Outpatient Insulin Management: An Interventional Evolution

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Disclosures

Compensated

Speaker’s Bureau:
Novo Nordisk Pharmaceuticals
Janssen Pharmaceuticals
Mist Pharmaceuticals
Medtronic Diabetes

Advisory Board:
Ultragenyx Pharmaceuticals
Novo Nordisk Pharmaceuticals

Non-Compensated

International Society of Clinical Densitometry (ISCD) Task Force Practice Analysis Committee for CCD Certification
Discussion Overview

Learning Objectives

• Highlight guidelines specific to initiating insulin therapy in type 1 and type 2 diabetes

• Underscore the pharmacokinetic attributes of currently-available insulin products

• Recognize and critique strategies related to insulin-specific management in type 1 and type 2 diabetes

• Highlight basic insulin pump operation and the goal of complimenting normal physiologic pancreatic function.

• Differentiate between the advantages and disadvantages of CSII vs. multiple daily injections for people with type 1 and type 2 diabetes.

• Discuss the benefits of CSII for a patient with insulin-requiring type 2 diabetes.

Key Phrases/Terms

• Physiologic versus Non-physiologic Therapies

• Standard Deviation

• Legacy Effect

• Time-in-Range
Trending Statistics

≈5,000 Adult and ≈900 Pediatric Board Certified Endocrinologists in the U.S.

≈3,900 Clinically Active

84.1 million with “Pre-diabetes”
30.3 million “Classic” diabetes

1 Endocrinologist per ≈29,300 (Pre- + Diabetic) Patients Nationwide

85% of Diabetes Care will require:

↓

Health Care Providers beyond Endocrinologists

• Primary Care Physicians
• Physician Assistants
• Nurse Practitioners


“The Whole is Greater Than the Sum of Its Parts”

Aristotle (Greek philosopher/scientist; 384 B.C. → 322 B.C.)

Defines the modern concept of **Synergy** and the T.E.A.M. acronym:

**T**ogether, **E**verything **A**chieves **M**ore.

Applies to physics, engineering, agriculture, business, and ......

...... **the chemistry and biology of insulin**
Evolution of a Therapeutic Breakthrough

**INSULIN**: Landmark Discovery

- 1921 – discovered insulin using dogs
- 1922 – 14-yr-old boy with diabetes, near death, first person to receive insulin
- 1923 – Nobel prize

**96 Years of Pharmacologic Milestones**

Insulin therapy development: A rich history, a good present, a bright future

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**On his discovery of Insulin** …

Insulin is **not a cure** for diabetes; it is a treatment. It enables the diabetic to burn sufficient carbohydrates, so that proteins and fats may be added to the diet in sufficient quantities to provide energy for the economic burdens of life.

— *Sir Frederick Grant Banting*
Greatest Historical Breakthroughs in Insulin Therapy

• **1973**: Development of Mono-component “Human” insulin
  - Purified pork insulin; new standard in purity.
  - Enzymatic conversion: Alanine (B30) → Threonine
  - Identical in structure to human insulin

• **1978**: Advancement of Recombinant DNA “Human” Insulin
  - Gene manipulation of E. coli to produce Bio-synthetic human insulin
  - Eliminated insulin allergy and immune-mediated lipoatrophy.
  - Humulin R and Humulin N (Eli Lilly)

• **1995**: Expansion to Insulin Analogues
  - Laboratory grown (E. coli/Baker’s Yeast) but genetically altered amino acid sequence)
  - Pharmaco-kinetic/-dynamic features striving to simulate “endogenous” insulin
  - Lispro is the first analogue produced – FDA approved 1996
Primary Goal of Insulin Treatment Strategies

- **Match pharmaco-kinetic/-dynamic profile of “endogenous insulin”:**
  - Timing precision; adherence; fewer injections
  - Reduce within-/between-patient variability in plasma glucose

![Graph showing glucose infusion rates over time for different insulin types.](image)

- **Tight glycemic control:**
  - Limit microvascular complications *(DCCT and UKPDS)*
  - **Reduce** glucose variability/standard deviation *(oxidative stress → O_2^- free radicals → endothelial damage)*
  - Minimize “Legacy Effect”
  - Achieve “Time-in-Range” *(HbA1C???)*

- **Minimal risk for exogenous side effects:**
  - hypoglycemia
  - weight gain

- **Achieve “Prospective” treatment models:**
  - Sliding Scale
  - Split-Mixed (both insulins provide potential basal and prandial effects)
  - Basal-Bolus
  - Pump Infusion Therapy
Major Adverse Effects of Insulin

