Type 2 Diabetes: An Update on Oral and Injectable Medications

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Family Medicine Grand Rounds
March 2021
Financial Disclosures

Research Grant Funding:
• Abbott Diabetes
• Novo Nordisk
Outline

• Glycemic Targets
• Diabetes Education: Nutrition, Exercise
• Type 2 DM Management
  • Guidelines
  • Medications
    • Shared decision-making / factors
    • Risks & benefits of specific medication classes
      • Cardiovascular outcomes
      • Renal outcomes
• Glucose Monitoring
Approach to Glycemic Control in Type 2 Diabetes Mellitus

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C.
Guidelines for Glycemic Control: What’s Best for the Patient?

- **A1C < 7% for most patients**
- **A1C goals may be adjusted based on risk (i.e. older adult, CAD, Stroke, Dementia)**
  - Individualize de-intensification based on hypoglycemia risk and other potential harmful effects
    - Examples…
      - < 7.5 to 8% → CAD, Stroke or > 70 years
      - < 8 to 8.5% → Dementia or other significant co-morbidities
- **A1C levels > 8.5% increase polyuria, polydipsia, renal dysfunction.**
Diabetes Education Outcomes – Clinical Benefits

Group-based diabetes education: 11 studies, 1532 patients

Primary Endpoint: A1C Change

Secondary Endpoints

- Weight Loss: -1.6 Kg @ 12-14 months
- Blood Pressure (SBP): -5 mmHg @ 4-6 mos
- Reduce DM Meds: NNT = 5

Type 2 Diabetes Management Guidelines

American Diabetes Association Standards of Medical Care in Diabetes—2020

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)
Type 2 Diabetes Management Guidelines: First-Line Therapy is Metformin
Biguanides (Metformin)

- **A1C Effect:** 1 to 2%
- **Reasons to Consider:**
  - Weight loss (2-3 kg)
  - PO Route
  - No Hypoglycemia
- **Side effects, Limiting Factors:**
  - GI side effects
  - Risk for lactic acidosis (rare)
    - Absolute: GFR < 30 (do not start with GFR < 45)
    - Relative: (1) Liver dysfunction, (2) Heart failure, (3) Age > 80 years, (4) Heavy alcohol intake
What About the Patient Who Doesn’t Tolerate Metformin?

Gastrointestinal side effects? Consider Metformin ER…

But a number of brands have been recalled…

A diabetes drug has been recalled because it contains high levels of cancer-causing agent

By Scottie Andrew, CNN

Updated 9:45 AM ET, Fri October 9, 2020

A diabetes drug has been recalled because it contains high levels of cancer-causing agent

By Scottie Andrew, CNN

Updated 9:45 AM ET, Fri October 9, 2020

An Indian pharmaceutical company is recalling some metformin tablets because they may contain higher-than-normal levels of a carcinogen.
Medications to Treat Type 2 Diabetes Mellitus

Type 2 Diabetes Management Guidelines: Shared Decision Making Based on Many Factors

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF

CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

ASCVD PREDOMINATES
- Established ASCVD
- Indicators of high ASCVD risk (age <55 years with coronary, carotid or lower extremity artery stenosis >50%, or LHV)

HF OR CKD PREDOMINATES
- Particularly HFrEF (LVEF <50%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

COMPPELLING NEED TO MINIMIZE HYPOGLYCEMIA

PREFERABLY
- GLP-1 RA with proven CVD benefit!
- SGLT2i with proven CVD benefit!

IF A1C above target
- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit!
  - DPP-4i if not on GLP-1 RA
  - Basal insulin
  - TZD
  - SU

COMPPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

COST IS A MAJOR ISSUE

SU6
TZD5

IF A1C above target
- If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain
- Preferably:
  - DPP-4i (if not on GLP-1 RA) based on weight neutrality

IF A1C above target
- Insulin therapy basal insulin with lowest acquisition cost
- Consider DPP-4i or SGLT2i with lowest acquisition cost

Consider the addition of SU or basal insulin:
- Choose second generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia
Type 2 Diabetes Mellitus: Second-Line Medication Choice…

• The choice for second-line therapy is not always straightforward. Consider based on multiple factors…
  • Change in A1C (efficacy)
  • Cost
  • Hypoglycemia risk
  • Side effects
  • Weight Change
  • Cardiovascular disease

ADA/EASD Guidelines. Diabetes Care. 2020
Sulfonylureas and Meglitinides

• **Examples**
  - Sulfonylureas: Glipizide, Glimepiride, Gliburide
  - Meglitinides: Repaglinide, Nateglinide

• **A1C Effect:** 1 to 2%

• **Reasons to Consider:**
  - Established, well-studied generic pill
  - Glinides → lower risk of hypoglycemia

• **Side effects, Limiting Factors:**
  - Hypoglycemia (erratic PO intake, elderly, renal dysfunction)
  - Weight gain (2 kg)
Skipping meals and increasing risk of low sugars?
Case of Hyperglycemia – What Might You Choose?

