Decoding what to do when your patient has Diabetes and Cardiovascular Disease

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Disclosures

• Consultation: Medtronic
• Honoraria: Sanofi
• Research Support: CU Foundation CWHR Fellowship (Lilly)
Case Study

• 41-year-old South Asian female
  – Initial visit after moving to town

• Past Medical History
  – T2DM, hypertension, dyslipidemia
  – Non-smoker

• Medications:
  – Metformin 1g bid
  – Lisinopril 20 mg qd
  – Hydrochlorothiazide 25 mg qd
  – Atorvastatin 10 mg

• Physical Exam:
  – 200 lbs, 5’10”, BMI 28.6
  – BP 156/78, Pulse 80, Resp 20

• Lab results:
  – A1C: 8.0%
  – FPG: 180 mg/dL
  – Lipids: Total cholesterol 160 mg/dL, LDL 125 mg/dL, HDL 35 mg/dL, TG 175 mg/dL
  – Urine albumin/creatinine ratio 13

Question: Where do we start?
Comprehensive cardiovascular risk reduction

- Type 2 Diabetes
- Hypertension
- Dyslipidemia

- Glucose control  ? Target?
- BP control      ? Target?
- Cholesterol control ? Target?

I got this....
But the devil is in the details
We need to address risk factors. How are we doing?
Cardiovascular (CV) Risk Factor Targets in Diabetes:

Percent at target levels for any one, two, or all three factors among the 2018 persons with diabetes:

<table>
<thead>
<tr>
<th></th>
<th>Any 1 of 3</th>
<th>Any 2 of 3</th>
<th>3 of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>41.1%</td>
<td>26.5%</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

Percent CVD risk reduction for being at target level among:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Blood pressure</th>
<th>LDL-C</th>
<th>HBA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>17%</td>
<td>33%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Percent lower adjusted risk of CVD events with one, two, or three risk factors at target level:

<table>
<thead>
<tr>
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<th>Any 1 of 3</th>
<th>Any 2 of 3</th>
<th>3 of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>36%</td>
<td>52%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Comprehensive CVD risk factor modification saves lives:

- Every encounter presents an opportunity
- Employ our educational support systems to ensure adherence
- Diabetes means polypharmacy
- **Don’t forget diet and physical activity !!!**
Prevention or delay is the best risk reduction

Age of onset

Opportunity for DM prevention and CVD risk mitigation

Men

Women

Good News: Events per individual are lower

Bad news: absolute numbers are up

NHIS Data 1990-2010; Modified from Gregg et al. NEJM 2014
https://www.cdc.gov/diabetes/statistics/cvd/fig1.gif
## CV Outcome trials (CVOT) History:
- **FDA objective:** SAFETY

### Year | Drug | Safety concerns and response
--- | --- | ---
1992 | Human proinsulin | Trials and development suspended
|  |  | CV issues and ↑ risk of acute myocardial infarction\(^a\)
2005 | Muraglitazar | ↑ Risk of death, major CV adverse events, CHF\(^b\)
2007 | Rosiglitazone | ↑ CV risk; withdrawn from market in many countries\(^c\)
2008 | – | FDA issued guidance document for the evaluation of CV risk\(^d\)
|  |  | Studies are required to demonstrate that **new anti-diabetic therapies do not increase CV** risk in comparison with existing therapies

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NE ws:

Diabetes Medicine prevents MACE

MACE= major adverse cardiac events

GLP-1 agonists and SGLT2 inhibitors decrease CV events:

