Injectable Therapies for Type 2 Diabetes Mellitus (T2DM) and Obesity

This presentation will:

• Explain the pathophysiological aspects of T2DM, and how defects can be addressed with injectable therapies.

• Outline incretin-based injectable therapies for T2DM and obesity management and discuss evidence from clinical trials.

• Describe established and newly available insulin therapies for treatment of T2DM.

• Describe how to intensify insulin regimens to achieve glycemic targets.
Injectable Therapies for T2DM and Obesity

GLP-1 RA

Insulin

GLP-1 RA = glucagon-like peptide-1 receptor agonist; T2DM = type 2 diabetes mellitus.
UKPDS: Beta-Cell Loss Over Time

Dashed line shows extrapolation forward and backward from years 0 to 6 from diabetes diagnosis, based on Homeostasis Model Assessment (HOMA) data from UKPDS.

The data points for the time of diagnosis (0) and the subsequent 6 years are taken from the obese subset of the UKPDS population and were determined by the HOMA model.

HOMA = homeostasis model assessment; OAD = oral anti-diabetic; T2DM = type 2 diabetes mellitus; UKPDS = United Kingdom Prospective Diabetes Study Group.

GLP-1 Modulates Numerous Functions in Humans

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

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

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

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

**Stomach**: Helps regulate gastric emptying

**Brain**: Promotes satiety and reduces appetite

GLP-1 = glucagon-like peptide-1.

Abnormal Insulin and Glucagon Responses Contribute to Hyperglycemia in Type 2 Diabetes

Mean ± SE
SE = standard error.

The Incretin Effect

Control subjects (n=8)

Type 2 diabetes (n=14)

Incretin Effect

Glucose-Dependent Actions of GLP-1: Effect in Subjects with Type 2 Diabetes

Data are mean ± SE. *P<0.05
GLP-1 = glucagon-like peptide-1; PBO = placebo; SE = standard error.

GLP-1 Infusion Normalizes Blood Glucose in Patients with Diabetes

GLP-1 = glucagon-like peptide-1.

Metabolism of GLP-1 and GIP

Dipeptidyl Peptidase-4 (DPP-4)
- Ubiquitous, specific protease
- Cleaves N-terminal dipeptide
- Inactivates > 50% of GLP-1 in ~1 min
  > 50% of GIP in ~7 min

Active hormones
GLP-1 [7-36NH₂]
GIP [1-42]

Inactive metabolites
GLP-1 [9-36NH₂]
GIP [3-42]

GLP-1 RA Increases 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

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

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

**Exenatide, Liraglutide, Albiglutide, Dulaglutide**

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

- Exenatide BID (twice daily)
- Liraglutide (once daily)
- Exenatide ER (weekly)
- Albiglutide (weekly)
- Dulaglutide (weekly)
- Lixisenatide (once daily)

BID = twice daily; ER = extended release; GLP-1 = glucagon-like peptide-1.
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**\(^4\)

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

Exenatide

- Exenatide BID: 5 mcg SC ≤ 60 min AC BID
- After 1 month: 10 mcg SC ≤ 60 min AC BID
- Supplied as pen (use: 1 per month)

- Exenatide ER: 2 mg SC QWK
- Available as single-dose tray or pen

AC = before meals; BID = twice daily; ER = extended release; SC = subcutaneously; QWK = every week.

Development of Exenatide: An Incretin Mimetic

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.

Glucose Control with Exenatide BID with/without Oral Agents

<table>
<thead>
<tr>
<th>Treatment†</th>
<th>N</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></td>
<td></td>
<td>PBO</td>
<td>EXE</td>
<td>MET</td>
<td>EXE + MET</td>
<td>SU</td>
<td>EXE + SU</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.2</td>
<td>8.2</td>
<td>8.7</td>
<td>8.6</td>
<td>7.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Δ A1C (%)</td>
<td></td>
<td>-0.2</td>
<td>-0.9</td>
<td>-0.8</td>
<td>-0.86</td>
<td>-0.89</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

*P<0.001 vs comparator.
†All exenatide dosages shown are 10 μg BID
A1C = glycated hemoglobin; BID = twice daily; EXE = exenatide; GLAR = glargine; MET = metformin; PBO = placebo; SU = sulfonylurea; TZD = thiazolidinedione.

