Role of DPP-4 Inhibitors, GLP-1 Agonists, and SGLT-2 Inhibitors in the treatment of Diabetes Mellitus Type 2

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Disclaimers

• I have not received money or gifts from medical device companies or from the pharmaceutical industry.

• I am currently utilizing a grant from the Valley Regional Hospital Foundation to implement a low carbohydrate high fat dietary intervention for the treatment of Diabetes Mellitus Type 2.

Learning Objectives

• For DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors:
  • Mechanism of action
  • Evidence and limitations
  • Diabetes Canada Guidelines
  • Evidence-based and patient-centred approach to prescribing
  • Touch on new models of understanding DM2 with their potential impact on treatment decisions

Outline of presentation

• Take a look at a few cases
• Review pathophysiology of DM2 and natural history
• Review evidence to individualize an A1c target
• Review mechanism of action of newer classes of diabetes medications
• Review efficacy and safety of these medications by looking at meta-analysis, RCTs, and evidence-based resources
• A look back at initial cases

Case 1

History
70 M presents to your office for routine follow-up for Diabetes Mellitus Type 2. He has had Diabetes for the past 3 years. There is no evidence of microvascular or macrovascular complications.

Past Medical History
Hypertension, COPD, Hyperlipidemia

Medications
Metformin 1000 mg BID, Atorvastatin 20mg a day, Perindopril 4mg a day

Social History
Non-smoker, on Pharmacare

Exam
BP 130/80, BMI 32

Labs
A1C: 8.5 (similar past 3 years), Creatinine B1, UACR negative

Case 1: What is the next best step for this 70 yr old patient with DM2 for the past 3 years with no complications, obesity, & A1c of 8.5?

A. Add a sulfonylurea as it has a reasonable safety profile and is the most cost effective medication.

A. Add a DPP-4 as it is the most likely to get the A1c down to goal (and is also the best tolerated)

A. Add a GLP-1 agonist as it is now the preferred second line agent to metformin based on decreased mortality and cardiovascular events seen in the LEADER trial.

A. Add a SGLT-2 inhibitor as it is now the preferred second line agent to metformin based on decreased mortality and cardiovascular events seen in the EMPA-REG trial.
Case 2

**History**
60 F with Diabetes Mellitus 2 for the past 5 years presents for routine follow up. Diabetes complicated by coronary artery disease (nSTEMI 6 years ago with complex 3VD) and an EF of 35%. She is frustrated that she is not losing weight. No recent hospital admissions.

**Past Medical History**
Obesity, Hypertension, Hyperlipidemia, OSA, CHF, urosepsis 2 yrs ago

**Medications:**
- Atorvastatin 20 mg
- ASA 81 mg
- metformin 1000 BID
- carvedilol 12.5 BID
- perindopril 4 mg daily
- furosemide 20 mg daily

**Exam**
BP 110/80, BMI is 34. Euvolemic on exam.

**Investigations:**
- A1c is 7.6
- LDL 1.8
- UACR 5
- Creatinine 120
- eGFR of 50

Case 2: What is the next best step for this 60 yr old patient with DM2 for the past 5 years with obesity, diffuse three vessel coronary artery disease, CHF, and an A1c of 7.6?

A. Add a sulfonylurea as it is cost effective and will do just as well as the newer agents at protecting against major adverse cardiovascular events.

B. Add Liraglutide, a GLP-1 agonist, due to its evidence for lowering major adverse cardiac events, weight loss effect, and no increased risk of urinary tract infections

C. Add Empagliflozin, a SGLT-2 inhibitor, due to evidence for lowering major adverse cardiac events including lowering risk of CHF admissions.

D. Intensify lifestyle therapy. Given A1c < 8.5 and presence of established CAD, there is concern about lowering A1c further due to increased mortality in the ACCORD trial (2008) for patients with established coronary artery disease.

