Combination Therapy for Type 2 Diabetes
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Educational Objectives

- Discuss the use of combination therapy using agents with complementary mechanisms of action
- Assess patient A1C in determining appropriate combination therapy
- Review the hierarchy of agents in treatment decision-making
- Understand the importance of individualized therapy
- Prescribe appropriate combination therapy for patients at high cardiovascular risk
- Summarize injectable combination therapies
Approach to Combination Therapy
A1C Levels in Patients With Diabetes

Many patients with diabetes remain above target levels
Role of A1C

- A1C is an indirect measure of average blood glucose levels over a period of approximately 3 months\(^1\)
- A1C serves as a highly predictive tool for diabetic complications\(^1\)
- Higher A1C targets may be required for individual patients (eg, the elderly) and can change over time\(^2\)
- Some studies have shown higher A1C levels in African Americans than non-Hispanic whites\(^1\)
- It is important to consider individualized SMBG and A1C levels when setting glucose targets\(^1,2\)

A1C, glycated hemoglobin; SMBG, self-monitoring of blood glucose.
A1C Targets: American Association of Clinical Endocrinologists

- When possible and achieved safely and affordably, AACE recommends an A1C target of ≤6.5%
- If adverse outcomes such as severe hypoglycemia result from this lower target, a target of >6.5% may be appropriate

A1C Targets: American Diabetes Association

- A1C <7% is an appropriate goal for many nonpregnant adults
- Select individual patients may target stricter A1C goals (<6.5%) if achievable without adverse effects
  - This includes patients treated only with lifestyle therapy or metformin, or those with more recent-onset diabetes, as well as those with longer projected life span and no CVD
- Other patients may require less rigid A1C goals (<8%), including patients with:
  - Lower life expectancy
  - History of hypoglycemia
  - Advanced vascular complications
  - Considerable comorbid conditions
  - Long-standing treatment-resistant diabetes

# A1C Targets, International Diabetes Organizations

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommended A1C Target</th>
</tr>
</thead>
</table>
| American Association of Clinical Endocrinologists<sup>1</sup> | ≤6.5%  
Based on safety and affordability; individualize where appropriate |
| American Diabetes Association/European Association for the Study of Diabetes<sup>2</sup> | ≤7%  
Most nonpregnant adults with adequate life expectancy; individualize based on patient characteristics and preferences and risk of adverse events |
| Diabetes Canada<sup>3</sup> | ≤6.5% Adults with low hypoglycemia risk, to reduce CKD and retinopathy risk  
≤7% Most adults  
7.1%-8.5% Elderly (+/- dementia), functionally dependent, at high risk for hypoglycemia, and/or with limited life expectancy |
| Latin American Diabetes Association<sup>4</sup> | ≤6.5% Young, no complications, at low risk for hypoglycemia  
<7% Individualize treatment |
| National Institute for Health and Care Excellence<sup>5</sup> | 6.5% If managed by lifestyle + diet +/- single drug  
7.0% If on a drug associated with hypoglycemia  
Consider less stringent target if patient has lower life expectancy, high hypoglycemia risk, and/or significant comorbidities |

A1C, glycated hemoglobin; CKD, chronic kidney disease.

5. NICE guideline. Updated May 2017. [https://www.nice.org.uk/guidance/ng28](https://www.nice.org.uk/guidance/ng28)
Individualization of Glycemic Targets

- Evidence supports tailoring glycemic goals to individual patients
- Therapeutic choices should be guided by patient attributes and medication mechanisms of action; consider factors such as disease duration, baseline A1C, and obesity status
- Other factors to consider include patient age, therapeutic goals, potential contraindications, and benefits vs risks of each regimen
  - A1C ≤6.5% for recent onset T2D without clinically significant ASCVD may lead to a reduction in lifetime risk of micro- and macrovascular complications
  - A1C >6.5% is recommended for patients with severe hypoglycemia, shorter life expectancy, advanced renal disease or macrovascular complications, significant comorbidities, or difficult-to-treat long-standing T2D

A1C, glycated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; T2D, type 2 diabetes.
2019 AACE Glycemic Control Algorithm

Key principles include:

• Individualized goals
• Inclusion of lifestyle therapy
• Prompt initiation of mono-, dual, or triple therapy (including insulin), based on A1C targets

Glycemic Target Individualization: American Diabetes Association

• Patient and disease factors used to determine optimal A1C targets
• Characteristics toward the left justify more stringent efforts to lower A1C
• Characteristics toward the right suggest less stringent efforts
• A1C 7% = 53 mmol/L

2019 ADA/EASD Glycemic Control Algorithm

- Takes into account whether the patient has:
  - Established ASCVD or CKD
  - A compelling need to minimize hypoglycemia and/or weight gain, or promote weight loss
  - Cost is also taken into account

A1C, glycated hemoglobin; ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; EASD, European Association for the Study of Diabetes.

If A1C rises to 48 mmol/mol (6.5%) on lifestyle interventions:
• Offer standard-release metformin
• Support the person to aim for an A1C level of 48 mmol/mol (6.5%)

FIRST INTENSIFICATION:
If A1C rises to 58 mmol/mol (7.5%):
• Consider dual therapy with:
  - Metformin and a DPP4i
  - Metformin and pioglitazone
  - Metformin and an SU
  - Metformin and SGLT2i
• Support the person to aim for an A1C level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION:
If A1C rises to 58 mmol/mol (7.5%):
• Consider triple therapy with:
  - Metformin, a DPP4i, and an SU
  - Metformin, pioglitazone, and an SU
  - Metformin, pioglitazone or an SU, and a SGLT2i
• Insulin-based treatment
• Support the person to aim for an A1C level of 53 mmol/mol (7.0%)

If standard-release metformin is not tolerated, consider a trial of modified-release metformin

If triple therapy is not effective, not tolerated, or contraindicated, consider combination therapy with metformin, an SU, and a GLP-1 mimetic for adults with T2D who:
• Have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian, and other minority ethnic groups) and specific psychological or other medical problems associated with obesity, or
• Have a BMI lower than 35 kg/m², and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related complications

If A1C rises to 48 mmol/mol (6.5%) on lifestyle interventions:
• Consider one of the following:
  - A DPP4i, pioglitazone, or an SU
  - An SGLT2i instead of a DPP4i if an SU or pioglitazone is not appropriate
• Support the person to aim for an A1C level of 48 mmol/mol (6.5%) for people on DPP4i, SGLT2i, or pioglitazone, or 53 mmol/mol (7%) for people on an SU

FIRST INTENSIFICATION:
If A1C rises to 58 mmol/mol (7.5%):
• Consider dual therapy with:
  - A DPP4i and pioglitazone
  - A DPP4i and an SU
  - Pioglitazone and an SU
• Support the person to aim for an A1C level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION:
If A1C rises to 58 mmol/mol (7.5%):
• Consider insulin-based treatment
• Support the person to aim for an A1C level of 53 mmol/mol (7.0%)
Agents Used in Combination Therapy
Sequential Management of Hyperglycemia: “Treatment to Failure”

• A stepwise treatment approach has traditionally been used to manage patients with T2D. New treatments are added only when acute symptoms become apparent.

