Oral Agents in Type 2 DM

CME Away
India & Sri Lanka
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• **Potential for conflict(s) of interest:**
  – None to declare
Faculty/Presenter Disclosure

- Faculty: Richard Bebb
- Relationships with commercial interests:
  - None to report
Learning Objectives:

- Review oral agents for diabetes
- Metformin is still a key medication
- Use drugs with CVD outcome data
- Review Diabetes Guidelines
- Issues specific to the Elderly
Case 1: 63 yr male

- FBG 6.2 & 6.8 mmol/L (111 & 122 mg/dl)
- BP 135/85
- A1c 6.8%
- Family history of premature CAD
He has which condition?

1) Impaired fasting glucose
2) Diabetes
3) Impaired glucose tolerance
4) Pre-diabetes
ADA Diagnosis of Diabetes

1) FPG > 6.9 mmol/l (8 hr fast) (126 mg/dl)
2) 2hr glucose post 75g OGTT >11.1 mmol/L (200 mg/dl)
3) Symptomatic hyperglycemia or hyperglycemic crisis with random glucose >11.1 mmol/L (200 mg/dl)
4) HgbA1c >6.4% (using NGSP certified standardized A1c measurement) (Increased risk for DM with A1c 5.7-6.4%)

Criteria 1 & 4 should be confirmed by repeat testing, unless unequivocal hyperglycemia
ADA 2018 Clinical Guidelines
Case 1:

- referred to DM education program
  - Diet advise, exercise prescription, SMBG
- HgA1c drops to 6.0%
- 18 months later HgbA1c 7.8%
What are our targets?

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>FPG/preprandial PG (mmol/L)</th>
<th>2-hour postprandial PG (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 7.0</td>
<td>4.0 – 7.0 (72-126 mg/dl)</td>
<td>5.0 – 10.0 (90-180 mg/dl)</td>
</tr>
</tbody>
</table>

- Goals individualized based on:
  - Age/life expectancy
  - Comorbid conditions
  - Known CVD or advanced microvascular complications
  - Hypoglycemia unawareness

ADA & CDA Guidelines
**Individualizing A1C Goals**

- **Most Patients with T1DM and T2DM**
  - A1C ≤6.5% may be considered in some patients with T2DM to further lower the risk of nephropathy and retinopathy which must be balanced against the risk of hypoglycemia.

- **Consider A1C 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 it is difficult to achieve an A1C ≤7.0%, despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy.

Adjusting Targets & Therapy for the Elderly
Risk of Diabetes Complications by A1C and Age at Diagnosis

Risk of Blindness

Risk of Renal Insufficiency

# Frequency of Emergency Room Visits for Hypoglycemia by Age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>Total estimated number of cases (95% CI)</th>
<th>Rate per 1,000 subjects for diabetic pop. (95% CI)</th>
<th>Rate per 1,000 visits at the emergency (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>401</td>
<td>1,550 (1,330, 1,780)</td>
<td>62 (53, 71)</td>
<td>1.7 (1.5, 2.0)</td>
</tr>
<tr>
<td>0-19</td>
<td>78</td>
<td>359 (229, 489)</td>
<td>-</td>
<td>0.9 (0.6, 1.2)</td>
</tr>
<tr>
<td>20-44</td>
<td>323</td>
<td>1,200 (1,020, 1,370)</td>
<td>-</td>
<td>2.3 (2.0, 2.7)</td>
</tr>
<tr>
<td>45-64</td>
<td>364</td>
<td>1,230 (1,060, 1,400)</td>
<td>19 (17, 22)</td>
<td>5.5 (4.7, 6.2)</td>
</tr>
<tr>
<td>65-74</td>
<td>219</td>
<td>845 (698, 991)</td>
<td>25 (20, 29)</td>
<td>10 (8.5, 12)</td>
</tr>
<tr>
<td>≥75</td>
<td>319</td>
<td>1,330 (1,090, 1,580)</td>
<td>54 (44, 64)</td>
<td>12 (9.4, 14)</td>
</tr>
</tbody>
</table>

Note: this table represents data gathered from the American National Hospital Ambulatory Medical Care between 1993 and 2005. USA = United States of America; CI = confidence interval. Ginde AA et al. Diabetes Care 2008; 31:511-3.
Drug-Induced Hypoglycemic Coma Is More Common in Elderly People with Type 2 Diabetes

Retrospective medical record review of individuals with diabetes who were admitted with drug-induced hypoglycemic coma or developed drug-induced hypoglycemic coma during hospitalization.