Case 3

**History**
50 year old male presents in routine follow up for Diabetes Mellitus Type 2 for the past 6 years and basal insulin therapy the past 5 1/2 years. Blood sugars are running 4 to 8 in the morning and 4 to 14 through the day.

**Past Medical History:**
No history of hypertension or dyslipidemia.

**Medications:**
- Metformin 1000 mg twice a day
- Glargine 14 units subcutaneous each night

**Social History:**
Retired from the military, no smoking, and a runner

**Exam:**
BP 120/80, BM 23, Appears thin, healthy and fit

**Labs:**
- A1c of 8.3,
- Creatinine is normal

Case 3: What is the next best step for this 50 yr old patient with DM2, normal BMI, who is on glargine for the past 5.5 yrs?

A. Add a sulfonylurea due to safety and cost.

B. Add a DPP-4 inhibitor due to tolerability and efficacy.

C. Add a GLP-1 agonist as it has more potent A1c reduction.

D. Add a SGLT-2 inhibitor as it has a very low risk causing lows while also preventing highs.

E. Check C-peptide and anti-GAD antibody

Pathophysiology of DM 2

**Curr Pharm Design, 2012;19 (13)**

Natural History of Diabetes Mellitus Type 2

**Figure adapted from American Association of Clinical Endocrinologists website; modified by MMINDRUM to include drug classes**
Heterogeneity of DM 2

Figure modified MMINDRUM March 2018 to include description of subtypes

UKPDS 10 year follow up for sulfonylurea or insulin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event Rate</th>
<th>RRR</th>
<th>ARR</th>
<th>Time (yrs)</th>
<th>NNT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DM endpoint</td>
<td>47.5%</td>
<td>52.2%</td>
<td>9%</td>
<td>4.7%</td>
<td>21</td>
<td>[15 to 28]</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>10.8%</td>
<td>14.2%</td>
<td>24%</td>
<td>3.4%</td>
<td>29</td>
<td>[19 to 42]</td>
</tr>
<tr>
<td>Diabetes related death</td>
<td>14.1%</td>
<td>17%</td>
<td>17%</td>
<td>2.9%</td>
<td>35</td>
<td>[29 to 47]</td>
</tr>
</tbody>
</table>

Microvascular disease: 11.3% vs 13.4% (16%) 3%

Diabetes related death: 13.1% vs 18.7% (30%) 5.6%


UKPDS 10 year follow up for metformin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event Rate</th>
<th>RRR</th>
<th>ARR</th>
<th>Time (yrs)</th>
<th>NNT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DM endpoint</td>
<td>42.6%</td>
<td>53.9%</td>
<td>21%</td>
<td>11.3%</td>
<td>9</td>
<td>[6 to 14]</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>11.3%</td>
<td>13.4%</td>
<td>16%</td>
<td>3%</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Diabetes related death</td>
<td>13.1%</td>
<td>18.7%</td>
<td>30%</td>
<td>5.6%</td>
<td>18</td>
<td>[13 to 24]</td>
</tr>
</tbody>
</table>


ACCORD Trial

Outcome | Event Rate (Annual) | RRR | ARR | Time (yrs) | NNT | 95% CI         |
--------|---------------------|-----|-----|------------|-----|---------------|
MACE    | 2.11%               | 2.29%| N/A | N/A        | N/A |               |
Mortality | 1.41%             | 1.14%| .23%| .24%       | N/A |               |
Hypoglycemia | 10.5%       | 3.5% | .45%| .7%        | N/A |               |

Individualizing A1C Targets

A target A1C ≤7.5% may be considered in some patients with type 2 diabetes to further lower the risk of microvascular and retinopathy which must be balanced against the risk of hypoglycemia.