• Earlier intensification with combination therapy is recommended to achieve and maintain target goals among patients with high A1C levels at baseline.

A1C, glycated hemoglobin; OAD, oral antidiabetic drug; T2D, type 2 diabetes.

Diabetes Duration

A1C (%)
To optimally manage T2D:

1. Therapy should be individualized based on known pathophysiologic defects

2. Multiple agents are necessary to target different aspects of this disorder

DPP4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitors; SU, sulfonylureas; T2D, type 2 diabetes; TZD, thiazolidinediones.

Adapted from DeFronzo RA. Diabetes 2009;58:773-795.
Type 2 Diabetes Pharmacotherapy

12 drug classes with different mechanisms of action

- **Insulin Replacement therapy**
- **GLP-1 RAs**
  - Stimulate beta cells, suppress glucagon
- **Sulfonylureas**
  - Increase insulin secretion, reduce hepatic insulin
- **DPP4i**
  - Restore incretin levels (GLP-1), increase insulin secretion, suppress glucagon
- **TZDs**
  - Reduce insulin resistance
- **Glinides**
  - Short-acting insulin secretagogue
- **Biguanide (metformin)**
  - Decrease gluconeogenesis
- **Amylin analog (pramlintide)**
  - Delay gastric emptying; suppress glucagon secretion
- **GLP-1 RAs**
  - Stimulate beta cells, suppress glucagon
- **SGLT2i**
  - Glycosuric effect
- **Colestevlam**
  - Resin binder/bile acid sequestrant
- **Alpha-glucosidase Inhibitors**
  - Delay glucose absorption
- **Bromocriptine**
  - Hypothalamic-pituitary reset; suppress hepatic glucose

DPP4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones.

### AACE: Profiles of Antidiabetic Medications for T2D

#### Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th>MET</th>
<th>GLP1-RA</th>
<th>SGLT2i</th>
<th>DPP4i</th>
<th>AGi</th>
<th>T2D (moderate dose)</th>
<th>SU</th>
<th>GLN</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPO</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
<td>Mild</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Loss</td>
</tr>
<tr>
<td>RENAL / GU</td>
<td>Contra-indicated if eGFR &lt;30 mL/min/1.73 m²</td>
<td>Exenatide</td>
<td>Not indicated for eGFR &lt;45 mL/min/1.73 m²</td>
<td>Genital Mycotic Infections</td>
<td>Dose Adjustment Necessary (Except Linagliptin)</td>
<td>Effective in Reducing Albuminuria</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
</tr>
<tr>
<td>GI Sx</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>CHF CARDIAC</td>
<td>Neutral</td>
<td>See #1</td>
<td>See #2</td>
<td>See #3</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>CHF Risk</td>
<td>Neutral</td>
</tr>
<tr>
<td>ASCVD</td>
<td>Neutral</td>
<td>See #1</td>
<td>See #2</td>
<td>See #3</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
<td>Stroke Risk</td>
<td>May Reduce</td>
<td>Possible</td>
<td>ASCVD Risk</td>
<td>Benefit</td>
</tr>
<tr>
<td>BONE</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>KETOACIDOSIS</td>
<td>Neutral</td>
<td>Neutral</td>
<td>DKA Can Occur in Various Stress Settings</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

AACE, American Association of Clinical Endocrinologists; ASCVD, atherosclerotic cardiovascular disease; AGi, alpha-glucosidase inhibitors; BCR-QR, bromocriptine quick release; CHF, congestive heart failure; COLSVL, colesevelam; CrCl, creatinine clearance; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide receptor agonist; GI Sx, gastrointestinal symptoms; GU, genito-urinary; MET, metformin; SLGT2i, sodium-glucose cotransporter 2 inhibitors; SU, sulfonylureas; T2D, thiazolidinediones.

## Combination Therapy: Major Second-Line Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucagon-like peptide-1</td>
<td>Mimic GLP-1, resulting in increased insulin secretion and inhibited glucagon secretion&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Promote weight loss and strong A1C-lowering with a relatively low risk of hypoglycemia&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>receptor agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium-glucose cotransporter-2</td>
<td>Target renal glucose reabsorption by inhibiting SGLT on the luminal membrane of tubular cells of the proximal convoluted tubule, promoting urinary secretion of glucose&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Significant reductions in A1C levels, and improved systolic blood pressure and body weight&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4</td>
<td>Prevent the breakdown of GLP-1 to increase insulin secretion and decrease glucagon secretion&lt;sup&gt;4,5&lt;/sup&gt;</td>
<td>Neutral risk of ASCVD and weight gain, low risk for hypoglycemia; modest A1C-lowering effects&lt;sup&gt;5,6&lt;/sup&gt;</td>
</tr>
<tr>
<td>inhibitors</td>
<td></td>
<td>Evidence suggests good safety profile in elderly and in patients with T2D and liver dysfunction due to fatty liver&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Directly decrease insulin resistance in adipose tissue, muscle, and the liver by activating the nuclear receptor, PPAR; this alters the transcription of several genes involved in glucose and lipid metabolism and energy balance&lt;sup&gt;5,8&lt;/sup&gt;</td>
<td>Strong A1C lowering, low hypoglycemia risk; low-cost&lt;sup&gt;5,6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Stimulate pancreatic beta-cell secretion of insulin by closing ATP-sensitive K+ channels in the cell membrane&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Potent A1C reductions and low cost&lt;sup&gt;6,10&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

A1C, glycated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; ATP, adenosine triphosphate; GLP-1, glucagon-like peptide-1; PPAR, peroxisome proliferator-activated receptor; SGLT, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

Initiation of Combination Therapy

• Metformin is the preferred first-line agent for the treatment of T2D\textsuperscript{1,2}
• Patients on metformin monotherapy who do not achieve glycemic targets should be started on combination therapy with additional agents, including insulin\textsuperscript{2}
• Combination therapy is often required and should include therapeutic agents with complementary mechanisms of action\textsuperscript{2}
• For patients with A1C >7.5% who are not on antihyperglycemic agents, metformin plus another agent in addition to lifestyle therapy should be initiated\textsuperscript{2}
• Although a medication’s efficacy declines somewhat when added as a third agent, the addition may be required to ensure effective treatment\textsuperscript{2}
• Symptomatic patients with A1C >9% are likely to achieve great benefit from the addition of insulin, although maximum doses with 2 or 3 other agents may be adequate if the patient has no significant symptoms\textsuperscript{2}

A1C, glycated hemoglobin; T2D, type 2 diabetes.
Combination Therapy: Glucose Control With Saxagliptin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Initial Combo w/ Metformin 24 Weeks</th>
<th>Add-on to Metformin 24 Weeks</th>
<th>Add-on to Metformin 18 Weeks</th>
<th>Add-on to Glyburide vs Uptitration 24 Weeks</th>
<th>Add-on to TZD 24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Monotherapy 24 Weeks¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>401</td>
<td>PBO</td>
<td>Met</td>
<td>Saxa + Met</td>
<td>Gly</td>
<td>Saxa + Gly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1306</td>
<td>Saxa + Met</td>
<td>Saxa + Met</td>
<td>Saxa + Met</td>
<td>Saxa + Gly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>743</td>
<td>Met</td>
<td>Saxa + Met</td>
<td>Sita + Met</td>
<td>Sita + Gly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>801</td>
<td>Met</td>
<td>Saxa + Met</td>
<td>Saxa + Met</td>
<td>Saxa + Gly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>768</td>
<td>Gly</td>
<td>Saxa + Met</td>
<td>Gly</td>
<td>Saxa + Gly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>565</td>
<td>TZD</td>
<td>Saxa + Gly</td>
<td>TZD</td>
<td>Saxa + Gly</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.9</td>
<td>8.0</td>
<td>9.4</td>
<td>9.4</td>
<td>8.1</td>
<td>7.7</td>
</tr>
<tr>
<td>Δ A1C (%)</td>
<td>-0.46</td>
<td>-0.2</td>
<td>-0.13</td>
<td>-0.62</td>
<td>-0.52</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

*P<0.0001 vs comparator.

