7:45 – 9 am

Evolving Insulin Therapy: Optimizing Care Through Proper Selection & Use

SPEAKERS

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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Andrew Ahmann, MD, MS: Research Support from Medtronic; Novo Nordisk Inc.; and sanofi-aventis U.S. Board and Advisory Panel Member for Janssen Pharmaceuticals, Inc. and Mannkind Corporation. Consultant for DexCom and Novo Nordisk Inc.
- Guillermo E Umpierrez, MD, FACP, FACE: No financial relationships to disclose.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Drug List

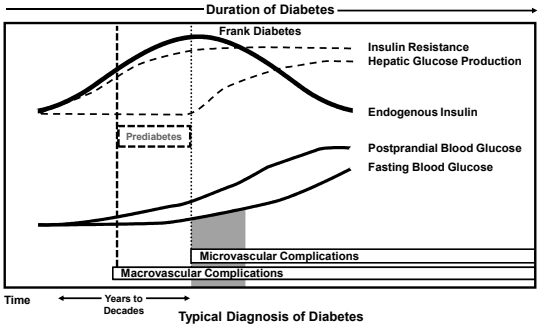
Generic Drug Name	US Trade Name
insulin aspart	Novolog, Novolog FlexPen,
insulin detemir	Levemir, Levemir Flexpen
insulin glargine	Lantus, Lantus SoloStar
U-300 insulin glargine	Toujeo
insulin glulisine	Apidra
insulin human regular	Humulin R, Novolin R
insulin human isophane (NPH)	Humulin N, Novolin N
insulin lispro	Humalog, Lispro-PFC
metformin	Glucophage
pioglitazone	Actos
sitagliptin	Januvia

Objectives

- Implement strategies for the timely initiation of insulin therapy to best achieve glycemic control in patients with type 2 diabetes
- Design insulin regimens that are appropriate and tailored to a patient's needs
- Recognize the barriers to insulin-mediated glucose control and apply strategies to overcome them
- Outline the pharmacokinetic/ pharmacodynamics profiles and evidence for emerging basal insulin for the treatment of type 2 diabetes

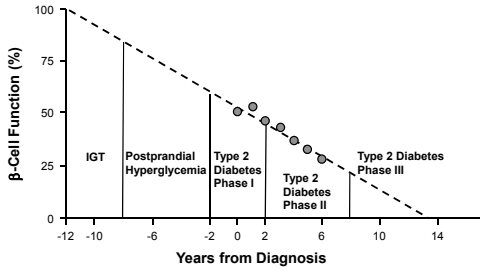
Progression of Type 2 Diabetes

Natural History of Type 2 Diabetes



Ramlo-Halsted BA, Edelman SV. *Clin Diabetes*. 2000;18(2):80-85.

Stages of Type 2 Diabetes
By Beta Cell Function



Adapted from Lebovitz H. *Diabetes Review*. 1999;7:139-53.

Glycemic Control & Complications

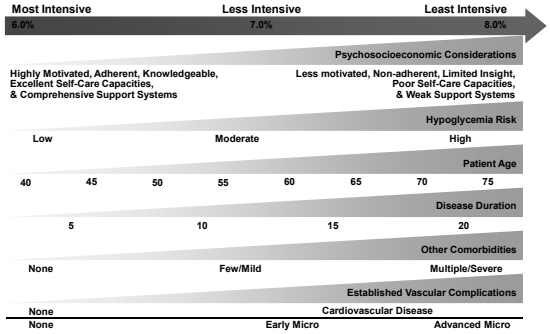
Type 2 Studies	Microvascular	Macrovascular	Mortality
DCCT/EDIC[1]			
UKPDS[2,3]	↓ / ↓	↔ / ↓	↔ / ↓
ACCORD[4,5]	↓	↔	↑
ADVANCE[6,7]	↓ / ↓	↔ / ↔	↔ / ↔
VADT[8]	↔	↔	↔

Observational Follow-up

1. http://diabetes.niddk.nih.gov/dm/pubs/control/ 2. Adapted from UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853. 3. Holman RR, et al. *N Engl J Med*. 2008;359:1577-1589. 4. Gerstein, et al. *NEJM*. 2008;358:2545-2559. 5. ACCORD Study Group. *NEJM*. 2010; 363:233-244. 6. Patel, et al. *NEJM*. 2008;358: 2560-2572. 7. Zoungas S, et al. *N Engl J Med*. 2014;371:1392-1406. 8. Duckworth, et al, NEJM 2009;360:129-139.