- **Hypoglycemia (unawareness)**
  - **DCCT Study** (Type 1 Diabetes)
    - Severe hypoglycemia in 26% of patients
    - 43% of episodes nocturnal
  - **UKPDS Study** (Type 2 Diabetes)
    - Insulin cohort: 2% of patients with at least 1 severe episode/year

- **Weight Gain** *(over “insulinization”; hypoglycemia/defensive snacking)*
  - **DCCT Study** (Type 1 Diabetes)
    - Intensive cohort with ≈ 10.5 lb. increase
  - **UKPDS Study** (Type 2 Diabetes)
    - Insulin Cohort with ≈ 5.1 lb. increase

- **Progression of Retinopathy with rapid glycemic control**
  - **Osmotic Hypothesis**: rapid decline in plasma glucose shifts water from a higher osmotic pressure interstitium to a lower intravascular osmotic space
  - **Synergistic Hypothesis**: insulin amplification + expression of vascular endothelial growth factor (by ischemic vessels) promotes retinal vascular proliferation.
  - **Higher Risk** = proliferative retinopathy + HbA1C ≥ 10%
1982-1993 DCCT Study: 3-fold increase in Hypoglycemia

**Trade-off between:** Reducing Complications & Minimizing Hypoglycemia

**Patients used:** Regular insulin /Intensive therapy via **Multiple Injections or Insulin Pump**

**Intensive Glycemic Control** Reduced Microvascular complications overall $\Rightarrow \approx 60\%$:
- Retinopathy $63\%$
- Neuropathy $60\%$
- Nephropathy $54\%$

By End of Study 42% of Intensively-Managed Patients on CSII Therapy

**DCCT Research Group, 1993**
1977-1997: United Kingdom Prospective Diabetes Study for Type 2 Diabetes ("Newly Diagnosed Patients")
Intensification of Therapy (i.e. sulfonylureas, insulin, MDI therapy)

HbA1C Reduction of \( \approx 1.0\% \)
Behavioral, Distribution and Absorption Considerations

• Molecular Character:
  • Human non-analogue versus analogue insulin → altered kinetic behavior
  • Fatty-acid side-chain:
    • dictates self-association/reversible albumin binding features
    • influences portal/peripheral/CNS distribution

• Product concentration:
  • U-100, U-200, U-300, U-500
  • absorption rate inverse to concentration

• Injection sites:

• Formulation design:
  • Protamination: “crystalline-based” protracted absorption (limited/variable)  NPH Insulin
  • pH-altered precipitation: protracted absorption (extended/less-variable)  Glargine Insulin (Lantus)
  • Non-precipitant (Fatty-acid side chain): protracted/reproducible absorption kinetics
    • Detemir Insulin (Levemir)
  • Zinc, Phenol, m-cresol components:
    • Self-association/conformational properties in-solution: multi-hexamers → di-hexamers → hexamers → monomers
    • Dissociation properties SQ → active insulin monomers

Degludec Insulin (Tresiba)
The Ideal Analogue Insulin

**Rapid-acting agents:**

- Replicate *first- and second-phase* endogenous kinetics
- High hexameric stability in solution; rapid dissociation into monomers post-SQ injection
- Match "action time" for meals
- **Predictable end-point** to minimize residual insulin conflicts (hypoglycemia)
- Prevent *ramifications of post-prandial hyperglycemia:*
  - Insulin “Over Correction” → post-prandial hypoglycemia (Pump; Basal-Bolus regimens)
  - Post-prandial-related CV Risk:
    - HbA1C 1% ↑ = 50% CV↑ = Type 1 DM
    - HbA1C 1% ↑ = 7.5% CV↑ = Type 2 DM

**24-hour Basal agents:**

- Achieve **steady-state** pharmacokinetics/dynamics
- Low peak:trough ratio
- Duration of action comfortably exceeds 24-hours
- Dosing frequency **not to exceed once daily**
- Low variability of action from injection to injection
- Able to mix with Rapid-acting insulin

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**Insulin Predictability of Basal Insulin**

- Pumps
- Gold Standard
- Detemir
- Glargine
- Intrasubject Variability
- NPH

Endogenous Insulin Kinetics

• Secretion is Bi-phasic

• Prandial First-phase Insulin Release:
  • begins within 2 minutes of nutrient ingestion
  • “buffers” postprandial glucose “spike”
  • earliest “flaw” in beta-cell function

