

Insulin Update 2017: Is Newer Better?

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Disclosures

- None

Learning Objectives

- Discuss insulin initiation in type 2 diabetes
- Present information on newly available insulins
- Compare effects and cost of different types of insulin

Case

- 62 yo woman, type 2 DM x 9 years, history of MI, dx with CHF last month- controlled
- Currently on metformin, glipizide, pioglitazone, liraglutide
- A1c 9.2%, BMI 42
- Normal renal, liver function
- Complains of fatigue

Question 1

- When starting basal insulin, which medication would you discontinue?
 - Metformin
 - Glipizide
 - Pioglitazone
 - Liraglutide

Question 2

- How much insulin would you start, and which would you choose?
 - .2u/kg, glargine since it has best A1c effect
 - 5units qhs, NPH since it has the best A1c effect
 - 10-15units qhs, NPH since it is the most cost effective
 - .1u/kg, NPH since it has the lowest risk of nocturnal hypoglycemia

Objectives

- Discuss insulin initiation in type 2 diabetes
- Present information on newly available insulins
- Compare effects and cost of different types of insulin

Key

- Analog: Modified human insulin to act faster or slower
- Short-acting:
 - Lispro: Humalog®
 - Aspart: Novolog®
 - Glulisine: Apidra®
 - Regular - Novolin®, Humulin®, Relion®
- Longer-acting :
 - NPH: Novolin®, Humulin®, Relion®
 - Glargine: Lantus®
 - Basaglar
 - U300: Toujeo®
 - Detemir: Levemir®
 - Degludec: Tresiba®
 - U100 and U200

Terminology

- Basal: “Covers” glucose levels between meals/overnight
 - Often what you start with in type 2 diabetes
- Bolus: “Covers” glucose levels that rise after eating meals/carbohydrate
- Distribution: generally, basal ~ 50% of total daily dose (TDD) and bolus ~ 50%
 - Generally, type 1 < 1u/kg; type 2 > 1u/kg as TDD

Considerations with Insulin

- Most effective for glucose control
- Risks:
 - Weight gain: 1-3 kg over 24 weeks Wallia A, Molitch M. JAMA 2014;311:2315
 - Hypoglycemia:
 - Severe hypoglycemia associated with 3.4-fold risk of death McCoy RG Diab Care 2012;35:1897
 - And recurrent episodes →hypo-unawareness
 - ↓ Quality of life, especially elderly
 - Fall-related fractures, car accidents and likely dementia

Options for insulin

Basal- Insulin	Onset	Peak	Duration	Cost
NPH	1-2 hrs	4-8 hrs	14-18 hrs	\$25-140
Detemir	1-4 hrs	4-6 hrs	12-20 hrs	\$240-370
Glargine	1-6 hrs	Flat/3 hrs	22-24 hrs/24-36 hrs (U300)	\$260-389
Degludec	1-9 hrs	10-12 hrs	42 hours	\$450-550
Bolus- Insulin	Onset	Peak	Duration	Cost
Regular	30-60 min	2-4 hrs	4-8 hrs	\$25-140
Aspart, lispro, glulisine	5-15 min	1-2 hrs	3-5 hrs	\$270-500
Inhaled	~ 15 min	~ 50 min	3 hours	\$320

Afrezza®

- Inhaled insulin
 - Pre-meal insulin
 - Max effect at 50min c/w 120 min with lispro
 - Duration of action 3 hours c/w 4 hours for lispro
 - Limited dosing flexibility
 - 4 and 8 unit cartridges
 - PFT monitoring needed
 - Contraindicated in asthma, COPD
 - Costly-\$320 for one kit



Yki-Jarvinen, Diab Care 2014;37:3235; Med Letter March 2015

New Basals- the "T's"

- Degludec (*Tresiba*®): 42 hours
 - Comes as U100 or U200
 - Transition 1:1 from long-acting (consider 20% decrease with BID or lower A1c)
 - Dosing flexibility (not given < every 8 hours)
- U300 Glargine (*Toujeo*®): 24-36 hours
 - Transition 1:1 from long-acting
 - Often requires dose ↑ 10-15% c/w regular glargine
 - Once daily, same time

Clinical Profiles

	Steady State	Max Dose	Units/pen	Pens/box	Cost
U300 Lantus	5 days	80 U	450	3 (1350)	\$350
U100 Degludec	2-3 days	80 U (1U adj)	300	5 (1500)	\$450
U200 Degludec	2-3 days	160 U (2U adj)	600	3 (1800)	\$560

My opinion on T-insulins

	Pros/considerations	Cons
Degludec	<ul style="list-style-type: none"> - Shift workers - Missed doses - BID long-acting - Variable BG 	<ul style="list-style-type: none"> - Cost, cost, cost
U300 Lantus	<ul style="list-style-type: none"> - Missed doses - BID long-acting - Variable BG 	<ul style="list-style-type: none"> - Cost, cost, cost - May require ↑ dosing