Relationship between A1c and Mortality

Case 1: Progression

- Metformin 500 mg po BID
- HgbA1c drops to 7.1%
- 6 months later HgbA1c increased to 7.6%
Was Metformin the correct first medication for him?

1) Yes
2) No
3) He should have been started on Combination Therapy
4) Not sure
Metformin:

- **UKPDS**: 36% Reduction in all cause mortality in overweight Type 2 (effect persisted for 8.5 yrs post trial)

- Rousel et al 2010: 19,691 pts with DM & CVD: 
eGFR 30 – 60; 36% reduction of all cause mortality 
CHF; 40% reduction of all cause mortality

UKPDS

Metformin Then and Now:

• **Old recommendations:**
  Metformin contraindicated if creatinine > 1.5 in men, or > 1.4 in women

• **New Recommendations:**
  eGFR > 45: OK to use metformin.
  eGFR 30 to 45 OK to continue, starting not recommended.
  eGFR < 30 contraindicated

**Take home Pearl:** Dose reduce – try not to discontinue
Metformin Use with IV Dye

- Previously: prior to any study requiring dye hold for 48 hours
- Now: hold and re-assess eGFR in 48 hours *only* if...
  - eGFR <60
  - Hx of liver disease
  - Hx of heart failure
  - Hx of alcoholism
  - Intra-arterial iodinated contrast
- eGFR >60 plus none of the above? **No need to hold metformin!**
Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review

Appendix Table 6. All-Cause Mortality Using Reference 20

<table>
<thead>
<tr>
<th>Group</th>
<th>OR (95% CI)</th>
<th>Patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>No metformin</td>
<td>1.0 (reference)</td>
<td>n₀ = 2937</td>
</tr>
<tr>
<td>Metformin</td>
<td>OR = 0.52 (0.37-0.71)</td>
<td>n₁ = 1530</td>
</tr>
</tbody>
</table>

OR = odds ratio.
Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review

**Appendix Table 5.** All-Cause Mortality Using Reference 18

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (95% CI)</th>
<th>Patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea monotherapy</td>
<td>1.0 (reference)</td>
<td>n₀ = 3615</td>
</tr>
<tr>
<td>Metformin monotherapy</td>
<td>HR₁ = 0.85 (0.75-0.98)</td>
<td>n₁ = 688</td>
</tr>
<tr>
<td>Metformin + sulfonylurea</td>
<td>HR₂ = 0.89 (0.82-0.96)</td>
<td>n₂ = 1549</td>
</tr>
</tbody>
</table>

HR = hazard ratio.
β-cell function declines over time

Diabetes diagnosis

Extrapolation of β-cell function prior to diagnosis

β-cell function (%, HOMA)

Years from diagnosis

Lebovitz HE. Diabetes Reviews 1999;7:139

HOMA = homeostasis model assessment
Diabetes and Insulin

If we all live to 150 yrs of age…………

1) 50% of us will have diabetes
2) 100% of us will have diabetes
3) 100% of us will have diabetes and be on insulin
4) The government will still be promising tax relief “next year”
Glycemic control deteriorates over time

**UKPDS**

- Conventional*
- Glyburide
- Metformin
- Insulin

**ADOPT**

- Rosiglitazone
- Metformin
- Glyburide

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*Years from randomisation

- 0
- 2
- 4
- 6
- 8
- 10

**Median A1C (%)**

- 6.2% – upper limit of normal range

**Recommended treatment target <7.0%†**

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*Diet initially then sulphonylureas, insulin and/or metformin if FPG>15 mmol/L; †ADA clinical practice recommendations.

UKPDS 34, n=1704

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Earlier and More Aggressive Intervention May Improve Patients’ Chances of Reaching Goals

OAD = oral antidiabetic agent.

