This presentation will:

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

• Develop strategies for appropriate initiation and intensification of insulin therapy for T2D.

• Evaluate the efficacy and safety of different formulations of insulin, including insulin-incretin combination products.
Update on Insulin-based Agents for T2D
Antihyperglycemic Monotherapy
Maximum Therapeutic Effect, Dependent Upon Initial A1C

<table>
<thead>
<tr>
<th>Medication</th>
<th>Baseline A1C</th>
<th>Reduction in A1C Level (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>8.5¹</td>
<td>-0.5</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>8.3-8.5²</td>
<td>-0.5</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>7.7³</td>
<td>-1.0</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>7.8-12.5⁴</td>
<td>-1.5</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>8.2-8.5⁵</td>
<td>-1.5</td>
</tr>
<tr>
<td>Exenatide</td>
<td>8.0⁶</td>
<td>-1.5</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>10.0-10.3⁷</td>
<td>-1.5</td>
</tr>
<tr>
<td>Repaglinide GITS</td>
<td>8.8-9.0⁸</td>
<td>-1.5</td>
</tr>
<tr>
<td>Glimepiride GITS</td>
<td>7.7⁹</td>
<td>-1.5</td>
</tr>
<tr>
<td>Glipizide GITS</td>
<td>8.3-8.8¹⁰</td>
<td>-1.5</td>
</tr>
<tr>
<td>Metformin</td>
<td>9.7-10.1¹¹</td>
<td>-1.5</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>7.8-8.3¹²</td>
<td>-2.0</td>
</tr>
<tr>
<td>Insulin</td>
<td>8.61-9.5¹³,¹⁴</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

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.

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**
  - Metformin
  - 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**
  - Metformin
  - 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
  - DUAL Therapy
- YES
  - INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

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

PROGRESSION OF DISEASE

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation
Current and Emerging Basal Insulins

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.
- Approved by the US FDA in February 2015.
# Basal Insulins

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>NPH Insulin</th>
<th>Insulin Glargine</th>
<th>Insulin Detemir</th>
<th>Biosimilar Insulin Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>2-4 hours</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Peak</strong></td>
<td>4-10 hours</td>
<td>No pronounced peak</td>
<td>Relatively flat</td>
<td>No pronounced peak</td>
</tr>
<tr>
<td><strong>Effective Duration</strong></td>
<td>10-16 hours</td>
<td>Up to 24 hours</td>
<td>Up to 24 hours</td>
<td>Up to 24 hours</td>
</tr>
</tbody>
</table>

NPH = neutral protamine hagedorn.

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.

# 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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>1-2 hrs</td>
<td>4-12 hrs</td>
<td>18-24 hrs</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></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 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.

**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

Risk of Hypoglycemia with Insulin Detemir

Hypoglycemic events per-patient per-year

Overall

Nocturnal*

$P < 0.001$

Detemir + OAD
NPH + OAD

* Any episode between 11 pm and 6 am

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

Basal Insulin Added to OADs Improves Glycemic Control (24 Week Non-Inferiority Trial of 973 Insulin-Naive T2DM Patients Inadequately Controlled on OADs)

A1C = glycated hemoglobin; OAD = oral anti-diabetic; T2DM = type 2 diabetes mellitus.

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>
</tbody>
</table>
| Delay in down-titration of BI with improved glycemia → hypoglycemia and pre-emptive eating | • Discuss this scenario with patient as glycemic control is re-established: “Less insulin is needed to maintain control than establish control”  
  • Reduction of OHAs, such as SUs or glinides, may also be required |

BI = basal insulin; OHA = oral hypoglycemic agent; PP = postprandial; SU = sulfonylurea.
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 ~19 hours
- Steady state in 3 to 4 days
- Duration of action > 24 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.
Cumulative Mean Number of Confirmed and/or Severe Hypoglycemia

Hypoglycemia at any time of the day (24 hours)*
- U300
- U100

Nocturnal hypoglycemia (00:00–05:59 hours)*
- U300
- U100

Rate ratio 0.86 (0.77 to 0.97) p=0.0116
Rate ratio 0.69 (0.57 to 0.84) P=0.0002

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

Insulin Degludec

• desB30 insulin acylated (16 carbon fatty acid chain) at LysB29
• Duration of action > 42 hours
• Half-life ~25 hours
  – Detectable for at least 5 days
• Steady state in 2-3 days

FDA = U.S. Food and Drug Administration.
Degludec vs Glargine U100 in Type 2 Diabetes

A1C = glycated hemoglobin.

