



Back to Insulin Basics: Solidifying Strategies to Overcome Barriers and Improve the Insulin Initiation Experience

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Learning Objectives

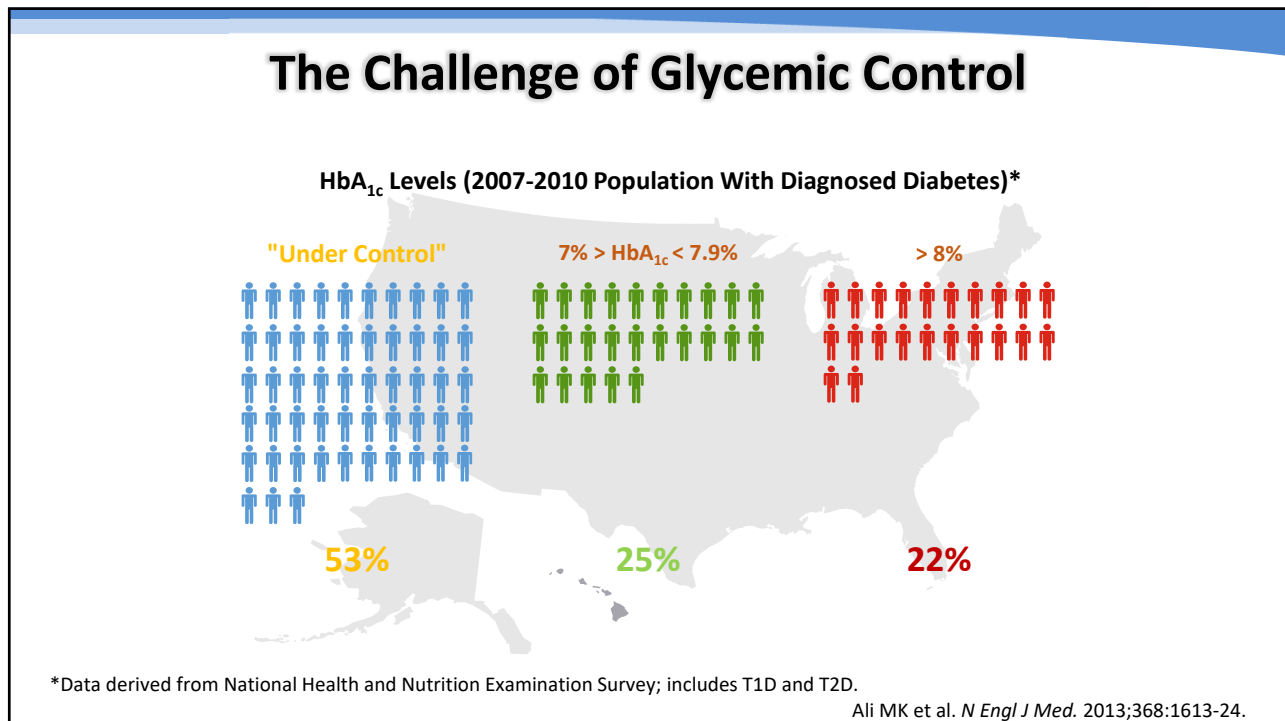
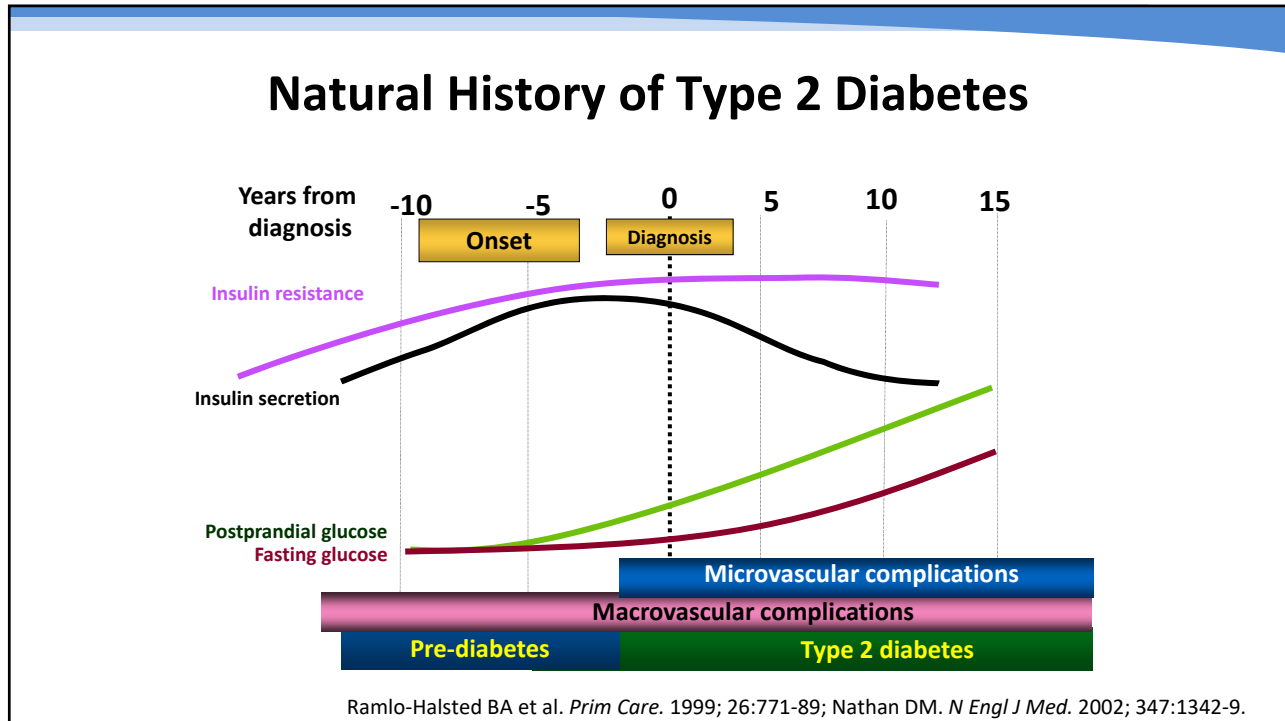
- Compare the clinical profiles of currently available insulin products with respect to dosing, variability, volume, and safety.
- Review best practices for initiating insulin therapies.
- Explain the concept of psychological insulin resistance.
- Review patient and healthcare provider barriers to overcoming therapeutic inertia.