A1C, glycated hemoglobin; Gly, glyburide; Met, metformin; PBO, placebo; Saxa, saxagliptin; Sita, sitagliptin; TZD, thiazolidinediones.

Combination Therapy: Glucose Control With Sitagliptin

Monotherapy vs Glipizide 52 Weeks
Initial Combo w/ Metformin 24 Weeks
Add-on to Metformin 24 Weeks
Add-on to Insulin 24 Weeks
Add-on to Pioglitazone vs Met + Pio 12 Months
Add-on to Rosiglitazone + Metformin 54 Weeks

N
1172
1091
701
641
151
278

Baseline A1C (%)
7.5
8.7
8.0
8.6
8.4
8.7
7.5
8.9
8.0
8.7
8.5
8.8

Δ A1C (%)
-0.7
-0.7
-0.02
0.0
-0.6
-1.4

* P<0.001 vs active comparator monotherapy. † P<0.001 vs active comparator dual therapy.
A1C, glycated hemoglobin; Glip, glipizide; Ins, insulin; Met, metformin; Pio, pioglitazone; Rosi, rosiglitazone; Sita, sitagliptin.

# Combination Therapy: Glucose Control With Albiglutide

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Add-on to Metformin</th>
<th>Add on to Pio +/- Met</th>
<th>Add-on to Met +/- SU +/- TZD</th>
<th>Add-on to Met +/- SU</th>
<th>Add-on to Basal Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>296</td>
<td>1049</td>
<td>310</td>
<td>841</td>
<td>779</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>8.0</td>
<td>8.1</td>
<td>8.2</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>0.2</td>
<td>0.27</td>
<td>0.36</td>
<td>0.28</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

$**P<0.0001$ vs placebo. $**P<0.001$ vs active comparators.

A1C, glycated hemoglobin; Albi, albiglutide; Glar, glargine; Glim, glimepiride; Lira, liraglutide; Met, metformin; PBO, placebo; Pio, pioglitazone; Rosi, rosiglitazone; Sita, sitagliptin; SU, sulfonylureas; TZD, thiazolidinediones.

Combination Therapy: Glucose Control With Dulaglutide

<table>
<thead>
<tr>
<th>Treatment†</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy 52 Weeks¹</td>
<td>7.6</td>
<td>-0.56 ***</td>
</tr>
<tr>
<td>Monotherapy 52 Weeks²</td>
<td>7.6</td>
<td>-0.78 **</td>
</tr>
<tr>
<td>Add-on to Metformin 26 Weeks³</td>
<td>8.1</td>
<td>-1.1 ***</td>
</tr>
<tr>
<td>Add-on to Pio + Met 52 Weeks⁴</td>
<td>8.1</td>
<td>-1.36 ***</td>
</tr>
<tr>
<td>Add-on to Met + SU 52 Weeks⁵</td>
<td>8.1</td>
<td>-1.08 ***</td>
</tr>
<tr>
<td>Add-on to Lispro 26 Weeks⁶</td>
<td>8.5</td>
<td>-1.41</td>
</tr>
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</table>

N

<table>
<thead>
<tr>
<th>Treatment†</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met</td>
<td>807</td>
</tr>
<tr>
<td>Dula</td>
<td>1098</td>
</tr>
<tr>
<td>Sita</td>
<td>599</td>
</tr>
<tr>
<td>Dula</td>
<td>976</td>
</tr>
<tr>
<td>Exe</td>
<td>807</td>
</tr>
<tr>
<td>Dula</td>
<td>884</td>
</tr>
</tbody>
</table>

A1C, glycated hemoglobin; Dula, dulaglutide; Exe, exenatide; Glar, glargine; Lira, liraglutide; Met, metformin; Pio, pioglitazone; Sita, sitagliptin; SU, sulfonylureas.

¹All dulaglutide dosages shown are 1.5 mg once weekly.

* P<0.02 vs glargine. ** P<0.01 vs metformin. *** P<0.001 vs comparator.

Combination Therapy: Glucose Control With Exenatide

<table>
<thead>
<tr>
<th>Treatment†</th>
<th>Monotherapy 24 Weeks¹</th>
<th>Add-on to Metformin 30 Weeks²</th>
<th>Add-on to Sulfonylurea 30 Weeks³</th>
<th>Add-on to TZD 16 Weeks⁴</th>
<th>Add-on to Metformin + SU 30 Weeks⁵</th>
<th>Add-on to Met + SU vs Glargine 26 Weeks⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>233</td>
<td>336</td>
<td>377</td>
<td>233</td>
<td>733</td>
<td>551</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>7.8 7.8</td>
<td>8.2 8.2</td>
<td>8.7 8.6</td>
<td>7.9 7.9</td>
<td>8.5 8.5</td>
<td>8.3 8.2</td>
</tr>
<tr>
<td>ΔA1C (%)</td>
<td>-0.2 -0.2</td>
<td>-0.9 -0.9</td>
<td>-0.8 -0.8</td>
<td>-0.86 -0.86</td>
<td>-0.89 -0.89</td>
<td>-0.9 -0.9</td>
</tr>
</tbody>
</table>

* P<0.001 vs comparator.
† All exenatide dosages shown are 10 μg BID.

A1C, glycated hemoglobin; Exe, exenatide; Glar, glargine; Met, metformin; PBO, placebo; SU, sulfonylureas; TZD, thiazolidinediones.