### Weight Reduction with Exenatide BID: Mono and Dual Combination Therapy

<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></td>
<td>N = 233</td>
<td>336</td>
<td>377</td>
<td>233</td>
<td>733</td>
<td>551</td>
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<tr>
<td>PBO</td>
<td>-1.4</td>
<td>-0.3</td>
<td>-0.6</td>
<td>-0.24</td>
<td>-1.75</td>
<td>1.8</td>
</tr>
<tr>
<td>EXE</td>
<td>-3.1 *</td>
<td>-2.8 *</td>
<td>-1.6 *</td>
<td>-1.6</td>
<td>-1.6</td>
<td>-2.3 *</td>
</tr>
<tr>
<td>MET</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>EXE + MET</td>
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<tr>
<td>SU</td>
<td></td>
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<tr>
<td>EXE + SU</td>
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<td>TZD</td>
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<tr>
<td>EXE + TZD</td>
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</table>

*P<0.05 vs comparator. **P<0.0001 vs glargine.

†All exenatide dosages shown are 10 μg BID.

**BID = twice daily; EXE = exenatide; GLAR = glargine; MET = metformin; PBO = placebo; SU = sulfonylurea; TZD = thiazolidinedione.**

Exenatide ER

- 2 mg SC every 7 days, with or without food
- Reconstituted w/ diluent; 23G x 5/16” needle
- Microsphere release; steady state: 6-7 wks
- A1C reduction vs BID exenatide: ~0.7%
- Not recommended as first-line Rx
- Add on to MET, SU, TZD, or combination
- Less nausea vs exenatide BID
- ↑ weight loss vs exenatide BID: 3.53 lbs vs 1.98 lbs at 24 wks

A1C = glycated hemoglobin; BID = twice daily; ER = extended release; lbs = pounds; MET = metformin; Rx = prescription; SC = subcutaneously; SU = sulfonylurea; TZD = thiazolidinedione.

### Glucose Control with Exenatide ER

<table>
<thead>
<tr>
<th></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 OAs +/- SU 26 Weeks⁴</th>
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</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>Treatment</td>
<td>EXE BID EXE ER SIT PIO MET EXE ER GLAR + OAs EXE ER + OAs LIRA + EXE ER + OAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>8.3 8.3</td>
<td>8.5 8.5 8.6 8.5</td>
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ΔA1C (%)

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### Notes

* Metformin, sulfonylurea, thiazolidinedione, or combination of any 2 of these agents.

† Metformin, sulfonylurea, metformin + sulfonylurea, or metformin + pioglitazone.

A1C = glycated hemoglobin; ER = extended release; EXE = exenatide; GLAR = glargine; LIRA = liraglutide; MET = metformin; OA = oral agent; PIO = pioglitazone; SIT = sitagliptin; SU = sulfonylurea.

**Weight Reduction with Exenatide ER**


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<th>Treatment (mg/day)</th>
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<td>PIO</td>
<td>MET</td>
<td>EXE + OAs</td>
<td>ER + OAs</td>
</tr>
</tbody>
</table>

**Δ Weight (kg)**

- Add-on to OAs* 30 Weeks¹: -3.6, -3.7
- Monotherapy vs OAs 26 Weeks²: -0.8, -2.0, -2.0
- Add-on to Metformin 26 Weeks³: -0.8, -2.3
- Add-on to MET +/- SU 26 Weeks⁴: -1.4, -2.6
- Add-on to OAs† 26 Weeks⁵: -3.6, -2.7

¹Metformin, sulfonylurea, metformin + sulfonylurea, or metformin + pioglitazone.

*Metformin, sulfonylurea, thiazolidinedione, or combination of any 2 of these agents.

BID = twice daily; ER = extended release; EXE = exenatide; GLAR = glargine; LIRA = liraglutide; MET = metformin; OA = oral agent; PIO = pioglitazone; SIT = sitagliptin; SU = sulfonylurea.
### Hypoglycemia with Exenatide ER

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Add-on to OAs* 30 Weeks¹</th>
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</tr>
<tr>
<td>EXE BID</td>
<td>EXE ER</td>
<td>SIT PIO MET EXE</td>
<td>SIT PIO EXE</td>
<td>GLAR + OAs EXE Er + OAs</td>
<td>LIRA + EXE Er + OAs</td>
</tr>
<tr>
<td>Patients reporting hypoglycemia (%)</td>
<td></td>
<td></td>
<td></td>
<td>31.0</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>6.1 5.4</td>
<td>3.1 3.7 4.1 5.2</td>
<td>3.0 1.0 1.0</td>
<td>8.9 11.0</td>
<td></td>
</tr>
</tbody>
</table>

¹Metformin, sulfonylurea, thiazolidinedione, or combination of any 2 of these agents.

†Metformin, sulfonylurea, metformin + sulfonylurea, or metformin + pioglitazone.

BID = twice daily; ER = extended release; EXE = exenatide; GLAR = glargine; LIRA = liraglutide; MET = metformin; OA = oral agent; PIO = pioglitazone; SIT = sitagliptin; SU = sulfonylurea.