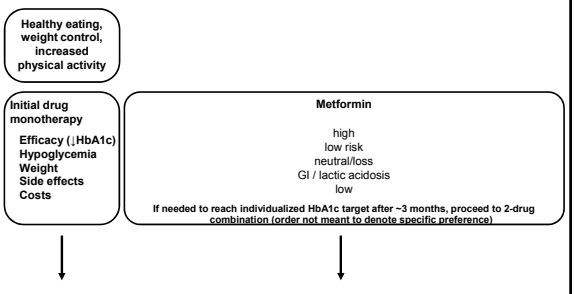
Recommendations for Advancing Therapy in Type 2 Diabetes

Individualizing A1C Targets for Patients with T2DM



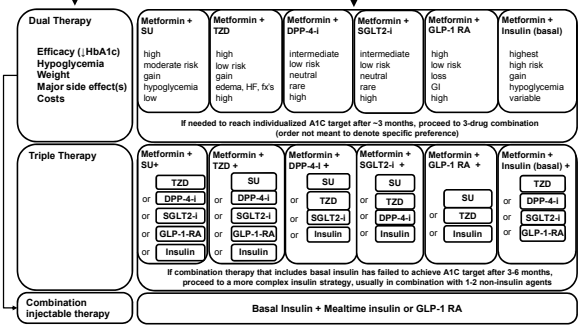
Data from Ismail-Beigi F, et al. *Ann Intern Med*. 2011;154(8):554-9.

ADA/EASD 2015 Guidelines



Adapted from American Diabetes Association. *Diabetes Care*. 2015;38(suppl 1):S41-S48.

ADA/EASD 2015 Guidelines
Cont'd



SGLT2-i = sodium-glucose cotransporter 2 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonists.

Adapted from American Diabetes Association. *Diabetes Care*. 2015;38(suppl 1):S41-S48.

Insulin as an Option

When to Consider Insulin in Type 2 Diabetes

- Basal insulin may be second agent after metformin
- When combination oral/injectable agents become inadequate
- High FPG or high PPG
- Unacceptable side effects of other agents
- Patient with advanced hepatic or renal disease
- Special circumstances (e.g., steroids, infection, pregnancy)
- Patient with hyperglycemia in the hospital
- "Severely" uncontrolled diabetes*

FPG = fasting plasma glucose; PPG = postprandial glucose.
***Defined as fasting glucose >250 mg/dL, random glucose > 300 mg/dL, A1C >10%, ketonuria, or symptomatic (polyuria, polydipsia, and weight loss) by ADA 2009 Consensus Statement. After glucose controlled, oral agents can be added and insulin withdrawn if preferred.**

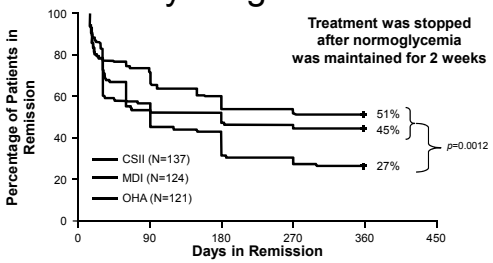
Nathan DM, et al. *Diabetes Care*. 2009; volume 32,193-203. Inzucchi SE, et al. *Diabetes Care*. 2012;35(6):1364-1379. ADA *Diabetes Care*. 2014:37(Suppl 1):S14-S80.

Why Consider Insulin Early?
The Benefits of Insulin

- The most predictable glucose reduction
  - Most effective
- Effective targeting of fasting glucose
  - Also enhances post-prandial insulin response as well
- Potential for preservation of beta cell function
  - Evidence of diabetes prevention in ORIGIN Trial
  - Evidence of improved insulin secretion when added to oral agents
  - Evidence of beta cell preservation/ prolonged remission when used early in T2DM
- Good safety record other than hypoglycemia
  - No evidence of increased cancer or heart disease with glargine in ORIGIN Trial

ADA. *Diabetes Care*. 2015;38 (suppl 1):S41-S48; Weng J, et al. *Lancet*. 2008;371:1753-60; Pennartz C, et al. *Diabetes Care*. 2011; 34:2048-2053. ORIGIN Trial Investigators, Gerstein HC, et al. *N Engl J Med*. 2012;367(4):319-28.