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

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.

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.

2. Peragallo V. *Diabetes Educ.* 2007;33:60S–65S.
New Insulin and Insulin + GLP-1 Receptor Agonist Combinations: Application and Therapeutic Efficacy

GLP-1 = glucagon-like peptide-1.
**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.
IDegLira: A Fixed Ratio Combination of Insulin Degludec and Liraglutide

- 1663 T2DM patients on MET ± PIO; 26 week open-label trial
- Patients achieving A1C <7%
  - IDegLira: 81%
  - DEG: 65%
  - LIRA: 60%
- IDegLira vs DEG
  - Weight change: -2.22 kg; \( P < .001 \)
  - Hypoglycemia: RR 0.68; \( P < .002 \)
- IDegLira vs LIRA
  - Weight change: 2.44 kg; \( P < .001 \)
  - Hypoglycemia: RR: 7.6; \( P < .001 \)

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.

Lixisenatide + Glargine: A1C

A1C = glycated hemoglobin; FDA = U.S. Food and Drug Administration; LOCF = last observation carried forward.

Insulin + GLP-1 Dual Therapies, Injection Devices
## Clinical Trial Results for IDegLira and IGlarLixi

<table>
<thead>
<tr>
<th>Study (N)</th>
<th>Patient population</th>
<th>Study duration (weeks)</th>
<th>Mean baseline A1C (% A1C reduction from baseline)</th>
<th>% patients with A1C ≤ 7.0%</th>
<th>Weight reduction from baseline (kg)</th>
<th>Hypoglycemia risk reduction (vs insulin alone)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDegLira</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUAL I (1,663, extension: 1,311)</td>
<td>Insulin-naive, not adequately controlled with metformin ± pioglitazone</td>
<td>26 + 26-week extension</td>
<td>8.3% (-1.8%)</td>
<td>78%</td>
<td>-0.5</td>
<td>37%</td>
</tr>
<tr>
<td>DUAL II (413)</td>
<td>Not adequately controlled with basal insulin (20–40 U) and metformin ± sulfonylureas/glinides</td>
<td>26</td>
<td>8.3% (-1.9%)</td>
<td>60%</td>
<td>-2.7</td>
<td>34%</td>
</tr>
<tr>
<td>DUAL V (557)</td>
<td>Not adequately controlled with insulin degludec (20–50 U) and metformin</td>
<td>26</td>
<td>8.8% (-1.8%)</td>
<td>72%</td>
<td>-1.4</td>
<td>57%</td>
</tr>
<tr>
<td><strong>IGlarLixi</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenstock et al (323)</td>
<td>Insulin-naive, not adequately controlled with metformin</td>
<td>24</td>
<td>8.0% (-1.7%)</td>
<td>84%</td>
<td>-1.0</td>
<td>Similar between groups</td>
</tr>
<tr>
<td>Rosenstock et al (1,170)</td>
<td>Not adequately controlled with metformin ± a 2nd oral antihyperglycemic drug</td>
<td>30</td>
<td>8.1% (-1.6%)</td>
<td>74%</td>
<td>-0.3</td>
<td>Similar between groups</td>
</tr>
<tr>
<td>Aroda et al (736)</td>
<td>Not adequately controlled with insulin glargine (maximum 60 U)</td>
<td>30</td>
<td>8.5% (-1.1%)</td>
<td>55%</td>
<td>-0.7</td>
<td>Similar between groups</td>
</tr>
</tbody>
</table>

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 titration


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
- According to the label, patients who are inadequately controlled on < 30U basal insulin or lixisenatide should start iGlarlixi at 15U insulin glargine (U-100 glargine)/ 5mcg lixisenatide once daily.


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