# Exenatide Extended Release: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events*</th>
<th>Patients (%)</th>
<th>Monotherapy</th>
<th>+ MET</th>
<th>+ MET +/- SU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EXE ER (n=248)</td>
<td>SIT (n=163)</td>
<td>PIO (n=163)</td>
<td>MET (n=246)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11.3</td>
<td>3.7</td>
<td>4.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.9</td>
<td>5.5</td>
<td>3.7</td>
<td>12.6</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>10.5</td>
<td>6.7</td>
<td>3.7</td>
<td>10.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>8.5</td>
<td>2.5</td>
<td>1.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Headache</td>
<td>8.1</td>
<td>9.2</td>
<td>8.0</td>
<td>12.2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7.3</td>
<td>1.8</td>
<td>4.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
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<tr>
<td>Fatigue</td>
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</tbody>
</table>

*Adverse events of interest occurring in ≥5% of patients receiving exenatide extended release.

ER = extended release; EXE = exenatide; GLAR = glargine; MET = metformin; PIO = pioglitazone; SIT = sitagliptin; SU = sulfonylurea.
Liraglutide

- Liraglutide: 0.6 mg SC QD x 1 week then 1.2 mg SC QD increase to 1.8 mg SC QD if needed
- Supplied as pen
- Use: 2-3 pens per month

QD = once daily; SC = subcutaneously.

Glucose Control with Liraglutide with/without Oral Agents

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy vs Glimepiride 52 Weeks¹</th>
<th>Add-on to Metformin 26 Weeks²</th>
<th>Add-on to Metformin 26 Weeks³</th>
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</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>746</td>
<td>1091</td>
<td>665</td>
<td>1041</td>
<td>821</td>
<td>581</td>
</tr>
<tr>
<td>Treatment</td>
<td>GLIM + MET</td>
<td>GLIM + LIRA + MET</td>
<td>GLIM + LIRA + MET</td>
<td>SU + LIRA + SU</td>
<td>SU + LIRA + SU</td>
<td>SU + LIRA + MET</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>8.4</td>
<td>8.4</td>
<td>8.5</td>
<td>8.4</td>
<td>8.4</td>
<td>8.3</td>
</tr>
</tbody>
</table>

ΔA1C (%)

-0.51
-1.14 *
-0.98
-1.00 *
-0.9
-1.50 **
-1.13 **
-0.5
-1.50 **
-1.09
-1.33 ***

*P<0.0001 vs monotherapy. **P<0.0001 vs dual therapy. ***P=0.0015 vs glargine. †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; SIT = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

Weight Reduction with Liraglutide: Mono and Dual Combination Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Monotherapy vs Glimepiride 52 Weeks(^1)</th>
<th>Add-on to Metformin 26 Weeks(^2)</th>
<th>Add-on to Metformin 26 Weeks(^3)</th>
<th>Add-on to Sulfonylurea 26 Weeks(^4)</th>
<th>Add-on to MET + TZD 26 Weeks(^5)</th>
<th>Add-on to MET + SU 26 Weeks(^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>746</td>
<td>1091</td>
<td>665</td>
<td>1041</td>
<td>821</td>
<td>581</td>
</tr>
<tr>
<td>GLIM</td>
<td>MET</td>
<td>GLIM + MET</td>
<td>LIRA + MET</td>
<td>SU</td>
<td>ROSI + LIRA + SU</td>
<td>MET + GLAR + LIRA + SU</td>
</tr>
<tr>
<td>LIRA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>746</td>
<td>1091</td>
<td>665</td>
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<td>821</td>
<td>581</td>
</tr>
<tr>
<td>GLIM</td>
<td>MET</td>
<td>GLIM + MET</td>
<td>LIRA + MET</td>
<td>SU</td>
<td>ROSI + LIRA + SU</td>
<td>MET + GLAR + LIRA + SU</td>
</tr>
<tr>
<td>LIRA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\Delta\) Weight (kg)

-4 -3 -2 -1 0 1 2 3

-4.00 -3.50 -3.00 -2.50 -2.00 -1.50 -1.00 -0.50 0.00 0.50 1.00 1.50 2.00 2.50 3.00

-4 -3 -2 -1 0 1 2 3

-4.00 -3.50 -3.00 -2.50 -2.00 -1.50 -1.00 -0.50 0.00 0.50 1.00 1.50 2.00 2.50 3.00

* \(P<0.0001\) vs glargine, rosiglitazone, sitagliptin, or SU. ** \(P<0.01\) vs metformin. *** \(P<0.05\) vs SU. † All liraglutide dosages shown are 1.8 mg QD.

GLAR = glargine; GLIM = glimepiride; LIRA = liraglutide; MET = metformin; QD = once daily; ROSI = rosiglitazone; SIT = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

Nausea Declined Over Time with Liraglutide Monotherapy

Patients (%)

Liraglutide Monotherapy vs SU

Liraglutide 1.2 mg (n=251)
Liraglutide 1.8 mg (n=246)
Glimepiride 8 mg (n=248)

Time (weeks)

SU = sulfonylurea.

