Basal/Bolus Insulin: Better Pattern Control in Type 2 Diabetes

Kim L Kelly, PharmD, BCPS, FCCP, CDTC, CPC, CEC
What we’ll cover

• Basal Insulin
  – Basal initiation
  – Basal alone vs. biphasic vs. prandial alone

• When basal isn’t enough
  – A1C control
  – Glycemic variability

• Methods of bolus initiation
  – Carbohydrate counting
  – Algorithm driven
  – Recommendations
Starting Insulin in People with T2DM
…back in the day

- After discovery of insulin various purifications and sources were used to make it easier to produce and administer
- Modifications were made to extend its activity
- Recombinant production of human insulin lessened some of the immunological effects
- Still…insulin therapy was delayed until ‘all other options were tried’ for T2DM
  - Insulin initiation was ‘bedtime NPH’
- Development of insulin analogs resulted in various products with longer or shorter activity
Original Treat to Target Trial
Basal Insulin Titration

- Physician titration of either NPH or glargine insulin performed weekly according to predefined algorithm
- Approximately 60% of patients achieved A1C < 7.0%

“Systematically titrating bedtime basal insulin added to oral therapy can safely achieve 7% HbA1c in a majority of overweight patients with type 2 diabetes with HbA1c between 7.5 and 10.0% on oral agents alone. In doing this, glargine causes significantly less nocturnal hypoglycemia than NPH, thus reducing a leading barrier to initiating insulin”.

Riddle MC, et al Diabetes Care 2003;26:3080
Self-Titration of Basal Insulin

Levemir TTT
Treat-to-Target
LANMET
Insight
GOAL-A1C
GOT
AT-LANTUS
H0t
INITIATE
GWAA
ALOHA
...and more
Basal Insulin Starts
“Do it Yourself” Approach

Patient Directed Basal Insulin Titration

- **Starting dose per package insert 10 units**
  - Treat to Target Trial “2-4-6-8” algorithm
    - Add 2, 4, 6, or 8 units of glargine weekly until mean FBG=100
  - ATLANTUS Study “3-2-1” algorithm
    - Add 2 units glargine every 3 days until mean FBG=100

- **Results**
  - No compromise in safety
  - Better outcomes
  - Patient satisfaction increased as control improved

Schaefer C, Insulin 2007; 2:154
Davies M, Diabetes Obesity & Metabolism 2008;10:387
Khunti K, Diabetes Obesity & Metabolism 2013;15:690
The 4-T Study

Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes

Rury R. Holman, M.B., Ch.B., F.R.C.P., Kerensa I. Thorne, M.Sc.,
Andrew J. Farmer, D.M., F.R.C.G.P., Melanie J. Davies, M.D.,
Joanne F. Keenan, B.A., Sanjoy Paul, B.D.S., and Jonathan

• Three-arm trial in 708 patients with type 2 diabetes from 58 UK and Irish centres
• Evaluating addition of three different analogue insulin regimens to dual oral antidiabetic therapy
• Open-label randomization to:
  − Twice a day biphasic insulin (NovoMix 30)
  − Three times a day prandial insulin (NovoRapid)
  − Once a day basal insulin (Levemir) before bed, with a morning injection added if necessary
Distribution of HbA1c Values

Proportion <6.5%
- Biphasic: 17.0%
- Prandial: 23.9%, \( p=0.08 \) vs. biphasic
- Basal: 8.1%, \( p=0.001 \) vs. biphasic, <0.001 vs. prandial

Proportion <7.0%
- Biphasic
- Prandial: 48.7%
- Basal: 27.8%

--- At baseline

Hypoglycemia (≥ Grade 2)* Over One Year

Mean at 1 year (events/patient/year)

- Biphasic: 5.7
- Prandial: 12.0, *p*<0.002 vs. biphasic
- Basal: 2.3, *p*=0.01 vs. biphasic, *p*<0.001 vs. prandial

*(symptoms with BG <3.1 mmol/l [56 mg/dL])*
**One Year Summary**

**Biphasic Insulin**
- 2 injections a day; 2 capillary BGs for titration
- HbA1c lowering equivalent to Prandial insulin
- More weight gain & hypoglycemia than Basal insulin but less for both than Prandial insulin

**Prandial Insulin**
- 3 injections a day; up to 7 capillary BGs for dose titration
- HbA1c lowering equivalent to Biphasic insulin
- More weight gain & hypoglycemia than Prandial or Basal