Managing the Patient with Diabetes

AT DIAGNOSIS OF TYPE 2 DIABETES

Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

A1C < 8.5%

- If not at glycemic target (2-3 mos)
- Start / Increase metformin

A1C ≥ 8.5%

- Start metformin immediately
- Consider initial combination with another antihyperglycemic agent

Symptomatic hyperglycemia with metabolic decompensation

Initiate insulin +/- metformin

If not at glycemic targets

Add an agent best suited to the individual:

Patient Characteristics
- Degree of hyperglycemia
- Risk of hypoglycemia
- Overweight or obesity
- Comorbidities (renal, cardiac, hepatic)
- Preferences & access to treatment
- Other

Agent Characteristics
- BG lowering efficacy and durability
- Risk of inducing hypoglycemia
- Effect on weight
- Contraindications & side-effects
- Cost and coverage
- Other

If not at target

- Add another drug from a different class; or
- Add bedtime basal insulin to other agent(s); or
- Intensify insulin regimen

Timely adjustments to and/or addition of antihyperglycemic agents Should be made to attain target A1c within 6 to 12 months
What to do next?

1. Improve lifestyle
2. Increase metformin to 1g TID
3. Add glyburide 2.5mg BID
4. Add pioglitazone 30mg QD
5. Add acarbose 50mg TID
6. Add sitagliptin 100mg QD
7. Add glargine 10 units SC Qhs
8. Add liraglutide 1.2 mg sc Qam
9. Add empagliflozin 10 mg QD
Conventional therapies can lead to weight gain

ADOPTE: up to 4.8 kg in 5 years

* Significant differences between the rosiglitazone group and the other treatment groups with the Hochberg adjustment

Kahn SE, et al. NEJM 2006;355:2427
RECORD: Time to Bone Fracture Event

Cumulative incidence (% SE)

Rosiglitazone (185 events)
RR: 1.57 (95% CI 1.26, 1.97); p<0.0001

Metformin/SU (118 events)

People at risk
Rosiglitazone 2,220 2,116 2,031 1,955 1,864 1,778 1,778 950
Metformin/SU 2,227 2,123 2,037 1,959 1,888 1,805 1,805 958

RECORD = Rosiglitazone Evaluated for Cardiovascular Outcome and Regulation of Glycaemia in Diabetes;
SE = standard error; RR = relative risk; SU = sulfonylurea
## Fractures in Men and Women

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rosiglitazone n=1,078</td>
<td>Control n=1,075</td>
<td>Risk ratio*</td>
<td>Rosiglitazone n=1,142</td>
</tr>
<tr>
<td>All</td>
<td>124 (154)</td>
<td>68 (78)</td>
<td>1.82</td>
<td>61 (71)</td>
</tr>
<tr>
<td>Upper limb</td>
<td>63 (78)</td>
<td>36 (39)</td>
<td>1.75</td>
<td>23 (24)</td>
</tr>
<tr>
<td>Distal lower limb</td>
<td>47 (49)</td>
<td>16 (17)</td>
<td>2.93</td>
<td>23 (24)</td>
</tr>
</tbody>
</table>

Number of participants (fractures)

Note: some people had more than one fracture, possibly in different areas.

*Interaction: p=0.1
What Are Incretins?

- Gut peptide hormones (GLP-1, GIP)
- Secreted in response to food ingestion
- Stimulate glucose-dependent insulin secretion
- Account for up to 60% of insulin response in healthy subjects

Incretin Drugs

- **GLP Agonists**
  - Exenatide
  - Liraglutide
  - Semaglutide
  - Albiglutide
  - Taspoglutide
  - Exenatide Lar
  - Lixisenatide

- **DPP 4 Inhibitors**
  - Vildagliptin
  - Sitagliptin
  - Saxagliptin
  - Alogliptin
  - Linagliptin
  - Dutogliptin
  - Metaglip
The Incretin Effect Is Reduced in Patients with Type 2 Diabetes

Mean ± SE; N=22 (14 patients with T2DM, 8 metabolically healthy control subjects).
*P ≤ 0.05 compared with respective value after oral glucose load (50g/400mL).
GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins

GLP-1 secreted upon the ingestion of food

Promotes satiety and reduces appetite

↓ Beta-cell workload

↑ Beta-cell response

Beta cells: Enhances glucose-dependent insulin secretion

β cells:
Enhances glucose-dependent insulin secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Stomach: Slows gastric emptying