Diabetes Epidemic

- Over 30 million Americans have Diabetes Mellitus
- 84 million have prediabetes and are at risk of progression to diabetes mellitus
- Diabetes is the leading cause of working-age blindness and amputations
- Estimated to cost \$327 billion in 2017

www.diabetes.org accessed January 10, 2020
American Diabetes Association. Economic Cost of Diabetes in the US in 2017. *Diabetes Care*. 2018 Mar; dci180007.

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When is Insulin Appropriate?

- A1C > 10% or blood glucose levels > 300 mg/dL
- Any time glycemic control is inadequate on other therapies
- Type 1 DM is suspected
- Ongoing metabolic catabolism
 - Weight loss
 - Ketosis
 - Very high triglycerides
- Pregnancy

American Diabetes Association. *Diabetes Care*. 2020;43(suppl 1):S98-S110.

Insulin Initiation: Therapeutic Inertia is Common

81,573 people with type 2 diabetes in the U.K. Clinical Practice Research Datalink
Identified between January 2004 and December 2006, with follow-up until April 2011.

- On 2 oral agents and A1C > 7%  > 7 years to start insulin!
- On 2 oral agents and A1C > 8%  > 6 years to start insulin!
- % therapy intensified correctly titrated over time period?  Only 6-25%

Khunti K et al. *Diabetes Care*. 2013;36:3411-17

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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
- Concerns about weight gain

Provider Barriers

- Therapeutic inertia
- Lack of insulin training, time, and/or support
- Fear of hypoglycemia
- Concerns about weight gain

Adapted from Funnell MM. *Clinical Diabetes*. 2007;25(1):36-38. Polonsky WH et al. *Curr Med Res Opin*. 2011;27(6):1169-74.

What Can We Do?

Increase Our Knowledge About Insulin

Improve Patient Ability to Start/Continue Insulin:

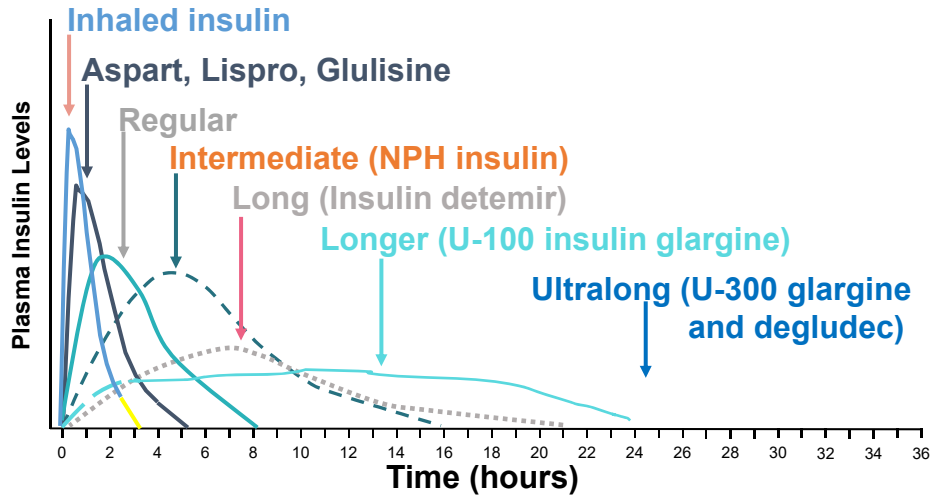
1. How to Overcome Psychological Insulin Resistance
2. Educational principles for insulin
 - How to instruct on injections

Know:

1. Insulin availability and cost
2. Relevant differences between insulins
3. Clinically appropriate initiation/titration

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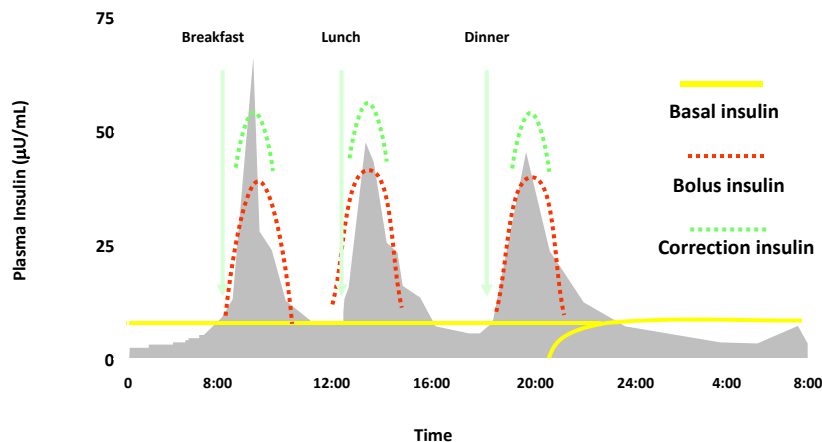
PK Profile of Currently Available Insulins



PK = pharmacokinetic; NPH = neutral protamine Hagedorn.

Adapted from Hirsh IB. *N Eng J Med.* 2005;352:174-83. Flood TM. *J Fam Pract.* 2007;56(suppl 1):S1-S12. Becker RH, et al. *Diabetes Care.* 2014;pii:DC_140006. <http://www.pdr.net/full-prescribing-information/> for affrezza and fiasp.

Understanding the Insulin Therapy Components



Adapted from Bray.

Moghissi ES et al; American Association of Clinical Endocrinologists; American Diabetes Association. *Endocr Pract.* 2009;15(4):353-69. Bray B. *Consult Pharm.* 2008;23(suppl B):17-23. Roberts G et al. *Med J Aust.* 2012;196(4):266-9. Umpierrez GE et al. *Diabetes Care.* 2011;34(2):256-61.

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Insulin Regimens: Learning the Lingo

- **Basal only (most common starting point)**
 - 1 injection (at bedtime or every 24 hours)
 - Added to oral agents
- **Basal Plus (usually 2-3 injections)**
 - Basal insulin injection
 - Adding one rapid-acting analog or inhaled insulin sequentially starting with largest meal; if inadequate control, then add 2nd rapid-acting injection to 2nd largest meal
- **Basal bolus (usually 4-5 injections)**
 - Basal insulin injection (once a day or split twice a day)
 - Rapid-acting insulin before each meal
- **Premixed**
 - 2 injections

American Diabetes Association. *Diabetes Care*. 2020;43(suppl 1):S98-S110.