Most patients with type 1 and type 2 diabetes

Consider 7.1-8.5% if:
- Limited life expectancy
- High level of functional dependency
- Extensive coronary artery disease at high risk of ischemic events
- Multiple co-morbidities
- History of recurrent severe hypoglycemia
- Hypoglycemia unawareness
- Longstanding diabetes for whom A1C ≥7.0% is difficult to achieve and is an absolute A1C ≥7.5% in a subgroup of patients

Relative goals
- Decrease A1C
- Avoid hypoglycemia
- Well tolerated and safe
- Weight loss or weight neutral
- Cost effective
- Pleiotropic effects
  - Decrease inflammatory markers
  - Improve endothelial function
  - Reduce hyperinsulinemia
  - Improve insulin sensitivity
  - Improve quality of life

Absolute Goals
- Reduce microvascular complications
- Retinopathy / Blindness
- Renal function: Dialysis
- Neuropathy / Amputations
- Cardiovascular Complications
  - Heart Attack
  - Stroke
- Cardiovascular mortality
- All cause mortality

DPP-4 Inhibitors, GLP-1 agonists, and SGLT-2 Inhibitors

DPP-4 Inhibitors
- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Trajenta)

GLP-1 Agonists
- Exenatide (Byetta, Bydureon)
- Liraglutide (Victoza)
- Dulaglutide (Trulicity)
- Semaglutide (Ozempic)

SGLT-2 Inhibitors
- Dapagliflozin (Forxiga)
- Canagliflozin (Invokana)
- Empagliflozin (Jardiance)

Combination Pills
- Metformin/sitagliptin (Janumet)
- Metformin/saxagliptin (Jentadueto)
- Metformin/linagliptin (Kazano)
- Metformin/dapagliflozin (Xigduo)
- Metformin/alogliptin (Kazano)
- Metformin/dapagliflozin (Xigduo)
- Metformin/saxagliptin (Kamblyza)
- Metformin/dapagliflozin (Xigduo)

GLP-1 Agonists & DPP-4 Inhibitors

Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes

- Meta-analysis of 27 randomized trials with ~11,000 patients
- Conclusion: when added to maximal metformin therapy, all non-insulin anti-diabetic drugs were associated with similar HgbA1c reductions but differed in their associations with weight gain and risk of hypoglycemia.

Adapted from: Diabetes. 2009; 58: 783-790 and
CADTH Network Meta-Analysis, comparative effectiveness

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>A1c</th>
<th>Weight (kg)</th>
<th>Systolic BP</th>
<th>OR of severe hypoglycemia</th>
<th>OR of SAEs</th>
<th>OR of withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4i</td>
<td>-0.58</td>
<td>0.18</td>
<td>-1.04</td>
<td>0.91</td>
<td>0.91</td>
<td>0.78</td>
</tr>
<tr>
<td>GLP-1a</td>
<td>-0.88</td>
<td>-1.44</td>
<td>-2.79</td>
<td>1.8</td>
<td>1.05</td>
<td>1.8</td>
</tr>
<tr>
<td>SGLT-2</td>
<td>-0.67</td>
<td>-2.21</td>
<td>-4.06</td>
<td>0.61</td>
<td>1.11</td>
<td>1</td>
</tr>
<tr>
<td>SUs</td>
<td>-0.7</td>
<td>2.11</td>
<td>2.84</td>
<td>6.4</td>
<td>0.96</td>
<td>0.74</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>-0.85</td>
<td>2.76</td>
<td>1</td>
<td>3</td>
<td>1.48</td>
<td>0.33</td>
</tr>
</tbody>
</table>

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CADTH Network Meta-Analysis, comparative effectiveness in cardiovascular safety trials

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>OR of MACE</th>
<th>OR of CV mortality</th>
<th>OR of Mortality</th>
<th>OR of CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4i</td>
<td>0.99</td>
<td>[0.68 to 1.45]</td>
<td>0.97</td>
<td>[0.83 to 1.2]</td>
</tr>
<tr>
<td>GLP-1a</td>
<td>0.87</td>
<td>[0.45 to 1.6]</td>
<td>0.86</td>
<td>[0.71 to 1.2]</td>
</tr>
<tr>
<td>SGLT-2</td>
<td>0.84</td>
<td>[0.46 to 1.67]</td>
<td>0.56</td>
<td>[0.47 to 0.95]</td>
</tr>
</tbody>
</table>

