MODERN DIABETES CARE: DON’T FORGET ABOUT INSULIN!

CA-AACE Hot topics in Diabetes
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Herbert I. Rettinger, M.D., FACE
President, Endocrinology Medical Group of OC, Inc
Clinical Professor of Medicine/Endocrinology
Past President, CA-AACE
DISCLOSURES

• Speaker - Sanofi Aventis

• Many of my slides were taken from a prior talk by Dr. Michael Bush - with his permission.
Natural History of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Obesity</th>
<th>IFG*</th>
<th>Diabetes</th>
<th>Uncontrolled hyperglycemia</th>
</tr>
</thead>
</table>

**Glucose (mg/dL)**
- 350
- 300
- 250
- 200
- 150
- 100
- 50
- 0

**β-Cell Function (%)**
- 150
- 100
- 50
- 0

**Active Treatment**
- Glucose
- Fasting Glucose
- Insulin Resistance
- Insulin Level

**Oral Agents, Injectables**

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*IFG = impaired fasting glucose

Adapted from International Diabetes Center (IDC) Minneapolis, Minnesota
Patient A.J.

- A.J. is a 56 year old hospital administrator. Her mother and father, both born in Mexico, had Type 2 DM and after gaining 15 lbs in the past 3 years, she started worrying about her risk of being “Pre-Diabetic.”

- A1c 6.3%
- FBS 115 mg/dl
Diabetes Prevention Program

n = 3224 Subjects with IGT
Cumulative Diabetes Incidence

Cumulative incidence of diabetes (%)

Years

Placebo
11%/yr

Metformin
7.8%/yr
↓31%

Lifestyle
4.8%/yr
↓58%

Diabetes Prevention Program

Patient A.J.

- She stays on metformin 850 mg bid for the next 3 years. Unfortunately, despite trying to lose weight, she gains 8 lbs and appears for a routine visit with a FBS of 168 mg/dl.
- Further tests show:
  - A1b 8.1%
  - TC 277  TG 301  HDL 26  LDL 146
  - Creatinine 1.5
  - Uma 66 mg/g Cr
- You add another agent
• Over the next few years, limited by her insurance and her unwillingness to take injections or “newer medicines,” the patient has been placed on:
  • Metformin 1000 bid
  • Pioglitazone 30 mg
  • Glimepiride 4 mg ½ tab BID ac
• She made little in diet changes
• DPP4i didn’t help and SGLT2i caused symptoms of vaginitis
• A1c had fallen to 6.8%, but is now up to 7.4% again.
• You think about insulin!
Patient A.J.

- Despite substituting an injectable GLP-1RA for the Sitagliptin, her A1c rises to 8.4%.
- *Is Insulin is the right choice now?*
When To Start Insulin in T2DM

— When combination OAD* inadequate,
— Side effects of OAD unacceptable,
— Patient wants more flexibility,
— Special circumstances (i.e. Steroids, infection, pregnancy),
— Patient with hepatic or renal disease,
— Patient with CAD, ↑ TG.

*OAD- oral anti-diabetic agents (or Other anti-diabetic agents)
PPG Contributes to 50% or More of Overall A1C When A1C Is 8.4 or Below

A1C Goal: Increasing Contribution of PPG as A1C Improves

INSULIN TACTICS

The Ideal Basal Insulin . . .

• Mimics normal pancreatic basal insulin secretion
• Long-lasting effect - around 24 hours or >
• Smooth, peakless profile
• Reproducible and predictable effects
• Reduced risk of nocturnal hypoglycemia
• Once-daily administration for convenience
• Able to reduce Hepatic Glucose Production
INSULIN TACTICS
Starting With Basal Insulin
Advantages

• 1 injection with no mixing
• Slow, safe, and simple titration
• Low dosage
• Limited weight gain
• Effective improvement in glycemic control
• Starting Dose = 1/10 body weight in pounds
  — i.e. Wt=160 pounds, starting dose = 16 units (Start low, go slow)
4T STUDY: Adding Insulin to Gain Control

708 T2DM on dual oral agents

First Phase

- Add biphasic insulin* twice a day
- Add prandial insulin* three times a day
- Add basal insulin* once (or twice) daily

Age (years) | 61.7  
Diabetes duration (years) | 9  
Body mass index (kg/m²) | 30.2  
A1C (%) | 8.6

4T STUDY: Glucose Profiles

- Biphasic
- Prandial
- Basal

ADDING ONCE A DAY BASAL INSULIN TO IMPROVE DIABETES CONTROL

BASAL TYPES

— Glargine
  ❖ U-100
  ❖ Lantus
  ❖ Basaglar ("bio-similar")
  ❖ U-300
  ❖ Toujeo