Type 2 DM: Building an Insulin Regimen

At Bedtime (NPH)
Or
Every 12-24 hours

Basal

↑
Long-acting insulin

- Convenient
- Minimizes # of injections/day
- Improves fasting blood glucose and glycemic control in majority of patients
- Similar glycemic control with less hypoglycemia versus more complex insulin regimens¹

Holman RR et al. Three year efficacy of complex insulin regimens in type 2 diabetes *N Engl J Med* 2007; 361:1736-47. Adapted from: Moghissi ES et al; American Association of Clinical Endocrinologists; American Diabetes Association. *Endocr Pract*. 2009;15(4):353-69. Clement S et al. *Diabetes Care*. 2004;27(2):553-91.

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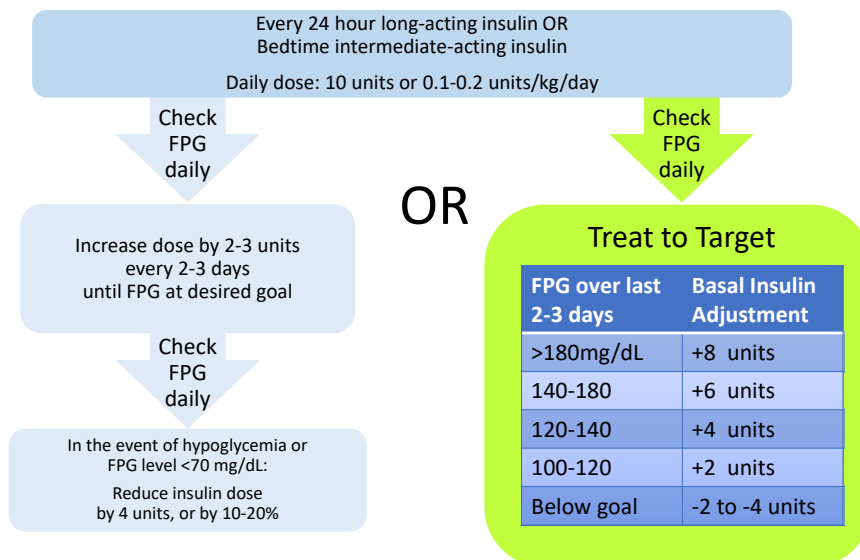
Currently Available* Insulins

Insulin	Time to Onset (hr)	Time to Peak Action (hr)	Duration of Action (hr)
Rapid-acting insulin			
Aspart, Lispro (U-100 , U-200), Glulisine	≤ 0.25	0.5-1.5	4-6
Aspart with niacinamide	< 0.2	0.5-1.5	4-6
Insulin human (inhaled)	< 0.2	0.75	1.5-4
Short-Acting insulin			
Insulin human regular (U-100)	0.5	3	8
Insulin human regular (U-500)	0.25	4-8	13-24
Intermediate-Acting insulin			
Human insulin isophane (NPH)	2-4	4-10	12-18
Long-Acting Insulins			
Detemir	3-4	6-8 (though relatively flat)	Up to 24
Glargine (U-100)	2-4	flat	20-24
Ultra-long Acting insulins			
Glargine (U-300)	6	flat	up to 36
Degludec (U-100, U-200)	1	flat	>42

Patient-specific onset, peak, and duration may vary from times listed in table. *Premix products not depicted

Hirsch IB. *N Engl J Med.* 2005; 352:174-83; Umpierrez GE et al. *J Clin Endocrinol Metab.* 2012; 97:16-38; Dansinger M. Types of insulin. June 21, 2016. www.webmd.com/diabetes/guide/diabetes-types-insulin (accessed 2020 Jan 24); Bennett JA. Insulin chart. July 17, 2015. Individual product prescribing information.

Starting Basal Insulin



FPG = fasting plasma glucose

Philis-Tsimikas. *A Adv Ther* 2013;30:607-22. ADA. *Diabetes Care.* 2020;43(suppl 1):S98-S110.

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United States Diabetes Organizations: Algorithms for Insulin Use to Achieve Glycemic Control

American Diabetes Association:

Pharmacologic Approaches to Glycemic Treatment

American Association of Clinical Endocrinologists/American College of Endocrinology:

Comprehensive Type 2 Diabetes Management Algorithm

AACE/ACE. *Endocrine Practice*. 2019;25(1):69-204.
American Diabetes Association. *Diabetes Care*. 2020;43(suppl 1):S98-S110.

National Diabetes Organizations: Glucagon Like Peptide-1 Receptor Agonist (GLP-1RA) Prior to Basal Insulin?

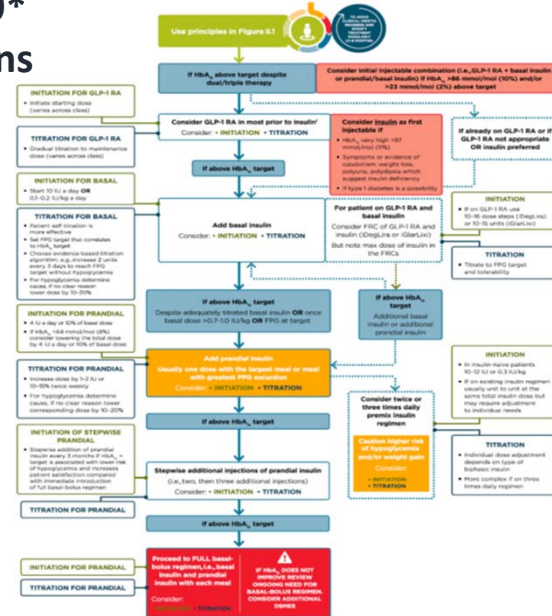
- Cardiovascular (CV) Outcome Trials:
 - Potential CV benefits with GLP-1 RA's
 - LEADER, SUSTAIN-6, REWIND, EXSCEL trials
 - Potential renal benefits
- Similar A1C reductions to basal insulin initiation
- If on optimized basal insulin, similar A1C reductions to mealtime insulin
- Less hypoglycemia versus basal insulin
- Weight loss in majority of patients
- Cost can be similar if newer agents are used
- When to Recommend Insulin First?
 - A1C is high (>10-11%)
 - Catabolism is present, which may indicate insulin deficiency
 - weight loss, ketosis, ongoing polyuria and/or polydipsia
 - Type 1 DM is suspected

AACE/ACE. *Endocrine Practice*. 2019;25(1):69-204
American Diabetes Association. *Diabetes Care*. 2020;43(suppl 1):S98-S110.

