Update on Agents for Type 2 Diabetes

This presentation will:

• Outline the clinical considerations in the selection of pharmacotherapy for type 2 diabetes, including degree of A1C lowering achieved, patient-specific concerns, adverse drug reactions, and contraindications

• Discuss the role and timing of combination therapy in achieving A1C goals

• Explain the implications of recent, large randomized clinical trials on clinical decision-making
Estimated Prevalence and Costs of Diabetes in the U.S., 2002-2012

- Medical expenditures for people with DM are 2.3 times higher than those without DM
- The primary driver of increased cost is the increasing prevalence of DM
- Despite the introduction of new classes of medications for DM treatment, anti-diabetic agents and supplies only account for 12% of medical expenditures

DM = diabetes mellitus.

AACE Diabetes Algorithm

• **Guide therapy based on A1C level**
  – Focus on lifestyle intensification at all levels

• **Important tenets:**
  – **Target A1C is <6.5%**
    • Based on associated lower risk of micro- and macrovascular complications
    • Recommend monitoring A1C quarterly, along with fasting and postprandial blood glucose, with intensification of therapy until goal A1C is achieved
    • Individualize A1C target based on comorbidities
    • Patient should monitor fasting and postprandial blood glucose levels
  – **Use agents with maximal efficacy, associated with lowest risk of hypoglycemia**
    • Sulfonylureas are therefore much lower in algorithm
    • Earlier use of incretin mimetics and DPP-4 inhibitors to stimulate insulin secretion without hypoglycemia

A1C = glycated hemoglobin; DPP-4 = dipeptidyl-peptidase 4
Approach to Management of Hyperglycemia

Adapted with permission from Ismail-Beigi F, et al. Ann Intern Med 2011;154:554-559
Main Pathophysiological Defects in T2DM

“The Ominous Octet”

- Impaired insulin secretion
- Decreased incretin effect
- Increased glucagon secretion
- Increased lipolysis
- Increased glucose reabsorption
- Decreased glucose uptake
- Increased hepatic glucose production
- Neurotransmitter dysfunction

DeFronzo RA. Diabetes. 2009 Apr;58(4):773-95.
Current Antihyperglycemic Medications

12 groups with different mechanisms of action

- Sulfonylureas
  - Generalized insulin secretagogue
- TZDs
  - Reduce peripheral insulin resistance
- Biguanide
  - Reduces hepatic insulin resistance
- DPP-4 inhibitors
  - Restore GLP-1 Levels
- Glinides
  - Restore postprandial insulin patterns
- Amylin analog
  - Suppresses glucagon
- α-Glucosidase inhibitors
  - Delay CHO absorption
- Colesevelam
  - Bile acid sequestrant
- Bromocriptine
  - Hypothalamic pituitary reset
- GLP-1 analogs
  - Stimulate beta-cells
  - Suppress glucagon
- Colesevelam
  - Bile acid sequestrant
- SGLT-2 inhibitors
  - Block renal glucose reabsorption

CHO = carbohydrate; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-dependent glucose cotransporters-2; TZD = thiazolidinedione.
GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGi
- SU/GLN

Entry A1C ≥ 7.5%

DUAL THERAPY*
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

If not at goal in 3 months proceed to Dual Therapy

TRIPLE THERAPY*
- GLP-1 RA
- SGLT-2i
- Basal Insulin
- DPP-4i
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS
NO
- DUAL Therapy
OR
- TRIPLE Therapy
YES
- INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND
- Few adverse events and/or possible benefits
- Use with caution

PROGRESSION OF DISEASE

COPYRIGHT © 2017 AACE  MAY NOT BE REPRODUCED IN ANY FORM WITHOUT EXPRESS WRITTEN PERMISSION FROM AACE.  DOI 10.4158/EP161682.CS

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation.
Algorithm to Achieve Glycemic Goals

Baseline A1C 6.5% - 7.5%

- Monotherapy may be effective in this range
  - Metformin first choice for monotherapy if no contraindications
  - Consider DPP-4 if ↑PP and FPG, GLP-1 if ↑↑PP, TZD if metabolic syndrome or NAFLD, AGI if ↑PP
  - Do not recommend secretagogue (SU or glinide) in this range due to risk of hypoglycemia; short-lived effect