• Prandial Second-phase Insulin Release:
  • sustained until normoglycemia is restored
  • suppresses hepatic glucose production

• Basal Insulin Maintenance
  • ≈ 50% of our total daily insulin;
  • suppresses lipolysis, proteolysis, and glycogenolysis
Ideal Rapid and Basal Insulins

**Insulin activity curves (AUC=1)**

- **Novolog**: $(4.26 \times 10^{-5})t^{1.32}e^{-t/1.57/25}$
- **FIAS**: $(3.11 \times 4)^{1.5}e^{-t/0.05}$

**Rapid- and Long-Acting Insulin Profiles**

- **Aspart, Lispro, Glulisine (2-4 hr)**
- **Regular insulin (6–8 hr)**
- **NPH (12–16 hr)**
- **Glargine (~24 hr)**
- **Degludec (>>24 hr)**
- **Detemir (~20–24 hr)**
# The Ideal Analogue Insulin

## Rapid-acting agents:

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>ONSET</th>
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<td>Humalog insulin</td>
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Hypoglycemia: 
The Limiting factor to Glycemic Control

- 101 Type 1 diabetic patients receiving basal-bolus insulin therapy enrolled
- CGM data collected to provide insight into glycemic variability.
- Patients **stratified equally by HbA1c values with CGM data** demonstrating
  - All HbA1c subgroups exhibit similar patterns of glycemic variability and SD of ≈50–60 mg/dL
  - The lower the HbA1c value, the longer the duration of hypoglycemia and nocturnal (23:00–6:00) hypoglycemia
- **Study implication:** A lower HbA1c is not associated with a lower SD but may lead to increased hypoglycemic episodes.

  - Group A: HbA1c ≤ 7.2 %
  - Group B: 7.2 % → 8.1 %
  - Group C: 8.2 % → 9.1 %
  - Group D: HbA1c > 9.2 %

Tsujino, T, Nishimura, R. The relationship between HbA1c values and the Occurrence of Hypoglycemia as Assessed by Continuous Glucose Monitoring in Patients with Type 1 Diabetes. Diabetol Metab Syndr. 2016; 8: 53.
Abstract:

The DCCT Trial established HbA1C as the gold standard of glycemic control, with levels ≤7% deemed appropriate for reducing the risk of vascular complications.

.......... Yet, even when A1Cs were comparable between intensively treated subjects and their conventionally treated counterparts, the latter group experienced a markedly higher risk of progression to retinopathy over time.

Our speculative explanation, based on the discovery that hyperglycemia-induced oxidative stress is the chief underlying mechanism of glucose-mediated vascular damage, was that glycemic excursions were of greater frequency and magnitude among conventionally treated patients, who received fewer insulin injections.

Subsequent studies correlating the magnitude of oxidative stress with fluctuating levels of glycemia support the hypothesis that glucose variability, considered in combination with A1C, may be a more reliable indicator of blood glucose control and the risk for long-term complications than mean A1C alone.
Should Minimal Blood Glucose Variability ("Time in Range") Become the Gold Standard

"Time In Range" CGM Bar Graph Summary

CGMS Analysis: HbA1C 6.1 → 6.3%  MDI Therapy
**Legacy Effect:** Contribution of HbA1C Over Time

Relative contribution of HbA1c values at different past-points in time to future risk of retinopathy progression

For HbA1C values 2.4 years ago, the relative contribution is ≈ 80%.

For HbA1C values of 6.5 and 8.4 years ago, the contribution is 50% and 25% respectively.

DCCT: Legacy Effect of Earlier Glucose Control
**UKPDS: Legacy Effect of Earlier Glucose Control**

**After median 8.5 years post-trial follow-up**

<table>
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<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
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<tr>
<td>Any diabetes related endpoint</td>
<td>RRR: 12%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>( P: 0.029 )</td>
<td>( 0.040 )</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 25%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>( P: 0.0099 )</td>
<td>( 0.001 )</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 16%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>( P: 0.052 )</td>
<td>( 0.014 )</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 6%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>( P: 0.44 )</td>
<td>( 0.007 )</td>
</tr>
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</table>

Analogue Insulins: Unique Considerations

- Insulin Aspart Rapid-acting (Novolog):
  - Single amino acid substitution at B28 (Proline → Aspartic Acid)
    - Humalog is a “molecular reversal” of proline (B28) and lysine (B29)
  - Zinc-based product; pH 7.2-7.6 (Humalog pH 7.0-7.8)
  - Comparatively faster onset compared to Humalog
  - Administer 5-10 min. before meal (Humalog 15 min.)

