Update on Oral Agents & Non-insulin Injectables for T2DM

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New Haven, CT
Update on Oral Agents & Non-insulin Injectables 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
• Weight-loss agents orlistat, lorcaserin, and phentermine/topiramate can prevent progression to T2DM
  – Improve BP, triglycerides, and insulin sensitivity
• Metformin and acarbose can reduce progression to T2DM by 25% - 30%
  – Use for prediabetes is off-label
  – Both are safe, confer CVD risk benefit; metformin is well tolerated
• TZDs prevented progression to T2DM in 60% - 75% of patients in clinical trials
  – Associated with adverse outcomes
• GLP-1 receptor agonists may be as effective as TZDs
  – Promote weight loss, but inadequate safety data
• TZDs and GLP-1 RAs reserved for patients not responding to conventional therapies or at highest risk for T2DM
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
UKPDS: Benefits of Glycemic Control

Every 1% decrease in A1C led to significant reductions in diabetes-related complications

- Risk of myocardial infarction: 14%
- Risk of diabetes-related death: 21%
- Risk of microvascular complications: 37%
- Risk of amputation or PVD death: 43%

Decrease was statistically significant for all comparisons shown


PVD=Peripheral Vascular Disease
# Approach to Management of Hyperglycemia

![Diagram](image-url)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>More stringent</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia, other adverse events</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Absent</td>
<td>Few / mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent</td>
<td>Few / mild</td>
</tr>
<tr>
<td>Resources, support system</td>
<td>Readily available</td>
<td>Limited</td>
</tr>
</tbody>
</table>

Pathogenesis of Type 2 Diabetes: The “Triad”

Insulin Resistance: Receptor And Post-receptor Defects

- Increased Glucose Production
- Insufficient Glucose Disposal

↑ Glucose

Liver → Pancreas

Peripheral Tissues (skeletal muscle)

Impaired Insulin Secretion

Main Pathophysiological Defects in T2DM
“The Ominous Octet”

- Islet β-cell: Impaired insulin secretion
- Islet α-cell: Increased glucagon secretion
- Decreased glucose uptake
- Increased hepatic glucose production
- Increased glucose reabsorption
- Decreased glucose uptake
- Increased lipolysis
- Increased glucose reabsorption
- Decreased incretin effect
- Neurotransmitter dysfunction

Decline in $\beta$-Cell Function with Diabetes Progression: UKPDS

$\beta$-Cell Function (%)

Rx: Insulin, Metformin, Sulfonylurea

Dashed line shows extrapolation forward and backward from years 0 to 6 based on HOMA data from UKPDS.

Insulin Resistance in Subjects with Varying Levels of Glycemia

Once established, insulin resistance remains relatively constant.


FPG=Fasting Plasma Glucose
Hepatic Insulin Resistance: Increased Hepatic Glucose Output


FPG=Fasting Plasma Glucose
## Current Antihyperglycemic Medications

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Amylin mimetics</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>GLP-1 receptor agonists</td>
</tr>
<tr>
<td>Metformin</td>
<td>DPP-4 inhibitors</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Dopamine agonists</td>
</tr>
<tr>
<td>Alpha-glucosidase Inhibitors</td>
<td>Bile acid sequestrants</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>SGLT2 inhibitors</td>
</tr>
</tbody>
</table>

CHO = carbohydrate; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-dependent glucose cotransporters-2;
Current Antihyperglycemic Medications

- Insulin
- Sulfonylureas
- Metformin
- Thiazolidinediones
- Alpha-glucosidase Inhibitors
- Meglitinides
- Amylin mimetics
- GLP-1 receptor agonists
- DPP-4 inhibitors
- Dopamine agonists
- Bile acid sequestrants
- SGLT2 inhibitors

CHO = carbohydrate; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-dependent glucose cotransporters-2;
HYPERGLYCEMIA

- Islet β-cell
  - Impaired insulin secretion
  - Decreased incretin effect

- Islet α-cell
  - Increased glucagon secretion

- Increased hepatic glucose production

- Increased lipolysis

- Increased glucose reabsorption

- Decreased glucose uptake

- Neurotransmitter dysfunction

Current Antihyperglycemic Medications

- **Insulin**
  - Impaired insulin secretion

- **DPP-4i**
  - Decreased incretin effect

- **GLP-1RA**
  - Decreased incretin effect

- **Metformin**
  - Increased hepatic glucose production

- **SGLT2i**
  - Increased glucose reabsorption

- **TZD’s**
  - Decreased glucose uptake

- **Increased glucagon secretion**
- **Increased lipolysis**
- **Defronzo RA. Diabetes. 2009 Apr;58(4):773-95.**
GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGi
- SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