- If monotherapy is unsuccessful, move on to dual oral rx; often need to augment reduction in PP BG to get to goal in this A1C range

DPP-4 = dipeptidyl peptidase-4; PP = post-prandial; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; TZD = thiazolidinedione; NAFLD = non-alcoholic fatty liver disease; AGI = alpha-glucosidase inhibitor; SU = sulfonylurea; A1C = glycated hemoglobin; SGLT-2 = sodium glucose transport-2
Algorithm to Achieve Glycemic Goals
Baseline A1C 7.6%-9.0%

- Dual therapy with metformin provides superior glycemic control over metformin alone.
- If dual oral rx is unsuccessful, consider triple therapy
- If triple oral rx fails to achieve A1C goal, initiate insulin

GLP-1 RA = glucagon-like peptide-1 receptor agonist
DPP4-I = dipeptidyl peptidase 4 inhibitor
TZD = thiazolidinedione
SGLT-2 = sodium glucose cotransporter 2 inhibitor
QR = quick-release
AG-I = alpha-glucosidase inhibitor
SU = sulfonylurea
GLN = glinide
Algorithm to Achieve Glycemic Goals

Baseline A1C >9.0%

If patient is asymptomatic with recent onset of disease and drug naïve, may consider starting with dual or triple oral regimens.

If symptomatic, start insulin.

Once A1C has improved to <7.5%, consider initiation of dual oral therapy with tapering and possible discontinuation of insulin rx.

**Targeted Sites of Action of Oral Anti-Hyperglycemic Drug Classes**

<table>
<thead>
<tr>
<th>Liver</th>
<th>Skeletal Muscle</th>
<th>Pancreas</th>
<th>Gut</th>
<th>Fat</th>
<th>Kidney</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Sulfonylureas</td>
<td>DPP-IV Inhibitors</td>
<td>α-Glucosidase inhibitors</td>
<td>TZDs</td>
<td>SGLT-2 inhibitors</td>
<td>Bromocriptine</td>
</tr>
<tr>
<td>TZDs</td>
<td>TZDs</td>
<td>Glinides</td>
<td>Biguanides</td>
<td>TZDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td></td>
<td>TZDs</td>
<td>Colesevelam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td>Amylin</td>
<td>GLP-1 RA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Glucose production**
- **Glucose uptake**
- **Insulin release**
- **Glucose absorption**
- **Insulin sensitivity**
- **Glucose reabsorption**
- **Glucose production**

DPP = dipeptidyl peptidase; SGLT-2 = Sodium-glucose co-transporter 2; TZD = thiazolidinediones

Clinical Considerations

• Combining therapeutic agents with different modes of action may be advantageous.

• In many if not most patients (unless contraindicated or intolerance has been demonstrated), use metformin, which increases insulin sensitivity, and/or insulin sensitizers such as TZDs, as part of the therapeutic regimen.

• Dosage of secretagogues or insulin should be adjusted as blood glucose levels decline when used in combination with metformin, TZD, DPP-4 inhibitors, and/or incretin mimetics (GLP-1 agonists).

TZD = thiazolidinediones; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1

Clinical Considerations

• The weight gain associated with thiazolidinediones in some patients may be partly offset by combination therapy with metformin

• If A1C is elevated and preprandial blood glucose measurements are at target levels, carefully assess postprandial glucose levels

• **Individualize treatment regimens!**
## Effect of Glucose-lowering Drugs on Patient Weight

<table>
<thead>
<tr>
<th>Therapeutic Options</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>↑</td>
</tr>
<tr>
<td>TZD&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>↑</td>
</tr>
<tr>
<td>Insulin&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>↑</td>
</tr>
<tr>
<td>Metformin&lt;sup&gt;7&lt;/sup&gt;</td>
<td>↔</td>
</tr>
<tr>
<td>DPP-4 inhibitor&lt;sup&gt;8&lt;/sup&gt;</td>
<td>↔</td>
</tr>
<tr>
<td>GLP-1 receptor agonist&lt;sup&gt;9&lt;/sup&gt;</td>
<td>↓</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors&lt;sup&gt;10&lt;/sup&gt;</td>
<td>↓</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium glucose co-transporter-2; TZD = thiazolidinedione