Adding Basal Insulin- ADA/EASD Algorithm

- Start 10U/day, or .1-.2units/kg/day
 - Bedtime or AM, depending on pattern/adherence
 - Usually with metformin +/- other agent
- Adjust 10-15% or 2-4U once/twice weekly to reach FPG target
 - Generally fasting goals of 80-130mg/dl
 - Maybe higher in certain populations
- For hypoglycemia: determine cause
 - ↓ dose by 4U or 10-20%

Trials that Compare Basal Initiation

- Treat to Target- NPH vs glargine ¹
 - **Equivalent** A1c with less nocturnal hypoglycemia in those using glargine
- Comparison of NPH and detemir ²
 - **Equivalent** A1c with less hypoglycemia (↓47%) and slightly less wt gain with detemir
- Degludec vs Glargine ³
 - **Equivalent** A1c, ↓ nocturnal hypos with degludec

1-Riddle MC, Diab Care 2003;26:3080; 2- Hermansen K, Diab Care 2006;29:1269; 3- Garber et al, Lancet 2012;379:1498

Algorithms are Aggressive

- Treat to Target trial:
 - Initial dose: 10units at bedtime (glargine or NPH)
 - Titrated weekly, based on mean fasting BG from prior 2 days:

➤ 180	+ 8 units
140-180	+ 6 units
120-140	+ 4 units
100-120	+ 2 units
< 56-72	- 2-4 units

Riddle MC et al, Diab Care 2003;26:3030

Managing Hypoglycemia



- Patient education
 - Symptoms, treatment, diet/carbohydrates
 - Rule of 15- 15 grams of fast-acting carb, recheck BG in 15 min
- Effect of exercise
- Adjustment of medication, monitoring
- Raising goals for glucose
- Avoidance of lows
 - Recovery of symptoms noted within 2 weeks

Seaquist ER et al, Diab Care 2013;36:1384

What about other agents when adding insulin?



- GLP1, DPP-4 SGLT-2, Metformin:
 - May reduce wt gain/dose needed
 - May worsen hypoglycemia risk
- Sulfonylurea (SU):
 - Better post-prandial BG, but ↑ hypoglycemia
 - Consider d/c when prandial insulin started
- TZDs:
 - Increased risk for edema with insulin

Wallia A, Molitch M. JAMA 2014;311:2315; Diab Care Supp 2017

Case continued



- Long discussion, started on Glargine (Lantus®) 15units qhs
 - Education with pharmacist, scheduled for follow up phone calls
- When she goes to the pharmacy, she is told she needs to substitute “generic glargine”

Basaglar®- Insulin Glargine

- Biosimilar in Europe, “follow on” in US
- 2 trials (ELEMENT 1 & 2)
 - Non-inferior, no difference in safety, weight, hypoglycemia
- Only available in pens (5/box)
 - Up to 80 units in single injection
- Cannot be substituted by pharmacies
- Cost: \$332.49 (Lantus®, \$389)

Blevins TC, Diab Obes Metab 2015; Rosenstock J, Diab Obes Metab 2015

Case continues...

- Substitutes Basaglar®, learns how to use insulin pens
- Titrates up over time, now on 45units at bedtime
- A1c dropped to 8.4% and holding
- What next?

BG Data

AM	Noon	Dinner	Hs
134	213	168	224
125	151	184	245
161	143	232	212
152	175	215	286
143	121	186	312

- Largest meal tends to be dinner, but not always
- Since starting insulin has gained 8#

When to add bolus?

- Basal should be 50% of total daily dose (TDD)
 - Estimate based on TDD 1-2u/kg/day
 - Consider if using > 60-70 units per day basal, or considering splitting glargine
 - A1c above goal
 - Start with largest meal

Add 1 rapid insulin injection before largest meal

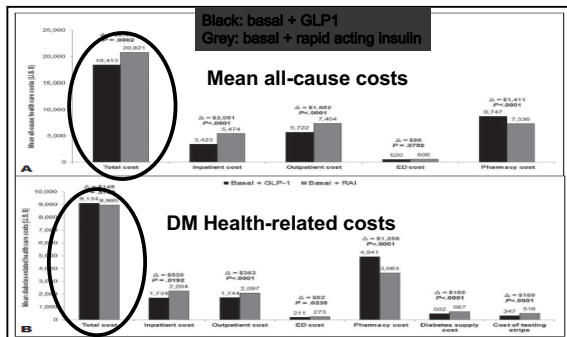
START: 4U, .1U/kg or 10% of basal; if A1c < 8% consider ↓ basal by same
ADJUST: ↑ dose by 1-2U or 10-15% 1-2x weekly until bg goal reached
For hypo: ↓ dose by 2-4U or 10-20%

ADA Supplement, 2017

Combinations instead of bolus?