Trial after trial supports CV benefit
# FDA-Mandated CV Outcomes Trials in T2DM

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR¹</th>
<th>EXAMINE²</th>
<th>TECOS³</th>
<th>CARMELINA⁴</th>
<th>CAROLINA⁵</th>
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</thead>
<tbody>
<tr>
<td>DPP4-i</td>
<td>saxaglaptin</td>
<td>alogliptin</td>
<td>sitagliptin</td>
<td>linagliptin</td>
<td>linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>glimepiride (SU)</td>
</tr>
<tr>
<td>N</td>
<td>16,492</td>
<td>5380</td>
<td>14,671</td>
<td>6979</td>
<td>6103</td>
</tr>
<tr>
<td>Results</td>
<td>2013</td>
<td>2013</td>
<td>2015</td>
<td>2018</td>
<td>2018</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>ELIXA⁶</th>
<th>LEADER⁷</th>
<th>SUSTAIN 6⁸</th>
<th>EXSCEL⁹</th>
<th>REWIND¹⁰</th>
<th>HARMONY¹¹</th>
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</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td>lixisenatide</td>
<td>liraglutide</td>
<td>semaglutide</td>
<td>exenatide LR</td>
<td>dulaglutide</td>
<td>albiglutide</td>
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<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>9340</td>
<td>2015</td>
<td>2016</td>
<td>2017</td>
<td>2018</td>
<td>2018</td>
</tr>
<tr>
<td>Results</td>
<td>2015</td>
<td>2015</td>
<td>2016</td>
<td>2017</td>
<td>2018</td>
<td>2018</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG¹²</th>
<th>CANVAS¹³</th>
<th>(CREDENCE¹⁴)</th>
<th>DECLARE¹⁵</th>
<th>VERTIS CV¹⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2-i</td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>ertugliflozin</td>
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<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>702</td>
<td>4330</td>
<td>4400</td>
<td>8246</td>
<td>8246</td>
</tr>
<tr>
<td>Results</td>
<td>2015</td>
<td>2017</td>
<td>2018</td>
<td>2018</td>
<td>2020</td>
</tr>
</tbody>
</table>

What does this mean for your practice?
PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

Glucose-lowering Medication in Type 2 Diabetes: Overall Approach

Pharmacologic Approaches to Glycemic Management: Standards of Medical Care in Diabetes - 2020. Diabetes Care 2020;43(Suppl. 1):S98-S110
Type 2 Diabetes and ASCVD or CHF

Pre-existing and high risk

...regardless of A1c

Pharmacologic Approaches to Glycemic Management:
Standards of Medical Care in Diabetes - 2020. Diabetes Care 2020;43(Suppl. 1):S98-S110
Case Study: 5 years later

- 46-year-old South Asian female
  - Recent hospitalization for ACS and PCI x1 noted, EF 40%
- Past Medical History
  - T2DM, hypertension, dyslipidemia
  - Non-smoker
- Medications:
  - Metformin 1g bid
  - Lisinopril 20 mg qd
  - Hydrochlorothiazide 25 mg qd
  - Atorvastatin 40 mg
- Physical Exam:
  - 200 lbs, 5’10”, BMI 28.6
  - BP 122/68, Pulse 80, Resp 20
- Lab results:
  - A1C: 6.8%
  - FPG: 140 mg/dL
  - Lipids: Total cholesterol 120 mg/dL, LDL 66 mg/dL, HDL 40 mg/dL, TG 70mg/dL
  - Urine albumin/creatinine ratio 35
  - Cr 1.1

GLP1 RA or SGLT2 inhibitor?
2008 FDA Guidance for Industry on Evaluating the Cardiovascular Risk of New Antidiabetic Therapies

Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus

4.4.3 Long-term safety and cardiovascular safety
Concerning CV events, the emphasis will be on major cardiovascular events (MACE) (CV death, non-fatal myocardial infarction and stroke) but hospitalisation for unstable angina could also be included in a composite endpoint if the main objective is to exclude a safety signal. It is important to ensure that these are adjudicated events. Other events such as revascularisation and/or worsening of heart failure will also be evaluated. Other safety outcomes (e.g. malignancies) should be chosen based on the known safety profile of the product class, the mechanism of action of the investigational drug and/or the non-clinical findings.

THE LANCET Diabetes & Endocrinology 2014

Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored

This omission is important because hospital admission for heart failure is a common and prognostically important cardiovascular complication of diabetes. Moreover, it is the one cardiovascular outcome for which the risk has been shown unequivocally to be increased by some glucose-lowering therapies. As such, we believe that heart failure should be systematically evaluated in cardiovascular outcome trials of all new glucose-lowering drugs.

