Diabetes and Heart Failure: Truth and Consequences

Jeffrey Unger, MD

Disclosures: None
Diabetes and Heart Failure: Truth and Consequences

Jeff Unger, MD, FAAFP, FACE
Diplomat, American Board of Family Practice
Fellow, American Association of Clinical Endocrinologists
Assistant Clinical Professor of Family Medicine, UC Riverside School of Medicine
Director, Metabolic Studies; Catalina Research Institute
Director, Unger Concierge Primary Care Medical Group
Rancho Cucamonga, CA

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Disclosures

Jeff Unger, MD, has disclosed that he is on the advisory board for Abbott Diabetes, Novo Nordisk Diabetes, as well as on the speakers bureau for Abbott and Novo Nordisk. Additionally, he owns stock in Novo Nordisk.

Stephen Brunton, MD, has disclosed that he is on the advisory board for Abbott Diabetes, Salix, Astra Zeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, Teva, and Esperion, as well as on the speakers bureau for Astra Zeneca, Boehringer Ingelheim, Janssen, Lilly, and Novo Nordisk.

Gregory Scott, PharmD, RPh, Editorial Support, disclosed no relevant financial relationship or interest with a proprietary entity producing, marketing, reselling or distributing health care goods or services.
Learning Objectives

After participating in this presentation, the learner will be able to:

• Assess patients with type 2 diabetes mellitus for cardiovascular (CV) risk, including heart failure
• Describe the results of cardiovascular outcomes trials of glucose-lowering medications for type 2 diabetes mellitus, focusing on heart failure
• Select glucose-lowering medication shown to be beneficial in patients with type 2 diabetes mellitus at risk of heart failure

Diabetes Mellitus as a Cardiovascular Risk Factor


Linear Relationship Between Glycemic Control and HF


10 studies involving 178,929 patients with diabetes and 14,176 incident cases of HF

RR, relative risk
Patients with T2DM are at greater Risk of developing HF and being hospitalized due to HF

<table>
<thead>
<tr>
<th>Patients with T2DM are 2.5x more likely to develop HF than people without T2DM \cite{1,2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of hospitalization from HF is 33% higher in patients with T2DM \cite{3}</td>
</tr>
<tr>
<td>Even with optimal glycemic management, patients with T2DM have a high risk of morbidity and mortality \cite{4}</td>
</tr>
</tbody>
</table>

\begin{itemize}
  \item \cite{1} Nichols GA, et al. \textit{Diabetes Care}. 2004;27(8):1879-1884.
  \item \cite{3} Cavender MA, et al. \textit{Circulation}. 2015;132:923-931.
\end{itemize}

\textbf{UKPDS: 1% HbA1c Decrease and Reduced Risk of Complications}

- Lower extremity amputation or fatal peripheral vascular disease (All P<0.0001)
- Cardiovascular complications
- Microvascular disease (All P<0.0001)
- Cataract extraction (All P<0.0001)
- Heart failure (All P<0.0001)
- Myocardial Infarction (All P<0.0001)
- Stroke (All P<0.0001)

\textbf{Initial Presentation of Cardiovascular Disease in T2DM}

- Unrelated Coronary Death
- Transient Ischemic Attack
- Unstable Angina
- Non-fatal Myocardial Infarction
- Heart Failure
- Coronary Disease Not Further Specified
- Stable Angina
- Stroke Not Further Specified
- Ischemic Stroke
- Peripheral Arterial Disease

\textit{Adjusted for age, sex, body mass index, deprivation, HDL cholesterol, total cholesterol, systolic blood pressure, smoking status, and statin and antihypertensive medications}

Worse Prognosis in Patients with HF and T2DM

Exercise Capacity is diminished in patients with HFpEF and T2DM

Patients with T2DM and HFpEF have worse outcomes
How Heart Failure Is Diagnosed

**Clinical Evaluation**
- History & Physical examination
- Risk scoring - Seattle Heart Failure Model, ADHERE

**Testing**
- CBC, electrolytes, urinalysis, BUN, SCr, glucose, fasting lipids, LFTs, TSH
- Biomarkers - BNP, NT-proBNP
- Chest X-ray
- 12-lead ECG
- 2-dimensional echocardiogram with Doppler
- Angiogram

All of the Major Risk Factors for HF are Associated with Diabetes

- Hypertension
- Sleep Apnea
- Advanced Age
- Dyslipidemia
- Anemia
- Coronary Heart Disease
- Chronic Kidney Disease

Heart Failure
Diabetes Mellitus

Type 2 Diabetes Mellitus

- Insulin Resistance
- Prediabetes
- Type 2 Diabetes Mellitus
- Vascular Complications

Treating Patients with T2DM is more than Glucose Control

There's also:
- Antiplatelet therapy
- Blood pressure
- Cholesterol
- Exercise
- Dietary