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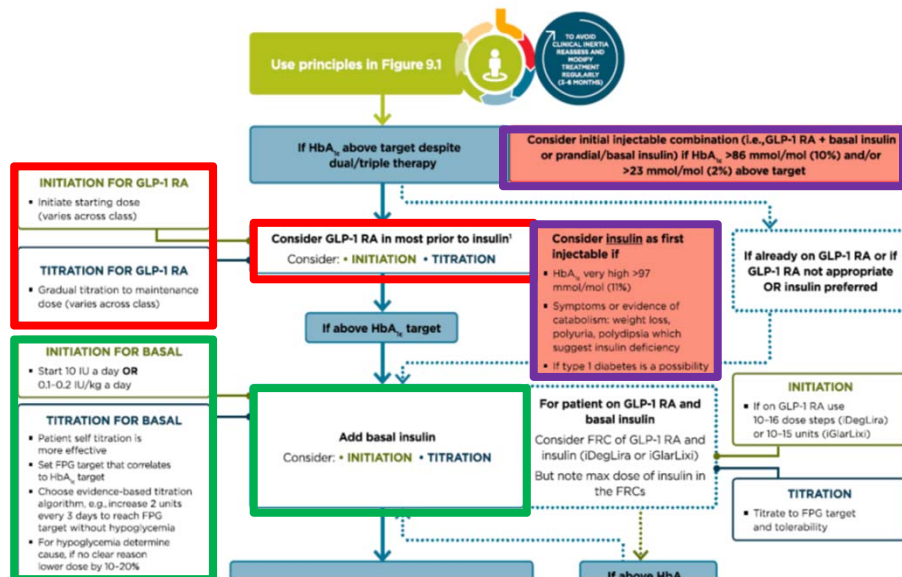
American Diabetes Association 2019* Injectable Therapy Recommendations

- *2019 algorithm presented
- 2020 guidelines similar, but 2019 provides more “guidance” such as:
 1. Initiation
 2. Titration
 3. Combination



Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care*. 2019;42(Suppl 1):S90-S102

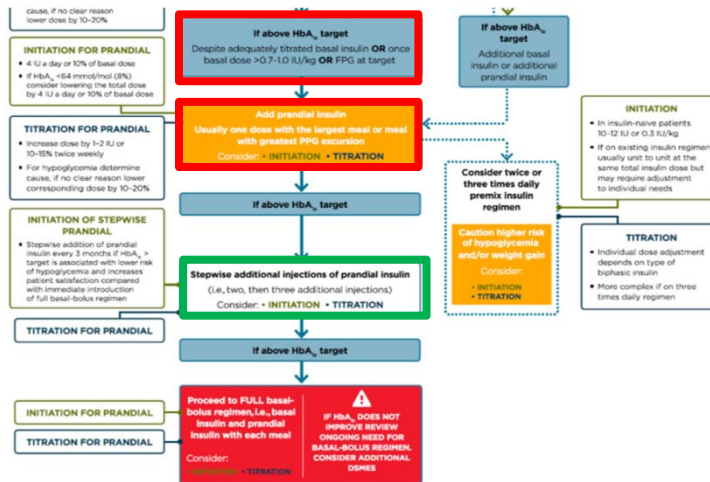
American Diabetes Association 2019 Injectable Therapy Recommendations



FRC= Fixed Ratio Combination. iDegLira- insulin degludec combined with liraglutide. iGlarLixi= insulin glargine combined with Lixianatide
Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2019. *Diabetes Care*. 2019;42(Suppl. 1):S90-S102

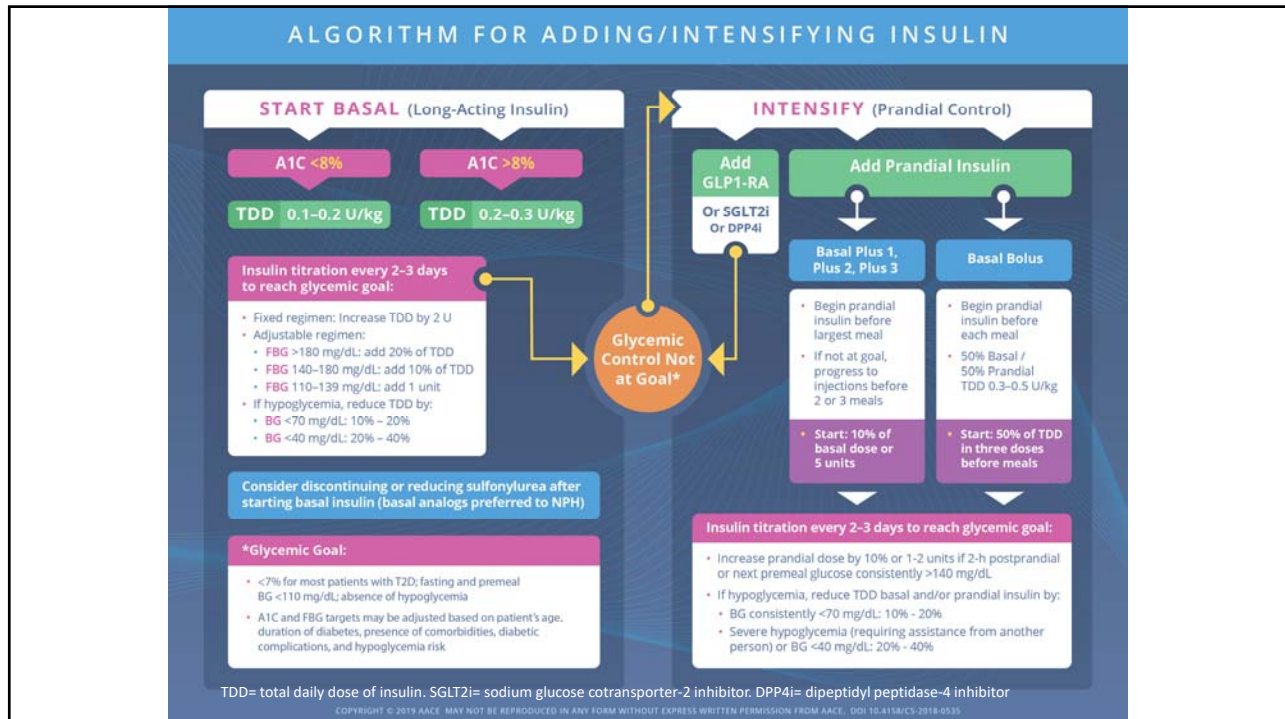
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American Diabetes Association 2019 Injectible Therapy Recommendations (p 2)



PPG= postprandial glucose. DSMES= Diabetes Self Management Education and Support.