Combination Therapy: Glucose Control With Exenatide ER

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Add-on to OAs* 30 Weeks①</th>
<th>Monotherapy vs OAs 26 Weeks②</th>
<th>Add-on to Metformin 26 Weeks③</th>
<th>Add-on to Met +/− SU 26 Weeks④</th>
<th>Add-on to OAs† 26 Weeks⑤</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>258</td>
<td>820</td>
<td>514</td>
<td>456</td>
<td>911</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>8.3 8.3</td>
<td>8.5 8.5 8.6 8.5</td>
<td>8.5 8.5 8.6</td>
<td>8.3 8.3</td>
<td>8.4 8.5</td>
</tr>
</tbody>
</table>

| Δ A1C (%) | -1.5 -1.5 -1.48 -1.53    | -1.15 -1.63                   | -0.9 -1.5 -1.50              | -1.3 -1.50                   | -1.48 -1.28                |

① Metformin, sulfonylurea, thiazolidinedione, or combination of any 2 of these agents.
② Metformin, sulfonylurea, metformin + sulfonylurea, or metformin + pioglitazone.
A1C, glycated hemoglobin; Exe, exenatide; ER, extended release; Glar, glargine; Lira, liraglutide; Met, metformin; OAs, oral agents; Pio, pioglitazone; Sita, sitagliptin; SU, sulfonylureas.
## Combination Therapy: Glucose Control With Liraglutide

### Monotherapy vs Glimepiride 52 Weeks\(^1\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glim</td>
<td>746</td>
<td>8.4</td>
</tr>
<tr>
<td>Lira</td>
<td></td>
<td>8.3</td>
</tr>
</tbody>
</table>

### Add-on to Metformin 26 Weeks\(^2\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met</td>
<td>1091</td>
<td>8.4</td>
<td>-0.51</td>
</tr>
<tr>
<td>Glim +</td>
<td></td>
<td>8.4</td>
<td>-0.98</td>
</tr>
<tr>
<td>Lira +</td>
<td></td>
<td>8.4</td>
<td>-1.14</td>
</tr>
</tbody>
</table>

### Add-on to Metformin 26 Weeks\(^3\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sita +</td>
<td>665</td>
<td>8.5</td>
<td>-1.50</td>
</tr>
<tr>
<td>Lira +</td>
<td></td>
<td>8.4</td>
<td>-1.50</td>
</tr>
</tbody>
</table>

### Add-on to Sulfonylurea 26 Weeks\(^4\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU</td>
<td>1041</td>
<td>8.4</td>
<td>-0.9</td>
</tr>
<tr>
<td>Rosi +</td>
<td></td>
<td>8.4</td>
<td>-0.44</td>
</tr>
<tr>
<td>Lira +</td>
<td></td>
<td>8.5</td>
<td>-1.13</td>
</tr>
</tbody>
</table>

### Add-on to Met + TZD 26 Weeks\(^5\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met +</td>
<td>821</td>
<td>8.4</td>
<td>-0.5</td>
</tr>
<tr>
<td>Glar +</td>
<td></td>
<td>8.6</td>
<td>-0.24</td>
</tr>
<tr>
<td>Lira +</td>
<td></td>
<td>8.3</td>
<td>-1.09</td>
</tr>
</tbody>
</table>

### Add-on to Met + SU 26 Weeks\(^6\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met +</td>
<td>581</td>
<td>8.2</td>
<td>-1.33</td>
</tr>
<tr>
<td>Glar +</td>
<td></td>
<td>8.3</td>
<td>***</td>
</tr>
</tbody>
</table>

---

**Key:**
- *P*<0.0001 vs monotherapy.
- **P*<0.0001 vs dual therapy.
- ***P*=0.0015 vs glargine.

\(^1\) All liraglutide dosages shown are 1.8 mg QD.

A1C, glycated hemoglobin; Glar, glargine; Glim, glimepiride; Lira, liraglutide; Met, metformin; QD, once daily; Rosi, rosiglitazone; Sita, sitagliptin; SU, sulfonylureas; TZD, thiazolidinediones.

**Combination Therapy: Glucose Control With Lixisenatide**

<table>
<thead>
<tr>
<th>Treatment†</th>
<th>Monotherapy 12 Weeks</th>
<th>Add-on to Metformin 24 Weeks</th>
<th>Add-on to Metformin 24 Weeks</th>
<th>Add-on to Pioglitazone 24 Weeks</th>
<th>Add-on to Stable Glargine ± Met 24 Weeks</th>
<th>Add-on to Titrated Glargine + OAs (Insulin-Naive Patients) 24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=361</td>
<td>484</td>
<td>639</td>
<td>484</td>
<td>495</td>
<td>446</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>8.1</td>
<td>8.0</td>
<td>8.0</td>
<td>8.1</td>
<td>8.4</td>
<td>7.6</td>
</tr>
<tr>
<td>Treatment†</td>
<td>PBO</td>
<td>Lixi</td>
<td>Exe BID + Met</td>
<td>Pio</td>
<td>Lixi + Pio</td>
<td>Glar + Lixi + Glar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ A1C (%)</td>
<td>-0.27</td>
<td>-0.73</td>
<td>-0.96</td>
<td>-0.34</td>
<td>-0.4</td>
<td>-0.4</td>
</tr>
</tbody>
</table>

*Noninferiority criteria met.
†All lixisenatide dosages shown are 20 µg QD, administered in a 2-step dose increase regimen.

A1C, glycated hemoglobin; Exe, exenatide; Glar, glargine; Lixi, lixisenatide; Met, metformin; OAs, oral agents; PBO, placebo; Pio, pioglitazone; QD, once daily.

## Combination Therapy

### Glucose Control With Canagliflozin

<table>
<thead>
<tr>
<th>Treatment* (mg/day)</th>
<th>N</th>
<th>Monotherapy 26 Weeks&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Add-on to Metformin 12 Weeks&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Add-on to Metformin 52 Weeks&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Add-on to Metformin + SU 52 Weeks&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Add-on to OAs +/- Insulin in CKD&lt;sup&gt;1&lt;/sup&gt; 26 Weeks&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PBO</td>
<td>Met</td>
<td>Sita + Met</td>
<td>Cana + Met</td>
<td>Glim + Met</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>584</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>451</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1452</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>755</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>269</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Baseline A1C (%)

- **P<0.001 vs placebo.

### Δ A1C (%)

- **P<0.001 vs baseline.

### Notes

- All canagliflozin dosages shown are 300 mg.
- Estimated glomerular filtration rate 30-50 mL/min/1.73 m².
- Met criteria for noninferiority and superiority (upper limit of confidence interval <0.0%).

A1C, glycated hemoglobin; Cana, canagliflozin; CKD, chronic kidney disease; Glim, glimepiride; Ins, insulin; Met, metformin; OAs, oral agents; PBO, placebo; Sita, sitagliptin; SU, sulfonylureas.

## Combination Therapy: Glucose Control With Dapagliflozin

### Monotherapy 24 Weeks

<table>
<thead>
<tr>
<th>Treatment* (mg/day)</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>7.8</td>
<td>-0.23</td>
</tr>
<tr>
<td>Dapa</td>
<td>8.0</td>
<td>-0.89</td>
</tr>
</tbody>
</table>

### Initial Combo with Metformin 24 Weeks

<table>
<thead>
<tr>
<th>Treatment* (mg/day)</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>9.1</td>
<td>-1.44</td>
</tr>
<tr>
<td>Dapa</td>
<td>9.1</td>
<td>-1.45</td>
</tr>
<tr>
<td>Dapa + Met</td>
<td>9.1</td>
<td>-1.98</td>
</tr>
</tbody>
</table>

### Add-on to Metformin 52 Weeks

<table>
<thead>
<tr>
<th>Treatment* (mg/day)</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>8.1</td>
<td>-0.52</td>
</tr>
<tr>
<td>Dapa</td>
<td>7.9</td>
<td>-0.52</td>
</tr>
<tr>
<td>Glip + Met</td>
<td>8.1</td>
<td>-0.97</td>
</tr>
<tr>
<td>Dapa + Met</td>
<td>8.3</td>
<td>-0.97</td>
</tr>
</tbody>
</table>