Liraglutide 3mg

- Approved 2010 for treatment of overweight/obesity
- Indications: adults with BMI ≥ 30 or BMI ≥ 27 kg/m² with one CV risk factor: hypertension, type 2 diabetes mellitus, hypercholesterolemia
- Approved with REMS: follow up and registry for MTC, breast cancer, CV safety
- Supplied as 3 mL pen, 6mg/mL (5 pens/mo)
- Dose titration: 0.6mg daily SC x 7 d; 1.2mg daily x 7 d; 1.8mg daily x 7 d; 2.4mg daily x 7 d; 3mg daily maintenance

BMI = body mass index; CV = cardiovascular; MTC = medullary thyroid cancer; REMS = Risk Evaluation and Mitigation Strategies; SC = subcutaneously.
Liraglutide 3mg

- Phase 3
- 56-week trials
- Proportion of patients achieving weight loss:

<table>
<thead>
<tr>
<th></th>
<th>≥ 5%</th>
<th>≥ 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide 3mg</td>
<td>62.3</td>
<td>33.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>34.4</td>
<td>15.4</td>
</tr>
</tbody>
</table>

Latest Once-weekly GLP-1 Receptor Agonists

- Albiglutide (modified GLP-1 fused to albumin)
- Dulaglutide (GLP-1 analog fused to IGG4)
- Semaglutide (structural analog of liraglutide)
  - Not FDA approved, in Phase 3 clinical trials
- Resistant to DPP-4 degradation
- Similar efficacy as exenatide ER
- A1C reduction 0.8% – 1.0%
- Studied with metformin, SU, pioglitazone, basal insulin
- Not recommended as first-line therapy

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; ER = extended release; FDA = U.S. Food and Drug Administration; GLP-1 = glucagon-like peptide-1; IGG4 = human immunoglobulin; SU = sulfonylurea.
Semaglutide

• Not FDA approved as of 11/2016
• Under investigation in the SUSTAIN phase 3 clinical trial program
• Long-acting GLP-1, once-weekly dosing
• Structurally similar to liraglutide

FDA = U.S. Food and Drug Administration; GLP-1 = glucagon-like peptide-1; SC = subcutaneously; SUSTAIN = Trial To Evaluate Outcomes with Semaglutide in Subjects with Type 2 Diabetes.
Semaglutide – Efficacy

• Semaglutide is a long-acting GLP-1 agonist
  - Not approved by the FDA as of 11/2016

• Six phase III clinical trials (the SUSTAIN phase III clinical trial program) examined semaglutide for safety and efficacy
  - Semaglutide causes significant reductions in A1C in patients with T2DM compared to sitagliptin, exenatide ER, and insulin glargine
  - Semaglutide reduced the risk of major CV events by 26% compared to placebo in patients with T2DM at high CV risk
  - In SUSTAIN 6, A1C was significantly lower in the semaglutide vs placebo group
  - Results confirmed semaglutide noninferiority

• Semaglutide use results in moderate weight loss; up to 5.3% of body weight

A1C = glycated hemoglobin; ER = extended release; FDA = U.S. Food and Drug Administration; GLP-1 = glucagon-like peptide-1; SUSTAIN = Trial To Evaluate Outcomes with Semaglutide in Subjects with Type 2 Diabetes; T2DM = type 2 diabetes mellitus.

Shown are Kaplan–Meier plots of the primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), nonfatal myocardial infarction (Panel B), nonfatal stroke (Panel C), and death from cardiovascular causes (Panel D). Insets show the same data on an expanded y axis.

SUSTAIN = Trial To Evaluate Outcomes with Semaglutide in Subjects with Type 2 Diabetes

LEADER: Liraglutide

- Over 9,000 high-risk patients with T2D or previous CV events
- Liraglutide use led to significant CV events reduction

CV = cardiovascular; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results; T2D = type 2 diabetes.
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
Metabolic Effects of GLP-1 in Patients with Type 2 Diabetes

• Improves glucose-dependent insulin secretion
• Decreases plasma glucagon concentration
• Decreases fasting and postprandial glucose concentration
• Lowers A1C


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

• Most frequent adverse effect of GLP-1 RAs is nausea, which occurs in up to one-third of patients and is usually self-limiting, although some patients cannot tolerate these agents.

• Nausea may be diminished by avoiding overeating and slowing the titration.

• Administering exenatide BID closer to mealtime can also decrease nausea.

BID = twice daily; GLP-1 RA = glucagon-like peptide-1 receptor agonist.
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.

Type 2 Diabetes and Pancreatitis Risk

- 2.8-fold increased risk of pancreatitis among patients with type 2 diabetes

Incidence per 100,000 patient-years

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.