CV = cardiovascular; MACE = major adverse cardiovascular events.
Hospitalization for HF Predominates Among Diabetes-Related Admissions

GLP-1 Receptor Agonists and Risk for Heart Failure

Risk reduction in HF hospitalisation by 9%, GLP-1 RA vs. placebo; NNT 312 (95% CI 165–2810)

<table>
<thead>
<tr>
<th>Hospital admission for heart failure</th>
<th>936/27,977 (3%)</th>
<th>1016/28,027 (4%)</th>
<th>0.91 (0.83–0.99)</th>
<th>312 (165 to 2810)</th>
<th>0.028</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elixia</td>
<td>122/3,034 (4%)</td>
<td>127/3,034 (4%)</td>
<td></td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>Leader</td>
<td>218/4,668 (5%)</td>
<td>248/4,672 (5%)</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Sustain-6</td>
<td>59/1,648 (4%)</td>
<td>54/1,649 (3%)</td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Exscel</td>
<td>219/7,356 (3%)</td>
<td>231/7,396 (3%)</td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>Harmony outcomes</td>
<td>79/4,731 (2%)</td>
<td>111/4,732 (2%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rewind</td>
<td>213/4,949 (4%)</td>
<td>226/4,952 (5%)</td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>Pioneer 6</td>
<td>21/1,591 (1%)</td>
<td>24/1,592 (2%)</td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
</tbody>
</table>

Hospitalization for Heart Failure: Effects of SGLT2 Inhibitors

- **EMPA-REG OUTCOME**
  - Empagliflozin
  - 9.4 vs 14.5 events/1000 p-y
  - HR: 0.65 (0.50-0.85)
  - 35%

- **CANVAS/CANVAS-R**
  - Canagliflozin
  - 5.5 vs 8.7 events/1000 p-y
  - HR: 0.67 (0.52-0.87)
  - 33%

- **DECLARE-TIMI 58**
  - Dapagliflozin
  - 6.2 vs 8.5 events/1000 p-y
  - HR: 0.73 (0.61-0.88)
  - 27%

References:
CREDENCE Results: Hospitalization for Heart Failure

Hazard ratio, 0.61 (95% CI, 0.47–0.80)  
\( P < 0.001 \)

Participants with an event (%)

<table>
<thead>
<tr>
<th>Months since randomization</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2199</td>
<td>2202</td>
</tr>
<tr>
<td>6</td>
<td>2165</td>
<td>2171</td>
</tr>
<tr>
<td>12</td>
<td>2122</td>
<td>2131</td>
</tr>
<tr>
<td>18</td>
<td>2043</td>
<td>2076</td>
</tr>
<tr>
<td>24</td>
<td>1735</td>
<td>1789</td>
</tr>
<tr>
<td>30</td>
<td>1147</td>
<td>1226</td>
</tr>
<tr>
<td>36</td>
<td>638</td>
<td>668</td>
</tr>
<tr>
<td>42</td>
<td>170</td>
<td>199</td>
</tr>
</tbody>
</table>

No. at risk

- Placebo: 2199, 2165, 2122, 2043, 1735, 1147, 638, 170
- Canagliflozin: 2202, 2171, 2131, 2076, 1789, 1226, 668, 199
# Heart Failure Hospitalization By Prior Heart Failure