### Add-on to Pioglitazone 24 Weeks

<table>
<thead>
<tr>
<th>Treatment* (mg/day)</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>8.3</td>
<td>-0.42</td>
</tr>
<tr>
<td>Dapa</td>
<td>8.4</td>
<td>-0.42</td>
</tr>
<tr>
<td>Pio + Dapa + Pio</td>
<td>8.7</td>
<td>0</td>
</tr>
</tbody>
</table>

### Add-on to Sitagliptin +/- Metformin 24 Weeks

<table>
<thead>
<tr>
<th>Treatment* (mg/day)</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>8.7</td>
<td>-0.50</td>
</tr>
<tr>
<td>Dapa + Sita +/- Met</td>
<td>8.7</td>
<td>-0.50</td>
</tr>
<tr>
<td>Pioglitazone + Met</td>
<td>8.5</td>
<td>-0.39</td>
</tr>
</tbody>
</table>

### Add-on to insulin +/- OAs 24 Weeks

<table>
<thead>
<tr>
<th>Treatment* (mg/day)</th>
<th>Baseline A1C (%)</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>8.6</td>
<td>-0.96</td>
</tr>
</tbody>
</table>

### Notes

- All dapagliflozin dosages shown are 10 mg.
- *P<0.001 vs placebo. **P<0.0001 vs comparator.

A1C, glycated hemoglobin; Dapa, dapagliflozin; Ins, insulin; Glip, glipizide; Met, metformin; OAs, oral agents; PBO, placebo; Pio, pioglitazone; Sita, sitagliptin.

## Combination Therapy: Glucose Control With Empagliflozin

<table>
<thead>
<tr>
<th>Treatment* (mg/day)</th>
<th>Monotherapy 24 Weeks¹</th>
<th>Add-on to Metformin 24 Weeks²</th>
<th>Add-on to Metformin 104 Weeks³</th>
<th>Add-on to Met + SU 24 Weeks⁴</th>
<th>Add-on to Pio +/- Met 24 Weeks⁵</th>
<th>Add-on to MDI insulin 52 Weeks⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>899</td>
<td>638</td>
<td>1549</td>
<td>669</td>
<td>499</td>
<td>563</td>
</tr>
<tr>
<td><strong>Baseline A1C (%)</strong></td>
<td>7.9</td>
<td>7.9</td>
<td>7.9</td>
<td>8.2</td>
<td>8.2</td>
<td>8.3</td>
</tr>
<tr>
<td><strong>ΔA1C (%)</strong></td>
<td>0.08</td>
<td>-0.13</td>
<td>-0.55</td>
<td>-0.17</td>
<td>-0.11</td>
<td>-0.81</td>
</tr>
</tbody>
</table>

* All empagliflozin dosages shown are 25 mg. ** P<0.001 vs placebo. *** P<0.05 vs active comparator.

A1C, glycated hemoglobin; Empa, empagliflozin; Ins, insulin; Glim, glimepiride; MDI, multiple dose injection; Met, metformin; PBO, placebo; Pio, pioglitazone; Sita, sitagliptin; SU, sulfonylureas.

### Fixed-Dose Combination Agents for T2D

<table>
<thead>
<tr>
<th>Single-pill oral</th>
<th>Injectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4i + biguanide&lt;sup&gt;1-3&lt;/sup&gt;</td>
<td>GLP-1 RA + basal insulin</td>
</tr>
<tr>
<td>Meglitinide + biguanide&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>SGLT2i + biguanide&lt;sup&gt;1,4-7&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>SU + biguanide&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>TZD + biguanide&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>SGLT2i + DPP4i&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>DPP4i + TZD</td>
<td></td>
</tr>
<tr>
<td>SU + TZD</td>
<td></td>
</tr>
</tbody>
</table>

- Evidence from retrospective pharmacy claims analyses suggests that adherence is improved with FDC compared with 2-pill combinations<sup>8-10</sup>
- Improved adherence has also been shown when switching from monotherapy to FDC, rather than separate pill combinations<sup>10</sup>

DPP4i, dipeptidyl peptidase-4 inhibitors; FDC, fixed-dose combination; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinediones.

## Approved Oral Fixed-Dose Combination Therapies

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Formulation</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4i + Biguanide1-3</td>
<td>Alogliptin, linagliptin, saxagliptin, or sitagliptin + metformin</td>
<td>Stimulates postprandial insulin, suppresses glucagon secretion + reduces hepatic gluconeogenesis</td>
</tr>
<tr>
<td>Meglitinide + biguanide1</td>
<td>Repaglinide + metformin</td>
<td>Increases insulin secretion + reduces hepatic gluconeogenesis</td>
</tr>
<tr>
<td>SGLT2i + biguanide1,4-7</td>
<td>Canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin + metformin</td>
<td>Reduces renal glucose absorption + reduces hepatic gluconeogenesis</td>
</tr>
<tr>
<td>SU + biguanide1</td>
<td>Glipizide or glyburide + metformin</td>
<td>Increases insulin secretion from pancreatic beta cells + reduces hepatic gluconeogenesis</td>
</tr>
<tr>
<td>TZD + biguanide1</td>
<td>Pioglitazone or rosiglitazone + metformin</td>
<td>Increases insulin sensitivity + reduces hepatic gluconeogenesis</td>
</tr>
<tr>
<td>SGLT2i + DPP4i1</td>
<td>Dapagliflozin + saxagliptin Empagliflozin + linagliptin Ertugliflozin + sitagliptin</td>
<td>Reduces renal glucose absorption + stimulates postprandial insulin, suppresses glucagon secretion</td>
</tr>
<tr>
<td>DPP4i + TZD</td>
<td>Alogliptin + pioglitazone</td>
<td>Stimulates postprandial insulin, suppresses glucagon secretion + increases insulin sensitivity</td>
</tr>
<tr>
<td>SU + TZD</td>
<td>Glimepiride + pioglitazone</td>
<td>Increases insulin secretion from pancreatic beta cells + increases insulin sensitivity</td>
</tr>
</tbody>
</table>

DPP4i, dipeptidyl peptidase-4 inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinediones.

## Efficacy of Second Therapy Added To Metformin

<table>
<thead>
<tr>
<th>Combination</th>
<th>Reduction in A1C vs metformin monotherapy*</th>
<th>Weight change</th>
<th>Hypoglycemia risk RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU/glinide + metformin</td>
<td>-0.68%</td>
<td>+2.6 kg</td>
<td>8.91 (1.46, 54.34)</td>
</tr>
<tr>
<td>SGLT2i + metformin</td>
<td>-0.47%</td>
<td>-2.0 kg</td>
<td>1.37 (0.64, 2.92)</td>
</tr>
<tr>
<td>TZD + metformin</td>
<td>-0.44%</td>
<td>+1.93 kg</td>
<td>1.60 (1.05, 2.46)</td>
</tr>
<tr>
<td>DPP4i + metformin</td>
<td>-0.44%</td>
<td>+0.38 kg</td>
<td>1.15 (0.84, 1.55)</td>
</tr>
</tbody>
</table>

*Weighted mean difference

CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; RR, relative risk; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinediones.