Early Insulin Increased Remission in Newly Diagnosed T2DM



Target glycemic control was achieved in less time (4 & 5.6 days) and in more CSII and MDI pts (97.1% & 95.2%) than OHA pts (9.3 days and 83.5%)

CSII = continuous subcutaneous insulin infusion; MDI = multiple daily insulin injections; OHA = oral hypoglycemic agents.

Weng J, et al. *Lancet*. 2008;371:1753-60.

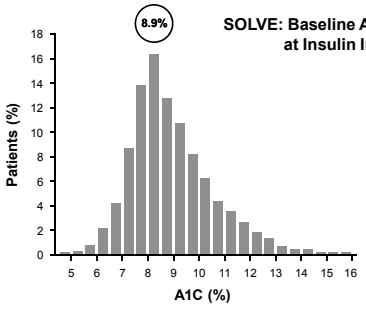
Barriers to Insulin Initiation and Adherence

Impediments to the Potential Benefit of Insulin Therapy in Type 2 Diabetes

- Provider inertia
  - Delay in progression of therapy to reach target
  - Worse with insulin than other agents
- Behavioral barriers to initiating insulin
  - Patients
  - Providers
- Objective limitations once initiated
  - Non-adherence
  - Hypoglycemia
  - Weight gain

Adapted from Funnell MM. *Clinical Diabetes*. 2007;25(1):36-38. Derr RL, et al. *Diabetes Spectrum*. 2007; 20(3):177-185. Karter AJ, et al. *Diabetes Care*. 2010;33(4):733-735.

Clinical Inertia Leads to Delayed Insulin Initiation



Data from Khunti K, et al. SOLVE Study Group. *Diabetes*. 2011;60(Suppl 1):A306.

Key Barriers to Insulin Therapy

Patient Barriers

- Patient reluctance
- Sense of failure
- Loss of independence
- Belief that insulin is ineffective
- Fear of injections
- Fear of hypoglycemia
- Weight gain

Provider Barriers

- Clinical inertia
- Lack of insulin training, time, and/or support
- Fear of hypoglycemia
- Weight gain

Adapted from Funnell MM. *Clinical Diabetes*. 2007;25(1):36-38. Polonsky WH, et al. *Curr Med Res Opin*. 2011;27(6):1169-1174.

Overcoming the Barriers to Insulin Therapy

- Avoid using insulin as a "threat," but a solution and discuss it as an option early
- Use insulin pens and regimens that offer maximum flexibility
- Give a "limited" trial of insulin
- Tell patient injection is less painful than finger stick and give an injection in the office
- **Teach patient to recognize and treat hypoglycemia, and use basal analog insulins to minimize hypoglycemia risk**
- Meet with dietitian before initiation of insulin

Kruger D, et al. *Diabetes Educ*. 2010;36(suppl 3):44S-72S. Funnell MM. *Clinical Diabetes*. 2007;25(1):36-38. Derr RL, et al. *Diabetes Spectrum*. 2007; 20(3):177-185.

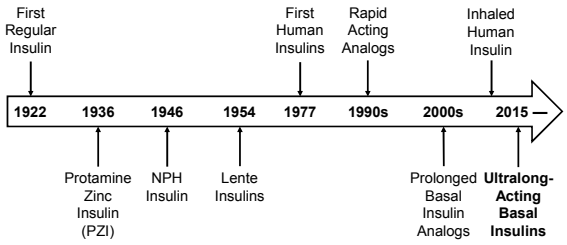
Overcoming the Barrier of Hypoglycemia with Insulin

- Less hypoglycemia with "basal only" approach
- Analog insulins reduce hypoglycemia; new ultralong-acting basal insulins greater reduction
- Appropriate dosing reduces hypoglycemia
- Choose the right target and right insulin for each individual
  - e.g., Higher targets for elderly or those with renal insufficiency
- Proper patient education is crucial
  - Learning to have consistent meals, adjust for exercise, monitor glucose, etc.

Morales J and Schneider D. *Am J Med*. 2014;127:S17-24. American Diabetes Association. *Diabetes Care*. 2015;38 (suppl 1):S41-S48.

Insulin Products

The Evolution of Insulin Products



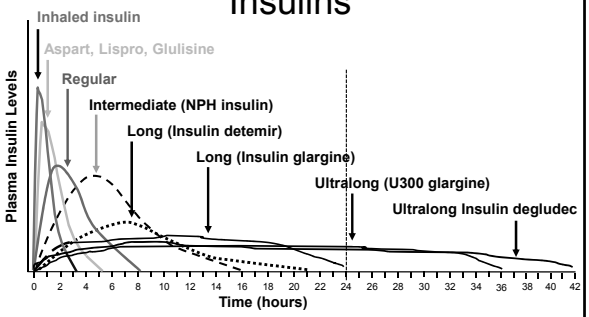
Tibaldi JM. *Am J Med*. 2014;127:S25-S38.