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>Hazard Ratio (95% C.I.)</th>
<th>Study</th>
<th>History of HF</th>
<th>No history of HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2i</td>
<td>Placebo</td>
<td><strong>Heterogeneity Q</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG Outcomes</td>
<td>40.7</td>
<td>52.4</td>
<td>0.75 (0.48, 1.19)</td>
<td>0.68 (0.55, 0.83)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>14.1</td>
<td>28.1</td>
<td>0.51 (0.33, 0.78)</td>
<td>0.59 (0.43, 0.82)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>27.7</td>
<td>37.2</td>
<td>0.73 (0.55, 0.96)</td>
<td>0.79 (0.57, 1.09)</td>
</tr>
<tr>
<td><strong>Fixed effects model for history of HF (p=0.0002)</strong></td>
<td>0.68 (0.55, 0.83)</td>
<td>0.71 (0.60, 0.83)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- EMPA-REG Outcomes: History of HF: 40.7 vs 52.4; Hazard Ratio: 0.75 (0.48, 1.19)
- CANVAS Program: History of HF: 14.1 vs 28.1; Hazard Ratio: 0.51 (0.33, 0.78)
- DECLARE-TIMI 58: History of HF: 27.7 vs 37.2; Hazard Ratio: 0.73 (0.55, 0.96)

- Fixed effects model for history of HF (p=0.0002) 0.68 (0.55, 0.83)


Data are not from head-to-head trials and should not be directly compared.
GLP1 RA and SGLT2 inhibitors save lives:

- Endocrinologists and cardiologists should start these agents
- In our health care delivery systems we should optimize PCP education to ensure optimal understanding, appropriate use and comfort with side effects
- Employ our educational support systems to ensure adherence and side effects mitigation/safety
- Improve policies to get these medications on formularies and affordable
Positive Sea Change:
GLP-1 Agonist
SGLT2 inhibitor

It’s a Glucose Medicine

It’s a Heart Medicine

It’s two medicines in One !!
Balancing Risks and Benefits for Personalized Goals

More Stringent Control
- No hypoglycemia
- Less complexity/polypharmacy
- Lifestyle or metformin only
- Short disease duration
- Long life expectancy
- No CVD

Less Stringent Control
- History of severe hypoglycemia
- High burden of therapy
- Longer disease duration
- Limited life expectancy
- Extensive co-morbidity
- CVD

NOW need to consider “diabetes” medications for CVD beyond glucose
In closing:

Efficacy of anti-hyperglycemic agents for ASCVD, CHF and renal disease changes the indications for these agents

Let’s discuss your patients and your challenges
Thank you for your time
SGLT2 inhibitors can cause DKA but you need to work at it:

- Endocrinologists and cardiologists should both initiate
- Be aware of high risk settings
STOP DKA Protocol

Symptomatic (e.g. lethargy, loss of appetite, nausea, abdominal pain) → STOP SGLT2

Test ketones* and glucose every 2-4 hours
(even if blood glucose is not elevated)

Oral ingestion of fluid and carbohydrates
(250–500 mL fluid every 2 hours and up to 30–60 g of carbohydrates every 2-4 hours)

Protocol instructions for supplemental insulin and carbohydrates
(see STOP DKA table)

*Ketosis/DKA may occur without an elevated blood glucose

Diabetes Self-management Education and Support

5.1 In accordance with the national standards for diabetes self-management education and support, all people with diabetes should participate in diabetes self-management education and receive the support needed to facilitate the knowledge, decision-making, and skills mastery necessary for diabetes selfcare. A

5.2 There are four critical times to evaluate the need for diabetes self-management education to promote skills acquisition in support of regimen implementation, medical nutrition therapy, and well-being: at diagnosis, annually, when complicating factors arise, and when transitions in care occur. E
Diabetes Self-management Education and Support

5.3 Clinical outcomes, health status, and well-being are key goals of diabetes self-management education and support that should be measured as part of routine care. C

5.4 Diabetes self-management education and support should be patient centered, may be given in group or individual settings and/or use technology, and should be communicated with the entire diabetes care team. A

5.5 Because diabetes self-management education and support can improve outcomes and reduce costs B, reimbursement by third-party payers is recommended. C
Diabetes Self-management Education and Support

Four critical time points have been defined when the need for DSMES is to be evaluated by the medical care provider and/or multidisciplinary team, with referrals made as needed:

1. At diagnosis
2. Annually for assessment of education, nutrition, and emotional needs
3. When new complicating factors (health conditions, physical limitations, emotional factors, or basic living needs) arise that influence self-management
4. When transitions in care occur