Risk of Hypoglycemia

• Plays a significant role in choice of agents in AACE algorithm
• For patients at highest risk of hypoglycemia, may consider close evaluation of agents chosen as well as therapeutic goal
• Patients with type 2 diabetes at highest risk of low blood glucose include those with:
  – Diabetes duration >15 years
  – Advanced macrovascular disease
  – Hypoglycemia unawareness
  – Limited life expectancy
  – Severe comorbidities

# Biguanides

## Metformin

| Mechanism       | Insulin sensitivity  
|                 | Hepatic glucose production  
|                 | FPG more than PPG  
| Efficacy        | A1C 1%-2%  
| Advantages      | No weight gain or hypoglycemia, potential weight loss  
| Disadvantages   | GI side effects  
|                 | Lactic acidosis *(rare)*  
| Contraindications | Renal disease; CHF  

Combinations available with SU, TZD, repaglinide, and DPP-4 inhibitors

A1C = glycated hemoglobin; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GI = gastrointestinal; PPG = post-prandial glucose; SU = sulfonylurea; TZD = thiazolidinedione

Metformin [package insert]. Princeton NJ; Bristol Myers Squibb; 2009.
## Sulfonylureas and Glinides

**Glipizide, Glimepiride, Glyburide**  
**Repaglinide, Nateglinide**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Insulin secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>FPG</td>
<td>↓</td>
</tr>
<tr>
<td>PPG</td>
<td>↑</td>
</tr>
</tbody>
</table>

| Efficacy           | Moderate           |

| Advantages         | Strong short term efficacy |

| Disadvantages      | Weight gain, hypoglycemia, tend to lose efficacy after several years |

| Contraindications  | Avoid in severe hepatic and renal impairment |

Combinations available with metformin, TZD

FPG = fasting plasma glucose; PPG = post-prandial glucose; TZD = thiazolidinedione

Higher Mortality Is Associated with Greater Exposure to Sulfonylureas

There was a greater risk of death associated with higher daily doses and better adherence for patients who used glyburide (HR = 1.3; 95% CI, 1.2-1.4), but not metformin (HR = 0.8; 95% CI, 0.7-1.1).

A retrospective, inception cohort study conducted in 5795 new users of oral glucose-lowering medications:

- Insulin or combination therapy were excluded
- Mean age: 66.3 years
- Mean follow-up: 4.6 years
- Main outcomes: all-cause mortality, death from acute ischemic event
**Thiazolidinediones**

**Pioglitazone, Rosiglitazone**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>↑ Insulin sensitivity, especially at muscle, lowers both FPG and PPG, but effect may be delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Moderate (↓ A1C 1.0%-1.5%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>No hypoglycemia, no reliance on renal excretion</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Fluid retention, edema, heart failure, weight gain, slow onset of action, bone fractures, macular edema, osteoporosis, anemia, and bladder cancer</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Class III or IV CHF or hepatic impairment w/ALT &gt;2.5 times upper normal limits</td>
</tr>
</tbody>
</table>

Combinations available with metformin and sulfonylurea

A1C = glycated hemoglobin; ALT = alanine aminotransferase; CHF = congestive heart failure; FPG = fasting plasma glucose; PPG = postprandial plasma glucose.
# Alpha-Glucosidase Inhibitors

**Acarbose, Miglitol**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>(\downarrow) Rate of gut polysaccharide breakdown, thereby slowing absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Modest ((\downarrow) A1C 0.5%-1.0%), PPG lowering</td>
</tr>
<tr>
<td>Advantages</td>
<td>Weight-neutral, non-systemic drug, targets post-prandial glucose</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Bloating, flatulence, diarrhea – (\downarrow) w/slow titration, frequent dosing</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Severe renal impairment, diabetic ketoacidosis, malabsorption, obstruction, inflammatory bowel, or conditions aggravated by gas production</td>
</tr>
</tbody>
</table>