And let's not forget:
- Smoking
- Weight
- Regular examination of:
  - Eyes, mouth/teeth, feet/skin, kidneys

Plus:
- Diabetes distress
- Quality of life

And now:
- Choose glucose-lowering medication shown to reduce cardiovascular risk (when possible)

Case Scenario: Fred

- 62 yo man diagnosed with T2DM 10 y ago (A1c 8.6%)
- 3 y history of mixed dyslipidemia
- Complains of occasional SOB, fatigue
- Currently:
  - A1c 7.5%
  - BMI 30.6 kg/m²
  - BP 160/95 mmHg
  - LDL-C 125 mg/dL
  - Triglycerides 364 mg/dL
  - Non-HDL-C 156 mg/dL
- Medications:
  - Metformin 1 g BID
  - Losartan 100 mg QD
  - Simvastatin 40 mg QD
  - ASA 81 mg QD

Case Scenario: Fred (cont)

- Diagnostic evaluation reveals Fred has heart failure with preserved ejection fraction
  - Ejection fraction 60%
The goal of cardiovascular safety trials is to demonstrate that the CV safety of the new glucose-lowering therapy is similar to placebo.

**Nomenclature**

- Primary vs secondary prevention
- Primary end point:
  - Composite of: CV death, non-fatal MI, and non-fatal stroke
Diabetes Medication CV Outcomes/Safety Trials

<table>
<thead>
<tr>
<th>DPP-4i</th>
<th>GLP-1RA</th>
<th>SGLT-2i</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>EXAMINE</td>
<td>Albiglutide*</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>CAMELINA</td>
<td>Dulaglutide</td>
</tr>
<tr>
<td></td>
<td>CAROLINA</td>
<td>Exenatide QW</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>SAVOR-TIMi3</td>
<td>Liraglutide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enalacetide</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>TECOS</td>
<td>Lixisenatide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Semaglutide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: All trials are randomized, double-blind, parallel, placebo-controlled, multicenter trials.

*Will no longer be available as of December 2019.

Case Scenario: Fred

- 62 yo man diagnosed with T2DM 10 y ago (A1c 8.6%)
- 3 y history of mixed dyslipidemia
- Complains of occasional SOB, fatigue

- Currently
  - A1c 7.5%
  - BMI 30.6 kg/m²
  - BP 160/95 mmHg
  - LDL-C 125 mg/dL
  - Triglycerides 164 mg/dL
  - Non-HDL-C 156 mg/dL

- Medications
  - Metformin 1 g BID
  - Losartan 100 mg QD
  - Simvastatin 40 mg QD
  - ASA 81 mg QD

Results of CV Outcomes Trials

<table>
<thead>
<tr>
<th>CV Safety</th>
<th>CV Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipeptidyl peptidase-4 inhibitors</td>
<td></td>
</tr>
<tr>
<td>Alogliptin</td>
<td>✓</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>✓</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>✓</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>✓</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-1 receptor agonists</td>
<td></td>
</tr>
<tr>
<td>Albiglutide*</td>
<td>✓</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>✓</td>
</tr>
<tr>
<td>Exenatide BID</td>
<td>Not required</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>✓</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>✓</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>✓</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>✓</td>
</tr>
<tr>
<td>Sodium glucose cotransporter-2 inhibitors</td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>✓</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>✓</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Will no longer be available as of December 2019.
Antihyperglycemic Medications Demonstrating Cardiovascular Benefit: SGLT-2 Inhibitors

### Canagliflozin (1 & 2 Prevention) - Endpoint

<table>
<thead>
<tr>
<th>Rate/100 patient-years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>2.69 (a)</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>0.55</td>
</tr>
<tr>
<td>CV death or HF hospitalization</td>
<td>1.63</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>8.94</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>0.55</td>
</tr>
</tbody>
</table>

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction

*Primary endpoint

Independent of prior stroke at baseline

### Dapagliflozin (1 & 2 Prevention) - Endpoint

<table>
<thead>
<tr>
<th>Rate/100 patient-years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>2.26</td>
</tr>
<tr>
<td>CV death or HF hospitalization</td>
<td>1.22</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>0.62</td>
</tr>
<tr>
<td>≥40% decrease in eGFR to &lt;60 mL/min/1.73 m², ESRD, or death from renal or CV cause</td>
<td>1.08</td>
</tr>
</tbody>
</table>

CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; MI, myocardial infarction

*Primary endpoint

Consistent across multiple groups, including history of ASCVD or heart failure

### Empagliflozin (2 Prevention) - Endpoint

<table>
<thead>
<tr>
<th>Rate/100 patient-years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>3.74 (b)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>1.94 (b)</td>
</tr>
<tr>
<td>CV death</td>
<td>1.24</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>0.94</td>
</tr>
<tr>
<td>HF hospitalization or CV death (excluding fatal stroke)</td>
<td>1.97</td>
</tr>
</tbody>
</table>