**Basal Insulin**
- 1 injection a day; 2 capillary BGs for titration
- More patients require a second insulin than Biphasic or Prandial
- Less HbA1c lowering than Biphasic or Prandial insulin
- Less weight gain & hypoglycemia than Biphasic or Prandial

For the full 3-year trial results, see: Holman RR, et al. New Engl J Med 2009;361:1736
So How Good is Basal Insulin Alone in T2DM?
Fasting & 2-Hour Post Challenge Plasma Glucose (PCPG)

- Both FPG and 2-hour PCPG increase as HbA1c increases
- 2-hour PCPG increases at a rate 4 X greater than FPG accounting for a greater proportion of the HbA1c value

Worle H. et al Arch Intern Med 2004:164;1927
Post Prandial Glucose (PPG)

- Loss in PPG control precedes worsening of overall control of type 2 diabetes
- PPG elevations may not be evident from changes in HbA1c

Monnier L, Colette C. Diabetes Care 2007; 30:263
In many studies, glycemic variability is an independent risk factor for a variety of diabetes complications!
Self-Titration of Basal + Bolus Insulin

PREFER
FULL-STEP
PREDICTIVE 303
ELEONOR
Initiateplus
PREDICTIVE ATLAS
Di@log
AUTONOMY
OPAL
Extra-STEP
ALOHA
...and more
In a review of 15 randomized controlled trials involving over 4,000 patients reviewing the outcomes of basal/bolus therapy with biphasic insulin therapy, there was a slightly more favorable HbA1c response with basal/bolus therapy with comparable rates of hypoglycemia for both modes of therapy.

Carbohydrate Counting?
Challenges of carbohydrate counting…

Self-Efficacy Links Health Literacy and Numeracy to Glycemic Control

Chandra Y. Osborn, PhD MPH1,2, Kerri Cavanaugh, MD MHS2,3, Kenneth and Russell L. Rothman, MD MPP1,2
1Division of General Internal Medicine
University of Washington, Seattle, WA
2Division of Diabetes, Endocrinology, and Nutrition
University of Washington, Seattle, WA
3Diabetes, Endocrinology, and Metabolism Division
University of Washington School of Medicine, Seattle, WA

Numeracy and Literacy Independently Predict Patients’ Ability to Identify Out-of-Range Test Results

Monitoring Editor: Gunther Eysenbach
Reviewed by Rebecca Britt and Dean Schiller

Numeracy and Dietary Intake in Patients With Type 2 Diabetes

Michael E. Bowen, MD, MPH, Kerri L. Cavanaugh, MD, MHS, Kathleen Wolff, MSN, BC-ACNS, BC-FNP, Dianne Davis, RD, LDN, CDE, Becky Gregory, MS, RD, LDN, CDE, and Russell Rothman, MD, MPP
University of Texas Southwestern Medical Center, Dallas, Texas
University School of Medicine, Nashville, Tennessee

1. J Health Commun 2010;15(suppl 2) 146-158

N=383; T1DM & T2DM; 3 clinics

- A significant relationship between health literacy, general numeracy and diabetes self-efficacy
- 31% had <9th grade literacy skills
- 69% had <9th grade numeracy skills
- Majority were on insulin

N=383; T1DM & T2DM; 3 clinics

- Health literacy and numeracy are each associated with greater diabetes self-efficacy
- Greater diabetes self-efficacy associated with lower HbA1c levels

N=383; T1DM & T2DM; 3 clinics

- Patients with lower numeracy consumed higher % of calories from carbohydrates
- Low numeracy was associated with inaccurate dietary reporting
Is there an alternative to carbohydrate counting?
Self-Titration of Insulin

Adjust to Target in Type 2 Diabetes

Comparison of a simple algorithm with carbohydrate counting for adjustment of mealtime insulin glulisine

RICHARD M. BERGENSTAL, MD
MARY JOHNSON, RN, CDE
MARGARET A. POWERS, PHD, RD, CDE
ALAN WYNNE, MD

ALEXANDRA VLAJNIC, MD
PRISCILLA HOLLANDER, MD
MARC RENDELL, MD

Table 1—Insulin glargine and insulin glulisine dose adjustment based on pattern of mealtime blood glucose values for the past week