Combinations available with sulfonylureas

A1C = glycated hemoglobin; PPG = post-prandial glucose

# Dopamine Receptor Agonist

## Bromocriptine QR

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Exact mechanism of action unclear, believed to reduce sympathetic tone, inflammation, and insulin resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Modest (↓ A1C 0.5%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>May decrease cardiovascular risk</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Hypotension, syncope, hypoglycemia, nausea</td>
</tr>
<tr>
<td>Contraindications</td>
<td>History of psychosis or during breastfeeding. Use caution with renal or hepatic impairment.</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; QR = quick-release

# Bile Acid Sequestrants

## Colesevelam

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Raises cholecystokinin, which slows gastric emptying and post-prandial glucose. Exact mechanism unknown, may be mediated via TGR5, and/or farnesoid X receptor (FXR/bile acid receptor) effects on intestinal glucose.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Modest (↓ A1C 0.5%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>↓ LDL-C (also FDA approved for LDL-C reduction) weight neutral, no hypoglycemia, can complement statin treatment in lowering LDL and cardiac event risk.</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Constipation, nausea, dyspepsia, myalgia, pharyngitis, ↑ triglycerides, drug interactions.</td>
</tr>
<tr>
<td>Contraindications</td>
<td>History of bowel obstruction, TGs &gt;500 mg/dL; history of hypertriglyceridemia-induced pancreatitis.</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride
GLP-1 Modulates Numerous Functions in Humans

**Brain:**
- Promotes satiety and reduces appetite

**Alpha cells:**
- Glucose-dependent postprandial glucagon secretion

**Liver:**
- Glucagon reduces hepatic glucose output

**Stomach:**
- Helps regulate gastric emptying

**Beta-cells:**
- Enhances glucose-dependent insulin secretion

**GLP-1:**
- Secreted upon the ingestion of food

GLP-1 = glucagon-like peptide-1.

# Characteristics of GLP-1 Agonists

*Exenatide, Liraglutide, Albiglutide, Dulaglutide*

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mimic prolonged action of GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Decrease A1C levels 0.5%–2.0%</td>
</tr>
<tr>
<td></td>
<td>(depends on entry of glucose into bloodstream from gut)</td>
</tr>
<tr>
<td>Dosing</td>
<td>Once- or twice-daily injection, weekly *</td>
</tr>
<tr>
<td>Side effects</td>
<td>Nausea, vomiting, weight loss</td>
</tr>
<tr>
<td>Main risk</td>
<td>C-cell thyroid tumors**, long-term safety unknown</td>
</tr>
<tr>
<td>Associated with</td>
<td>Pancreatitis possible</td>
</tr>
</tbody>
</table>

*Dosing depends on GLP-1 agonist

**With liraglutide, in rodents only

A1C = glycated hemoglobin; GLP-1 = glucagon-like peptide-1.

Exenatide [package insert]. San Diego, CA; Amylin Pharmaceuticals; 2010.; Tanzeum (albiglutide) [prescribing information].
# Marketed GLP-1 RAs

<table>
<thead>
<tr>
<th></th>
<th>Exenatide BID</th>
<th>Liraglutide</th>
<th>Exenatide ER</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
<th>Lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Byetta®</td>
<td>Victoza®</td>
<td>Bydureon®</td>
<td>Tanzeum™ (US)</td>
<td>Trulicity®</td>
<td>Adlyxin™ (US)</td>
</tr>
<tr>
<td>Description</td>
<td>Synthetic exendin-4, a peptide identified in H. suspectum that activates GLP-1 and is resistant to DPP-4 degradation</td>
<td>GLP-1 modified(^a) to be resistant to DPP-4 degradation</td>
<td>Exenatide contained in a hydrolyzable polymer microspheres for extended release</td>
<td>An albumin fusion protein made of 2 copies of modified human GLP-1</td>
<td>A fusion protein with 2 disulfide-linked human GLP-1 analog sequence chains, connected by a small peptide linker to human immunoglobulin G4 (IGG4)</td>
<td>A peptide containing 44 amino acids, amidated at the C-terminal amino acid (position 44)</td>
</tr>
<tr>
<td>Half-life</td>
<td>2.4 hours</td>
<td>13 hours</td>
<td>&gt; 1 week</td>
<td>5 days</td>
<td>5 days</td>
<td>3 hours</td>
</tr>
<tr>
<td>Dosing</td>
<td>2X daily, before meals</td>
<td>1X daily, any time</td>
<td>1X weekly</td>
<td>1X weekly</td>
<td>1X weekly</td>
<td>1X daily, before 1st meal</td>
</tr>
</tbody>
</table>

\(^a\) Amino acid substitution and addition of acyl chain.