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction

*Primary endpoint

Independent of prior MI and/or stroke at baseline
## Antihyperglycemic Medications Demonstrating Cardiovascular Benefit: GLP-1 Receptor Agonists

### Dulaglutide (1 & 2 Prevention)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rate/100 patient-years</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>2.35</td>
<td>2.66</td>
<td>0.88 (0.79-0.99)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.52</td>
<td>0.69</td>
<td>0.76 (0.61-0.95)</td>
</tr>
<tr>
<td>New macroalbuminuria, sustained decline in eGFR ≥30% or chronic renal replacement therapy</td>
<td>3.47</td>
<td>4.07</td>
<td>0.85 (0.77-0.93)</td>
</tr>
</tbody>
</table>

*Primary endpoint


### Liraglutide (1 & 2 Prevention)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rate/100 patient-years</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>3.4</td>
<td>3.9</td>
<td>0.87 (0.78-0.97)</td>
</tr>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke, revascularization, or hospitalization for UA or HF</td>
<td>5.3</td>
<td>6.0</td>
<td>0.88 (0.78-0.99)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>2.1</td>
<td>2.5</td>
<td>0.85 (0.76-0.95)</td>
</tr>
<tr>
<td>CV death</td>
<td>1.2</td>
<td>1.6</td>
<td>0.78 (0.69-0.88)</td>
</tr>
<tr>
<td>Microvascular event</td>
<td>2.0</td>
<td>2.3</td>
<td>0.84 (0.71-0.99)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>1.5</td>
<td>1.9</td>
<td>0.78 (0.61-1.00)</td>
</tr>
</tbody>
</table>

*Primary endpoint *NNT=66 over 3 years *NNT=98 over 3 years


### Semaglutide (1 & 2 Prevention)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rate/100 patient-years</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>3.24</td>
<td>4.44</td>
<td>0.74 (0.63-0.88)</td>
</tr>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke, revascularization, hospitalization for UA or HF</td>
<td>6.17</td>
<td>8.36</td>
<td>0.74 (0.63-0.88)</td>
</tr>
<tr>
<td>All-cause death, nonfatal MI, nonfatal stroke</td>
<td>3.66</td>
<td>4.81</td>
<td>0.77 (0.65-0.92)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.80</td>
<td>1.31</td>
<td>0.61 (0.48-0.78)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>2.50</td>
<td>3.85</td>
<td>0.65 (0.50-0.84)</td>
</tr>
<tr>
<td>New or worsening nephropathy</td>
<td>1.86</td>
<td>3.06</td>
<td>0.64 (0.41-0.99)</td>
</tr>
</tbody>
</table>

*Primary endpoint

NNT=45 over 2 years


---

Antihyperglycemic Medications Demonstrating Cardiovascular Benefit: GLP-1 Receptor Agonists (cont)
## Effect of Selected Glucose-Lowering Medications on Heart Failure Hospitalization Rate/100 patient-years

<table>
<thead>
<tr>
<th></th>
<th>Rate/100 patient-years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SGLT-2 Inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>0.55</td>
<td>0.87</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>0.62</td>
<td>0.85</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>0.94</td>
<td>1.45</td>
</tr>
<tr>
<td><strong>GLP-1 Receptor Agonist</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dulaglutide⁴</td>
<td>0.83</td>
<td>0.91</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>1.76</td>
<td>1.61</td>
</tr>
</tbody>
</table>

⁴HF hospitalization or urgent visit

## Summary & Implications for Primary Care

- Reducing cardiovascular risk is the key treatment objective for patients with diabetes
- Available evidence shows that medications from 3 classes do not pose an increased risk of major adverse cardiovascular events
- Available evidence shows that the following medications reduce the risk of key cardiovascular outcomes
  - SGLT-2 inhibitors: canagliflozin, dapagliflozin, empagliflozin
  - GLP-1 RAs: albiglutide, dulaglutide, liraglutide, semaglutide

## New Paradigm in Diabetes Treatment

[Image of a flowchart or diagram related to diabetes treatment]
Patients with T2DM and Established ASCVD or CKD

Case Scenario: Fred

- 62 yo man diagnosed with T2DM 10 y ago (A1c 8.6%)
- 3 y history of mixed dyslipidemia
- Complains of occasional SOB, fatigue
- Currently
  - A1c 7.5%
  - BP 160/95 mmHg
  - LDL-C 125 mg/dL
  - Triglycerides 154 mg/dL
  - Non-HDL-C 156 mg/dL
- Medications
  - Metformin 1 g BID
  - Losartan 100 mg QD
  - Simvastatin 40 mg QD
  - ASA 81 mg QD

Diagnosed with HFpEF

For patients with type 2 diabetes mellitus and established coronary heart disease, which one of the following treatment goals should be optimized?

1. A1c
2. blood lipids
3. blood pressure
4. cardiovascular risk reduction
Diabetes and Heart Failure: Truth and Consequences

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