— Detemir
  ❖ Levemir

— Degludec
  ❖ Tresiba (U-100, U-200)
ADDING ONCE A DAY BASAL INSULIN TO IMPROVE DIABETES CONTROL

**BASAL TYPES**

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  - Levemir
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  - Tresiba (U-100, U-200)

**TIMING & TITRATE**

Levemir is generally given hs, sometimes twice a day in equal doses

Glargine insulins are usually given hs or in AM

Degludec is given any time, may be variable

**BUT the dose is always adjusted to control the FASTING BLOOD SUGAR**
STARTING BASAL INSULIN
Titrating To The Right Dose

• ALGORITHM 1
  — Start with 10 units at bedtime.
  — Physician or staff increases doses weekly by 2u (120-140 mg/dl) or 4u (140 - 180 mg/dl) or 6u (> 180 mg/dl)

• ALGORITHM 2
  — Start with a calculated dose of units (FBS in mg/18)
  — Patient increases dose daily by 2u if FBS > 120 mg/dl

• Prandial treatment (pills or prandial insulin) was either continued at the onset or could be added at week 12

DAVIES: Diabetes Care (2005), 28: 1282–1288
Mean FBG Compared with Mean Insulin Glargine Dose (IU) in Per-Protocol Population Receiving Algorithm 1 or 2

What are the differences among the basal insulins?
U-100 Glargine Equivalent (Basaglar) vs U-100 Glargine (Lantus) in Insulin-naive Patients With T2DM

- Equivalent change in A1C (−1.48% vs −1.54%, LY vs GLAR, \( P = \text{NS} \))
- Equivalent insulin dose (0.42 vs 0.44 U/kg, LY vs GLAR, \( P = \text{NS} \))
- Equivalent weight gain (2.0 vs 2.2 kg, LY vs GLAR, \( P = \text{NS} \))

\( \text{a} \) n = 221 (LY), n = 236 (GLAR), mean age = 58 y, duration of diabetes = 11 y, BL A1C = 8.4–8.5%, BL wt = 89–91 kg, BL BMI = 32 kg/m\(^2\); \( \text{b} \) plasma glucose ≤ 70 mg/dL or sign or symptom of hypoglycemia; \( \text{c} \) between bedtime and waking; \( \text{d} \) requiring assistance, baseline to month 6.

U-100 Glargine Equivalent (Basaglar) vs U-100 Glargine (Lantus) in Insulin-naive Patients With T2DM

Overall Hypoglycemia

Nocturnal Hypoglycemia

Severe Hypoglycemia

- Equivalent change in A1C (–1.48% vs –1.54%, LY vs GLAR, P = NS)
- Equivalent insulin dose (0.42 vs 0.44 U/kg, LY vs GLAR, P = NS)
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INSULIN GLARGINE U-300 (Toujeo)

- Concentrated insulin with smaller depot surface area\(^a\)
- Flatter, prolonged PK and PD profiles
- Onset is 6 h, half-life is \(~23\) h, duration 4 d\(^c\)
  - FDA-approved February 25, 2015
GLARGINE U-300 vs U-100
Edition Studies Pooled Analysis

- Comparable improvement in glycemic control
- Significantly lower confirmed (< 70 mg/dL) and/or severe hypoglycemia at
- Weight gain was
  - U300 (0.51 kg)
  - U300 (0.85 U/kg)

12% increase in

Upon injection, phenol diffuses quickly and phenol links up via single side-chain contacts. Long multi-hexamer chains assemble. Zinc diffuses slowly causing individual hexamers to disassemble, releasing monomers. Monomers are absorbed from the depot into the circulation.


INSULIN DEGLUDEC (Tresiba)

desB30 insulin
- Acylated (16 carbon fatty acid chain) at LysB29

PK
- Onset: 2 to 4 h
- Half life: ~25 h
- Duration of action: ≥ 42 h
- Steady state: ~3 to 4 d
- Detectable: ≥ 5 d
- 36-h stable level

FDA approval in 2015

DEGLUDEC vs GLARGINE U-100
Insulin Naïve Patients at 1 Year

- Similar HbA₁c and weight changes
  - -1.1% vs -1.2% (P = .40)
  - 2.4 kg vs 2.1 kg (P = .28)
- Similar overall hypoglycemia
  - 1.5 vs 1.9 events/y (NS)
- Lower nocturnal hypoglycemia with degludec (graph)

*1030 patients with T2D; †Once daily, U100; ‡Hypoglycemia defined as plasma glucose < 56 mg/dL or severe per ADA definition; §Nocturnal, occurring between 0100 h and 0559 h.
DEGLUDEC VARIABLE DOSING

*687 patients with T2D in a 26-wk, randomized, open-label, parallel-group, treat-to-target trial; 
†Dosing schedule provided for a maximum dosing interval of 40 h and a minimum dosing interval of 8 h; 
‡Morning defined as time period from waking up to first meal of day; 
§Evening defined as time period from start of evening meal to bedtime.