Alpha cells: ↓ Postprandial glucagon secretion

Incretin mimetics and DPP-4 inhibitors: major differences

<table>
<thead>
<tr>
<th>Properties/effect</th>
<th>Incretin mimetics</th>
<th>DPP-4 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycaemia</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Maintained counter-regulation by glucagon in hypoglycaemia</td>
<td>Yes</td>
<td>Not tested</td>
</tr>
<tr>
<td>Inhibition of gastric emptying</td>
<td>Yes</td>
<td>Marginal</td>
</tr>
<tr>
<td>Effect on body weight</td>
<td>Weight loss</td>
<td>Weight neutral</td>
</tr>
<tr>
<td>Side effects</td>
<td>Nausea</td>
<td>None observed</td>
</tr>
<tr>
<td>Administration</td>
<td>Subcutaneous</td>
<td>Oral</td>
</tr>
</tbody>
</table>

SAVOR-TIMI 53
Primary Endpoint
Composite of CV death, MI, or ischemic stroke

HR (95% CI) = 1.00 (0.89-1.12)
P < 0.001 for non-inferiority
P = 0.99 for superiority

Saxagliptin met the primary endpoint of non-inferiority but not superiority when compared to placebo

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53.
SAVOR-TIMI 53
Major Secondary Endpoints

<table>
<thead>
<tr>
<th>Cardiovascular Endpoints</th>
<th>Placebo (N=8212)</th>
<th>Saxagliptin (N=8280)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>260 (2.9)</td>
<td>269 (3.2)</td>
<td>1.03 (0.87–1.22)</td>
<td>0.72</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>278 (3.4)</td>
<td>265 (3.2)</td>
<td>0.95 (0.80–1.12)</td>
<td>0.52</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>141 (1.7)</td>
<td>157 (1.9)</td>
<td>1.11 (0.88–1.39)</td>
<td>0.38</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>81 (1.0)</td>
<td>97 (1.2)</td>
<td>1.19 (0.89–1.60)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>228 (2.8)</td>
<td>289 (3.5)</td>
<td>1.27 (1.07–1.51)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hospitalization for coronary revascularization</td>
<td>459 (5.6)</td>
<td>423 (5.2)</td>
<td>0.91 (0.80–1.04)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

CI = confidence interval; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53.
EXAMINE
Primary Endpoint

Composite of death from CV causes, non-fatal MI, or non-fatal stroke

HR (95% CI) = 0.96 (≤1.16)
P < 0.001 for non-inferiority
P = 0.32 for superiority

Alogliptin was non-inferior but not superior to placebo with respect to the primary endpoint

## EXAMINE: Major Safety Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=2679)</th>
<th>Alogliptin (N=2701)</th>
<th>Hazard Ratio for Alogliptin Group (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Components of primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>111 (4.1)</td>
<td>89 (3.3)</td>
<td>0.79 (0.60–1.04)</td>
<td>0.10</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>173 (6.5)</td>
<td>187 (6.9)</td>
<td>1.08 (0.88–1.33)</td>
<td>0.47</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>32 (1.2)</td>
<td>29 (1.1)</td>
<td>0.91 (0.55–1.50)</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Principal secondary end-point §</strong></td>
<td>359 (13.4)</td>
<td>344 (12.7)</td>
<td>0.95 (≤1.14)†</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Other end-points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>173 (6.5)</td>
<td>153 (5.7)</td>
<td>0.88 (0.71–1.09)</td>
<td>0.23</td>
</tr>
<tr>
<td>Death from cardiovascular causes¶</td>
<td>130 (4.9)</td>
<td>112 (4.1)</td>
<td>0.85 (0.66–1.10)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hospital admission for heart failure</td>
<td>89 (3.3)</td>
<td>106 (3.9)</td>
<td>1.19 (0.90–1.58)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*P values for testing the superiority of alogliptin to placebo were calculated with the use of a Cox regression analysis.

† The parenthetical value is the upper boundary of the one-sided repeated CI, at an alpha level of 0.01.

§ The secondary endpoint was a composite of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or urgent revascularization due to unstable angina within 24 hours after hospital admission.