- GLP1 + basal vs bolus + basal
 - With GLP1 comparable A1c, less hypoglycemia, weight loss Eng, C. The Lancet 2014
- SGLT2I + basal vs pbo + basal
 - A1c reduction (.5%), wt loss (2kg) Rosenstock J, Diab Obes Metab 2015
- TZD also an option
 - ↑ fluid retention, weight gain when used with insulin- be careful

Cost Data



Total health costs for \$18,413 (GLP1) vs \$20,821 (RAI), but diabetes costs were similar.

Dalal MR, Endo Prac 2015

New Combinations

- Degludec/Liraglutide
 - Xultophy®, \$981/box
 - 1unit insulin:3.6mg GLP1
 - Starting dose:
 - 16unit doses (16uD:.58mgL)
 - A1c lowering:
 - -1.9% c/w -1.44% (degludec) or -1.28% (liraglutide)
- Glargine/lixisenatide
 - Soliqua®, \$656/box
 - 3:1 fixed ratio
 - Pen with 15-60 units, 1 unit increments
 - If < 30units/d, start with 15u; if 30-60u, start 30 units
 - A1c lowering:
 - -1.1% vs .6% with glargine alone

Case #1

- Before she can start on an additional agent, she is told by her insurance she needs to transition back to NPH insulin
- How do you do this?

Don't Overlook NPH and Regular

- Among privately insured adults + DM2
 - 19% using analogs in 2000, c/w 96% in 2010
 - From 2001 → 2015:
 - lispro vials \$35 → \$234, human insulin \$20 → \$131
- Marketing **BIG** with insulin analogs
 - Cited as being more physiologic, less hypoglycemia
- **BUT** no difference in A1c, outcomes or complications

Tylee T, Hirsch I, JAMA 2015

Switching to NPH and Regular

- With BID Glargine/levemir, can transition 1:1 to NPH
 - NPH best given at bedtime c/w dinner
 - Remember midday peak (so may need less meal insulin with lunch)
- Once daily glargine to NPH
 - NPH needs to be BID
 - Many options (depending on patterns):
 - 2/3 in the AM, 1/3 in the PM
 - ½ in the AM, ½ in the PM
 - Monitoring is key



Mealtime insulin

- When switching to Regular insulin from analog:
 - Same dose as analog insulin, given with meals (or 30 minutes prior to eating)
 - Beware sliding scales
 - Takes motivation, education and monitoring to determine doses
- Consider referral to teach how to mix insulin (reduce injection frequency)



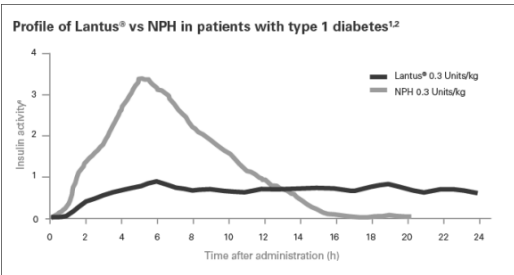
Crossover Study with Regular Insulin

- 100 pts with type 2 dm randomized
 - 1st: inject pre-meal insulin 20min prior to eating
 - 2nd: taken at time of eating
- Difference in A1c only .08% (NS)
 - No difference in hypoglycemia, BG profile
- Treatment satisfaction much higher taking insulin with meal (rather than 20 min prior)
 - Preferred by 86% of participants

When high doses aren't working

- 42 year-old, morbidly obese, type 2 diabetes for 8 years
- A1c 10%, limited monitoring/engagement
 - Checking 3-4x per week, all > 200mg/dl
- Glargine 65units BID, lispro 5units with meals
 - Five injections per day

Comparison of Glargine vs NPH



Options to consider

- NPH, rather than glargine
 - Consider when doses > 1u/kg basal Bota VM, 2012 Endo Practice 18:e49
 - Transition 1:1, watch for midday hypoglycemia
- More meal insulin
 - Would consider increase to get ratio closer to 50/50 of TDD
 - Could calculate TDD based on 1.5-2u/kg
- Consider adding metformin, SGLT2I, GLP1
- Make sure he is taking injections
 - Does he have the right size syringes? Mixing?

Options for Insulin Resistance

- Consider in those:
 - Using > 2u/kg/day, >200units/day and A1c>8%
- Includes:
 - U500: 5x concentrated regular, hybrid of basal/bolus insulin
 - Now available in pens- less complex
 - 2 pens = \$550, one vial \$1,415
 - U300 Glargine (Toujeo), U200 Degludec (Tresiba)

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THE END