PENS FOR THE NEW BASAL INSULINS

**Glargine pens**
- **U300 pen**
  - Delivers ≤ 80 U/injection in increments of 1 U

**Degludec pens**
- **U100 pen**
  - Delivers ≤ 80 U/injection in increments of 1 U
- **U200 pen**
  - Delivers ≤ 160 U/injection in increments of 2 U

- Pens do not require calculation; simply dial to the number of units prescribed
- For titration, recommended time between dose increases is 3 to 4 d
### Summary

#### BASAGLAR
- 100 units/mL
- Biologically equivalent to U-100 glargine
- Compared with U-100 glargine:
  - Equally effective
  - *Equivalent* hypoglycemia
  - Equivalent weight gain

#### TOUJEO
- 300 units/mL
- Same molecule as U-100 glargine but more concentrated
- Compared with U-100 glargine:
  - Equally effective
  - *Less* hypoglycemia
  - Equivalent weight gain

#### TRESIBA
- 100 or 200 units/mL
- Novel molecular configuration
- Compared with U-100 glargine\(^a\):
  - Equally effective
  - *Less* hypoglycemia\(^b\)
  - Equivalent weight gain

- **Ultralong-acting basal insulins** have a *flatter time-action profile*, with less glycemic variability, and may be less likely to cause hypoglycemia than first-generation insulin analogues.

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\(^a\) Significantly less overall hypoglycemia in insulin-naive patients.

\(^b\) Significantly less nocturnal hypoglycemia in insulin-naive patients.
The patient is started on bedtime basal insulin, starting on 10 units.

Her glimepiride is stopped.

Her pioglitazone is stopped.

Metformin is continued.

She is advised to increase her dose by 2 units every 2-4 days until her FBS is under ...

She has office visits every 2-4 weeks, encouraging and guiding her.

After three months, her FBS is fine, but A1c is still 7.2%.
LIKELIHOOD OF REACHING A1C <7% AFTER STARTING BASAL INSULIN

Percentage of patients who reached A1c ≤7% during each 3-month interval from 3 to 24 months after first BI prescription among those who have not achieved A1c ≤7% until beginning of interval and were still on BI treatment and remained in the Explorys system (n=5936)

- 1169 (19.7%) patients achieved glycemic control in the first 6 months.
- 431 (10.9%) achieved glycemic control in the next 3 months.
- 131 (5.7%) in the following 3 months.
- 31 (1.9%) achieved glycemic control between 12-15 months.
- 18 (3.1%) between 15-18 months.
- 12 (3.1%) between 18-21 months.
- 8 (3.5%) between 21-24 months.

Patients reaching glycemic control:

<table>
<thead>
<tr>
<th>Time on therapy (months)</th>
<th>Patients reaching glycemic control</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–6</td>
<td>1169 (19.7%)</td>
</tr>
<tr>
<td>6–9</td>
<td>431 (10.9%)</td>
</tr>
<tr>
<td>9–12</td>
<td>131 (5.7%)</td>
</tr>
<tr>
<td>12–15</td>
<td>31 (1.9%)</td>
</tr>
<tr>
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<td>12 (3.1%)</td>
</tr>
<tr>
<td>21–24</td>
<td>8 (3.5%)</td>
</tr>
</tbody>
</table>
As Patients Get Closer to Goal, the Need to Manage PPBS Increases

Increasing Contribution of PPG as A1C Improves

Adapted from Monnier L, Lapinski H, Collette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of Type 2 diabetic patients: variations with increasing levels of HBA(1c). *Diabetes Care.* 2003;26:881-885.
When Basal Is Not Enough

- Add basal insulin and titrate
- Basal plus GLP-1 RAs
- Lifestyle changes plus various Medications
WHAT ABOUT ADDING A GLP-1 ANALOG?
Basal Insulin and GLP1-RA in One Injection!
COMBINING GLP1-RA WITH BASAL INSULIN
When Basal Is Not Enough

ADD PRANDIAL INSULIN

Basal
Add basal insulin and titrate

Basal plus
GLP-1 RAs

Lifestyle changes plus various Medications
CONTROL POST-PRANDIAL AS WELL AS FASTING BLOOD SUGAR

The postprandial state lasts 4 hours immediately following the start of a meal. Cumulative duration of postprandial states is approximately 12 hours (a full half-day).