Therapeutics Review Recommendations; 2017 (4) 1 - 20

CADTH Cost Analysis

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Example</th>
<th>Cost/day</th>
<th>Cost/day + Test strips</th>
<th>ICUR vs Metformin ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4i</td>
<td>Linagliptin 5 mg</td>
<td>$2.85</td>
<td>$3.62</td>
<td>$178,127</td>
</tr>
<tr>
<td>GLP-1a</td>
<td>Exanatide 20 mg</td>
<td>$4.41</td>
<td>$5.17</td>
<td>$119,997</td>
</tr>
<tr>
<td>SGLT-2</td>
<td>Empagliflozin 2.5 mg</td>
<td>$2.92</td>
<td>$3.69</td>
<td>$100,459</td>
</tr>
<tr>
<td>Sulfonylurals</td>
<td>Glyburide 10 mg</td>
<td>$0.22</td>
<td>$1.17</td>
<td>$38,643</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>0.5 u/kg</td>
<td>$3.7</td>
<td>$5.48</td>
<td>$324,968</td>
</tr>
<tr>
<td>Metformin</td>
<td>2000 mg</td>
<td>$0.29</td>
<td>1.06</td>
<td>N/A</td>
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</tbody>
</table>

Therapeutics Review Recommendations; 2017 (4) 1 - 20

DPP-4, GLP-1 Agonists, SGLT-2 Inhibitors and Cardiovascular Outcomes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Study</th>
<th>MACE</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxagliptin</td>
<td>SAVOR TIMI 53</td>
<td>~16K at high CV risk over 2 yrs</td>
<td>non-inferior</td>
<td>CHF (NNH 148)*</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>EXAMINE</td>
<td>5.3K w/ recent ACS over 1.5 yrs</td>
<td>non-inferior</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>TECOS</td>
<td>14.6K w/ CAD over 3 yrs</td>
<td>non-inferior</td>
<td></td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>ELIXA</td>
<td>6K w/ recent ACS over ~2 yrs</td>
<td>non-inferior</td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>LEADER</td>
<td>9.3K in high CV risk over ~4 yrs</td>
<td>superior</td>
<td>See next slides</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>SUSTAIN-6</td>
<td>3.2K at high CV risk over 2 yrs</td>
<td>non-inferior</td>
<td>See next slides</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>EMPA-REG</td>
<td>7K at high CV risk over 3 yrs</td>
<td>superior</td>
<td>See next slides</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>CANVAS</td>
<td>10K at high CV risk over 3 yrs</td>
<td>non-inferior</td>
<td>See next slides</td>
</tr>
</tbody>
</table>


*CHF admission rate of 3.5% vs. 2.8%; HR of 1.27; CI 1.07-1.51; p=0.007

LEADER Trial

- 9340 patients with Type 2 DM and high cardiovascular risk randomized to liraglutide or placebo
- Age >50 with any arterial disease, CKD, Class II/III CHF,
- Or age 60 with positive UACR, HTN with LVH, or systolic/diastolic dysfunction
- Median follow up of 3.8 yrs
- Average age was 64, BMI of 32, average duration of DM was 13 yrs, entry A1c of 8.7
- A1c decreased by 0.4% compared to placebo
- Body weight decreased by 2.3 kg
- Systolic BP decreased by 1.2 mm Hg
- Primary composite outcome in time to first occurrence of death from cardiovascular causes, non fatal MI, or non-fatal stroke


LEADER Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event Rate</th>
<th>RRR</th>
<th>ARR</th>
<th>Time [yrs]</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>13%</td>
<td>14.9%</td>
<td>12%</td>
<td>1.9%</td>
<td>52.6</td>
</tr>
<tr>
<td>CV Death</td>
<td>4.7%</td>
<td>6.0%</td>
<td>32%</td>
<td>1.3%</td>
<td>76.9</td>
</tr>
<tr>
<td>DM</td>
<td>4.7%</td>
<td>5.3%</td>
<td></td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>8.2%</td>
<td>9.6%</td>
<td>15%</td>
<td>1.4%</td>
<td>71.4</td>
</tr>
</tbody>
</table>