• An 87 year old female presents to your clinic for follow-up for T2DM.
  • She has a history of diabetes for about 6 years duration. She also has hypertension, hyperlipidemia, chronic kidney disease, and dementia.
• Her current diabetes regimen includes metformin 1000 mg BID.
  • She tolerates dosing; no changes for the last 6 years.
• Hemoglobin A1C is 9.1% & GFR 42

Do you add to the regime? If so, what might you recommend? **Sulfonylurea increases hypoglycemia risk,** **Meglitinide** less so….
Type 2 Diabetes Mellitus: Second-Line Medication Choice…

• The choice for second-line therapy is not straightforward and based on multiple factors…

  • Change in A1C (efficacy)
  • Cost
  • Hypoglycemia risk
  • Side effects
  • Weight Change
  • Cardiovascular disease

ADA Guidelines. Diabetes Care. 2020
Second-Line Therapy Considerations: Minimize Hypoglycemia

Consider one of the following medication classes:

- Thiazolidinediones
- SGLT-2 Inhibitors
- GLP-1 Receptor Agonists
- DPP-4 Inhibitors
DPP-4 Inhibitors

• Examples:
  • Sitagliptin (Januvia)
  • Saxagliptin (Onglyza)
  • Linagliptin (Tradjenta)
  • Alogliptin (Nesina)

• A1C Effect: 0.5 to 0.9%

• Reasons to Consider: (1) PO Route (2) well-tolerated
  (3) No Hypoglycemia (4) No weight gain

• Side effects, Limiting Factors: (1) Cost (2) Modest A1C benefit,
  (3) CHF in saxa- and alogliptin (4) Low likelihood of pancreatitis
  (5) Joint pains (6) No positive or negative cardiovascular impact
DPP-4 Inhibitors and Cardiovascular Outcomes Trials

DPP-4 Inhibitors Demonstrate No Cardiovascular Benefit
A second case…

Diabetes & CVD – What do you Choose?

• A 68 year old male presents to clinic for management of type 2 diabetes mellitus of 10 years duration. He also has a history of hypertension, hyperlipidemia & coronary artery disease.

• Current regimen includes:
  • Metformin 1000 mg BID & Glipizide 10 mg BID
  • He moderates carbohydrates and exercises 5 days/week.

• Hemoglobin A1C is 8.4%

Do you add to current regimen?
If so, what medication might you choose?
Improving glycemic control has not been shown to improve cardiovascular outcomes in type 2 diabetes mellitus....
Cardiovascular Outcome Trials for Individual Medications – Impacting Choice?

2013
- EMPA-REG OUTCOME
  - n = 7,020
  - 3-P MACE

2015
- EXAMINE
  - n = 5,380
  - 3-P MACE
- TECOS
  - n = 14,671
  - 4-P MACE

2016
- SUSTAIN-6
  - n = 3,297
  - 3-P MACE
- CANVAS Program
  - n = 30,132
  - 3-P MACE

2017
- LEADER
  - n = 9,340
  - 3-P MACE
- FREEDOM-CVO
  - n = 4,156
  - 4-P MACE

2018
- CARMELINA
  - n = 7,003
  - 3-P MACE
- PIONEER 6
  - n = 3,176
  - 3-P MACE
- VERTIS CV
  - n = 8,000
  - 3-P MACE

2019
- CAROLINA
  - n = 6,072
  - 3-P MACE
- REWIND
  - n = 9,901
  - 3-P MACE
- CREDENCE
  - n = 4,464
  - ESRD, doubling of creatinine, renal/CV death
- DECLARE-TIMI 58
  - n = 17,276
  - 3-P MACE; CV death + HF hospitalization

2020
- Dapa-HF
  - n = 4,500
  - CV death, HF hospitalization, urgent HF visit
- DAPA-CKD
  - n = 4,000
  - ≥50% sustained decline in eGFR or reaching ESRD, CV death, or renal death
- EMPEROR-Preserved
  - n = 4,126
  - CV death or HF hospitalization
- EMPOWER-Reduced
  - n = 3,850
  - CV death or HF hospitalization

DPP-4 inhibitors
SGLT2 inhibitors
GLP-1 receptor agonists
Insulin
TZD
α-Glucosidase inhibitor

Cefalu WT et al, Diabetes Care, 2018
Type 2 Diabetes Mellitus: Second-Line Medication Choice...