Current Available Insulins

Insulin Type	Onset	Peak, h	Duration of Action, h
Rapid-acting analogs			
Insulin lispro, aspart, glulisine	15 min	0.5-1.5	3-5
Insulin human inhaled	12-15 min	~1.0	2.5-3.0
Short-acting			
Regular human (U-100)	30-60 min	2-4	5-8
Regular human (U-500)	30-60 min	4-8	14-15
Intermediate-acting			
Human NPH insulin	1-3 h	6-12	12-24
Long-acting (basal)			
Insulin glargine	2-4 h	No pronounced peak	20-24
Insulin detemir	1-3 h	6-8	18-20
Ultralong-acting (basal)			
Insulin glargine U-300	**Develops over 6 h**	**Nearly peakless**	**≤36**
Insulin degludec (U-100/ U-200)	**30-90 min**	**Nearly peakless**	**>42**

Walia M and Molitch M. *JAMA*. 2014;311:2315-2325. http://www.pdr.net. Accessed April 5, 2015. Nasrallah SN, et al. *Clin Med Insights Endocrinol Diabetes*. 2012:5:31–37.

PK Profile of Currently Available Insulins



PK = pharmacokinetic; NPH = neutral protamine Hagedorn.

Adapted from Hirsch IB. *NEJM*. 2005;352:174-183. Flood TM. *J Fam Pract*. 2007;56(suppl 1):S1-S12. Becker RH, et al. *Diabetes Care*. 2015;38:637-643. http://www.pdr.net/full-prescribing-information/afrezza?druglabelid=3540. Accessed April 5, 2015. Hompesch M, et al. Clin Ther. 2014;36(4):507-15.

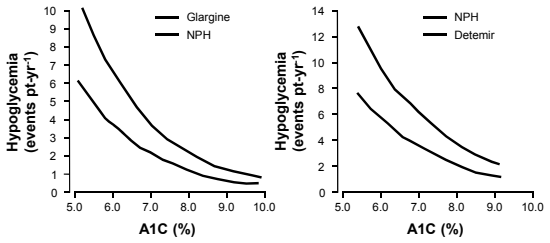
Current Available Premixed Insulins

Insulin Type	Onset	Peak, h	Duration of Action, h
70% NPH/ 30% Regular	0.5-1 h	3-12 (dual)	10-16
75% NPL / 25% Lispro	5-15 min	1-4 (dual)	10-16
50% NPL / 50% Lispro	5-15 min	1-4 (dual)	10-16
70% NPA / 30% Aspart	5-15 min	1-4 (dual)	10-16
70% Degludec / 30% Aspart	5-15 min	1-4	>42

Walia M and Molitch M. *JAMA*. 2014;311:2315-2325. PL Detail-Document, Comparison of Insulins and Injectable Diabetes Meds. Pharmacist's Letter/Prescriber's Letter. March 2015.

Hypoglycemia Reduced with Basal Insulin Analogs

No Difference in A1C but Reduced Hypoglycemia



Little S, et al. *Diabetes Technol Ther*. 2011:13(suppl 1):S53-S64.

Preferential Glucose Effect of Insulins

- Rapid-acting/short-acting insulin (meal-time insulins)
  - Reduces predominantly postprandial glucose (PPG)
  - Ideal for controlling postprandial hyperglycemia
- Intermediate-acting (NPH)
  - Reduces mostly fasting plasma glucose (FPG)
  - Not an ideal basal insulin due to intermediate duration of action
- Long-acting/ultralong-acting (basal insulins)
  - Reduces essentially only FPG, little effect on PPG
  - Not useful in patients with well control FPG

Monnier L, et al. *Diabetes Care*. 2003;26:881-885. Walia M and Molitch M. *JAMA*. 2014;311:2315-2325.