<table>
<thead>
<tr>
<th>Mean of last 3-day fasting SMBG mg/dl</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;180 mg/dl</td>
<td>Increase 8 units</td>
</tr>
<tr>
<td>140–180 mg/dl</td>
<td>Increase 6 units</td>
</tr>
<tr>
<td>120–139 mg/dl</td>
<td>Increase 4 units</td>
</tr>
<tr>
<td>95–119 mg/dl</td>
<td>Increase 2 units</td>
</tr>
<tr>
<td>70–94 mg/dl</td>
<td>No change</td>
</tr>
<tr>
<td>&lt;70 mg/dl</td>
<td>Decrease by the same number of units as insulin glulisine increase that titration week or up to 10% of total insulin glargine dose</td>
</tr>
</tbody>
</table>

Bergenstal RM et al Diabetes Care 2008;31:1305-1310
Self Titration of Insulin  
- Outcomes -

- One of the first studies to evaluate the use of carbohydrate counting in patients with type 2 diabetes
- Using a simple algorithm to adjust mealtime insulin glulisine each week based on SMBG patterns was as effective as adjusting mealtime insulin using insulin-to-carb ratios
- Both approaches yielded a reduction of about 1.5% in HbA1c; no significant differences in mean HbA1c change or % patients achieving HbA1c goals

Bergenstal RM et al  
Diabetes Care  2008;31:1305-1310
Current ADA Recommendations

- Published annually by the American Diabetes Association (ADA)
- Treatment recommendations developed jointly with the European Association for the Study of Diabetes (EASD)
<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin</th>
<th>Healthy eating, weight control, increased physical activity, and diabetes education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td></td>
<td>high</td>
</tr>
<tr>
<td>Hypo risk</td>
<td></td>
<td>low risk</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td>neutral / loss</td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td>GI / lactic acidosis</td>
</tr>
<tr>
<td>Costs</td>
<td></td>
<td>low</td>
</tr>
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If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Dual therapy†</th>
<th>Metformin</th>
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</tr>
<tr>
<td>Hypo risk</td>
<td>moderate risk</td>
<td>low risk</td>
<td>intermediate</td>
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<td>low risk</td>
<td>high</td>
</tr>
<tr>
<td>Weight</td>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>neutral</td>
<td>gain</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>Side effects</td>
<td>hypoglycemia</td>
<td>edema, HF, fxs</td>
<td>GU, dehydration</td>
<td>GI</td>
<td>hypoglycemia</td>
<td>variable</td>
</tr>
<tr>
<td>Costs</td>
<td>low</td>
<td>low</td>
<td>high</td>
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If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

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<tr>
<th>Triple therapy</th>
<th>Metformin</th>
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<td>high</td>
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If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-I:

<table>
<thead>
<tr>
<th>Combination injectable therapy†</th>
<th>Metformin</th>
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Insulin Transition Algorithm ADA/EASD

Basal insulin
(usually with metformin +/- other non-insulin agent)
- Start: 10 U/day or 0.1–0.2 U/kg/day
- Adjust: 10–15% or 2–4 U once-twice weekly to reach FBG target.
- For hypo: Determine and address cause; dose by 4 U or 10–20%.

If not controlled after FBG target is reached (or if dose >0.5 U/kg/day), treat PPG excursions with mealtime insulin. (Consider initial GLP-1-RA trial.)

Add 1 rapid insulin* injection before largest meal
- Start: 4 U, 0.1 U/kg, or 10% basal dose. If HbA1c<8%, consider basal by same amount.
- Adjust: dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
- For hypo: Determine and address cause; corresponding dose by 2–4 U or 10–20%.

Add ≥2 rapid insulin* injections before meals (“basal–bolus”)
- Start: 4 U, 0.1 U/kg, or 10% basal dose/meal.
  - If HbA1c<8%, consider basal by same amount.
  - Adjust: dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
  - For hypo: Determine and address cause; corresponding dose by 2–4 U or 10–20%.

Change to premixed insulin* twice daily
- Start: Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.
- Adjust: dose by 1–2 U or 10–15% once-twice weekly until SMBG target reached.
- For hypo: Determine and address cause; corresponding dose by 2–4 U or 10–20%.

If not controlled, consider basal–bolus.
Current AACE Recommendations

• Updated by AACE/ACE for 2015
• Algorithms for Pre-diabetes, Glycemic Control, Intensifying Insulin, Cardiovascular Risk Factors, Diabetes Medication Profiles
Post Prandial Targets

ADA = 180 mg/dL

IDF = 160 mg/dL

AACE/ACE = 140 mg/dL
316 patients with T2DM
- Poorly controlled on glargine +/- OADs (HbA1c > 6.5% and FPG > 121 mg/dL)

A single injection of glulisine added either at breakfast or at main meal
- 28% got control with breakfast dose
- 34% got control with main meal dose