Combination Triple Therapy: MET + DAPA + SAXA vs MET + SITA

**OBJECTIVE**: Assess safety and long-term efficacy of early addition of DAPA plus SAXA to MET as compared to a dual therapy strategy with SITA in patients with T2D inadequately controlled with metformin monotherapy (A1C 8.0% to 10.5%).

**METHODS**: Multinational, randomized, double-blind, active-controlled, double-dummy parallel-group phase 3b trial conducted in 6 countries. MET + DAPA + SAXA (n=232) and MET + SITA (n=232). Primary endpoint: Mean change in A1C, baseline to week 26.

**CONCLUSIONS**: Triple therapy with MET + DAPA + SAXA led to significantly improved glycemic control compared with conventional dual therapy.

A1C, glycated hemoglobin; DAPA, dapagliflozin; MET, metformin; SAXA, saxagliptin; SITA, sitagliptin; T2D, type 2 diabetes.

**OBJECTIVE:** Assess whether a novel, initial triple combination therapy MET + DAPA + SAXA is efficacious and tolerable compared with conventional stepwise add-on therapy (MET, followed by SU and DPP4i) in drug-naïve patients with recent-onset, uncontrolled T2D (A1C 8.0% to 10.5%).

**METHODS:** Open-label, prospective, randomized, comparator-controlled trial. Primary endpoint is the proportion of patients with A1C <6.5% at 104 weeks, without hypoglycemia, weight gain, or adverse events resulting in discontinuation.

---

**Eligible patients**
- Drug-naïve T2D
- A1C ≥8.0%, <10.5%
- Age 18-65 years
- BMI ≥23 kg/m² and <35 kg/m²

**Screening**

**1:1 randomization**

**Initial triple combination therapy group**

**Conventional stepwise therapy group**

**Assessment of primary and secondary outcomes, adverse events**

**Randomization**

**Treatment**

**Analysis**

---

A1C, glycated hemoglobin; DAPA, dapagliflozin; DPP4i, dipeptidyl peptidase-4 inhibitors; MET, metformin; SAXA, saxagliptin; SU, sulfonylureas; T2D, type 2 diabetes; Triple AXEL, Rivaroxaban Versus Warfarin in Acute Ischemic Stroke With Atrial Fibrillation.

Combination Quadruple Therapy: MET + SU + DPP4i, With SGLT2i

**OBJECTIVE:** To compare the safety and effectiveness of empagliflozin and dapagliflozin as components of a quadruple OAD agent regimen in patients with poorly controlled T2D (A1C 7.5% to 12%).

**METHODS:** Open-label, 52-week prospective, observational study.

**CONCLUSIONS:** Both SGLT2i significantly lowered A1C levels and were safe and effective when added as a 4th OAD agent in patients with T2D concurrently treated with 3 other OAD agents (MET + SU + DPP4i).

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A1C, glycated hemoglobin; DPP4i, dipeptidyl peptidase-4 inhibitors; MET, metformin; OAD, oral antidiabetic agent; SGLT2i, sodium-glucose cotransporter 2 inhibitors; SU, sulfonylurea; T2D, type 2 diabetes.

Injectable Combination Therapies
Considerations for Adding Insulin Therapy

• Basal insulin, the most convenient first-line insulin regimen, can be used in combination with metformin and other anti-hyperglycemic agents\(^1,2\)

• Basal insulin’s primary action is to prevent the liver from producing glucose, thus ensuring normal glucose levels overnight and between meals\(^1\)

• Patients on basal insulin who do not achieve A1C target levels should be considered for combination injectable therapy\(^1,2\)

A1C, glycated hemoglobin.

Basal Insulin as Add-on to Oral Antidiabetic Drugs in Patients With T2D

Combination of 2 or 3 OADs

Basal Insulin Therapy

START BASAL (Long-Acting Insulin)

A1C <8%

TDD: 0.1-0.2 U/kg

A1C >8%

TDD: 0.2-0.3 U/kg

A1C, glycated hemoglobin; OAD, oral antidiabetic agent; T2D, type 2 diabetes; TDD, total daily dose.
Basal Insulin Added to OADs Improves Glycemic Control: “Treat to Target” Trials

A1C (%)

N=756
Baseline A1C 7.5% to 10.0%
Treated with 1 or 2 OADs (MET, SU, or TZD)

N=973
Baseline A1C 7.0% to 10.5%
Treated with OADs, including MET

24 Weeks of Treatment

A1C, glycated hemoglobin; MET, metformin; NPH, neutral protamine Hagedorn insulin; OAD, oral antidiabetic agent; SU, sulfonylureas; TZD, thiazolidinediones.
Basal Insulin + GLP-1 RA: Complimentary Clinical Effects

**Combined effect is to decrease both fasting blood glucose and postprandial glucose excursions**

**Basal insulin**
- ↑ Peripheral glucose uptake
- ↓ Hepatic glucose production

Result:
- Fasting blood glucose control

**GLP-1 RA**
- ↑ Glucose-dependent insulin release
- ↓ Glucagon secretion
- Slowing of gastric emptying

Result:
- Postprandial blood glucose control

↑ Body weight
- Relatively high hypoglycemia risk

↓ Body weight
- Low hypoglycemia risk

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A1C, glycated hemoglobin; GLP-1 RA, glucagon-like peptide-1 receptor agonist.
Considerations for Combination Injectable Therapy

Initiate basal insulin if A1C above target despite dual/triple therapy (usually metformin + non-insulin agents)

If A1C not controlled (>10% or 2% over target), consider combination injectable therapy

Add rapid-acting (bolus) insulin before largest meal

If A1C not controlled, advance to basal-bolus

Advance to ≥2 rapid-acting premeal insulin injections (basal-bolus)

Add GLP-1 RA (iDegLira or iGlarLixi)

If not tolerated or A1C target not reached, start 2-injection regimen by adding prandial insulin

If goals not met, consider changing to alternative insulin regimen

Change to premixed insulin twice daily (before breakfast and supper)

If A1C not controlled, advance to third injection

Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)

A1C, glycated hemoglobin; GLP-1 RA, glucagon-like peptide-1 receptor agonist; iDegLira, insulin degludec and liraglutide; iGlarLixi, insulin glargine and lixisenatide.