BID = twice daily; DPP-4 = dipeptidyl peptidase-4; ER = extended release; E.U. = European Union; GLP-1 = glucagon-like peptide-1; IGG4 = human immunoglobulin; U.S. = United States.

GLP-1 Devices

• All GLP-1 RAs are available in pre-filled pens\(^1\)
  – Weekly GLP-1 RAs (exenatide ER, albiglutide, and dulaglutide) are available in single-dose pens
  – Weekly GLP-1 RAs (exenatide BID, liraglutide, and lixisenatide) are available in multi-dose pens

• Various studies have examined patient preferences
  – Lixisenatide and liraglutide pens have higher patient satisfaction compared to exenatide\(^2\)
  – Dulaglutide is the only weekly GLP-1 RA available in a ready-to-use formula that does not require reconstitution\(^3\)

• New technology is being developed for an implantable, continuous subcutaneous delivery system for GLP-1 RAs\(^4\)

---

Exenatide (Exendin-4)

- Synthetic version of salivary protein found in the Gila monster
- Approximately 50% identity with human GLP-1
  - Binds to known human GLP-1 receptors on β cells in vitro
  - Resistant to DPP-4 inactivation
- Administered twice daily

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.
Liraglutide

• Injected SC once-daily
• Acylated GLP-1 (C-16 fatty acid, palmitic acid, on position 26)
• Liraglutide is extensively bound to plasma protein (greater than 98%)
• 97% homology to GLP-1
• Endogenously metabolized without specific organ as major route of elimination

GLP-1 = glucagon-like peptide-1; SC = subcutaneously.

Albiglutide

• 30 mg SC QWK
• Increase to 50 mg SC QWK if needed
• Supplied as single-dose prefilled pen

QWK = every week; SC = subcutaneously.

Dulaglutide

- 0.75 mg SC QWK
- Increase to 1.5 mg SC QWK if needed
- Supplied as single-dose prefilled pen or prefilled syringe

QWK = every week; SC = subcutaneously.

Nausea Declined Over Time with Liraglutide Monotherapy

Patients (%)

0.0  3.5  7.0  10.5  14.0  17.5

Time (weeks)

SU = sulfonylurea.

Safety: Medullary Thyroid Cancer Risk

- All GLP-1 RAs are contraindicated in patients with a personal or family history of MTC or MEN2 because of the occurrence of c-cell tumors in rodents.
- The c-cell tumor risk in humans is unknown, because human relevance could not be determined in clinical trials.
- The value of routine calcitonin and/or ultrasound monitoring is uncertain.
- Patients with thyroid nodules or elevated serum calcitonin levels identified for other reasons should be sent to an endocrinologist.
- To monitor potential associations, report MTC to state cancer registry, regardless of treatment.

GLP-1 RA = glucagon-like peptide-1 receptor agonist; MEN2 = multiple endocrine neoplasia 2; MTC = medullary thyroid cancer.

Safety: Renal Impairment

• Renal impairment affects the clearance of exenatide BID & ER, but not that of liraglutide, albiglutide or dulaglutide.

• Hypovolemia due to nausea and vomiting may worsen renal function.

• Renal impairment with GLP-1 RAs has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration.

BID = twice daily; ER = extended release; GLP-1 RA = glucagon-like peptide-1 receptor agonist.
Safety: Pancreatitis

- Pancreatitis has been reported with all incretin-based therapies, although no causal relationship has been established.
- Patients should know signs and symptoms of pancreatitis and stop taking incretin-based therapies if signs and symptoms occur.
- If pancreatitis is confirmed, therapy should not be restarted.