Comparative InsulinTrials in T2DM

Summary of Key Findings

- Any insulin will lower glucose and A1C
- All insulins are associated with some weight gain and some risk of hypoglycemia
- The larger the doses and the more aggressive the titration, the lower the A1C, but often with a greater possibility of hypoglycemia
- Long-acting insulin analogs reduce the incidence of nocturnal hypos
- Rapid-acting insulin analogs reduce postprandial glucose excursions (compared with corresponding human insulins [NPH, Regular]) and tend to reduce hypoglycemia but they generally do not result in clinically significantly lower A1C
- Premixed insulin preparations are effective in reducing A1C but are associated with more hypoglycemia and weight gain than using individual short and long-acting insulin

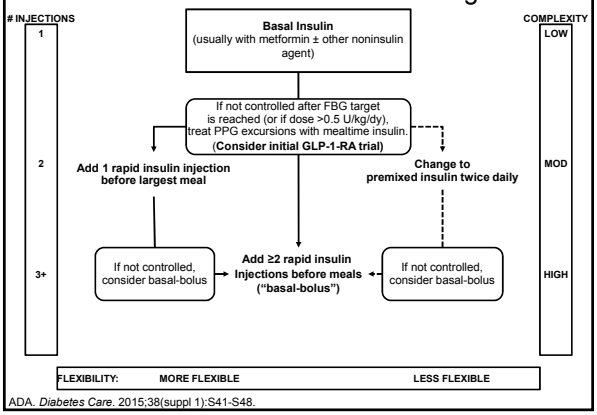
Inzucchi SE, et al. *Diabetologia*. 2012;55:1577-96.

Insulin Regimens and Selection

Insulin Options In Type 2 Diabetes

- Basal only
  - 1 injection
  - Added to oral agents
- Basal plus
  - 2 injections or 1 injection + 1 inhalation
  - Adding one rapid acting analog sequentially starting with largest meal
- Basal bolus
  - 4 injections or 1 injection + 3 inhalations
  - Rapid acting analog before each meal
- Pre-mixed
  - 2 injections

ADA Recommendations for Advancing Insulin



ADA. *Diabetes Care*. 2015;38(suppl 1):S41-S48.

Start with Basal Insulin Added to Oral Agents

- **Benefits**
  - Effective in reaching A1c goals for most
  - Convenient – once daily and easy titration
  - Proven safe (particularly with glargine)
    - ***Origin Trial showed no increased risk of CVD or cancer***
    - ***Low risk of hypoglycemia***, particularly with analog basal insulins
  - Therefore, addresses several barriers to insulin use
- **Dosing**
  - **Start** – 10 units per day or 0.1-0.2 units per kg per day
  - **Adjust** – ↑ by 10-15% or 2-4 U once or twice weekly to reach target
  - **For Hypoglycemia** – Assess cause and correct or ↓ dose 4 U or 10-20%

ORIGIN Investigators. *N Engl J Med*. 2012; 367:319-328. American Diabetes Association. *Diabetes Care*. 2015; 38(suppl 1)S41-S48.

Adding Insulin to OADs Improves Glycemic Control (Results of Large RCTs)

Study	Treatment	Baseline A1C	Resulting A1C
STEPWISE (2011) 48 weeks[1]	DET + 0-3 ASP*	8.9	7.5
	DET + 0-3 ASP†	8.7	7.2
4-T (2007) 52 weeks[2]	ASP TID[a]	8.6	7.2[b]
	BIASP BID[a]	8.6	7.3[b]
	DET QD[a]	8.4	7.6
DURABLE (2011) 24 weeks[3]	LM 75/25 BID	8.7	7.1
	GLAR QD	8.7	7.3

***Measured PPG; †Estimated meal size.**
[a]A second type of insulin could be added beginning at 24 weeks if HbA1C ≥ 8.0% on 2 consecutive readings or > 10%; [b]*p*<0.001 vs DET QD; [c]*p*<0.05 vs BIASP; [d]*p*<0.025 vs BIASP.

1. Meneghini L, et al. *Endocr Pract*. 2011;17:727-736. 2. Holman RR, et al. *N Engl J Med*. 2007;357: 1716-1730. 3. Buse JB, et al. *Diabetes Care*. 2011;34:249-55

When Basal Alone Is Not Enough

When A1C values are still not at target

AND…

- Basal insulin dose titrated to 0.4-0.6 units/kg/day
- Fasting BG levels at or approaching target
- Post-prandial BG values remain above target

Options:

- Advance insulin therapy with additional prandial insulin
- Add GLP-1 agonist therapy if tolerated, not contraindicated and is affordable for the patient

BG = blood glucose.

American Diabetes Association. *Diabetes Care*. 2015;38(suppl 1):S41-S48.