- Insulin Glulisine (Apidra):
  - “Dual Substitution”: Lysine → Asparagine (B3) and Glutamic acid → Lysine (B29)
  - “Zinc-Free” formulation accelerates dissociation rate
  - Onset of action < 10 minutes

- Insulin Aspart Fast-acting (FIASP):
  - Novolog insulin product with 2.5 minute onset of action
  - Nicotinamide added to solution to accelerate absorption
  - Arginine included as a “stabilizer”
Analogue Insulins: Unique Considerations

- **Insulin Detemir (Levemir):** FDA approved June 16, 2005 (Lantus April 20, 2000)
  - Genetically crafted using Baker’s Yeast (*Saccharomyces cerevisiae*)
  - **Molecular Design:**
    - 14-carbon fatty acid (*myristic acid*) moiety covalently bound to Lysine (B29)
  - Only insulin to exhibit a **weight-sparing effect**:
    - “Non-precipitant” formulation offers less within-subject variability → less hypoglycemia
    - **C-14 carbon moiety** facilitates blood-brain-barrier penetration → hypothalamic satiety centers
    - **C-14 carbon moiety** encourages reversible-albumin-binding capability → hepatic insulin extraction → limits peripheral lipogenesis
Analogue Insulins: Unique Considerations

- Insulin Glargine U-300 (Toujeo) – “concentrated” form of Glargine U-100
  - **Molecular Design:**
    - 2 arginine amino acids attached to B-chain C-terminus and A21 substitution (asparagine → glycine).
    - Compact Insulin Formulation/smaller surface area
    - Formulation reduces dissolution rate
    - “Near-Flat” PK/PD profile → more gradual onset → prolonged release.
  - Starting dose is 1:1 match with any current analogue basal agent or 80% of NPH dose.
  - Transitioning from Glargine U-300 → Glargine U-100: Glargine U-100 dose ≈80% of Glargine U-300 dose.
- **BRIGHT 24-week Study (June 2018):** Toujeo Non-Inferior compared to Tresiba:
  - HbA1C reduction
  - Hypoglycemic event rate (23%)
  - Hypoglycemic incidence rate (26%)
Analogue Insulins: Unique Considerations

- **Insulin Degludec (Tresiba)**
- **Molecular design:**
  - Threonine (B-30) on insulin B-chain cleaved
  - 16-carbon fatty diacid side chain attached to Lysine (B-29) using Glutamate spacer.
- 25-hour ½-life; 100% steady-state after 8 injections (90% after 4 injections)
- Peak level achieved by 8-12 hours
- Lasts up to 42-hours (detected in blood → 96 hours).
- **SWITCH Study (July 2017): Tresiba** with less Hypoglycemia/Nocturnal Hypoglycemia vs. Lantus
  - SWITCH 1 (Type 1 DM): 35% Overall; 36% Nocturnal
  - SWITCH 2 (Type 2 DM): 30% Overall; 42% Nocturnal
Tresiba Mechanism of Action
Benefits of Early Insulin Therapy

• **Preserve Beta-cell function:**
  • restoration of “first-phase” insulin release?

• **Improve Lipid Metabolism**

• **Reduced mortality Post-MI:**
  • Post-prandial glycemic control?

• **Early control → “anti-inflammatory” mechanisms**, reducing macrovascular/microvascular risk:
  • Suppression of intranuclear transcription factor κβ → transcription of proinflammatory cytokines

• **Studies suggest:** early tight control achieves and sustains **glycemic stability for extended periods** with less medication.

• **UKPDS (Type 2 DM):** B-cell failure progressive
  • **At time of diagnosis** – 50% normal beta-cell function likely exists
  • By the **time insulin therapy implemented** – 25% function exists
  • **53% of patients treated with SUs** required insulin therapy by 6-years → 80% by 9-years

• Reduced morbidity → Net cost reduction

• Diabetes-related costs ≈15% of the U.S. health-care budget
### 2018 ADA General Recommendations: Pharmacological Therapy in Type 2 Diabetes

**Start with Monotherapy unless:**

- A1C is greater than or equal to 9%, consider Dual Therapy.
- A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).