SUSTAIN - 6

- Double blind non-inferiority trial
- 3297 patients to once weekly semaglutide or placebo
- Mean age 65, DM for average of 13.9, mean A1c of 8.7
- High risk patients: 60% with established CAD
- Followed for 2 yrs


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event Rate</th>
<th>RRR</th>
<th>ARR</th>
<th>Time (yrs)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>6.5%</td>
<td>8.85%</td>
<td>25.9%</td>
<td>2.35%</td>
<td>43.5*</td>
</tr>
<tr>
<td>CV Death</td>
<td>2.7%</td>
<td>2.8%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Mortality</td>
<td>3.8%</td>
<td>2.6%</td>
<td>NA</td>
<td>NA</td>
<td>N/A</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>3%</td>
<td>1.8%</td>
<td>66%</td>
<td>1.2%</td>
<td>NNH 83</td>
</tr>
</tbody>
</table>

*notes: mostly due to decreased risk of non-fatal stroke 1.6% vs 2.7%, HR of 0.61 [0.38 to 0.99]; more retinopathy and less nephropathy; more insulin in the placebo group

EMPA-REG Trial

- 7020 patients with DM2 with CAD
- Duration: 3.1 yrs
- Randomized to empagliflozin or placebo
- Mean age of 63, mean BMI 31, more than 50% had DM2 for >10 yrs,
- Glucose target was 6.5 to 7% in accordance with aggressive standard of care.
- Primary composite endpoint was
- A1c improved around 0.5% in empagliflozin


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event Rate</th>
<th>RRR</th>
<th>ARR</th>
<th>Time (yrs)</th>
<th>NNT 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>10.5%</td>
<td>12.2%</td>
<td>14%</td>
<td>1.7%</td>
<td>58.8</td>
</tr>
<tr>
<td>CV Death</td>
<td>3.7%</td>
<td>5.9%</td>
<td>38%</td>
<td>2.2%</td>
<td>45.5</td>
</tr>
<tr>
<td>CHF</td>
<td>2.7%</td>
<td>4.1%</td>
<td>35%</td>
<td>1.4%</td>
<td>71.4</td>
</tr>
<tr>
<td>Mortality</td>
<td>5.7%</td>
<td>8.3%</td>
<td>32%</td>
<td>2.6%</td>
<td>38.5</td>
</tr>
</tbody>
</table>

EMPA-REG harms

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event Rate</th>
<th>RRR</th>
<th>ARR</th>
<th>Time (yrs)</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urosepsis</td>
<td>0.1%</td>
<td>0.4%</td>
<td>2.83</td>
<td>0.3</td>
<td>333</td>
</tr>
<tr>
<td>Genital infection (female)</td>
<td>2.6%</td>
<td>10%</td>
<td>3.84</td>
<td>7.4</td>
<td>13.5</td>
</tr>
<tr>
<td>Genital infection (male)</td>
<td>1.5%</td>
<td>5.0%</td>
<td>8.47</td>
<td>3.5</td>
<td>28.6</td>
</tr>
</tbody>
</table>

EMPA-REG medication adjustments

<table>
<thead>
<tr>
<th>Participants with additional:</th>
<th>Placebo</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose lowering medications</td>
<td>31.5%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Insulin</td>
<td>11.5%</td>
<td>5.8%</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>8.3%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Sultonylurea</td>
<td>7.0%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>2.9%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

EMPA-REG alternative hypothesis

1. Empagliflozin decreases mortality and serious adverse events when added to standard of care.

2. The more aggressive use of other glucose lowering medications in the placebo group increases mortality and serious adverse events.