Benefits of Basal Insulin/GLP-1 RA Fixed Ratio Combinations

- Target both FPG and PPG to improve glycemic control (vs individual components)
- No individual risks of hypoglycemia vs basal insulin alone (despite improved glycemic control)
- Weight neutrality or loss
- Slow up-titration reduces gastrointestinal effects vs GLP-1 RA alone
- A simplified regimen—reduced complexity vs premixed and basal bolus regimens may increase patient adherence

FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; PPG, postprandial plasma glucose.
GLP-1 RA Plus Insulin: Systematic Review

Results from 7 RCTs and 15 clinical practice or observational studies including at least 30 patients with T2D

GLP-1 RA, glucagon-like peptide-1 receptor agonist; RCT, randomized clinical trial; T2D, type 2 diabetes.
Fixed-Ratio Combinations of Basal Insulin and GLP-1 RA

- **iGlarLixi 100/33**
  - Insulin glargine and lixisenatide injection
  - Approved by FDA November 2016
  - Indication: Adults with T2D inadequately controlled on basal insulin (<60 units daily) or lixisenatide
  - 1 unit contains:
    - 1 U insulin glargine and
    - 0.33 mcg lixisenatide (a GLP-1 RA)
  - Administered SC once daily
  - Starting dose: 15 or 30 units (15 or 30 U insulin glargine and 5 or 10 mcg lixisenatide)
  - SoloStar pen

- **iDegLira 100/3.6**
  - Insulin degludec and liraglutide injection
  - Approved by FDA November 2016
  - Indication: Adults with T2D inadequately controlled on basal insulin (<50 units daily) or liraglutide
  - 1 unit contains:
    - 1 U insulin degludec and
    - 0.036 mg liraglutide (a GLP-1 RA)
  - Administered SC once daily
  - Starting dose: 16 units (16 U insulin degludec and 0.58 mg liraglutide)
  - FlexTouch pen

FDA, US Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SC, subcutaneous; iDegLira, insulin degludec and liraglutide; iGlarLixi, insulin glargine and lixisenatide; T2D, type 2 diabetes.

iDegLira (100/3.6) in Patients With T2D Inadequately Controlled on Basal Insulin Alone

26-week, randomized, double-blind study in patients with T2D inadequately controlled on basal insulin + MET (± SU/glinide)

• T2D
• ≥18 years of age
• A1C 7.5%-10%
• BMI ≥27 kg/m²
• Basal insulin 20-40 U + MET ± SU/glinide

1:1 Randomization

iDegLira + MET
(n=199)

iDeg + MET (n=199)

iDegLira and iDeg initiated at 16 U and titrated to FPG target of 72-90 mg/dL, to maximum dose of 50 U

26-week treatment period

Primary Endpoint: Change in A1C at week 26

A1C, glycated hemoglobin; FPG, fasting plasma glucose; iDeg, insulin degludec; iDegLira, insulin degludec and liraglutide; MET, metformin; SU, sulfonylureas; T2D, type 2 diabetes.

iDegLira (100/3.6) in Patients With T2D Inadequately Controlled on Basal Insulin Alone

Change in A1C after 26 weeks of therapy:

A1C targets and composite endpoints:

- **60%** of patients in the iDegLira arm achieved A1C <7.0% (vs 23% with iDeg)
- **40%** of patients in the iDegLira arm achieved A1C <7.0% with no confirmed hypoglycemia during final 12 weeks of treatment and with no weight gain (vs 8.5% with iDeg)
Glucose Control With iDegLira

*Per protocol maximum dose: 50 units/day (no maximum dose of degludec alone was specified in the insulin naïve trial).

A1C, glycosylated hemoglobin; iDeg, insulin degludec; iDegLira, insulin degludec and liraglutide; Lira, liraglutide; NI, noninferior; OAs, oral agents; S, superior.

iGlarLixi (100/33) in Patients With T2D Inadequately Controlled With Oral Agents

30-week, randomized, open-label study in patients on metformin ± 2nd oral agent

- T2D
- ≥18 years of age
- A1C 7.5%-10%
- MET ± 2nd OA

4-week run-in phase

2:2:1 Randomization

- iGlarLixi + MET (n=469)
- iGlar + MET (n=467)
- Lixi + MET (n=234)

30-week treatment period

iGlarLixi and iGlar initiated at 10 U and titrated to FPG target of 80-100 mg/dL, to maximum dose of 60 U

Primary Endpoint: Change in A1C at week 30

A1C, glycated hemoglobin; FPG, fasting plasma glucose; iGlar, insulin glargine; iGlarLixi, insulin glargine and lixisenatide; Lixi, lixisenatide; MET, metformin; T2D, type 2 diabetes.

iGlarLixi (100/33) in Patients With T2D Inadequately Controlled With Oral Agents

Change in A1C after 30 weeks of therapy:

- **74%** of patients in the iGlarLixi arm achieved an A1C <7.0% (vs 59% with glargine and 33% with lixisenatide)
- **54%** of iGlarLixi patients achieved an A1C <7.0% with no documented symptomatic hypoglycemia (vs 44% with glargine and 31% with lixisenatide)
- **32%** of iGlarLixi patients achieved an A1C <7.0% with no weight gain and no documented symptomatic hypoglycemia (vs 19% with glargine and 26% with lixisenatide)

Glucose Control With iGlarLixi

Per protocol maximum dose: 60 units/day.
A1C, glycated hemoglobin; iGlarLixi, insulin glargine and lixisenatide; OAs, oral agents.
Combination Therapy for Patients With High Cardiovascular Risk
Combination Therapy: Patients With High CV Risk

- Substantial historical evidence indicates that intensive, ongoing glucose control in newly diagnosed T2D patients may decrease long-term CVD rates\(^1\)

- In 2008, FDA guidance mandated CV safety assessment of all new antihyperglycemic agents\(^2\)
  - RCT studies required to demonstrate that study drug was not associated with more major adverse CV events than placebo (noninferiority)
    - Some studies tested for superiority if noninferiority criteria were met
  - **Primary outcome:** Composite of CV death, nonfatal MI, and nonfatal stroke
    - Some studies included additional endpoints

- Several studies of SGLT-2 inhibitors and GLP-1 RA have shown superiority compared with placebo.

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CV, cardiovascular; CVD, cardiovascular disease; FDA, US Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MI, myocardial infarction; RCT, randomized controlled trial; SGLT-2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

Summary of Published DPP4i Cardiovascular Outcomes Trials

<table>
<thead>
<tr>
<th></th>
<th>EXAMINE*</th>
<th>SAVOR-TIMI 53</th>
<th>TECOS</th>
<th>CARMELINA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome, HR (95% CI)</strong></td>
<td>0.96 (≤1.16)‡</td>
<td>1.00 (0.89-1.12)</td>
<td>0.98 (0.88-1.09)</td>
<td>1.02 (0.89-1.17)</td>
</tr>
<tr>
<td><strong>CV death, HR (95% CI)</strong></td>
<td>0.79 (0.60-1.04)</td>
<td>1.03 (0.87-1.22)</td>
<td>1.03 (0.89-1.19)</td>
<td>0.96 (0.81-1.14)</td>
</tr>
<tr>
<td><strong>Fatal or nonfatal MI, HR (95% CI)</strong></td>
<td>1.08 (0.88-1.33)</td>
<td>0.95 (0.80-1.12)</td>
<td>0.95 (0.81-1.11)</td>
<td>1.12 (0.90-1.40)</td>
</tr>
<tr>
<td><strong>Fatal or nonfatal stroke, HR (95% CI)</strong></td>
<td>0.91 (0.55-1.50)</td>
<td>1.11 (0.88-1.39)</td>
<td>0.97 (0.79-1.19)</td>
<td>0.91 (0.67-1.23)</td>
</tr>
<tr>
<td><strong>All-cause mortality, HR (95% CI)</strong></td>
<td>0.88 (0.71-1.09)</td>
<td>1.11 (0.96-1.27)</td>
<td>1.01 (0.90-1.14)</td>
<td>0.98 (0.84-1.13)</td>
</tr>
<tr>
<td><strong>HF hospitalization, HR (95% CI)</strong></td>
<td>1.27 (1.07-1.51)</td>
<td>1.00 (0.83-1.20)</td>
<td>0.90 (0.74-1.08)</td>
<td></td>
</tr>
</tbody>
</table>

‡ The parenthetical value is the upper boundary of the one-sided repeated CI, at an alpha level of 0.01. * Numerical imbalance (not statistically significant) with increased hospitalizations for heart failure with alogliptin.