MET or other 1st-line agent + 2nd-line agent

If not at goal in 3 months proceed to Triple 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

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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

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

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

If symptomatic, start insulin

### Healthy eating, weight control, increased physical activity & diabetes education

#### Metformin

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>low risk</td>
<td>neutral/loss</td>
<td>GI / lactic acidosis</td>
<td>low</td>
</tr>
</tbody>
</table>

*If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):*

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Dual therapy</th>
<th>Triple therapy</th>
<th>Combination injectable therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Hypo risk</td>
<td>Weight</td>
<td>Side effects</td>
</tr>
<tr>
<td>high</td>
<td>moderate risk</td>
<td>gain</td>
<td>hypoglycemia</td>
</tr>
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#### Metformin

<table>
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<th>Efficacy</th>
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<td>neutral</td>
<td>loss</td>
<td>low</td>
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*If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):*

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Sulfonlurea</th>
<th>Thiazolidinedione</th>
<th>DPP-4 Inhibitor</th>
<th>SGLT2 Inhibitor</th>
<th>GLP-1 RA</th>
<th>Insulin (basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>Metformin</td>
<td>moderate risk</td>
<td>low risk</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Metformin</td>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>low</td>
<td>low</td>
<td>gain</td>
</tr>
<tr>
<td>Metformin</td>
<td>hypoglycemia</td>
<td>edema, HF, fxs</td>
<td>rare</td>
<td>GU, dehydration</td>
<td>high</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>Metformin</td>
<td>low</td>
<td>low</td>
<td>rare</td>
<td>high</td>
<td>variable</td>
<td></td>
</tr>
</tbody>
</table>

*If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:*

<table>
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<tr>
<th>Metformin</th>
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<td>low</td>
<td>high</td>
<td>high</td>
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<td>low</td>
<td>rare</td>
<td>high</td>
<td>variable</td>
<td></td>
</tr>
</tbody>
</table>

*2015 Update to ADA-EASD Position Statement*
## T2DM GUIDELINES: ADA-EASD vs. AACE

<table>
<thead>
<tr>
<th></th>
<th>ADA-EASD</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focus</strong></td>
<td>Glycemia</td>
<td>Comprehensive (CV risk, wt, preDM)</td>
</tr>
<tr>
<td><strong>Gen’l A1c target</strong></td>
<td>&lt;7.0%</td>
<td>&lt;6.5%</td>
</tr>
<tr>
<td><strong>Monotherapy</strong></td>
<td>metformin</td>
<td>various</td>
</tr>
<tr>
<td><strong>Combination tx</strong></td>
<td>@ A1c 9.0%</td>
<td>@ A1c 7.5%</td>
</tr>
<tr>
<td><strong>Therapeutic choices</strong></td>
<td>More narrow</td>
<td>More broad</td>
</tr>
<tr>
<td><strong>Updates</strong></td>
<td>Every 3 years (?)</td>
<td>Annual</td>
</tr>
</tbody>
</table>
# Biguanides

## Metformin

| Mechanism | Insulin sensitivity  
|           | \( \uparrow \)  
|           | Hepatic glucose production  
|           | \( \downarrow \)  
|           | 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

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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**

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

---

# 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; decreases atherosclerotic events.</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.

Strategies for Enhancing GLP-1 Action

• **DPP-4 inhibitors** (oral therapies)
  – Inhibit actions of DPP-4
  – Sitagliptin, saxagliptin, linagliptin, alogliptin

• **GLP-1 receptor agonists** (injectable therapies)
  – Short acting: exenatide BID, liraglutide, lixisenatide
  – Long acting: exenatide QR, albiglutide, dulaglutide
  – Under investigation: semaglutide and ITCA 650
Inhibition of DPP-4 Increases Active Incretin Levels, Enhancing Downstream Incretin Actions

Active GIP
Active GLP-1

DPP-4

$DPP-4$ inhibitor

Inactive GIP
Inactive GLP-1

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

Glucose control improved

GIP = glucose-dependent insulino tropic peptide

Umpierrez et al. Endocrine Practice 2014
# 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; pancreatitis</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