Inhibition of DPP-4 Increases Active Incretin Levels, Enhancing Downstream Incretin Actions

- **Increased insulin secretion**
- **Decreased glucagon release**

**DPP-4** → **DPP-4 inhibitor**

**GIP = glucose-dependent insulino tropic peptide**

Umpierrez et al. Endocrine Practice 2014
## Characteristics of DPP-4 Inhibitors

**Alogliptin, Linagliptin, Saxagliptin, Sitagliptin**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Inhibit enzymatic degradation of GLP-1 and GIP; glucose-dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Decrease A1C levels 0.6%–0.9%</td>
</tr>
<tr>
<td>Dosing</td>
<td>Once daily</td>
</tr>
<tr>
<td>Side effects</td>
<td>Headaches, nasopharyngitis</td>
</tr>
<tr>
<td>Main risk</td>
<td>Viral infection; long-term safety unknown</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1

Comprehensive Efficacies of DPP-4s

Placebo-corrected Change From Baseline In A1C: Monotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>ΔHbA1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>12.5mg/25mg</td>
<td>-0.56/-0.59</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>5mg/5mg</td>
<td>-0.6/-0.7</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>5mg/5mg</td>
<td>-0.4/-0.6</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100mg/100mg</td>
<td>-0.6/-0.6</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>50mg BID/50mg</td>
<td>-0.5/-0.7</td>
</tr>
</tbody>
</table>

The current DPP-4s have comparative efficacy

Sodium Glucose Co-Transporter 2

Reabsorption of glucose is mediated by SGLTs in proximal convoluted tubule
  – Independent of insulin

• SGLT2 and SGLT1
  – Located on luminal surface of epithelial cells lining proximal convoluted tubule

• SGLTs in other organs
  – 2: liver
  – 1: small intestine

90% glucose is reabsorbed in S1 by SGLT2
  Low affinity, high capacity transporter

10% reabsorbed in S3 by SGLT1
  High affinity, low capacity transporter

Bays, H. Diabetes Therapy, 2013
# SGLT2 Inhibitors

**Canagliflozin, Dapagliflozin, Empagliflozin**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Inhibits sodium-glucose transport protein subtype 2 (SGLT2) which is responsible for at least 90% of glucose reabsorption in the kidney causing blood glucose is eliminated in the urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Modest ( ( \downarrow ) A1C 0.8-1.2%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>Insulin-independent glucose reduction, Low risk of hypoglycemia, Weight loss (to 4% BW), Blood pressure-lowering</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Osmotic diuresis causing Polyuria and lightheadedness, Bacterial urinary tract infections (≈5%), Fungal genital infections (≈10%), Increased LDL cholesterol, Hyperkalemia (canagliflozin), Bladder cancer concerns (dapagliflozin)</td>
</tr>
<tr>
<td>Contraindications</td>
<td>History of genital fungal infections, caution in chronic kidney disease</td>
</tr>
</tbody>
</table>

Efficacy of SGLT2 Inhibitors as Monotherapy

Δ A1C, %

<table>
<thead>
<tr>
<th></th>
<th>CANA¹</th>
<th></th>
<th>DAPA²</th>
<th></th>
<th>EMPA³</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>-1.03</td>
<td>-0.23</td>
<td>-0.66</td>
<td>-0.78</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>-0.77</td>
<td>-0.77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P<0.001 vs PBO for all

¹ Phase 3 trials, BL A1C 7.8% to 8.1%, 24-26 weeks.

Weight Effects with SGLT2 Inhibitors\textsuperscript{a} as Monotherapy

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
 & CANA\textsuperscript{1} & DAPA\textsuperscript{2} & EMPA\textsuperscript{3} \\
\hline
PBO & -0.5 & -2.2 & -0.3 \\
100 & -2.5\textsuperscript{b} & -2.8 & -2.3 \textsuperscript{b,c} \\
300 & -3.4\textsuperscript{b} & -3.2 & -2.5 \textsuperscript{b,c} \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} None of the agents listed are approved for weight reduction.\textsuperscript{4}  
\textsuperscript{b} Greater than PBO (P < .05).  
\textsuperscript{c} Greater than SITA (P < .05).