¶ Included are deaths that occurred as primary end-point events and deaths that occurred after a non-fatal primary end-point event.

CI = confidence interval

TECOS

Primary Endpoint

Time from randomization to the first confirmed CV-related death, non-fatal MI, non-fatal stroke, or UA requiring hospitalization

Sitagliptin was non-inferior but not superior to placebo with respect to the primary endpoint

HR (95% CI): 0.98 (0.89, 1.08)
P = 0.645

CV = cardiovascular; MI = myocardial infarction; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UA = unstable angina.

## TECOS
### Major Secondary Endpoints

<table>
<thead>
<tr>
<th>Secondary end point</th>
<th>Placebo (N=7266)</th>
<th>Sitagliptin (N=7250)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CV death</strong></td>
<td>366 (5.0)</td>
<td>380 (5.2)</td>
<td>1.03 (0.89–1.19)</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Hospitalization for unstable angina</strong></td>
<td>129 (1.8)</td>
<td>116 (1.6)</td>
<td>0.90 (0.70–1.16)</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Fatal or non-fatal MI</strong></td>
<td>316 (4.3)</td>
<td>300 (4.1)</td>
<td>0.95 (0.81–1.11)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Fatal or non-fatal stroke</strong></td>
<td>183 (2.5)</td>
<td>178 (2.4)</td>
<td>0.97 (0.79–1.19)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Death from any cause</strong></td>
<td>537 (7.3)</td>
<td>547 (7.5)</td>
<td>1.01 (0.90–1.14)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Hospitalization for heart failure</strong></td>
<td>229 (3.1)</td>
<td>228 (3.1)</td>
<td>1.00 (0.83–1.20)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

CV = cardiovascular; MI = myocardial infarction; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin.
SGLT2 Inhibitors: Cause glucosuria
SGLT2 Inhibitors: Mechanism of Action

Normal human kidneys reabsorb ~180 g of filtered glucose/day

GLU = facilitative glucose transporter. SGLT = sodium-dependent glucose transporter.

A1C Reductions Across Continuum of T2DM = 0.6-1.1% from Baseline with Dapa and Cana

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin</th>
<th>Canagliflozin (^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monotherapy(^1)</td>
<td>Add-on to Met(^2)</td>
</tr>
<tr>
<td>Baseline A1C</td>
<td>7.92</td>
<td>8.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>5 mg</th>
<th>10 mg</th>
<th>Placebo</th>
<th>5 mg</th>
<th>10 mg</th>
<th>Placebo</th>
<th>5 mg</th>
<th>10 mg</th>
<th>Placebo</th>
<th>5 mg</th>
<th>10 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline A1C</td>
<td><strong>-0.77</strong></td>
<td>*-0.89</td>
<td>*-0.84</td>
<td>*-0.63</td>
<td><strong>-0.82</strong></td>
<td>*-0.90</td>
<td><strong>-0.78</strong></td>
<td><strong>-1.03</strong></td>
<td><strong>-1.06</strong></td>
<td><strong>-1.07</strong></td>
<td><strong>-1.08</strong></td>
<td><strong>-1.09</strong></td>
</tr>
<tr>
<td>Add-on to Met</td>
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</table>

*B*p < 0.0001 vs. placebo. **p = 0.0005 vs. placebo. ***p < 0.001 vs. placebo.

Bargraph denotes individual trials and is not intended for comparisons between dapagliflozin and canagliflozin.

SGLT2i Have Greater A1c Efficacy Than DPP-4i Especially At Higher Baseline A1C

CANA 300 mg was more effective than SITA 100 mg in patients with baseline A1C between 7.5% and 8.5% and in patients with baseline A1C ≥ 8.5%

Matthews et al. ADA Poster Presentation June 2014; San Francisco CA (1096-P)
Sustained Body Weight Reduction with Add-on Dapagliflozin vs. Add-on Glipizide* in Patients Taking Metformin (104 weeks)

Baseline weight
DAPA + MET: 88.4 kg
Sulfonylrea + MET: 87.6 kg

Baseline weight
DAPA + MET: 88.4 kg
Sulfonylrea + MET: 87.6 kg

Week 104 weight
DAPA + MET: +1.36 kg (0.88, 1.84)
Sulfonylrea + MET: -3.70 kg (-4.16, -3.24)

Between-group difference: -5.06 kg (95% CI; -5.73, -4.4)

Sample size per time point
DAPA + MET: 400
SU + MET: 401

*Glipizide is approved and authorized for use but is not marketed in Canada.
Additional Benefits of SGLT2 Inhibitors

Reduction in blood pressure

• BP reduction
• 3-4 mmHg
Empagliflozin improves beta cell function in patients with IFG

What are the possible adverse effects of SGLT2 inhibition?