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><strong>Mechanism</strong></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><strong>Efficacy</strong></td>
<td>Modest ((\downarrow) A1C 0.8-1.2%)</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Insulin-independent glucose reduction, Low risk of hypoglycemia, Weight loss (to 4% BW), Blood pressure-lowering</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></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><strong>Contraindications</strong></td>
<td>History of genital fungal infections, caution in chronic kidney disease</td>
</tr>
</tbody>
</table>

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SGLT2 Inhibitors Safety: Adverse Reactions

• The most frequent adverse effects of SGLT2 inhibitors (occurring in ≥5% patients) are female genital mycotic and urinary tract infections

• Patients may also experience increased urination, dehydration, or nasopharyngitis

SGLT2 = sodium-glucose cotransporter-2
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
EMPA-REG OUTCOME: Primary outcome (3-point MACE)

HR 0.86  
(95.02% CI 0.74, 0.99)  
\( p=0.0382^* \)

N=7020 (T2DM + CVD)

EMPA-REG OUTCOME: CV death

HR 0.62
(95% CI 0.49, 0.77)
p<0.0001

All-cause death:
HR 0.68 (95% CI 0.57, 0.82) P<0.0001

EMP A-REG OUTCOME: Hospitalization for heart failure

**HR 0.65**  
(95% CI 0.50, 0.85)  
*p=0.0017*

## Secondary Outcome: Incident or worsening nephropathy and its components

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy</td>
<td>525/4124</td>
<td>388/2061</td>
<td>0.61 (0.53, 0.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New onset macroalbuminuria</td>
<td>459/4091</td>
<td>330/2033</td>
<td>0.62 (0.54, 0.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Doubling of serum-creatinine*</td>
<td>70/4645</td>
<td>60/2323</td>
<td>0.56 (0.39, 0.79)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
<td>13/4687</td>
<td>14/2333</td>
<td>0.45 (0.21, 0.97)</td>
<td>0.0409</td>
</tr>
</tbody>
</table>

*Accompanied by eGFR (MDRD) ≤45 mL/min/1.73m².

Cox regression analyses.

Mixed model repeated measures analysis. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
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GLP1-RA Increase Active Incretin Levels

**Normal Physiology**

Active GLP-1

DPP-4

Inactive GLP-1

**GLP-1 RA**

DPP-4 inhibitor

Resistance

Increased circulating GLP-1 levels

- Increased insulin secretion
- Decreased glucagon release

Glucose control improved

GLP-1 = glucagon-like peptide-1; GLP1-RA = glucagon-like peptide-1 receptor agonist; DPP-4 = dipeptidyl peptidase 4

Umpierrez et al. Endocrine Practice 2014
# GLP-1 Receptor Agonists

**Exenatide, Liraglutide, Albiglutide, Dulaglutide, Lixisenatide**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Activates GLP-1 receptors (increases glucose-dependent insulin secretion; decreases glucagon secretion; slows gastric emptying; decreases appetite)</th>
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<tbody>
<tr>
<td>Efficacy</td>
<td>Decrease A1C levels 1-1.5%</td>
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<tr>
<td>Dosing</td>
<td>Once-twice daily; once weekly</td>
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<tr>
<td>Side effects</td>
<td>Nausea, vomiting; ?retinopathy</td>
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<tr>
<td>Main risk</td>
<td>Long-term safety unknown</td>
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</table>

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

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio.

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.
SUSTAIN 6: Cardiovascular Outcomes

A Primary Outcome

- Hazard ratio, 0.74 (95% CI, 0.58–0.95)
- P<0.001 for noninferiority
- P=0.02 for superiority

B Nonfatal Myocardial Infarction

- Hazard ratio, 0.74 (95% CI, 0.51–1.08)
- P=0.12

C Nonfatal Stroke

- Hazard ratio, 0.61 (95% CI, 0.38–0.99)
- P=0.04

D Death from Cardiovascular Causes

- Hazard ratio, 0.98 (95% CI, 0.65–1.48)
- P=0.92

No. at Risk

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Key Clinical Considerations

• Individualize the A1c target (tighter for younger, healthier; looser for older and more infirm.)

• Individualize the treatment regimen, based on patient characteristics, costs, complexity and patient preferences.

• Minimize adverse effects, especially hypoglycemia risk and weight gain.

• *New concept:* Favor drugs with evidence-based benefits in those with CVD (and renal) disease.