Insulin Regimens – Basal Plus

Advantages

- **Basal plus**
  - Two injections only, bolus typically targeted to largest meal of day
  - Adherence is greater for twice daily than more frequent dosing
  - Eliminates the barrier of lunch dosing
  - Nearly as effective in lowering A1c as full basal bolus therapy in many

Disadvantages

- **Basal plus**
  - May not cover all prandial needs
  - May not reach goal in some patients

Plank J, et al. *Arch Intern Med*. 2005;165:1337-44. Horvath K, et al. *Cochrane Database Syst Rev*. 2007;(2):CD005163. Davies M, et al. *Diabetes Care*. 2005;28:1282-8. Yki-Ja¨rvinen H, et al. *Diabetes Care*. 2007;30:1364-9. Crasto W, et al. *Postgrad Med J*. 2009;85:257-267.

How to Intensify Using the Basal Plus Approach

- Choose a "target" meal to initiate prandial insulin
  - Breakfast or the largest meal of the day
- **Start** – rapid acting insulin analog
  - 4 U, 0.1 U/kg or 10% of basal dose 10-15 minutes before meal
  - If A1c is <8.0% consider decreasing basal by 10%
- **Adjust** –
  - Increase dose 1-2 units or 10-15% once or twice weekly until SMBG following that meal is at target
    - 2-h PPG -> target < 180 mg/dl
    - Next pre-prandial or HS BG -> target < 130 mg/dl
- **For Hypoglycemia** –
  - Determine cause and correct; ↓ corresponding dose by 2-4 units or 10-20%
- Once titrated to goal, if A1C remains above target add 2nd prandial dose

American Diabetes Association. Diabetes Care. 2015;38(suppl 1):S41-S48.

Insulin Regimens – Basal Bolus

Advantages

- **Basal bolus**
  - Flexible regimen, basal plus bolus whenever eating meal, allows for correction insulin use
  - **Appropriate** for patients willing to do multiple injections daily with frequent BG monitoring and capable of managing the complexity

Disadvantages

- **Basal bolus**
  - Many injections, adds complexity to daily insulin regimen
  - May impact adherence

Plank J, et al. *Arch Intern Med*. 2005;165:1337-44. Horvath K, et al. *Cochrane Database Syst Rev*. 2007;(2):CD005163. Davies M, et al. *Diabetes Care*. 2005;28:1282-8. Yki-Ja¨rvinen H, et al. *Diabetes Care*. 2007;30:1364-9. Crasto W, et al. *Postgrad Med J*. 2009;85:257-267.

Insulin Regimens – Pre-Mixed

Advantages

- **Pre-mixed**
  - Can minimize daily injection number
  - **Appropriate** for patients that cannot use basal bolus, wanting only 2 injections, and who have regular lifestyles, eat similar amounts at similar times each day (similar total calories and similar content for carbohydrate/fat/protein)

Disadvantages

- **Pre-mixed**
  - Fixed ratio, does not allow flexibility in dosing, increased risk of hypoglycemia

Plank J, et al. *Arch Intern Med*. 2005;165:1337-44. Horvath K, et al. *Cochrane Database Syst Rev*. 2007;(2):CD005163. Davies M, et al. *Diabetes Care*. 2005;28:1282-8. Yki-Ja¨rvinen H, et al. *Diabetes Care*. 2007;30:1364-9. Crasto W, et al. *Postgrad Med J*. 2009;85:257-267.

Strategies for Insulin Selection

- **Convenience** (once daily vs. twice or three times daily)
- **Proven safety**
  - Analogs – ORIGIN study showed low hypoglycemic risk, no adverse CV effects, and no cancer risk[1]
  - NPH – a little more hypoglycemic risk than analogs[2]
- **Adverse Effects** (Hypoglycemia, weight gain)
- **Cost**
  - NPH $
  - Analogs $$-$$$
- **Insurance coverage**
  - Analogs – coverage varies and may require prior authorization

1. ORIGIN Trial Investigators. *N Engl J Med*. 2012;367(4):319-28. 2. Riddle M, et al. *Diabetes Care*. 2003; 26:3080-3086.

New Ultralong-Acting Basal Insulin: U300 Glargine and Insulin Degludec

Characteristics of the Ideal Basal Insulin

- Pharmacodynamic profile should be flat (peakless)
- Low risk of hypoglycemia
- Duration of action of 24 hours
- Low variability within individual patients

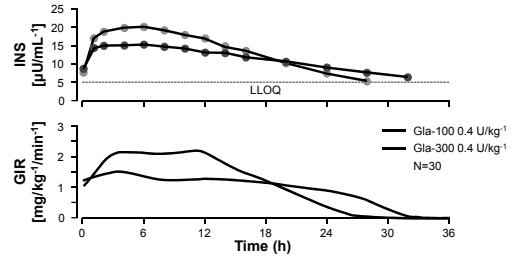
Arnolds S, et al. *Int J Clin Pract*. 2010;64(10):1415-1424.