- Genital Mycotic Infections (GMI)
- Urinary Tract Infections (UTI)
- Volume-related adverse effects

Rare DKA (Beware Latent Type 1)
EMPA-REG

- 7020 pts in RCT for median of 3.1 years
- Lower CV event rate in empagliflozin group (10.5 vs. 12.1%, HR 0.86) with lower rate of death from CV causes and hospitalization for heart failure.
- Long term protection of kidney function.
- Increased rate of genital infections.

N Engl J Med 2015; 373:2117-2128
EMPA-REG CV Outcomes

Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
P=0.04 for superiority

N Engl J Med 2015; 373:2117-2128
CANVAS

- Population: 10,142 DM2 with high CV risk
- Intervention: canagliflozin vs. placebo
- Outcome: CV death, nonfatal MI or stroke at 188 weeks
- Results: 27 vs 31 per 1000 pt-yrs [HR 0.86, P<0.001], reduced progression of albuminuria.
- Note: Higher risk of amputation (6.3 vs 3.4 per 1000 pt-yrs)
Primary MACE Outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

Hazard ratio 0.86 (95% CI, 0.75-0.97)
p < 0.0001 for noninferiority
p = 0.0158 for superiority

No. of patients
Placebo 4347 4153 2942 1240 1187 1120 789
Canagliflozin 5795 5566 4343 2555 2460 2363 1661

Years since randomization

Patients with an event (%)

Intent-to-treat analysis

CANVAS Program
# Large CV Outcomes Trials in Diabetes (Non-Insulin)

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELINA</th>
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<tr>
<td>DPP4-i</td>
<td>saxagliptin</td>
<td>alogliptin</td>
<td>sitagliptin</td>
<td>linaglaptin</td>
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<td>Comparator</td>
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<td>sulfonylurea</td>
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<td>2018</td>
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<th>REWIND</th>
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<tr>
<td>GLP1-RA</td>
<td>liraglutide</td>
<td>lixisenatide</td>
<td>semaglutide</td>
<td>exenatide LR</td>
<td>dulaglutide</td>
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<td>6,000</td>
<td>8,400</td>
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<tr>
<td>Results</td>
<td>2016</td>
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<td>2018</td>
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<tr>
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<th>EMPA-REG</th>
<th>VAS</th>
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<tr>
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<td>empaglifozin</td>
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<td>dapaglifozin</td>
<td>eptuglifozin</td>
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<td>placebo</td>
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<tr>
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<td>4300</td>
<td>22,200</td>
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<tr>
<td>Results</td>
<td>2015</td>
<td>2017</td>
<td>2019</td>
<td>2020</td>
</tr>
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</table>
EMPA-REG renal outcomes

Incident or worsening nephropathy

Cumulative Probability of Event (%)