The choice for second-line therapy is not straightforward and based on multiple factors...

- Change in A1C (efficacy)
- Cost
- Hypoglycemia risk
- Side effects
- Weight Change
- Cardiovascular disease
GLP-1 Receptor Agonists

• **Examples:**
  - Exenatide (Byetta / Bydureon)
  - Liraglutide (Victoza)
  - Lixisenatide (Adlyxin)
  - Dulaglutide (Trulicity)
  - Semaglutide (Ozempic SQ & Rybelsus PO)

• **A1C Effect:** - 0.5 to 1.5%

• **Reasons to Consider:** (1) Weight loss (1 to 4.5 kg) (2) Cardiovascular outcomes (3) Minimal Hypoglycemia

• **Side effects, Limiting Factors:** (1) Cost (2) Gastrointestinal side effects (nausea 39%, diarrhea 21%, vomiting 16%) (3) Thyroid c-cell tumors unlikely

Increase insulin secretion; Decrease glucagon; Increase satiety Slow gastric emptying
Weight Loss in T2DM & GLP-1 RA

Madsbad S & Holst JJ. Diabetes, Epidemiology, Genetics, Pathogenesis, Diagnosis, Prevention and Treatment. 2018
## Summary of GLP-1 RA Cardiovascular Outcomes Trials

### Study Baseline Characteristics Primary Outcome

<table>
<thead>
<tr>
<th>GLP-1 RA: Study name</th>
<th>No. of patients</th>
<th>Median follow-up (years)</th>
<th>% with CV disease*</th>
<th>% of statin use</th>
<th>Baseline age</th>
<th>Baseline HgA1c</th>
<th>Baseline BMI</th>
<th>Primary composite CV outcome HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lixisenatide: ELIXA</td>
<td>6068</td>
<td>2.1</td>
<td>100%</td>
<td>93%</td>
<td>60.3</td>
<td>7.7%</td>
<td>30.1</td>
<td>1.02 (0.89 to 1.17)</td>
<td>0.81</td>
</tr>
<tr>
<td>Liraglutide: LEADER</td>
<td>9340</td>
<td>3.8</td>
<td>81%</td>
<td>72%</td>
<td>64.3</td>
<td>8.7%</td>
<td>32.5</td>
<td>0.87 (0.78 to 0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Semaglutide: SUSTAIN-6</td>
<td>3297</td>
<td>2.1</td>
<td>60%</td>
<td>73%</td>
<td>64.6</td>
<td>8.7%</td>
<td>32.8</td>
<td>0.74 (0.58 to 0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Exenatide QW: EXSCEL</td>
<td>14752</td>
<td>3.2</td>
<td>73.1%</td>
<td>74%</td>
<td>62.0</td>
<td>8.0%</td>
<td>31.8</td>
<td>0.91 (0.83 to 1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Albigrutide: Harmony</td>
<td>9463</td>
<td>1.6</td>
<td>100%</td>
<td>84%</td>
<td>64.1</td>
<td>8.7%</td>
<td>32.3</td>
<td>0.78 (0.68 to 0.90)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Dulaglutide: REWIND</td>
<td>9901</td>
<td>5.4</td>
<td>31.5%</td>
<td>66%</td>
<td>66.2</td>
<td>7.2%</td>
<td>32.3</td>
<td>0.88 (0.79 to 0.99)</td>
<td>0.026</td>
</tr>
<tr>
<td>Oral semaglutide: PIONEER 6</td>
<td>3183</td>
<td>1.3</td>
<td>84.7%</td>
<td>85%</td>
<td>66.0</td>
<td>8.2%</td>
<td>32.3</td>
<td>0.79 (0.57 to 1.11)</td>
<td>0.17</td>
</tr>
</tbody>
</table>
Cardiovascular Endpoints: GLP-1 RA Agonists