New Insulin Glargine U-300

- U-300 insulin glargine offers a smaller depot surface area leading to a reduce rate of absorption
- **Provides a flatter and prolonged pharmacokinetic and pharmacodynamic profiles and more consistency**
- Half-life is ~23 hours
- Steady state in 4 days
- **Duration of action ≤36 hours**
- **Associated with less hypoglycemia especially nocturnal hypoglycemia**
- **FDA approved February 2015**

Garber AJ. *Diabetes Obesity Metab*; [Epub ahead of print; published online 31 Oct 2013]. Owens DR, et al. *Diabetes Metab Res Rev*. 2014;30(2):104-19. Steinstraesser A, et al. *Diabetes Obes Metab*. 2014 Feb 26. [Epub ahead of print]. http://www.australianprescriber.com/magazine/19/3/76/8. Accessed March 11, 2014. http://www.medpagetoday.com/Endocrinology/Diabetes/46690. Accessed January.

Pharmacokinetic and Pharmacodynamics of U300 Glargine vs U100 Glargine



U300 glargine displays a more even and prolonged PK/PD profile compared with U100 glargine, offering blood glucose control beyond 24 hours

LLOQ = lower limit of quantification; GIR = glucose infusion rate; PK = pharmacokinetic; PD = pharmacodynamic.

Becker RH, et al. *Diabetes Care*. 2014;pii:DC_140006.

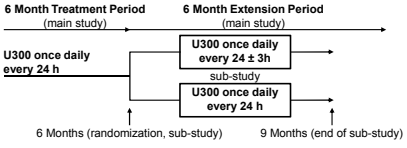
U300 Glargine vs U100 Glargine in T2DM:
Meta-Analysis of Phase III Trials EDITION 1, 2, & 3

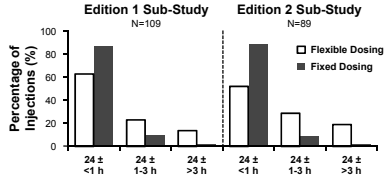
	Baseline to Month 6		RR (95% CI)
	Glar U300 (N=1247)	Glar U100 (N=1249)	
A1C (%), LS mean	-1.02	-1.02	NS
Weight (kg), LS mean	0.49	0.75	*P*=0.058
Any hypo in 24 hr*	67.8	73.8	0.92 (0.87-0.96)
Any nocturnal hypo*	31.7	41.3	0.77 (0.69-0.85)
Confirmed BG <54 mg/dL or severe hypo*	26.9	33.3	0.81 (0.72-0.90)
Confirmed nocturnal BG <54 mg/dL or severe hypo*	9.7	13.2	0.73 (0.59-0.91)

***% people ≥1 event.**
LS = least squares; RR = relative risk; BG = blood glucose; CI = confidence interval.

Ritzel RA, et al. Presentation 963, 50th EASD Annual Meeting, September 15-19, 2014, Vienna, Austria.

Flexible vs Fixed Dosing U300 Glargine:
Sub-Studies of Phase III Trials





- **No difference in A1C between flexible- vs fixed-dosing**
- **No difference in severe or nocturnal hypoglycemia within each sub-study**

Ritzel R, et al. Presentation 919-P 74th ADA Scientific Sessions June 13-17, 2014, San Francisco, CA. http://ada.scientificposters.com/epsAbstractADA.cfm?id=6. Accessed August 15, 2014.

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

1. http://www.pdr.net/full-prescribing-information/toujeo?druglabelid=3688. Accessed March 26, 2015.
2. http://www.pdr.net/drug-summary/lantus?druglabelid=520. Accessed March 26, 2015.