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2019. *Diabetes Care*. 2019;42(Suppl 1):S90-S102



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Comparing the New Generation of Basal Insulins

Insulin Degludec and Insulin Glargine (U-300)

U-300 Insulin Glargine

- Smaller depot surface area reduces rate of absorption
 - Half-life ~ 23 hours
 - Steady state in 4 days
 - Duration of action ≤ 36 hours
- Only available in pens
- U-300 insulin glargine pen is white with green label
 - 300 U/mL, 1.5 mL pen, Max 80 units/ injection, Dose 1 unit increments
- U-300 insulin glargine MAX pen is white with green STRIPES on the label
 - 300 U/mL, 3 mL pen, Max 160 units/injection, Dose 2 unit increments



<https://www.pdr.net/drug-summary/Toujeo-insulin-glargine-3688>. Accessed 2020 Jan 14.
<https://www.pdr.net/search-results?q=insulin%20glargine>. Accessed 2020 Jan 14.

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U-100, U-200 Insulin Degludec

- Prolonged action due to dihexamer and multihexamer formations and albumin binding
 - Duration of action >42 hours
 - Half-life ~24 hours
 - Steady state in 2-3 days
- Only available in pens
- U-100 degludec pen is blue with green label
 - 100 units/mL, 3mL, Max 80 units per injection, Dose 1 unit increment
 - U-200 degludec pen is blue with green STRIPES on label
 - 200 units/mL, 3 mL, Max dose per injection is 160 units, 2 unit increments



Tresiba package Insert, Novo-Nordisk, Bagsvaerd, Denmark, December 2019

<https://www.pdr.net/drug-summary/Tresiba-insulin-degludec-3796>. Accessed 14 January 2020

Cardiovascular Safety of New Generation Basal Insulins

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Cardiovascular Outcome Trial Insulin Degludec vs. Insulin Glargine

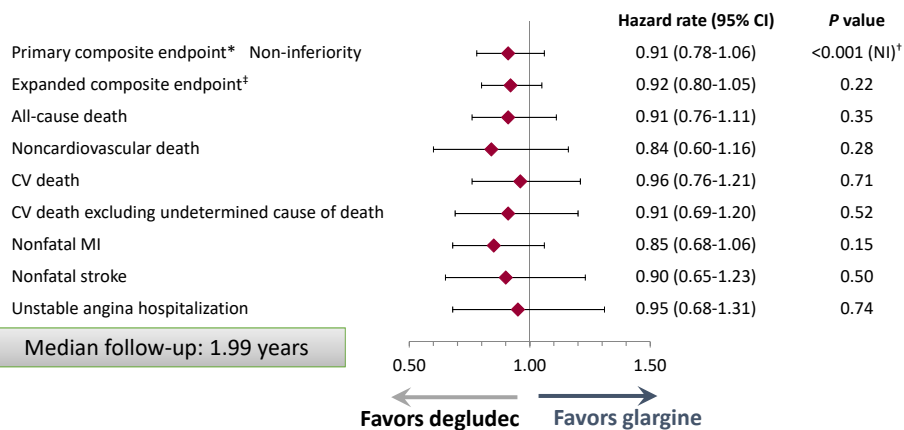
DEVOTE Study Design

- n=7637 patients with T2DM at high risk of CV events
 - Age ≥50 years with with CVD or renal disease
 - Age ≥60 years with ≥1 CV risk factor
- Randomization
 - U-100 insulin degludec: n=3818
 - U-100 insulin glargine: n=3819
- Noninferiority study: prespecified margin <1.3 for upper bound of 95% CI of the HR for the primary endpoint; superiority tested if noninferiority criterion met
 - Primary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke
 - Key secondary endpoints
 - Adjudicated severe hypoglycemia
 - Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina
 - All-cause death

Marso SP et al. *N Engl J Med.* 2017;377:723-32.

Cardiovascular Outcomes: Insulin Degludec vs. Glargine

DEVOTE CVOT Outcomes (n=7637)



*CV death, nonfatal MI, or nonfatal stroke; †Confirmed noninferiority; superiority, P=0.21.

‡CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; NI, noninferiority.

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Insulin Glargine (U-300) vs. Insulin Glargine (U-100): Meta-analysis of Phase III Trials

	Baseline to Month 6		RR (95% CI)
	Glargine U-300 (n=1247)	Glargine U-100 (n=1249)	
A1c (%), LS mean	-1.02	-1.02	NS
Weight (kg), LS mean	0.51	0.79	p = 0.039
Any nocturnal hypoglycemia*	2.1	3.06	0.69 (0.57-0.84)
Confirmed BG <70 mg/dL or severe hypoglycemia any time of day*	15.22	17.77	0.86 (0.77-0.97)
Severe hypoglycemia any time of day*	0.11	0.11	0.98 (0.51-1.86)

* = events per participant-year, RR = relative risk, CI = confidence interval, LS = least squares, BG = blood glucose.