**Lixisenatide**
- **Primary outcome**: No difference (13.4 vs. 13.2%)
- **Death, CV causes**: No difference (7.0 vs. 7.4%)
- **Death, All cause**: No difference (5.2 vs. 5.1%)

**Liraglutide**
- **Primary outcome**: 13% reduction (13.0 vs. 14.9%)
- **Death, CV causes**: 22% reduction (4.7 vs. 6.0%)
- **Death, All cause**: 15% reduction (8.2 vs. 9.6%)

**Exenatide**
- **Primary outcome**: No difference (11.4 vs. 12.2%)
- **Death, CV causes**: No difference (4.6 vs. 5.2%)
- **Death, All cause**: No difference (6.9 vs. 7.9%)
### Cardiovascular Endpoints: GLP-1 RA Agonists

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary Outcome</th>
<th>Death, CV causes</th>
<th>Death, Any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semaglutide</td>
<td>26% reduction (6.6 vs. 8.9%)</td>
<td>No difference (2.7 vs. 2.8%)</td>
<td>No difference (3.8 vs. 3.6%)</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>12% reduction (12.0 vs. 13.4%)</td>
<td>No difference (10.8 vs. 12.0%)</td>
<td>No difference</td>
</tr>
<tr>
<td>Semaglutide PO</td>
<td>No difference (3.8 vs. 4.8%)</td>
<td>51% reduction (0.9 vs. 1.9%)</td>
<td>49% reduction (1.4 vs. 2.8%)</td>
</tr>
</tbody>
</table>
Consider GLP-1 RA Over Bolus Insulin When Basal Insulin Has Failed
Type 2 Diabetes Mellitus: Second-Line Medication Choice...

The choice for second-line therapy is not straightforward and based on multiple factors...

- Change in A1C (efficacy)
- Cost
- Hypoglycemia risk
- Side effects
- Weight Change
- Cardiovascular disease

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CHF, OR ESRD

CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

ASCVD PREDOMINATES
- Established ASCVD
- Indicators of high ASCVD risk
  - Age ≥65 years with coronary, carotid, or lower extremity arterial stenosis >50%
  - LVH

PREFERABLY
- GLP-1 RA with proven CVD benefit
- SGLT2i with evidence of reducing HF and/or CVD progression in CVD or eGFR adequate
- GLP-1 RA considered or if eGFR less than adequate, add GLP-1 RA with proven CVD benefit

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
- GLP-1 RA with good efficacy for weight loss
- SGLT2i

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

If HbA1c above target
- GLP-1 RA
- SGLT2i

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain

PREFERABLY
- DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
- SU
- TZD
- Basal insulin
SGLT-2 Inhibitors

• **Examples:**
  - Dapagliflozin (Farxiga)
  - Canagliflozin (Invokana)
  - Empagliflozin (Jardiance)
  - Ertugliflozin (Steglatro)

• **A1C Effect:** - 0.5 to 1%

• **Reasons to Consider:** (1) Weight loss (1 to 2 kg) (2) Cardio-renal outcomes (3) PO route (4) Minimal hypoglycemia

• **Side effects, Limiting Factors:** (1) Euglycemic DKA (<1%) (2) Genitourinary infections (2%) (3) Cost (4) Limitations in GFR levels to start medications (4) LE amputations

Reduce Glucose Reabsorption
Weight Loss and SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Duration (week)</th>
<th>N</th>
<th>Treatment arms</th>
<th>Bodyweight change from baseline (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SGLT2 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bays et al. 2014 [29]</td>
<td>12</td>
<td>376</td>
<td>Placebo, Canagliflozin 50 mg, Canagliflozin 100 mg, Canagliflozin 300 mg</td>
<td>- 1.1, - 1.9, - 2.8, - 2.4</td>
</tr>
<tr>
<td>Napolitano et al. 2014 [82]</td>
<td>8</td>
<td>30</td>
<td>Placebo + diet (~ 500 cal), Remogliflozin etaborate 250 mg + diet (~ 500 cal), Sergliflozin etaborate 1,000 mg + diet (~ 500 cal)</td>
<td>- 5.1, - 7.6, - 6.1</td>
</tr>
<tr>
<td>Ramirez-Rodriguez et al. 2018 [23]</td>
<td>12</td>
<td>24</td>
<td>Placebo, Dapagliflozin 10 mg</td>
<td>- 1.0, - 3.0</td>
</tr>
<tr>
<td><strong>SGLT2 inhibitors + GLP1-RA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lundkvist et al. 2016 [83]</td>
<td>24</td>
<td>50</td>
<td>Placebo, Dapagliflozin 10 mg + Exenatide 2 mg</td>
<td>- 0.4, - 4.5</td>
</tr>
<tr>
<td>Lundkvist et al. 2017 [21]</td>
<td>52</td>
<td>50</td>
<td>Dapagliflozin 10 mg + Exenatide 2 mg</td>
<td>- 5.7</td>
</tr>
</tbody>
</table>