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<tr>
<th>Monotherapy</th>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
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<tbody>
<tr>
<td><strong>Efficacy</strong>^1</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td><strong>Hypo Risk</strong></td>
<td>low risk</td>
<td></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>neutral/loss</td>
<td></td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>GL/Lactic acidosis</td>
<td></td>
</tr>
<tr>
<td><strong>Costs</strong>^3</td>
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If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

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<tr>
<td><strong>Weight</strong></td>
<td>gain</td>
<td>neutral loss</td>
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If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtide insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

**Combination Injectable Therapy** (See Figure 8.2)
2018 ADA General Recommendations: Pharmacological Therapy in Type 2 Diabetes

Combination injectable therapy for type 2 diabetes.

American Diabetes Association Dia Care 2017;40:864-874
2018 AACE General Recommendations: Pharmacological Therapy in **Type 2 Diabetes**

### Glycemic Control Algorithm

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<th>INDIVIDUALIZE GOALS</th>
<th>LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)</th>
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<tbody>
<tr>
<td>A1C ≤ 6.5% For patients without concurrent serious illness and at low hypoglycemic risk</td>
<td><strong>Entry A1C &lt; 7.5%</strong></td>
<td>NO</td>
</tr>
<tr>
<td>A1C &gt; 6.5% For patients with concurrent serious illness and at risk for hypoglycemia</td>
<td><strong>Entry A1C ≥ 7.5%</strong></td>
<td>YES</td>
</tr>
<tr>
<td><strong>Entry A1C &gt; 9.0%</strong></td>
<td><strong>MONOTHERAPY</strong>*</td>
<td>---</td>
</tr>
<tr>
<td>Metformin</td>
<td><strong>DUAL THERAPY</strong>*</td>
<td>---</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>GLP-1 RA</td>
<td>---</td>
</tr>
<tr>
<td>SGLT-2i</td>
<td>SGLT-2i</td>
<td>---</td>
</tr>
<tr>
<td>DPP-4i</td>
<td>DPP-4i</td>
<td>---</td>
</tr>
<tr>
<td>TZD</td>
<td>TZD</td>
<td>---</td>
</tr>
<tr>
<td>AGI</td>
<td>Basal Insulin</td>
<td>---</td>
</tr>
<tr>
<td>SU/GLN</td>
<td>Colesvelam</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Bromocriptine QR</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>AGI</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>SU/GLN</td>
<td>---</td>
</tr>
<tr>
<td>If not at goal in 3 months proceed to Dual Therapy</td>
<td>If not at goal in 3 months proceed to Dual Therapy</td>
<td>---</td>
</tr>
<tr>
<td><strong>TRIPLE THERAPY</strong>*</td>
<td><strong>MET or other 1st-line agent + 2nd-line agent</strong></td>
<td>---</td>
</tr>
<tr>
<td>MET or other 1st-line agent</td>
<td>GLP-1 RA</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>SGLT-2i</td>
<td>---</td>
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<td>DPP-4i</td>
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<td></td>
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<td></td>
<td>Basal Insulin</td>
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</tr>
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<td></td>
<td>Colesvelam</td>
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<tr>
<td></td>
<td>AGI</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>SU/GLN</td>
<td>---</td>
</tr>
<tr>
<td>If not at goal in 3 months proceed to Triple Therapy</td>
<td>If not at goal in 3 months proceed to or intensify insulin therapy</td>
<td>---</td>
</tr>
</tbody>
</table>

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

---

* Order of medications represents a suggested hierarchy of usage; strength of recommendation.

---

PROGRESSION OF DISEASE

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2018 AACE General Recommendations: Pharmacological Therapy in Type 2 Diabetes

Algorithm for Adding/Intensifying Insulin

START BASAL (Long-Acting Insulin)

- **A1C < 8%**
  - TDD < 0.1–0.2 U/kg

- **A1C > 8%**
  - TDD 0.2–0.3 U/kg

Insulin titration every 2-3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
  - If hypoglycemia, reduce TDD by:
    - BG < 70 mg/dL: 10% – 20%
    - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

**Glycemic Goal:**

- <7% for most patients with T2D; fasting and premal
- BG < 110 mg/dL: absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

INTENSIFY (Prandial Control)

- Add GLP-1 RA
- Or SGLT-2i
- Or DPP-4i

Insulin titration every 2-3 days to reach glycemic goal:

- **Basal Plus 1, Plus 2, Plus 3**
  - Begin prandial insulin before largest meal
  - If not at goal, progress to injections before 2 or 3 meals
  - Start: 10% of basal dose or 5 units

- **Basal Bolus**
  - Begin prandial insulin before each meal
  - 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
  - Start: 50% of TDD in three doses before meals

*Glycemic Control Not at Goal*

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%
Injectable Insulin Strategies