When Basal Is Not Enough

Basal
Add basal insulin and titrate

Basal plus
Add prandial insulin at one meal

Basal plus GLP-1 RAs

Lifestyle changes plus various Medications
“BASAL-PLUS”
ADDING MEAL INSULIN TO ONLY ONE MEAL

When Basal is Not Enough

- Basal bolus
  Add prandial insulin at each meal

- Basal plus
  Add prandial insulin at one meal

- Basal
  Add basal insulin and titrate

- Basal plus GLP-1 RAs

- Lifestyle changes plus various Medications
BASAL-BOLUS INSULIN STRATEGY
BASAL/GLP1RA vs BASAL/BOLUS

Billing LK et al. Diabetes Care Publish Ahead of Print, published online February 26, 2018
# Current Options Among Insulin Products

<table>
<thead>
<tr>
<th>Type</th>
<th>Basal Insulins</th>
<th>Prandial Insulins</th>
<th>Premixed Insulins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human(^1)</td>
<td>• U-100 NPH</td>
<td>• U-100 regular human insulin (RHI) • U-500 RHI • Technosphere inhaled insulin</td>
<td>• U-100 70/30 RHI</td>
</tr>
<tr>
<td>Analogue(^1)</td>
<td>• U-100 glargine equivalent(^a) • U-100 detemir • U-100 degludec • U-200 degludec • U-300 glargine</td>
<td>• U-100 glulisine • U-200 lispro</td>
<td>• U-100 70/30 degludec/aspart</td>
</tr>
</tbody>
</table>

### Even Newer?

- All recently approved insulins are *only* available in pens\(^1,e;\) red text denotes which insulins are *only* available in prefilled pens.
- Analogue insulins are associated with less hypoglycemia than human insulins, although these differences are not always statistically significant\(^2\).

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\(^a\) In the US, U-100 glargine equivalent is not approved as a biosimilar product.\(^3\)

Humalog U-200® (Insulin lispro U-200)

- First concentrated ultra-rapid insulin
- PK/PD equivalent to Humalog U-100
- Pen:
  - Contains twice as much insulin
  - Dosed in 1 unit increments
  - Single dose still capped at 60 units
- 1:1 dose conversion with other bolus insulin

“AFREZZA” – Inhaled Insulin
U-500 REGULAR INSULIN

The U-500 syringe can dose up to 250 units (0.5 mL) of U-500 insulin per injection. Each line on the syringe corresponds to 5 units of U-500 insulin.

Guide for Dosing U-500 Insulin

<table>
<thead>
<tr>
<th>If the patient needs</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 200 U/day</td>
<td>U-100 insulin</td>
</tr>
<tr>
<td>200-300 U/day</td>
<td>b.i.d. regimen of U-500 insulin</td>
</tr>
<tr>
<td>300-750 U/day</td>
<td>t.i.d. regimen of U-500 insulin</td>
</tr>
<tr>
<td>750-2,000 U/day</td>
<td>t.i.d. regimen of U-500 insulin plus a fourth dose at bedtime</td>
</tr>
<tr>
<td>More than 2,000 U/day</td>
<td>insulin pump</td>
</tr>
</tbody>
</table>

Source: National Institutes of Health
“Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant, like the opening of aqueducts. Life is short, unpleasant and painful, thirst unquenchable, drinking excessive, and disproportionate to the large quantity of urine, for yet more urine is passed......the patients are affected by nausea, restlessness and burning thirst, and within a short time they expire.”

Aretaeus of Cappadocia
Insulin discovered......
1921
Banting and Best

& Marjorie

Banting & Best
HYPOGLYCEMIA

• When you start insulin, be sure to review possibility of low blood sugar.
• Need to carry fast sugar food.
• DOCUMENT!!
“Symptoms of Hypoglycemia Are Like Falling in Love For the First Time!!!”

• You get nervous and jittery,
• You get hot and sweaty,
• Your heart starts beating rapidly,
• And lastly –
• You want to say something intelligent, but only gibberish comes out!!

H. Rettinger, M.D, FACE.
TAKE HOME POINTS

• NPH is superseded by synthetic analogues: insulin glargine, detemir, degludec which provide a peakless profile, better reproducibility and consistency → lower risk of hypoglycemia

• Insulin pens. Give first injection in office.

• Diabetes is a progressive disease. Many will need insulin.

• Be aware of cultural taboos and misconceptions.

• Start with a simple regimen and build as needed.
WE ARE GETTING CLOSER TO GOAL!!!

THANK YOU FOR YOUR KIND ATTENTION