Rationale for Using Incretin-Based Therapies in the Treatment of Type 2 Diabetes

• Incretins play a key role in maintaining glucose homeostasis
• Incretin effects are diminished in patients with type 2 diabetes
• Incretin-based therapies
  – Target multiple defects of type 2 diabetes, including those not addressed by traditional medications
  – Do not cause hypoglycemia
  – Have favorable effects on weight
**Summary: GLP-1 Receptor Agonists**

- Good glycemic efficacy, glucose-dependent action
- Complement the actions of oral antihyperglycemic agents
- Can be used as monotherapy if MET is contraindicated and in combination with other oral agents and/or insulin
- Favorable weight effects and low hypoglycemic risk
- Consider patient risk factors and educate patients about potential risks and/or adverse effects (e.g., nausea, history of thyroid tumors, pancreatitis)
  - No increased risk of pancreatitis relative to other antihyperglycemic agents
  - Potential for gastrointestinal side effects
  - Cardioprotective (LEADER trial)

GLP-1 = glucagon-like peptide-1; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results; MET = metformin.
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

If not at goal in 3 months proceed to Dual Therapy

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 Triple Therapy

Entry A1C > 9.0%

TRIPLE 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 or intensify insulin therapy

SYMPTOMS
- NO
- YES

DUAL Therapy or TRIPLE Therapy

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

SYMPTOMS
- NO
- YES

DUAL Therapy
- OR
- INSULIN
± Other Agents

TRIPLE Therapy

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

PROGRESSION OF DISEASE
Antihyperglycemic Monotherapy
Maximum Therapeutic Effect, Dependent Upon Initial A1C

A1C = glycated hemoglobin; GITS = gastrointestinal therapeutic system.

When To Start Insulin in T2DM

- When combination oral/injectable agents become inadequate
- Unacceptable side effects of oral/injectable agents
- Patient wants more flexibility
- Special circumstances (i.e. steroid use, infection, pregnancy)
- Patients with hepatic or renal disease,
- Patients with CAD, ↑TG

CAD = coronary artery disease; T2DM = type 2 diabetes mellitus; TG = triglycerides.

Insulin Therapy in Type 2 Diabetes: Current Strategies

- **Basal insulin therapy**
  - Long-acting insulin analog once daily
  - Intermediate-acting NPH at bedtime

- **Human or analog insulin (prandial or premixed w/ intermediate)**
  - Once daily at largest meal
  - Twice daily (breakfast and dinner)
  - Three times daily (with each meal)

- **Intensive insulin therapy**
  - Basal +
  - Rapid-acting analog insulin
    - Once daily at largest meal
    - Twice daily at meals
    - Three times daily (with each meal)

- **Insulin pump therapy**

NPH = neutral protamine hagedorn.

Current and Emerging Basal Insulins

**Human insulins (intermediate-acting)**
- U-100 NPH

**Analogues (long-acting)**
- U-100 glargine
- U-100 detemir
- U-100 biosimilar glargine

**Analogues (ultra-long-acting)**
- U-300 glargine
- U-100 degludec
- U-200 degludec

FDA = U.S. Food and Drug Administration; NPH = neutral protamine hagedorn.

Blue boxes indicate FDA Approval

- Approved by the US FDA in December, 2016.
- Approved by the US FDA in September 2015.
- Not currently approved by the US FDA.
## Comparison of Available Insulins (Per Prescribing Information)

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular insulin (R)</td>
<td>30-60 min</td>
<td>2-5 hrs</td>
<td>5-8 hrs</td>
</tr>
<tr>
<td><strong>Rapid-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>15-30 min</td>
<td>30-90 min</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Insulin lispro U-200</td>
<td>15-30 min</td>
<td>30-90 min</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>10-20 min</td>
<td>40-50 min</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>20-30 min</td>
<td>30-90 min</td>
<td>1-2.5 hrs</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td>1-2 hrs</td>
<td>4-12 hrs</td>
<td>18-24 hrs</td>
</tr>
<tr>
<td>NPH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>1-1.5 hrs</td>
<td>relatively flat</td>
<td>up to 24 hrs</td>
</tr>
<tr>
<td>Insulin glargine U-300</td>
<td>6 hrs</td>
<td>flat</td>
<td>up to 24 hrs</td>
</tr>
<tr>
<td>Biosimilar insulin glargine</td>
<td>6 hrs</td>
<td>relatively flat</td>
<td>Up to 24 hrs</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>1-2 hrs</td>
<td>relatively flat</td>
<td>up to 24 hrs</td>
</tr>
<tr>
<td>Insuline degludec</td>
<td>1 hr</td>
<td>3-4 days</td>
<td>up to 24 hrs</td>
</tr>
<tr>
<td><strong>Premixed Insulins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular/NPH insulin 70/30</td>
<td>30 min</td>
<td>2-12 hrs</td>
<td>14-24 hrs</td>
</tr>
<tr>
<td>Lispro protamine 75/25, 50/50</td>
<td>15 min</td>
<td>0.5-2.5 hrs</td>
<td>16-20 hrs</td>
</tr>
<tr>
<td>Biphasic insulin aspart 70/30</td>
<td>10-20 min</td>
<td>1-4 hrs</td>
<td>up to 24 hrs</td>
</tr>
</tbody>
</table>