References:

US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/.
SGLT2 Inhibitors Safety: Warnings and Precautions

• SGLT2 inhibitor use may be associated with hypotension, ketoacidosis, impaired renal function, hypoglycemia, and increased LDL-C
  – Patients should be closely monitored, particularly those with a history of, or at risk for, these conditions

• Dapagliflozin should not be used in patients with a history of bladder cancer

• Canagliflozin may be associated with hyperkalemia and bone fracture
  – Bone fracture risk should be considered before use, and potassium levels should be monitored during use

LDL-C = low-density lipoprotein cholesterol; SGLT2 = sodium-glucose cotransporter-2
## CVD Outcomes in ACCORD, ADVANCE, and VADT

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th></th>
<th>ADVANCE</th>
<th></th>
<th>VADT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Standard</td>
<td>Intensive</td>
<td>Standard</td>
<td>Intensive</td>
<td>Standard</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.1%</td>
<td>8.1%</td>
<td>7.5%</td>
<td>7.5%</td>
<td>9.4%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Final</td>
<td>6.4%</td>
<td>7.5%</td>
<td>6.4%</td>
<td>7.0%</td>
<td>6.9%</td>
<td>8.4%</td>
</tr>
<tr>
<td>CVD/year</td>
<td>2.1%</td>
<td>2.3%</td>
<td>2.0%</td>
<td>2.1%</td>
<td>3.8%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

ACCORD = The Action to Control Cardiovascular Risk in Diabetes study; ADVANCE = The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial; CVD = cardiovascular disease; VADT = Veterans Affairs Diabetes Trial

Clear Findings from EMPA-REG

- EMPA-REG studied a high-risk group of people
  - Mean age 63 years
  - Type 2 diabetes X 10 years; mean A1C 8.1%
  - Proven CV disease with prior heart failure in 10%
  - eGFR between 30-60 mL/min in 20%
  - Cardioprotective Rx (statins 77%, ACEi 81%, ASA 83%)
  - MACE event rate ~ 4%/year, CV death rate ~ 1.8%/year

- In 7,020 such people, empagliflozin (10 or 25 mg/day)
  - Clearly reduces CV death and heart failure hospitalization
  - Starts to reduce these outcomes within 3 months

- There is no clear MI or stroke effect over 3 years of treatment
  - The “composite” outcome may not be relevant
  - The effect on its 3 components appears heterogeneous

ASA = aspirin; ACEi = angiotensin-converting enzyme inhibitors; CV = cardiovascular; eGFR = estimated glomerular filtration rate; MACE = Major Adverse Cardiac Events; MI = myocardial infarction.

### 3- and 4-Point MACE

<table>
<thead>
<tr>
<th>Event</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Point MACE</td>
<td>490 / 4687</td>
<td>282 / 2333</td>
<td>0.86 (0.74, 0.99)</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV Death</td>
<td>172 / 4687</td>
<td>137 / 2333</td>
<td>0.62 (0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-Fatal MI</td>
<td>213 / 4687</td>
<td>121 / 2333</td>
<td>0.87 (0.70, 1.09)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-Fatal Stroke</td>
<td>150 / 4687</td>
<td>60 / 2333</td>
<td>1.24 (0.92, 1.67)</td>
<td>0.1638</td>
</tr>
<tr>
<td>4-Point MACE</td>
<td>599 / 4687</td>
<td>333 / 2333</td>
<td>0.89 (0.78, 1.01)</td>
<td>0.0795</td>
</tr>
</tbody>
</table>

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction.

*95.02% CI and one-sided p-value.

Empa-Reg: Reduction in All-Cause Mortality

HR 0.68
(95% CI 0.57, 0.82)
\( p<0.0001 \)

Empa-Reg: Reduction in CHF admissions

LEADER Trial: Primary Outcome

First occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke in the time-to-event analysis in patients with type 2 diabetes and high CV risk.

Hazard ratio, 0.87 (95% CI, 0.78–0.97)
P<0.001 for noninferiority
P=0.01 for superiority

CI = confidence interval; CV = cardiovascular; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results.

Marso SP et al., NEJM 2016
LEADER - Cardiovascular Death

Cumulative incidences were estimated with the Kaplan–Meier method, and hazard ratios with Cox proportional-hazard regression model. Data analyses are truncated at 54 months because <10% of patients had an observation time beyond 54 months.

CI = confidence interval; HR = hazard ratio.