**SGLT-2 Inhibitor**
1-2 Kg weight loss

**SGLT-2 + GLP-1**
4 Kg weight loss

Pereira M & Eriksson J. Drugs 2019
### Cardiovascular Endpoints: SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Empagliflozin</th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Ertugliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td>CHF Hospitalization</td>
<td>Death (Any Cause)</td>
<td></td>
</tr>
<tr>
<td>14% Reduction (10.5 vs. 12.1%)</td>
<td>Reduced by 35%</td>
<td>Reduced 38%</td>
<td></td>
</tr>
<tr>
<td>14% Reduction (26.9 vs. 31.5%)</td>
<td>Reduced by 33%</td>
<td>Reduced 22%</td>
<td></td>
</tr>
<tr>
<td>No difference (8.8 vs. 9.4%)</td>
<td>Reduced by 27%</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>No difference (11.9 vs 11.9%)</td>
<td>Reduced by 30%</td>
<td>No difference</td>
<td></td>
</tr>
</tbody>
</table>

#### Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Matheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Ulf C. Brodin, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

#### Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., B.Ch., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Nigoci Pondaia, M.D., Ph.D., Wayne Law, U.S.L., Lorraine Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group

#### Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes


#### Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

Renal Endpoints with Empagliflozin

Change in Glomerular Filtration Rate
Renal Endpoints: SGLT-2 Inhibitors

**Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes**

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitzbett, M.D., Erich Bluemki, Ph.D., Stefan Hassel, Ph.D., Michael Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Meier, M.D., Uri C. Broedl, M.D., and Silvio E. Heilachi, M.D., for the EMPA-REG OUTCOME Investigators

- **EMPA REG**
  - > 39% reduction in incident or worsening nephropathy

**Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes**

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngoc Tran, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehu Dera, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group

- **CANVAS PROGRAMME**
  - > 40% reduction in composite of >40% reduction in eGFR, requirement for RRT and death from renal causes

**Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes**


- **DECLARE TIMI 58**
  - > 24% reduction in composite of > 40% decrease in eGFR rate to < 60 ml/min, new ESRD or death from renal or CV causes

**Empagliflozin with Ertugliflozin in Type 2 Diabetes**


- **VERTIS CV**
  - > 39% reduction in composite of sustained decline in eGFR of at least 50%, ESKD, or death from renal or CV causes

- **DAPA CKD**
  - > 40% reduction in composite of sustained decline in eGFR of at least 40%, dialysis/transplant or renal death

**CREDENCE**

-> 30% reduction in dialysis, transplantation, or sustained GFR of < 15 in those with GFR 30-90 at trial start

**EMPEROR REDUCED**

Perkovic V et al. NEJM 2019

-> Empa reduced eGFR rate of decline
A Third Case…
Newly Diagnosed Diabetes

• A 58 year old male presents to your clinic with new-onset hyperglycemia.

• Experiencing polyuria and weight loss over the last three weeks. On the night prior to his visit, he worked an overnight shift and glucose measured 423 mg/dl. Denies blurred vision, nausea, vomiting or shortness of breath.

• His medical history includes: Hypertension, Obesity, Hyperlipidemia. No CAD.
A Third Case…
Newly Diagnosed Diabetes

Physical exam.

- Pulse 74
- BP 134/67
- BMI 31.1
- Otherwise unremarkable

Lab Values

- Glucose 379 mg/dl
- Hemoglobin A1C 12.3%
- Urine ketones - Negative

What Do You Recommend?

- Consider Type 1 Diabetes
- Consider Insulin with A1C > 10%
When To Consider **Insulin** in Type 2 Diabetes Mellitus?