Ritzel RA et al. *Diabetes Obes Metab* 2015; 17:859-67

Degludec vs. Glargine (U-100): Meta-analysis

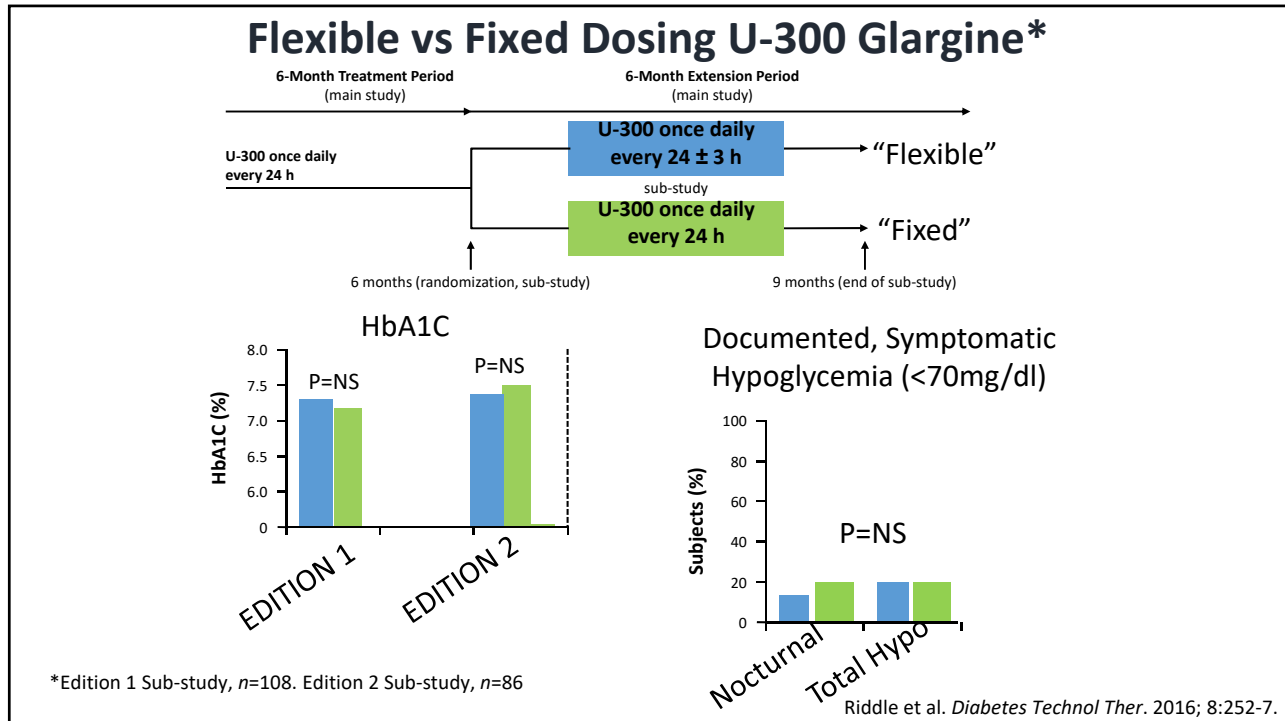
Insulin Degludec (U-100) vs. Insulin Glargine (U-100) 5 type 2 DM studies and 2 Type 1 DM studies

	Degludec vs. Glargine	95% CI
Attain FPG target of 90mg/dl without Nocturnal Hypoglycemia	Odds Ratio 1.82	1.49-2.22
Nocturnal confirmed ⁺ hypoglycemia	Rate Ratio 0.68	0.57-0.82

⁺ confirmed= 12AM to 6AM. PG <56mg/dL

Russel-Jones D et al. *Nutri Metab Card Dis*. 2015;25:898-905.

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Flexible vs. Fixed Insulin Degludec Dosing: BEGIN FLEX Trial

- Trial design:** 26-week, randomized, open-label, parallel-group, treat-to-target trial in patients with type 2 diabetes
- Primary outcome:** non-inferiority of flexible* insulin degludec dosing (8-40 hour intervals between doses) compared with glargine

Randomized
Background of Oral Meds
If on Basal insulin switched
Unit for Unit

Insulin Glargine (U-100) Daily

Insulin Degludec (U-100) Daily

Insulin Degludec (U-100)
Given in a FLEX* pattern

*FLEX= changing dosing interval: 36-40 hours between injections then 8-12 hours between injections throughout study

Meneghini et al. *Diabetes Care.* 2013;36:858.

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BEGIN FLEX- A1C Outcomes

	A1C				A1C: Attain <7%		
	Baseline	CHANGE 26 weeks	P value			At 26 weeks	P value
Glargine Daily	8.4%	-1.26	P=NS	Glargine Daily	43.9%	P=NS	
Degludec Daily	8.4%	-1.07		Degludec Daily	40.8%		
Degludec FLEX	8.5%	-1.28		Degludec FLEX	38.9%		

Meneghini et al. *Diabetes Care*. 2013;36:858.

Head-to-Head Trials: Insulin Degludec vs. U-300 Insulin Glargine

	Insulin?	CV Safety	Randomized	Real-World	Sponsor
DEVOTE	U300 IG U100 ID	✓			Novo
BRIGHT	U300 IG U100 ID		✓		Sanofi
DELIVER Naïve D	U300 IG ID (strength not stated)			✓	Sanofi
CONCLUDE	U300 IG U200 ID		✓		Novo
CONFIRM	U300 IG U100 or U200 ID			✓	Novo

U-300 IG= U-300 insulin glargine; U-100 or U-200 ID= insulin degludec

Rosenstock et al. *Diabetes Care*. 2018;41:2147-54. Cheng A et al. *Diabet Obes Metab*. 2020;1-9. Philis-Tsimikas. European Association for the Study of Diabetes 2019. Barcelona, 19 September 2019 Sullivan SD et al. *Diabet Obes Metab*. 2019;21:2123-32. Tibaldi J et al. *Diabetes Obes Metab*. 2019;21:1001-9.

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Insulin Degludec vs. Insulin Glargine (U-300)

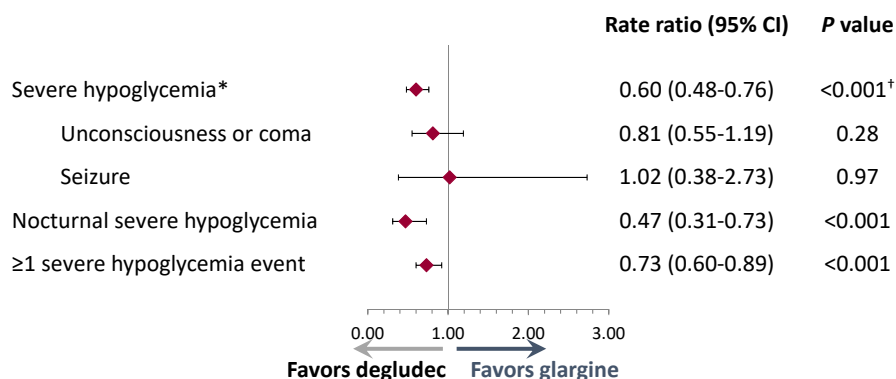
	Duration (weeks)	A1C (%)		ALL Hypo (95% CI)	Nocturnal Hypo (95% CI)	Severe Hypo (95% CI)
		GLAR	DEG			
BRIGHT	24	-1.64	-1.59	0.88 (0.66-1.17)	0.99 (0.74-1.32)	1 episode GLAR U300
		P=NS				
CONCLUDE	88	DEG -0.1% (-0.18- -0.02)		0.88 (0.73-1.06)	0.63 (0.48-0.84)	0.2 (0.7-0.57)
		P=0.02				
DELIVER Naïve D	24	-1.67	-1.58	0.94 (0.54-1.37)	Not reported	
		P=NS				
CONFIRM	24	-1.22	-1.48	0.64 (0.47-0.88)		
		P=0.029				

Hypo=hypoglycemia; Glar: insulin glargine; Deg: insulin degludec

Rosenstock et al. *Diabetes Care*. 2018;41:2147-54. Cheng A et al. *Diabetes Obes Metab*. 2020;1-9. Philis-Tsimikas. EASD 2019. Barcelona, 19 September 2019 Sullivan SD et al. *Diabetes Obes Metab*. 2019;21:2123-32. Tibaldi J et al. *Diabetes Obes Metab*. 2019; 21:1001-9.