NPH = neutral protamine hagedorn.
Oral agents plus **Basal Insulin at Bedtime**

- Continue oral agent(s) at same dosage
- Add single, evening BASAL insulin dose (10 U or 0.2/kg)
- Adjust dose by SMBG
  - goal FBS < 130 mg/dl

**FBS** = fasting blood sugar; **NPH** = neutral protamine hagedorn; **SMBG** = self-monitoring of blood glucose.
Insulin Analogs More Closely Match the Physiologic Insulin Profile Than Human Insulin

- **Bolus (meal-related) insulin analogs**
  - Rapid absorption
  - Peak action coincides with peak carbohydrate absorption

- **Basal insulin analogs**
  - Slow and steady rate of absorption
  - Protracted action

Insulin Glargine vs NPH Insulin Added to Oral Therapy: FPG and A1C (756 Patients Previously Treated with 1-2 OHAs and A1C>7.5%)

Mean daily insulin dose
Insulin glargine: 47 units
NPH: 42 units

A1C = glycated hemoglobin; FPG = fasting plasma glucose; NPH = neutral protamine hagedorn; OHA = oral hypoglycemic agent.

Treat to Target Trial: Frequency of Hypoglycemia

NPH = neutral protamine hagedorn; PG = plasma glucose; RRR = relative risk reduction.

Risk of Hypoglycemia with Insulin Detemir

Hypoglycemic events per-patient per-year

* Any episode between 11 pm and 6 am

P < 0.001

NPH = neutral protamine hagedorn; OAD = oral anti-diabetic.

Simple Way to Start Basal Insulin

Bedtime or morning: long-acting insulin OR
Bedtime: intermediate-acting insulin
Daily dose: 10 units or 0.2 units/kg

Check FBG Daily

Increase dose by 2 units every 3 days until FBG is 70–130 mg/dL
If FBG is >180 mg/dL, increase dose by 4 units every 3 days

Continue regimen and check A1C every 3 months

In the event of hypoglycemia or FBG level <70 mg/dL
Reduce bedtime insulin dose by 4 units, or by 10% if >60 units

A1C = glycated hemoglobin; FBG = fasting blood glucose.

When Basal is Not Enough
Optimizing Insulin Therapy For Glycemic Control

Basal insulin titration every 2 – 3 days to reach glycemic goal:
• Add 2 U
or
• FBG > 180 mg/dL: 20%
• FBG 140-180 mg/dL: 10%
• FBG 110-139 mg/dL: add 1 U

Consider prandial coverage if:
• A1C not at goal on total daily basal insulin dose > 0.3 U/kg
Increase prandial insulin when:
• 2h postprandial or next premeal glucose BG consistently 140-180 mg/dL

Lifestyle changes plus metformin
(±1, ±2, ±3 agents)

A1C = glycated hemoglobin; BG = blood glucose; FBG = fasting blood glucose.
# Pitfalls and Caveats in the Use of Basal Insulin (BI)

<table>
<thead>
<tr>
<th>The Challenge</th>
<th>The Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uptitrating dose based on elevated pre-supper blood glucose → nocturnal hypoglycemia</td>
<td>• Post-lunch hyperglycemia is the culprit; only titrate BI based upon fasting blood glucose</td>
</tr>
<tr>
<td>Over-reliance on BI to control PP hyperglycemia when added to non-prandial agents (eg, metformin, thiazolidinediones)</td>
<td>• As both fasting and PP hyperglycemia are present, consider use of a prandial agent before/at time of BI addition</td>
</tr>
<tr>
<td>Delay in down-titration of BI with improved glycemia → hypoglycemia and pre-emptive eating</td>
<td>• Discuss this scenario with patient as glycemic control is re-established: “Less insulin is needed to maintain control than establish control”</td>
</tr>
<tr>
<td></td>
<td>• Reduction of OHAs, such as SUs or glinides, may also be required</td>
</tr>
</tbody>
</table>

BI = basal insulin; OHA = oral hypoglycemic agent; PP = postprandial; SU = sulfonylurea.
DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT = sodium-dependent glucose cotransporters; TDD = transdermal drug delivery.
Treating to Target in Type 2 Diabetes (4-T) 3-year Results