- No Specific timing – Early or Late in disease course
- Glucose “toxicity” or “severe hyperglycemia”
  - Fasting glucose > 250 mg/dL or random glucose >300 mg/dL
  - Hemoglobin A1C > 10%
  - Ketonuria (Type 1 diabetes mellitus – admission for DKA)
  - Symptoms consistent with hyperglycemia – polyuria, polydipsia, weight loss
- Coexisting medical conditions
  - Pregnancy -> multiple daily insulin injections
  - Glucocorticoids -> Pair kinetics of steroids and insulin
Long-Acting Insulins: Kinetics & Clinical Outcomes…

Starting Basal Insulin Therapy in Type 2 Diabetes Mellitus

• **When / How Much to Start?**
  - Once daily – HS most common
  - Start with 10 units/day or 0.1 to 0.2 units/kg/day

• **Titrate Regimen: Key to Control**
  - Increase dose by 2 units (or 10-15%) once to twice weekly
  - Target fasting targets (80-130 mg/dL)
  - Assess for hypoglycemia

• If bolus insulin is required, consider carbohydrate ratio with correction factor -> **Consider bolus calculators / pens or insulin pump**

• **Diabetes Education is key!**

---

American Diabetes Association. Diabetes Care. 2020
Insulin pens: Diabetesnext.com
Insulin Risks: Weight gain & Hypoglycemia

- Weight gain is common
  - Average weight gain (UKPDS study -> approximately 4 kg)
- Hypoglycemia risk is increased with…
  - Advanced age, microvascular complication, erratic food intake
  - Cognitive impairment
  - Lower body mass index (insulin sensitivity)
  - Alcohol use
  - Coexisting chronic illnesses – liver and renal failure
- Review hypoglycemia symptoms and treatment
Treating Hypoglycemia – Rule of 15’s

• Check blood glucose if experiencing symptoms
• If blood glucose is low (below 70 mg/dL):
  • Treat with 15 grams of fast-acting sugar (simple carbohydrate)
    • ½ cup (4 ounces) of juice
    • 6 ounces of regular soda (NOT Diet)
    • 1 Tablespoon sugar or honey
    • Glucose/dextrose tablets (3 – 4 tablets)
• Re-check blood glucose after 15 minutes
Glucose Monitoring in Type 2 DM: Not Insulin-Requiring

- Benefits of glucose monitoring are mixed and recommendation should be individualized
  - Consider in those titrating medications, high A1C, risk of low sugars
Glucose Monitoring in Type 2 DM: Not Insulin-Requiring


Figure 4. Forest plot of comparison: 1 SMBG (self-monitoring of blood glucose) vs control (6 months follow-up), outcome: 1.1 HbA1c [%].

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SMBG Mean [%]</th>
<th>SD [%]</th>
<th>Total Mean [%]</th>
<th>SD [%]</th>
<th>Total Weight</th>
<th>Mean Difference IV, Random, 95% CI [%]</th>
<th>Mean Difference IV, Random, 95% CI [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnett 2008</td>
<td>-1.15</td>
<td>1.14</td>
<td>311</td>
<td>-0.91</td>
<td>1.29</td>
<td>299 22.0%</td>
<td>-0.24 [-0.43, -0.05]</td>
</tr>
<tr>
<td>Davidson 2005</td>
<td>-0.8</td>
<td>1.6</td>
<td>43</td>
<td>-0.6</td>
<td>2.1</td>
<td>45 5.8%</td>
<td>-0.20 [-0.58, 0.18]</td>
</tr>
<tr>
<td>DiGEM trial 2007 (1)</td>
<td>-0.15</td>
<td>0.81</td>
<td>301</td>
<td>-0.08</td>
<td>0.73</td>
<td>152 12.7%</td>
<td>-0.07 [-0.22, 0.08]</td>
</tr>
<tr>
<td>Fontbome 1988</td>
<td>-0.36</td>
<td>3.14</td>
<td>68</td>
<td>-0.5</td>
<td>1.54</td>
<td>68 8.3%</td>
<td>0.14 [-0.69, 0.97]</td>
</tr>
<tr>
<td>Francisco 2011</td>
<td>-1.2</td>
<td>1.81</td>
<td>46</td>
<td>-0.7</td>
<td>0.7</td>
<td>16 7.9%</td>
<td>0.05 [-0.92, 0.08]</td>
</tr>
<tr>
<td>Guerci 2003</td>
<td>-0.9</td>
<td>1.54</td>
<td>345</td>
<td>-0.5</td>
<td>1.54</td>
<td>344 18.3%</td>
<td>-0.40 [-0.63, -0.17]</td>
</tr>
<tr>
<td>Kleefstra 2010</td>
<td>-0.18</td>
<td>0.67</td>
<td>22</td>
<td>0.07</td>
<td>0.75</td>
<td>18 7.0%</td>
<td>-0.25 [-0.70, 0.20]</td>
</tr>
<tr>
<td>Muchmore 1994</td>
<td>-1.54</td>
<td>1.46</td>
<td>12</td>
<td>-0.85</td>
<td>1.87</td>
<td>11 0.9%</td>
<td>-0.69 [-2.07, 0.69]</td>
</tr>
<tr>
<td>SMBG study group 2002</td>
<td>-1</td>
<td>1.06</td>
<td>113</td>
<td>-0.54</td>
<td>1.41</td>
<td>110 11.3%</td>
<td>-0.46 [-0.79, -0.13]</td>
</tr>
</tbody>
</table>