Hazard ratio, 0.61 (95% CI, 0.53–0.70)
P<0.001

Wanner, NEJM June 2016
Effects of Canagliflozin on Cardiovascular, Renal, Hospitalization, and Death Events in the Integrated CANVAS Program.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin (N=5795)</th>
<th>Placebo (N=4347)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of participants per 1000 patient-yr</td>
<td></td>
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<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>11.6</td>
<td>12.8</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9.7</td>
<td>11.6</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7.1</td>
<td>8.4</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>11.2</td>
<td>12.6</td>
<td>0.89 (0.73–1.09)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>7.9</td>
<td>9.6</td>
<td>0.87 (0.69–1.09)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>118.7</td>
<td>131.1</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or hospitalization for heart failure</td>
<td>16.3</td>
<td>20.8</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.3</td>
<td>19.5</td>
<td>0.87 (0.74–1.01)</td>
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<tr>
<td>Progression of albuminuria</td>
<td>89.4</td>
<td>128.7</td>
<td>0.73 (0.67–0.79)</td>
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<tr>
<td>40% reduction in eGFR, renal-replacement therapy, or renal death</td>
<td>5.5</td>
<td>9.0</td>
<td>0.60 (0.47–0.77)</td>
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</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>CV death, nonfatal myocardial infarction,</td>
<td></td>
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<tr>
<td>or nonfatal stroke</td>
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<tr>
<td>CV death</td>
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<tr>
<td>Nonfatal myocardial infarction</td>
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<td>Nonfatal stroke</td>
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</tr>
<tr>
<td>Hospitalization for heart failure</td>
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<tr>
<td>CV death or hospitalization for heart failure</td>
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<tr>
<td>All-cause mortality</td>
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<tr>
<td>Progression to macroalbuminuria*</td>
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<tr>
<td>Renal composite*</td>
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</table>

*CANVAS Program endpoints comparable with EMPA-REG OUTCOME.

Favors SGLT2i | Favors Placebo
Bromocriptine (0.8 - 4.8 mg OD)

- Decreases PC sugars - mechanism not clear how? central
- > 10% GI, CNS side effects
- Ergot drug - re: drug interactions
- CYP 3A4 metabolism
- Has CV outcome data
- Has not been well accepted in guidelines
Change in HbA1c in Bromocriptine (0.8 to 4.8 mg OD in am) and placebo-treated diabetic subjects.

Ralph A. DeFronzo
Diabetes Care
2011;34:789-794
Kaplan-Meier plot of time to first cardiovascular (MACE) event (myocardial infarction, stroke, and death) in type 2 diabetic subjects treated with bromocriptine or placebo for 52 weeks.
## Diabetes Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>Efficacy</th>
<th>Hypo risk</th>
<th>Wt change</th>
<th>CV risk lower?</th>
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<tr>
<td>Metformin</td>
<td>+++</td>
<td>0</td>
<td>-</td>
<td>+</td>
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<td>SU</td>
<td>++</td>
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<td>0</td>
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<td>DPP4</td>
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<td>0</td>
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<td>0</td>
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<td>TZD</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>+?</td>
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<td>SGLT2</td>
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<tr>
<td>GLP1</td>
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<td>0</td>
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<tr>
<td>Insulin</td>
<td>++++</td>
<td>+++</td>
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# Medical and Surgical Interventions Shown to Delay or Prevent T2D

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Follow-up Period</th>
<th>Reduction in Risk of T2D (P value vs placebo)</th>
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<tbody>
<tr>
<td><strong>Antihyperglycemic agents</strong></td>
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<tr>
<td>Metformin</td>
<td>2.8 years</td>
<td>31% (P&lt;0.001)</td>
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<tr>
<td>Acarbose</td>
<td>3.3 years</td>
<td>25% (P=0.0015)</td>
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<tr>
<td>Pioglitazone</td>
<td>2.4 years</td>
<td>72% (P&lt;0.001)</td>
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<tr>
<td>Rosiglitazone</td>
<td>3.0 years</td>
<td>60% (P&lt;0.0001)</td>
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<tr>
<td>Insulin glargine</td>
<td>6 years + follow-up</td>
<td>23% (P=0.014)</td>
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<tr>
<td>Liraglutide, 3.0 mg</td>
<td>3.0 years</td>
<td>66% (P&lt;0.0001)</td>
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<tr>
<td><strong>Weight loss interventions</strong></td>
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<tr>
<td>Orlistat</td>
<td>4 years</td>
<td>37% (P=0.0032)</td>
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<tr>
<td>Phentermine/topiramate</td>
<td>2 years</td>
<td>79% (P&lt;0.05)</td>
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<tr>
<td>Bariatric surgery</td>
<td>10 years</td>
<td>75% (P&lt;0.001)</td>
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What to do next?

1. Improve lifestyle
2. Increase metformin to 1g TID
3. Add glyburide 2.5mg BID
4. Add pioglitazone 30mg QD
5. Add acarbose 50mg TID
6. Add sitagliptin 100mg QD
7. Add glargine 10 units SC Qhs
8. Add liraglutide 1.2 mg sc Qam
9. Add empagliflozin 10 mg QD