<table>
<thead>
<tr>
<th>Hypoglycemia Grade 2 or 3</th>
<th>No. of Events/Patient/Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic Insulin</td>
<td>2</td>
</tr>
<tr>
<td>Prandial Insulin</td>
<td>6</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>1</td>
</tr>
</tbody>
</table>

P < 0.001
New Basal Insulin Formulations

Glargine U-300
Degludec
High Concentration Glargine (U300)

- U300 insulin glargine offers a smaller depot surface area leading to a reduced rate of absorption
- Provides a flatter and prolonged pharmacokinetic and pharmacodynamic profiles and more consistency
- Half-life is ~23 hours
- Steady state in 4 days
- Duration of action ≤36 hours
U300 Glargine vs U100 Glargine in Type 2 Diabetes

Mean change in A1C for both treatment groups
-0.83%

No difference in A1C change

Lower rate of severe or confirmed hypoglycemia, particularly overnight

<table>
<thead>
<tr>
<th>Time period</th>
<th>U100</th>
<th>U300</th>
<th>RR with U300</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>Nocturnal</td>
<td>57.5%</td>
<td>44.6%</td>
<td>0.78</td>
</tr>
<tr>
<td>9 weeks – 6 mo</td>
<td>Nocturnal</td>
<td>46.0%</td>
<td>36.1%</td>
<td>0.79</td>
</tr>
<tr>
<td>0-6 months</td>
<td>24 hours</td>
<td>87.8%</td>
<td>81.9%</td>
<td>0.93</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; CI = confidence interval; LOCF = last observation carried forward; RR = rate ratio.

Ritzel et al. Diabetes Obes Metab. 2015. 17:859-867.
U-300 Insulin Glargine

- Only available in pens
  - 300 U/mL, 1.5 mL
  - Max dose per shot is 80 units with 1 unit increments using current pen
  - New pen in development will allow a max dose of 240 units

- U-300 glargine pen is white and green with the concentration highlighted in orange to distinguish it from U-100 glargine purple and gray

Flexible vs Fixed Degludec Once-Daily Dosing in Adults with T2DM: Efficacy and Hypoglycemia at 26 Weeks

A N = 457; DEG + OADs (not specified). FIXED, administered with evening meal daily; FLEX, administered 8-40 hours apart; Hypoglycemia, plasmaglucose < 56 mg/dL or severe per ADA definition.

A1C = glycated hemoglobin; BL = baseline; DEG = insulin degludec; EPY = events per year; OAD = oral anti-diabetic; QD = once daily; T2DM = type 2 diabetes mellitus.

Insulin Degludec

- Only available in pens
  - 100 U/mL (3.0 mL), max dose per injection 80 units
  - 200 U/mL (3.0 mL), max dose per injection 160 units

- Degludec U-100 pen is yellow and blue while the U-200 is green and blue with the concentration highlighted in blue

- Individualize dose

New Insulin and Insulin + GLP-1 Receptor Agonist Combinations: Application and Therapeutic Efficacy

GLP-1 = glucagon-like peptide-1.
Postprandial Hyperglycemia Persists After Basal Therapy

164 patients with baseline A1c $\geq 7.5\%$ on diet, oral agents, or insulin. Mealtime hyperglycemia persists after 3 months of intensive treatment.

A1C = glycated hemoglobin.

Lixisenatide Combined with Basal Insulin Improves Glycemic Control with Less Weight Gain in T2DM Over 24 Weeks

A1C = glycated hemoglobin; INS = insulin; LIXI = lixisenatide; PBO = placebo; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

IDegLira: A Fixed Ratio Combination of Insulin Degludec\textsuperscript{a} and Liraglutide

A1C = glycated hemoglobin; DEG = insulin degludec; FDA = U.S. Food and Drug Administration; LIRA = liraglutide; MET = metformin; PIO = pioglitazone; RR = ratio risk; T2DM = type 2 diabetes mellitus.

\textsuperscript{a} IDegLira and insulin degludec are not FDA approved for clinical use.

Insulin + GLP-1 Dual Therapies

- Two combination therapies were approved by the FDA in 2016
  - Insulin degludec/liraglutide (IDegLira)
  - Insulin glargine/lixisenatide (IGlarLixi)
- Studies indicate that combining insulin with GLP-1 receptor agonist therapy:
  - Provides comparable or in many cases improved A1C control compared with either drug alone
  - Promotes weight loss or weight neutrality compared to weight gain with insulin alone
  - Provides comparable or improved risk of hypoglycemic episodes compared with insulin alone
  - Results in improved FPG compared with either drug alone


A1C = glycated hemoglobin; FDA = U.S. Food and Drug Administration; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1.
Insulin + GLP-1 Dual Therapies, Injection Devices
Insulin Degludec/Liraglutide (IDegLira)