3. A combination of 1 and 2.


CANVAS trial

- 10,000 patients at high CV risk
- Man age 63 yrs, mean duration of DM was 13.5
- 65% had CV disease
- Randomized to canagliflozin or placebo
- Followed for 3.5 years
- Primary outcome was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke.

Selected Diabetes Canada Guidelines, 2016 interim update

1. If A1C <8.5% and glycemic targets are not achieved with lifestyle management within 2 to 3 month, metformin should be initiated Grade A, Level 1A

2. Metformin should be initial drug in monotherapy for overweight patients Grade A, Level 1A

3. If symptomatic hyperglycemia with metabolic decompensation start insulin +/- metformin Grade A, Consensus

4. Additional therapies should be added to metformin, or used in combination with each other based on table http://guidelines.diabetes.ca/update Grade D, Consensus

5. In adults with CVD in whom glycemic targets are not met, an antihyperglycemic agent with demonstrated CV benefit should be added to reduce major CV events

- Empagliflozin Grade 1, Level 1A
- Linagliptin if age <50 Grade 1, Level 1A
- Linagliptin if age >50 Grade D, Consensus

Selected antihyperglycemic agents and Renal Function

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event Rate/1000pt yr</th>
<th>Time (yrs)</th>
<th>NNT 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>26.9</td>
<td>3.5</td>
<td>223</td>
</tr>
<tr>
<td>CV Death</td>
<td>11.6</td>
<td>9</td>
<td>n/a</td>
</tr>
<tr>
<td>CHF</td>
<td>5.5</td>
<td>9</td>
<td>287</td>
</tr>
<tr>
<td>Mortality</td>
<td>17.3</td>
<td>3.4</td>
<td>NHN 346</td>
</tr>
<tr>
<td>Amputation</td>
<td>6.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Add another agent best suited to the individual by prioritizing patient characteristics:

- **Priority Characteristic**
  - Clinical cardiovascular disease
  - Risk of hypoglycemia
  - Overweight or obesity
  - CV disease or multiple risk factors
  - Comorbidities (renal, CHF, hepatic)
  - Preferences & access to treatment

- **Choice of Agent**
  - Antihyperglycemic agent with demonstrated CV outcome benefit (empagliflozin, liraglutide)

- Degree of hyperglycemia
- Risk of hypoglycemia
- Overweight or obesity
- CV disease or multiple risk factors
- Comorbidities (renal, CHF, hepatic)
- Preferences & access to treatment

- Consider relative A1C lowering
- Weight loss or weight neutral
- Effect on cardiovascular outcome
- See therapeutic considerations;
  - Consider eGFR
  - See cost column; consider access

Alogliptin
- Not recommended
- 50 mg
- 6.25 mg
- 12.5 mg

Acarbose
- Not recommended
- 25 mg

Alogliptin
- Not recommended
- 50 mg
- 6.25 mg
- 12.5 mg

Albiglutide
- 50 mg
- 30 mg

Albiglutide
- 50 mg
- 30 mg

Alogliptin
- Not recommended
- 50 mg
- 6.25 mg
- 12.5 mg
Add another class of agent best suited to the individual (agents listed in alphabetical order):

<table>
<thead>
<tr>
<th>Class</th>
<th>Relative to Metformin</th>
<th>Effect in Cardiovascular Outcome Trial</th>
<th>Other Therapeutic Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C Lowering</td>
<td>None</td>
<td>None</td>
<td>Improved postprandial control, GI side effects</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>None</td>
<td>Decrease in A1C with reduced DPP-4 levels</td>
<td>Caution with saxagliptin in heart failure</td>
</tr>
<tr>
<td>GLP-1R agonists</td>
<td>Neutral</td>
<td>Rare to None</td>
<td>Improved postprandial control, GI side effects</td>
</tr>
<tr>
<td>Insulin</td>
<td>None</td>
<td>None</td>
<td>Neutral (glar)</td>
</tr>
<tr>
<td>Insulin secretagogue: Sulfonylurea</td>
<td>None</td>
<td>None</td>
<td>Yes, Yes, Yes, Yes, Yes</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Neutral</td>
<td>Rare to None</td>
<td>Superiority in T2DM patients with clinical CVD, Neutral GI side effects</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Neutral</td>
<td>Rare</td>
<td>CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect</td>
</tr>
<tr>
<td>Weight loss agent</td>
<td>None</td>
<td>None</td>
<td>GI side effects</td>
</tr>
</tbody>
</table>