CI, confidence interval; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin; CV, cardiovascular; DPP4i, dipeptidyl peptidase-4 inhibitors; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; HF, heart failure; 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; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin

### Summary of Published SGLT-2i Cardiovascular Outcomes Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EMPA-REG OUTCOME</th>
<th>CANVAS/CANVAS-R</th>
<th>DECLARE - TIMI 58</th>
<th>CREDENCE‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE outcome (HR [95% CI])*</td>
<td>0.86 (0.74-0.99)</td>
<td>0.86 (0.75-0.97)</td>
<td>0.93 (0.84-1.03)**</td>
<td>0.80 (0.67-0.95)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.62 (0.49-0.77)</td>
<td>0.87 (0.72-1.06)</td>
<td>0.98 (0.82-1.17)</td>
<td>0.78 (0.61-1.00)</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.87 (0.70-1.09)</td>
<td>0.89 (0.73-1.09)</td>
<td>0.89 (0.77-1.01)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>1.18 (0.89-1.56)</td>
<td>0.87 (0.69-1.09)</td>
<td>1.01 (0.84-1.21)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.68 (0.57-0.82)</td>
<td>0.87 (0.74-1.01)</td>
<td>0.93 (0.82-1.04)</td>
<td>0.83 (0.68–1.02)</td>
</tr>
<tr>
<td>Heart failure hospitalization</td>
<td>0.65 (0.50-0.85)</td>
<td>0.67 (0.52-0.87)</td>
<td>0.73 (0.61-0.88)</td>
<td>0.61 (0.47–0.80)</td>
</tr>
</tbody>
</table>

*MACE outcome: cardiovascular death, non-fatal MI, non-fatal stroke (primary outcome in EMPA-REG, CANVAS/CANVAS-R, and DECLARE-TIMI 58, secondary outcome in CREDENCE). **Additional primary outcome in DECLARE-TIMI 58: CV death and hospitalization for heart failure, HR= 0.83 (0.73–0.95). ‡ CREDENCE enrolled patients with diabetic kidney disease. Primary outcome included composite of end-stage kidney disease (dialysis for at least 30 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 m² sustained for at least 30 days), doubling of the serum creatinine level, or death from renal or cardiovascular disease. The primary outcome was lower in those receiving canagliflozin HR= 0.7 (0.59-0.82).

CANVAS, Canagliflozin Cardiovascular Assessment Study; CANVAS-R, A Study of the Effects of Canagliflozin (JNJ-28431754) on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus; CV, cardiovascular; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; MI, myocardial infarction; SGLT2, sodium-glucose cotransporter 2. CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation.

## Summary of Published GLP-1 RA Cardiovascular Outcomes Trials

<table>
<thead>
<tr>
<th></th>
<th>LEADER</th>
<th>SUSTAIN-6</th>
<th>EXSCEL</th>
<th>ELIXA</th>
<th>HARMONY</th>
<th>REWIND</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong>, HR (95% CI)</td>
<td>0.87 (0.78-0.97)</td>
<td>0.74 (0.58-0.95)</td>
<td>0.91 (0.83-1.00)</td>
<td>1.02 (0.89-1.17)</td>
<td>0.78 (0.68-0.90)</td>
<td>0.88 (0.79-0.99)</td>
</tr>
<tr>
<td>CV death, HR (95% CI)</td>
<td>0.98 (0.65-1.48)</td>
<td>0.88 (0.76-1.02)</td>
<td>0.98 (0.78-1.22)</td>
<td>0.93 (0.73-1.19)</td>
<td>0.91 (0.78-1.06)</td>
<td>0.91 (0.78-1.06)</td>
</tr>
<tr>
<td>Fatal or nonfatal MI, HR (95% CI)</td>
<td>0.74 (0.51-1.08)</td>
<td>0.97 (0.85-1.10)</td>
<td>1.03 (0.87-1.22)</td>
<td>0.75 (0.61-0.90)</td>
<td>0.96 (0.79-1.15)</td>
<td>0.96 (0.79-1.15)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke, HR (95% CI)</td>
<td>0.86 (0.73-1.00)</td>
<td>0.61 (0.38-0.99)</td>
<td>0.97 (0.85-1.10)</td>
<td>1.03 (0.87-1.22)</td>
<td>0.75 (0.61-0.90)</td>
<td>0.96 (0.79-1.15)</td>
</tr>
<tr>
<td>All-cause mortality, HR (95% CI)</td>
<td>0.86 (0.71-1.06)</td>
<td>1.05 (0.74-1.50)</td>
<td>0.85 (0.70-1.03)</td>
<td>1.12 (0.79-1.58)</td>
<td>0.86 (0.66-1.14)</td>
<td>0.76 (0.62-0.94)</td>
</tr>
<tr>
<td>HF hospitalization, HR (95% CI)</td>
<td>0.87 (0.73-1.05)</td>
<td>1.11 (0.77-1.61)</td>
<td>0.94 (0.78-1.13)</td>
<td>0.96 (0.75-1.23)</td>
<td>0.86 (0.69-1.09)</td>
<td>0.86 (0.77-1.01)</td>
</tr>
</tbody>
</table>

CV, cardiovascular; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL, Exenatide Study of Cardiovascular Event Lowering Trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HARMONY, Harmony Outcomes (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus); HF, heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI, myocardial infarction; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes.

Summary

- Historically, therapeutic recommendations have focused on stepwise escalation—the addition of agents over time in response to treatment failure.
- Current evidence supports earlier initiation of combination therapy, based on A1C targets:
  - A1C is highly predictive of diabetes complications.
  - A1C targets should be individualized to specific patient characteristics:
    - Internationally, A1C targets range from $\leq 6.5\%$ to $8.5\%$, depending on patient attributes.
- Metformin is the preferred first-line agent:
  - Start combination therapy when patient A1C is above target.
  - Incorporate agents with complementary mechanisms of action.
  - Add agents with cardiorenal protection (ie, SGLT-2 inhibitor or GLP-1 RA) in high-risk patients.

Conclusions

• Health care professionals should consider patient-specific risk factors when determining antihyperglycemic treatment regimens for patients with T2D
• Such patient-specific risk factors include, but are not limited to, disease duration, baseline A1C level, life expectancy, obesity, comorbidities, cardiovascular risk, and age
• Affordability of treatment is also a concern
• Treatment has been shown to be more effective when tailored to patient comorbidities and specific adverse event profiles
• Recent clinical evidence supports the safety and efficacy of the earlier initiation of combination therapy in patients with T2D

A1C, glycated hemoglobin; T2D, type 2 diabetes.