Hypoglycemia: Insulin Degludec versus Glargine

DEVOTE CVOT Safety Outcomes (n=7637)



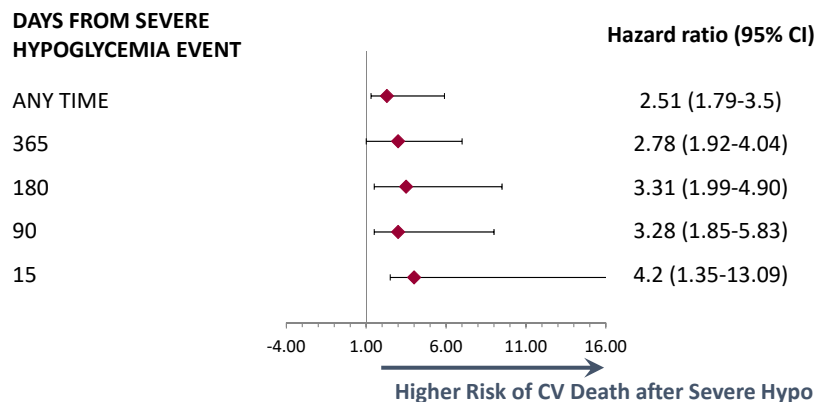
*Episode requiring assistance from another person to actively administer carbohydrate or glucagon or take other corrective actions. CI, confidence interval.

Marso SP et al. *N Engl J Med*. 2017;377:723-32.

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Severe Hypoglycemia Increases Risk of CV Death

DEVOTE CVOT Outcomes



*Episode requiring assistance from another person to actively administer carbohydrate or glucagon or take other corrective actions.
CI=confidence interval

Pieber TR et al. *Diabetologia*. 2018;61:58-65.

How Can We Best Help Our Patients Understand This Complex Information?

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What Patients Need to Know

- Insulin
 - Storage and expiration
- Preparation of insulin product
 - Syringe and vial?
 - Pen device?
- Choosing syringes or pen needles
- How to properly use the device
- How to dispose of the device

Basal Insulin Delivery Options

Insulin	Concentration	Vial	Pen	Max Dose per pen injection	Relative Cost "AWP"
NPH	U-100	X	X	60	\$
Glargine	U-100	X	X	80	\$\$
Glargine	U-300		X	160 "MAX pen"	\$\$
Detemir	U-100	X	X	80	\$\$\$
Degludec	U-100	X	X	80	\$\$\$\$
Degludec	U-200		X	160	\$\$\$\$
Regular Human	U-500	X	X	300	\$\$

AWP= average wholesale price

Product package insert. ADA Standards of Medical Care in Diabetes 2020. *Diabetes Care*. 2020;43:S98-S110.

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Expiration of Products

Products/Device	Refrigerated	Unrefrigerated	Once Used (opened)
Vials			
Insulin lispro, aspart, glulisine, glargine	Expiration Date	28 days	28 days
Insulin human R or N (Humulin)		31 days	31 days
Insulin human R or N (Novolin)	Expiration Date	42 days	42 days
Insulin human R (U-500)		40 days	40 days
Pens			
Insulin lispro, aspart, glulisine	Expiration Date	28 days	Do not refrigerate
Insulin glargine (U-100)			28 days
Insulin human R (U-500)			
Vials and pens			
Insulin detemir	Expiration Date	42 days	Do not refrigerate
Insulin degludec (U-100 or U-200)			42 days
Insulin glargine (U-300)	Expiration Date	56 days	56 days

<http://www.pdr.net/browse-by-drug-name>. Accessed 2020 Jan 10.

Insulin Pen Injection Technique

- Dial dose of insulin on the pen
 - Air in insulin chamber? Remove first
 - Ensure proper dose appears in the “dosing window”
- Screw on pen needle (remove outer/inner cap)
- Smoothly insert pen needle flush to skin, use 90° angle
- Depress the button to release insulin into SC tissue
- Delay withdraw of needle for 5 to 10 seconds after dose is delivered
 - Ensures full dose is delivered
- Pen may leak if needle kept on pen
- Always have the patient demonstrate back their technique

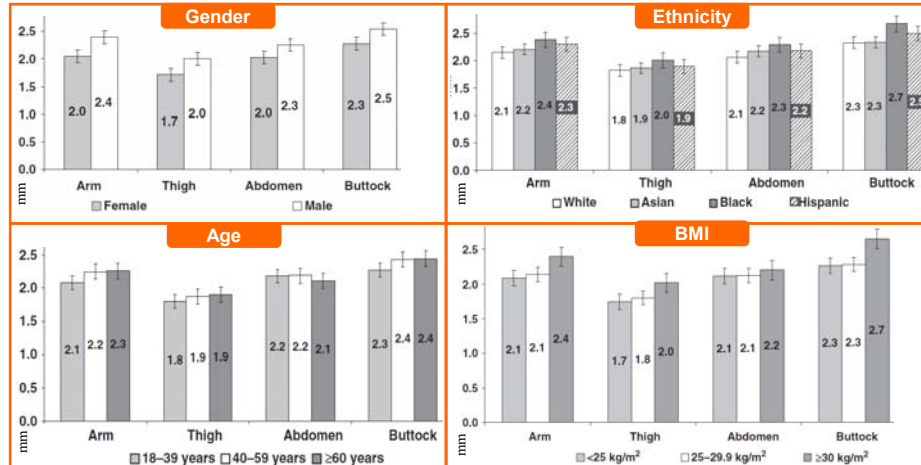


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Pen Needle Selection

Skin Thickness is Highly Consistent Among Patients

- Approximately 2-2.5 mm* (1.25-3.25 mm) regardless of gender, age, ethnicity, BMI
- Short needle should work for majority of patients