- A fixed-ratio combination of basal insulin insulin degludec and the GLP-1 receptor agonist liraglutide
- Indicated for adults with T2DM not adequately controlled with insulin or liraglutide alone
- Once-daily subcutaneous injection administration
- Recommended dose ranges from 16 U insulin degludec/0.58 mg liraglutide to 50 U insulin degludec/1.8 mg liraglutide
- Same contraindications as liraglutide (personal or family history of MTC)
- Studies underway to assess efficacy/safety of once- or twice-weekly administration


GLP-1 = glucagon-like peptide-1; MTC = medullary thyroid cancer; T2DM = type 2 diabetes mellitus
Insulin Glargine/Lixisenatide (IGlarLixi)

- A fixed-ratio combination of basal insulin glargine and the GLP-1 receptor agonist lixisenatide
- Indicated for adults with T2DM not adequately controlled with insulin or lixisenatide alone
- Once-daily subcutaneous injection administration
- Recommended dose ranges from 30 U insulin glargine/10 mcg lixisenatide to 60 U insulin glargine/20 mcg lixisenatide


GLP-1 = glucagon-like peptide-1; T2DM = type 2 diabetes mellitus
Key Points: Insulin Initiation

• Diabetes is a progressive disease and many individuals with T2DM eventually need insulin to control their blood glucose

• There are cultural taboos and misconceptions regarding insulin therapy; it is important to understand and acknowledge patients' specific concerns and design individualized treatment plans that fit their needs

• Start with a simple regimen, such as a once-daily basal insulin analog, and up-titrate the dose based on FPG; if A1C remains high when FPG is in the target range, add a DPP-4 inhibitor, a GLP-1 RA, or mealtime insulin

2. Peragallo V. Diabetes Educ. 2007;33:60S–65S.

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GLP-1 RA = glucagon-like peptide-1 receptor agonist; T2DM = type 2 diabetes mellitus.
Real-world Choices Depend on the Patient

- Injection frequency preference
  - Some patients may prefer premix
- Frequency of self-monitoring of blood glucose
- Variability of lifestyle, including meal timing and carbohydrate content of meals
- Presence of postprandial hyperglycemia
- Patient’s ability to follow the prescribed regimen
- Educational and emotional support available to patient
- Cost of analogue insulin options may be nearly double that of NPH or regular insulin

NPH = neutral protamine hagedorn.
Reasons Patients Avoid Insulin

- Lack of knowledge
- Cultural taboos and family beliefs
- Fear of needles or injection pain
- Fear of hypoglycemia and/or weight gain
- Inconvenience
- Sense of personal failure
- Diabetes seen as worse or more serious once insulin is initiated
- Fear that insulin causes complications and/or that insulin will impose constant demands on patient
Strategies to Overcome Patient Barriers to Insulin Use

- **Starting insulin** – get help from Certified Diabetes Educators, dietitians, pharmacists; consider group instruction

- **Needle phobia** – show fine needles, pens, demonstrate technique

- **Convenience** – use pens or other devices

- Begin therapy with **simple regimen** – detemir or glargine pen at bedtime

The Basal-Bolus Insulin Concept

• **Basal insulin**
  – Controls glucose production between meals and overnight
  – Nearly constant levels
  – 50% of daily needs

• **Bolus insulin (mealtime or prandial)**
  – Limits hyperglycemia after meals
  – Immediate rise and sharp peak at 1-hour postmeal
  – 10% to 20% of total daily insulin requirement at each meal

• **For ideal insulin replacement therapy,** each component should come from a different insulin with a specific profile

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Starting Basal/Bolus Therapy

• **Starting insulin dose** is based on weight
  = 0.3-0.5 units/kg

• **Basal dose** (glargine/detemir/NPH)
  = 50% of starting dose at bedtime

• **Bolus dose** (meal dose)
  = 50% of starting dose divided between meals
  (rapid-acting analog or Regular insulin)

NPH = neutral protamine hagedorn.

Example: Starting Multiple Daily Injections in 100-kg Patient with Moderate Insulin Resistance

• **Starting dose** = 0.5 x weight in kg
  - 0.5 x 100 kg = 50 units

• **Basal dose** = 50% of starting dose at bedtime
  - 50% of 50 units = 25 units at bedtime

• **Total bolus dose** = 50% of starting dose evenly distributed 1/3 at each meal
  - 25 units ÷ by 3 meals = 8 units before meals (TID)
Summary

- Many patients on basal insulin therapy will ultimately require treatment intensification

- Current options include:
  - Addition of mealtime control via addition of prandial insulin, leading to multiple daily insulin therapy
  - Switch to premix insulin
  - Add a DPP-4 inhibitor or a GLP-1 agonist

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

Injectable Therapies for T2DM

Thank You!