Hypoglycemia low and comparable between groups

Mean insulin dose at end of 24 weeks
- Breakfast group  11.2 Units
- Main meal group  12.0 Units

• Patients who achieved HbA1c < 6.5%
  – Total 30.7%
  – Breakfast injection 27.8%
  – Main meal injection 33.8%

• Patients who achieved HbA1c < 7.0%
  – Total 44.1%
  – Breakfast injection 36.5%*
  – Main meal injection 52.2%*

* Statistically significant difference between groups

**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

**Intensify** (prandial control)
- Add GLP-1 RA or SGLT-2i or DPP-4i
- Add Prandial Insulin
  - TDD: 0.3–0.5 U/kg
  - 50% Basal Analog
  - 50% Prandial Analog
  - Less desirable: NPH and regular insulin or premixed insulin

**Glycemic Control Not at Goal**
- 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 basal insulin started (basal analogs preferred to NPH)

**Glycemic Goal:**
- <7% for most patients with T2DM; fasting and premeal 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

**Insulin titration every 2–3 days to reach glycemic goal:**
- Increase prandial dose by 10% for any meal if the 2-hr postprandial or next premeal glucose is > 180 mg/dL
- Premixed: Increase TDD by 10% if fasting/premeal BG > 180 mg/dL
- If fasting AM hypoglycemia, reduce basal insulin
- If nighttime hypoglycemia, reduce basal and/or pre-supper or pre-eveing snack short/rapid-acting insulin
- If between-meal daytime hypoglycemia, reduce previous premeal short/rapid-acting insulin
A Bolus Insulin Titration Algorithm

**Patient Adjusted Bolus Insulin:** Bolus schedule based on Pre-meal glucoses for the meal following the meal where the bolus was given. For example the need to modify the pre-breakfast bolus was determined by the pre-lunch glucose reading the previous day as follows:

Daily titration schedule:

- If yesterday’s pre-lunch glucose was $>114\text{mg/dL}$
  - Add $1$ unit to the breakfast bolus today
- If yesterday’s pre-lunch glucose was $85–114\text{mg/dL}$
  - No additional insulin to the breakfast bolus today
- If yesterday’s pre-lunch glucose was $56–84\text{mg/dL}$
  - Decrease today’s breakfast bolus by $1$ unit
- If yesterday’s pre-lunch glucose was $<56\text{mg/dL}$
  - Decrease today’s breakfast bolus by $2$ units

Edelman S, et al. **AUTONOMY:** The First Randomized Trial Comparing Two Patient-Driven Approaches to Initiate and Titrate Prandial Insulin Lispro in Type 2 Diabetes. Diabetes Care 2014;37:2132
AUTONOMY Trial: Adjusting Mealtime Insulin at Every Meal

AUTONOMY Trial: Adjusting Mealtime Insulin at Every Meal

Study A (N=528)

Study B (N=578)

New Developments in Insulin Therapy

• Increased duration basal insulins
  – Insulin glargine 300 U (Toujeo®)
  – Insulin degludec (Tresiba®)*
• Inhalation insulin (Afrezza®)
• Insulin Pumps in Type 2 diabetes
  – ‘Traditional, durable’ insulin pumps (Opt2Mise trial)
  – Patch pumps
• Adding GLP-1 Agonists

* Not Approved by FDA
Recommendations
Recommendations for Insulinization

- Emphasize lifestyle intervention; minimize weight gain and PPG excursions
- Provide each patient with a written insulin protocol as a point of reference
- Allow patients to actively titrate their insulin dose
- Teach patients how to identify and appropriately manage hypoglycemia
- When initiating basal insulin, use 0.2 U/kg/day as the starting dose
- If not controlled after FPG target is reached or if the total dose is >0.5 U/kg, treat PPG excursions with mealtime insulin
- If A1C level not at target after 3 months of basal + bolus, add second injection
- Patients on basal/bolus insulin therapy should use paired glucose testing to fine-tune their treatment regimens

Unger J. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2011:4 253
American Diabetes Association Diabetes Care 2015;38(Suppl. 1):S41–S48
Additional Recommendations…

• Keep it simple!
• Discontinue sulfonylureas and meglitinides before starting insulin
• Test the patient’s numeracy and understanding of the algorithm (“if your blood glucose is X, then how much [insulin] would you give yourself”)
• If possible ‘calendarize’ the algorithm (calendar software is inexpensive and adds one more level of simplicity)
  • Call the patient to see how things are going
  • Consider the cost of your regimen (work with a pharmacist to estimate costs of regimen and co-pays)
THANK YOU!