Non-Physiologic

• Split-Mixed Regimens:
  • NPH + “analogue”-R or “Human Regular”-R”
  • Each provides a basal and prandial effect
  • Example → Morning mixed dose:
    • R contributes primary prandial-effect for breakfast, secondary prandial for lunch, and basal effect post-breakfast
    • NPH contributes basal-effect post-breakfast and lunch, and primary prandial effect for lunch
  • Requires meticulous attention to life-style organization
  • Risk of “Late-morning overlap” → hypoglycemia

• Sliding Scale Protocols:
  • Should be avoided
  • Retrospective decision-making

Physiologic

• Intensified Regimens
  • True Basal Insulin + OAD agents
  • True Basal Insulin + “selective Prandial” insulin

  • Basal-Bolus + “correction insulin”
    • Dosing flexibility
    • Predetermined versus Calculated dosing
    • More efficient post-prandial recovery
    • Prospective intervention
    • Avoid “Insulin Stacking”
Basal-Bolus Protocol

Developing a “Recipe”

- When initiating Basal-Bolus regimen, reduce calculated basal dose by 20% to avoid hypoglycemia:
  - 1/3 will receive correct dose
  - 1/3 will need more
  - 1/3 will need less

Clinical considerations:

- If using “correction insulin” between meals:
  - Remain aware of “insulin-stacking”

- If using “correction insulin” ≤ 3-hours after a prandial dose, reduce the “correction” by 50%.

- If exercising early in the post-prandial period (1-3 hours), reduce the prandial insulin dose by 75%
# Typical Basal-Bolus Protocol

<table>
<thead>
<tr>
<th>Mealtime Insulin: FIASP</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Correction: FIASP</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80 mg/dL</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>81-120 mg/dL</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>121-160 mg/dL</td>
<td>1</td>
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<td>1</td>
<td>0</td>
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<td>161-200 mg/dL</td>
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<tr>
<td>201-250 mg/dL</td>
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<td>3</td>
<td>3</td>
<td>0</td>
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<tr>
<td>251-300 mg/dL</td>
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<td>301-350 mg/dL</td>
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<tr>
<td>351-400 mg/dL</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>&gt;401 mg/dL</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

**Basal Insulin: TRESIABA**  | 25
The Problem with “Sliding Scales”

• Little evidence for therapeutic efficacy

• Fluctuating glucose levels more harmful → oxidative stress → vascular endothelial damage

• Meal time insulin is “comprehensively” based on an isolated value (activity, caloric variability, “other stressors” NOT CONSIDERED)

• “Skipping a dose” when glucose is below a cutoff point leaves patient without insulin for hours

• Failure to individualize insulin protocols (i.e. age, weight, type of insulin, time of day, caloric variability, type of diabetes??)

• Incorporating basal insulin will not offset peaks and dips in blood glucose

The Problem with “Sliding Scales”

RABBIT 2: Glycemic Control With Basal-Bolus vs Sliding-Scale Insulin

N=130 insulin-naïve hospitalized nonsurgical patients with T2DM

n=9 with BG >240 mg/dL

Blood glucose (mg/dL)

Admit 1 2 3 4 5 6 7 8 9 10

100 150 200 250 300

Days of therapy

1 2 3 4 5 6 7

Baseline

Blood glucose (mg/dL)

Admit 1 2 3 4 5 6 7

100 150 200 250 300

Sliding-scale

Basal-bolus

*P<.01; †P<.05; ‡Long-acting insulin (glargine) once daily + short-acting insulin (glulisine) before meals, total dose 0.4 unit/kg (BG 140-200 mg/dL) or 0.5 unit/kg (BG 201-400 mg/dL).


RALS = Remote Automated Laboratory System.

Umpierrez, GE., Smiley, D. Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes (RABBIT 2 Trial). Diabetes Care 30:2181–2186, 2007

CGMS Technology reflects Interstitial Glucose
CGM sensors should be worn continuously

CGM indicated as an **adjunct to SMBG and does not replace SMBG**

**SMBG**
(Self Monitoring Blood Glucose)
“Snapshot” of Blood Glucose
Potential 20% error rate

- Measures **Capillary Whole Blood glucose**
  - 1-12+ Readings per day

**CGM**
Rate change
Pattern/Trend Recognition → 24-hour surveillance
10.5% difference with paired laboratory reading

- Measures **Interstitial fluid glucose**
  - Up to 288 readings per day

• CGM and SMBG measure glucose in different compartments
Insulin Pump Technology: A Brief History