Total (95% CI)            | 1261          |        | 1063          | 100.0% |             | -0.26 [-0.39, -0.13]                   |                                        |

Heterogeneity: Tau² = 0.01; Chi² = 11.29, df = 8 (P = 0.19); I² = 29%
Test for overall effect: Z = 3.99 (P = 0.0001)

(1) Both intervention groups are combined
Glucose Monitoring in Type 2 DM: Not Insulin-Requiring

• Benefits of glucose monitoring are mixed and recommendation should be individualized
  • Consider in those titrating medications, high A1C, risk of low sugars
  • No consistent benefit with metformin

• Maximizing monitoring impact…
  • Targeted feedback
    • A1C < 7%: Fasting glucose < 130 & 2 hours post-prandial < 180
    • Immediate feedback for dietary modifications
  • Hypoglycemia monitoring
    • Monitor fasting, pre-lunch or pre-dinner levels.
Continuous Glucose Monitoring (CGM)

• Continuous Glucose monitoring in T1DM and multiple daily insulin injections in T2DM

• Professional or personal use.

• Consider in patients w/:
  • Multiple low sugars
  • At-risk for low sugars
  • Discordant data -- meter and A1C
Continuous Glucose Monitoring: Reports

**AGP Report**
December 7, 2019 - December 20, 2019 (14 Days)

**GLUCOSE STATISTICS AND TARGETS**

<table>
<thead>
<tr>
<th>Glucose Ranges</th>
<th>Targets</th>
<th>% of Readings (Time/Day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 70 mg/dL</td>
<td>Less than 4%</td>
<td>57 min</td>
</tr>
<tr>
<td>Below 54 mg/dL</td>
<td>Less than 1%</td>
<td>14 min</td>
</tr>
<tr>
<td>Above 180 mg/dL</td>
<td>Less than 25%</td>
<td>6h 0min</td>
</tr>
<tr>
<td>Above 250 mg/dL</td>
<td>Less than 5%</td>
<td>1h 12min</td>
</tr>
</tbody>
</table>

**Ranges And Targets For**

- **Type 1 or Type 2 Diabetes**

**Average Glucose** 141 mg/dL
**Glucose Management Indicator (GMI)** 6.7 %
**Glucose Variability** 31.6%

**TIME IN RANGES**

- **Very High** >250 mg/dL: 1% (14min)
- **High** 181-250 mg/dL: 18% (4h 19min)
- **Target Range** 70-180 mg/dL: 78% (18h 43min)
- **Low** 54-69 mg/dL: 3% (43min)
- **Very Low** <54 mg/dL: 0% (0min)

Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial.
Type 2 Diabetes Management

• Set an A1C target
• Diabetes education is Effective!!
  • Medical nutrition therapy, medication & injectable teaching
  • Epic Order: “Diabetes Education Referral”
• Annual Diabetes Screening is important…
  • Hemoglobin A1C
    • POC A1C testing
  • Diabetes Eye Exam
    • Retinal Camera at 2020 SM Blvd → Epic Order: “Remote Fundus”
  • Urine microalbumin (UMA)
  • Comprehensive foot exam (removed from Health Maintenance)
Type 2 Diabetes Management: Take Home Points

- Set an A1C target
- DM education is key!
- Start with Metformin
  - Consider Extended Release → Note recent recall
- Second-line therapy choice is based on multiple factors
  - Cost
  - Side effects
  - Weight gain / weight loss
  - Hypoglycemia risk
  - Cardiovascular (and renal) impact
THANK YOU!!