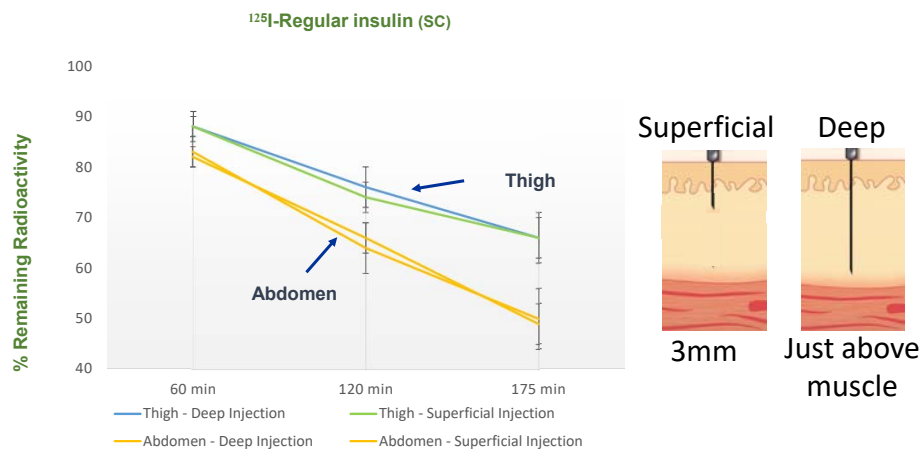


*Mean skin thickness results with 95% confidence intervals combined at all 4 injection sites
BMI=body mass index

Gibney M et al. *Curr Med Res Opin.* 2010;26(6):1519-30.

Absorption of regular insulin is consistent across Deep versus Superficial SC injection

Regular insulin is absorbed at similar rates at both sites, whether injected into deep or superficial subcutaneous tissue



Frid A et al. *Diabetic Medicine.* 1992;9:236-9.

Back to Insulin Basics: Solidifying Strategies to Overcome Barriers and Improve the Insulin Initiation Experience

Insulin Initiation: We Must Address Patients' Concerns

- Are there other treatment options the patient could try first?
- Does insulin mean my diabetes is getting worse?
- I'm scared of needle pain
 - I don't want to get "hooked on the needle"
- I'm worried about developing low blood glucose levels

These are logical concerns!

Adapted from Allen NA et al. *J Clin Transl Endocrinol.* 2016;7:1-6.

Overcoming Psychological Insulin Resistance

- Use motivational interviewing skills
 - "So what you are telling me is..."
- Avoid using insulin as a "threat"
 - Use insulin as the **solution**
 - Discuss it openly
 - Avoid gestures/facial expression that it is a bad thing
 - Promise a reassessment after a "limited" time trial
- Recommend insulin pens and higher gauge, shorter pen needles
- Demonstrate how to use the device, then have patient teach back device and injection technique in the office/pharmacy
- Manage expectations
 - Tell patient that injection is less painful than finger stick
 - Most patients do not feel pain with higher gauge, short needles
- Teach patient to recognize and treat hypoglycemia

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“Q&A” About Diabetes and Insulin

Provider	To Patient	For Patient-Outcome “What’s in it for me?”
Diabetes is progressive and over time the ability to make insulin can be diminished	<p>What are your fears or concerns if insulin would be necessary?</p> <p>If your body does not make enough insulin, the pills often are not enough to normalize your blood glucose. Insulin may be necessary to normalize it.</p>	<p>-This may mean you feel less fatigue</p> <p>-You may have more energy</p> <p>-You will be at lower risk of some serious complications</p>
I can’t do this.	What concerns about taking/potentially taking insulin are the most difficult for you?	Taking insulin is a series of steps, we can work together until the steps come together

Adapted from: Polonsky WH et al. *Int J Clin Pract.* 2017;71(8):e12973.

“Q&A” About Diabetes and Insulin

Concern	Answers
<p>What have you heard about insulin?</p> <p>This stuff can kill you! My ____ started insulin, and was dead three years later</p>	<p>Did ____ die from a low sugar reaction?</p> <p>It is likely insulin was started too late and that ____ had high blood sugars for a very long time, which puts people at risk for a lot of serious complications. Keeping your blood sugar at goal can decrease your risks of having these complications</p>
What side effects should I expect?	<p>Insulin may cause a low blood sugar reaction. Testing your blood sugar at home is important, especially if you think you are having the signs/symptoms of low blood glucose (REVIEW: Testing, Hypoglycemia)</p>

Adapted from: Polonsky WH et al. *Int J Clin Pract.* 2017;71(8):e12973.

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“Q&A” About Diabetes and Insulin

Concern	Answer
I'm afraid of needles	Most people have a fear of needles, that's normal, but just to be clear, insulin isn't addictive.
"I don't want to get hooked on the needle"	Are there addiction concerns with you or a family member I should be aware of? Let's try an injection together and see how you do.
So if I get better, can I stop insulin?	Well let's try it for a couple of weeks and see where we are at...many people have to continue with insulin, but we will take it one week at a time.
This is so overwhelming	Yes, it is a lot of new information. Are there questions we can answer now that may help get you started?
I can't remember all those steps at once!	You don't have to remember everything at once. Let's try a step at a time....

Adapted from: Polonsky WH et al. *Int J Clin Pract.* 2017;71(8):e12973.

Key Takeaways

- Inadequate glycemic control is common
- Timely initiation and titration of insulin helps the majority of patients achieve A1C goals
 - Therapeutic inertia is common with initiation and titration of insulin
- Understand the needs of your patient when starting basal insulin products
 - Cost?
 - Ease of use?
 - Avoidance of hypoglycemia?
 - Allaying common fears?

Back to Insulin Basics: Solidifying Strategies to Overcome Barriers and Improve the Insulin Initiation Experience

Key Takeaways

- Newer basal insulin choices with advantageous pharmacokinetics may improve ease of use and minimize hypoglycemia
- Conduct a motivational interview “Q&A” with your patient to improve the insulin initiation experience

Select References

- American Diabetes Association. Pharmacologic approaches to glycemic treatment. Standards of medical care in diabetes – 2020. *Diabetes Care*. 2020; 43(suppl 1):S98-110.
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