Dr. Arnold Kadish, 1963
First Prototype Insulin Pump
Delivers Insulin and Glucagon

1976
Mill Hill Infusor
Battery-operated syringe
allows continuous release of insulin

1983
MiniMed® 502 Pump
Medtronic’s First pump
(502A improves size/programming)

1992
MiniMed® 506 Pump
Offered meal bolus memory
and daily insulin totals
Insulin Pump Technology

November 2011
Tandem t:slim X2™ + G6® CGM

November 2012
Omnipod Tubeless Insulin Pump

September 2016
MiniMed® 670G Pump
Pump Basics

• Size of a pager

• Insulin is stored in a disposable cartridge (reservoir) and delivered by a small catheter inserted into the SQ fat layer

• The catheter (part of an infusion set) and insulin reservoir are removed and changed every 2-3 days

• Only ONE type of Insulin is used (Humalog, Novolog, Apidra .......... Fiasp??)

• Infusion-set attachment sites (SQ fatty skin layer) are the same used for MDI therapy:
  • abdomen, back of the arms, upper buttocks, and thighs
Insulin Pumps Can Deliver **Customized Basal Infusion Rates** at Increments as low as 0.01 units/hour over 24-hours to Modulate Hepatic Gluconeogenesis, avoid Nocturnal Hypoglycemia, etc.

Upon entering food **carbohydrate content** and **blood sugar level**, pumps accurately calculate “**pre-meal**” and glycemic target “**correction**” insulin requisites.

CSII Reduces Incidents of Severe Hypoglycemia

Severe hypoglycemic episodes: CSII vs MDI

<table>
<thead>
<tr>
<th>Study</th>
<th>Events per hundred patient-years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudolph 2002</td>
<td>19 (CSII) 73 (MDI)</td>
<td>&lt;0.0003</td>
</tr>
<tr>
<td>Bode 1996</td>
<td>138 (CSII) 134 (MDI)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Boland 1999</td>
<td>76 (CSII) 134 (MDI)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

In the 5-Nations Study
CSII Improved HbA1C
without Increased Risk of Hypoglycemia

GINSS ; Type 1 DM; CSII vs. MDI with NPH
CSII Helps Reduce Daily Insulin Requirements in Type 2 Patients

<table>
<thead>
<tr>
<th>Insulin</th>
<th>A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before CSII</strong></td>
<td><strong>Post 1-Yr CSII Use</strong></td>
</tr>
<tr>
<td>Patient 1</td>
<td>630 u/day</td>
</tr>
<tr>
<td>Patient 2</td>
<td>402 u/day</td>
</tr>
<tr>
<td>Patient 3</td>
<td>218 u/day</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Patient 4 is not included in this analysis because he was not on CSII for 1 year.</td>
</tr>
</tbody>
</table>

Neilsen et al., Diabetes Educator 2005 Vol. 31
Pump Pros and Cons

PROS

• “Micro-Management” of Insulin Delivery $\rightarrow$ Less glucose variability (standard deviation)
• Reduction in number and severity of hypoglycemic episodes $\rightarrow$ improved quality of life
• No injections; discreetness of insulin administration
• Reduced hospitalizations due to hypoglycemia/DKA
• Patient generally becomes better educated & more independent
• Bolus calculator, prevents insulin stacking; provides precision of dosing $\rightarrow$ up to 25-30% less insulin

CONS

• Mechanical device attached to body
• Perception of weight gain (not necessarily so)
• Extra cost of pump and supplies
• Time and personnel needed to initiate, supervise, and fine-tune therapy (patient participation crucial)
• More rapid (not more frequent) onset of DKA if insulin delivery interrupted for extended periods.
• Infusion site infections (rare) or irritation, leading to inadequate insulin absorption (minimized by maintaining scheduled visits for remedial care and education).
Choosing the Right Candidate

- **Patient is motivated** to accelerate their management and invest time to learn.
- **MDI/Basal-Bolus regimen** no longer meets treatment goals.
- Patient experiencing .......
  - Frequent hypoglycemia; Hypoglycemic unawareness
  - Unpredictable fluctuations in blood glucose levels
  - Gastroparesis
- Children/young adults who desire more **life-style flexibility**
- Challenging glycemic control with adolescent “growth spurt”
- Preconception planning and pregnancy
Pump Technology Options

V-Go Insulin Delivery System

- Wearable insulin delivery device for adults managing Type 2 diabetes.
- Does not require batteries, electronics, or software to function.
- Does not have tubes, cannulas, monitors, or alarms.
- Insulin advances via spring-activated hydraulic system