**CADTH**

1. For patients without CVD, a sulfonylurea should be added to metformin if inadequate glycemic control on metformin alone.

2. For patients with established CVD, CADTH recommends empagliflozin based on their current review.

**CADTH limitations**

- Many studies could not be included in the meta-analysis as metformin was not the base therapy
- 20% of studies were felt to have a high risk of bias
- Several studies used A1c goal of <6.5% as adequate control
- Little evidence of clinically important endpoints, little evidence of long term diabetes related complications (low event rates in individual studies)

**Case 1**

**History**

60 F with Diabetes Mellitus 2 for the past 5 years presents for routine follow up. Diabetes complicated by coronary artery disease (nSTEMI 6 years ago with complex 3VD) and an EF of 35%. She is frustrated that she is not losing weight. No recent hospital admissions.

**Past Medical History**

Obesity, Hypertension, Hyperlipidemia, OSA, CHF, Urosepsis 2 yrs ago

**Medications**

Atorvastatin 20mg a day, Perindopril 4mg a day

**Exam**

BP 110/80, BMI 32

**Labs**

A1c: 8.5 (similar past 3 years), Creatinine 80, UACR-negative

**Case 2**

**History**

40 Yr Diabetes Mellitus 2 for the past 3 years presents for routine follow up. Diabetes complicated by coronary artery disease (STEMI 6 years ago with complex 3VD) and an EF of 30%. She is frustrated that she is not losing weight. No recent hospital admissions.

**Past Medical History**

Obesity, Hypertension, Hyperlipidemia, OSA, CHF, corsac rule 3 yrs ago

**Medications**

Atorvastatin 20mg, ASA 81mg, metformin 1000 bid, carvedilol 12.5 bid, pantoprazole 4 mg daily, and furosemide 20 mg daily

**Exam**

BP 110/80, BMI 34. Euvolemic on exam.

**Investigations**

A1c 8.5, LDL 1.6, UACR 5, Creatinine 120, eGFR of 50
Case 2: What is the next best step for this 60 yr old patient with DM2 for the past 5 years with obesity, diffuse three vessel coronary artery disease, CHF, and an A1c of 7.6?

A. Add a sulfonylurea as it is cost effective and will do just as well as the newer agents at protecting against major adverse cardiovascular events.

B. Add Liraglutide, a GLP-1 agonist, due to its evidence for lowering major adverse cardiac events, weight loss effect, and no increased risk of urinary tract infections.

C. Add Empagliflozin, a SGLT-2 inhibitor, due to evidence for lowering major adverse cardiac events including lowering risk of CHF admissions.

D. Intensify lifestyle therapy. Given A1c < 8.5 and presence of established CAD, there is concern about lowering A1c further due to increased mortality in the ACCORD trial (2008) for patients with established coronary artery disease.

Case 3: What is the next best step for this 50 yr old patient with DM2, normal BMI, who is on glargine for the past 5.5 yrs?

A. Add a sulfonylurea due to safety and cost.

A. Add a DPP-4 inhibitor due to tolerability and efficacy.

A. Add a GLP-1 agonist as it has more potent A1c reduction.

A. Add a SGLT-2 inhibitor as it has a very low risk causing lows while also preventing highs.

A. Check C-peptide and anti-GAD antibody.

Role of DPP-4 Inhibitors, GLP-1 Agonists, and SGLT-2 Inhibitors in the treatment of Diabetes Mellitus Type 2

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