U-300 Insulin Glargine Dosing

- **Insulin-Naive Patients:**
  - Type 1 Diabetes – Start with 1/3 to 1/2 of the total daily insulin dose calculated by using 0.2-0.4 U/kg/day; give the remainder of the total daily insulin dose as a short-acting insulin and divide between each daily meal
  - Type 2 Diabetes – Start with 0.2 U/kg/day
- **Type 1 or Type 2 Diabetes:**
  - Changing from once daily long-acting or intermediate-acting insulin:
    - Initial dose can be the same as the once daily long-acting dose; for patients controlled on U-100 insulin glargine, expect that a higher daily dose of U-300 glargine will be needed to maintain the same level of glycemic control
  - **Changing from twice daily NPH insulin:**
    - **Initial dose is 80% of the total daily NPH dosage**

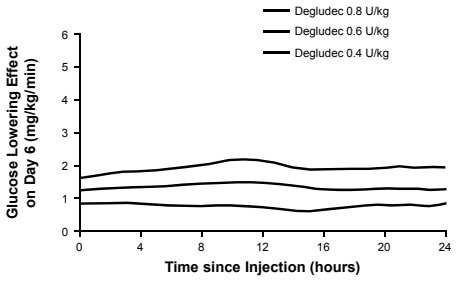
http://www.pdr.net/drug-summary/toujeo?druglabelid=3688. Accessed March 28, 2015.

New Insulin Degludec

- desB30 insulin acylated (16 carbon fatty acid chain) at LysB29
- **Has a prolonged pharmacokinetic and pharmacodynamic profiles, offering more consistency**
- **Duration of action >42 hours**
- Half-life ~25 hours
  - Detectable for at least 5 days
- Steady state in 2-3 days
- **FDA approved September 2015**

Garber AJ. *Diabetes Obesity Metab*; [Epub ahead of print; published online 31 Oct 2013]. Owens DR, et al. *Diabetes Metab Res Rev*. 2014;30(2):104-19.

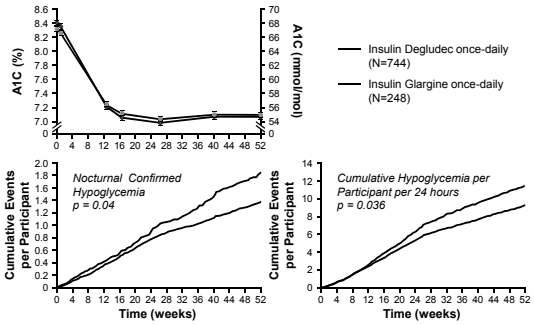
Pharmacodynamics of Degludec



Josse RG and Woo V. *Diabetes Obes Metab*. 2013;15(12):1077-1084.

Degludec vs U100 Glargine In Type 2 DM

Equal Efficacy, Less Nocturnal Hypoglycemia and Less Overall Documented Hypoglycemia with Degludec



Garber AJ, et al. *Lancet*. 2012;379(9285):1498-1507.

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

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. Accessed October 6, 2015.

When Might Ultralong-Acting Insulin Be Considered?

- Patient wanting basal insulin with the lowest risk of hypoglycemia
- Patient experiencing nocturnal hypoglycemia with current basal insulins
- Patient on current basal insulins not lasting throughout the day

Emerging Basal Insulins

Basal Insulins in Development
PEGylated Insulin Lispro*

- Polyethylene glycol polymer covalently attached to lispro
- Half-life 2-3 days
- Steady state in 7-10 days
- **Duration of action >36 hours**
- Phase II-III clinical trials
- Not likely to be reviewed by FDA until 2016

***Not FDA approved.**

Garber AJ. *Diabetes Obesity Metab*; [Epub ahead of print; published online 31 Oct 2013]. Owens DR, et al. *Diabetes Metab Res Rev*. 2014;30(2):104-19. Accessed March 11, 2014. Sinha VP, et al. *Diabetes Obesity Metab*. 2014;16(4):344-350. https://www.clinicaltrials.gov/ct2/results?term=LY2605541&Search=Search.

Summary

- T2DM is marked by progressive beta cell dysfunction requiring progressive pharmacological therapy to maintain glucose control
- Available guidelines promote stepwise advancement of therapy that includes basal insulin as an option after metformin
- Early use of insulin appears to retard progression of beta cell loss and promotes improvement in 1st and 2nd phase insulin secretion

Summary Continued

- Clinical inertia particularly impacts insulin initiation and exposes patients to unnecessary glucose exposure and diabetes complications
- Insulin regimens should be tailored to the patient's preferences and needs taking into consideration the pros and cons of each regimen
- The real and the perceived threat of hypoglycemia are major barriers among the multiple barriers to appropriately advancing therapy
- New ultralong-acting basal insulin U-300 glargine and those in development appear to offer further advantages in more consistent 24 hour coverage and reduced hypoglycemia risk