Insulin Delivery for Type 2 Diabetes worn like a patch

- It's worn like a patch; Discreet
- Simply place on skin (such as arm or stomach area), click a button, and wear it 24-hours
- Use ONE type of insulin (Humalog, Novolog, Apidra)
- Can translate into 30% less insulin per day
- “Just Stick It and Click It”
Pump Technology Options

**Tandem: t:slim X2™ Pump + Dexcom G6® CGM**
- Touchscreen technology; smallest pump available
- Capable of remote software updates
- Integrated Dexcom G6® CGM with Basal-IQ™ Technology:
  - Acquire Glycemic Data without finger sticks.
  - High and Low alert settings indicate when glucose is above or below a preset target range.
  - **NEW Predictive Low Glucose Suspend Algorithm:** Reduces frequency and duration of hypoglycemic events by predicting glucose levels 30 minutes ahead and suspending insulin if expected to drop below 80 mg/dL.
- Compatible with iPhone, iPad, iPod touch, any Android Device using OS version 6.0 or later, Android wear watches, Apple watch, etc.

**Omnipod Tubless Insulin Pump**
- Built-in 200-unit insulin reservoir, angled infusion set
- Weighs <30 grams
- A Tubeless, Waterproof*, Bluetooth®-Enabled Pod
- Bluetooth®-Enabled Blood Contour Next One Glucose Meter
- Color Touch-Screen Personal Diabetes Manager
- **NEW Omnipod Dash™ System**
  - Mobile applications for quick/easy access to Smartphone Personal Diabetes Manager
  - Ability to share status information by Smartphone with up to 12 people.
  - **Today View Widget** allows single-screen viewing of CGM and insulin delivery information on iOS mobile device.
- Available early 2019
Pump Technology Options

MinMed 630G + Guardian™ Sensor 3

SmartGuard® Technology

- **High Limit**
  - The high limit can be set from 100 to 400 mg/dL.

- **Low Limit**
  - This can be set from 60 to 90 mg/dL.

- **Alert before High**
  - Receive an alert any time the sensor glucose is predicted to reach preset high limit.

- **Time before High**
  - Determines number of minutes (5-30) before reaching high limit that patient receives an Alert.

- **Alert on high**
  - Receive an alert any time sensor glucose reaches or exceeds high limit.

- **Alert before Low**
  - Receive an alert when sensor glucose is predicted to reach low limit in 30 minutes.

- **Alert on Low**
  - Receive an alert when sensor glucose reaches/falls below preset low limit.

- **Suspend on Low**
  - Pump temporarily stops delivering insulin when sensor glucose reaches/falls below pre-set low limit.

MinMed 630G + Guardian™ Link 3 Transmitter

Alert Before Low & High Features

![Graph showing glucose levels and alert thresholds]

- **Prompt action may avoid low or reduce duration**
  - *A confirmatory fingerstick test is required prior to taking action.

Graph is approximate.
Threshold Suspend/Suspend-On-Low

Threshold Suspend

- Automatically suspends all insulin delivery when sensor values reach or fall below Suspend Threshold
- Suspend Threshold is set based on your needs
Pump Technology Options

MiniMed 670G System: WORLD’S FIRST HYBRID CLOSED LOOP SYSTEM

- **SmartGuard® HCL technology (Guardian® Sensor 3) offers 3 levels of personalization:**
  - **Predictive Alerts** → Alert Before High, Alert Before Low and Alert On Low options
  - **Suspend Features** → **BEFORE Low → ON Low:**
    - Suspend **BEFORE LOW**: Proactively avoids lows/rebound highs by stopping insulin 30 minutes before a pre-selected low limit is reached, then automatically resumes insulin once glucose levels recover all without bothersome alerts.
    - Suspend **ON LOW**: Pump temporarily stops delivering insulin when sensor glucose reaches/falls below pre-set low limit.
  - **Auto Mode**: automatically adjusts basal insulin delivery every 5 minutes based upon glucose level to maintain target range of 120 mg/dL, for 24-hours.
Smart Guard™ Technology: Suspend-Before-Low
Pump or MDI: Which Is Better?

CSII offers advantages over MDI therapy, but .....

• Properly selecting pump candidates and adequately training them is key to optimal outcomes.

• As technology continues to advance new challenges and opportunities for patients and practitioners will predictably arise.

• **No better time than the present** to become familiar with pump technology and related operational skill set, as the number of patients with **both Type 1 and Type 2 Diabetes** desiring and using pumps will continue to grow.