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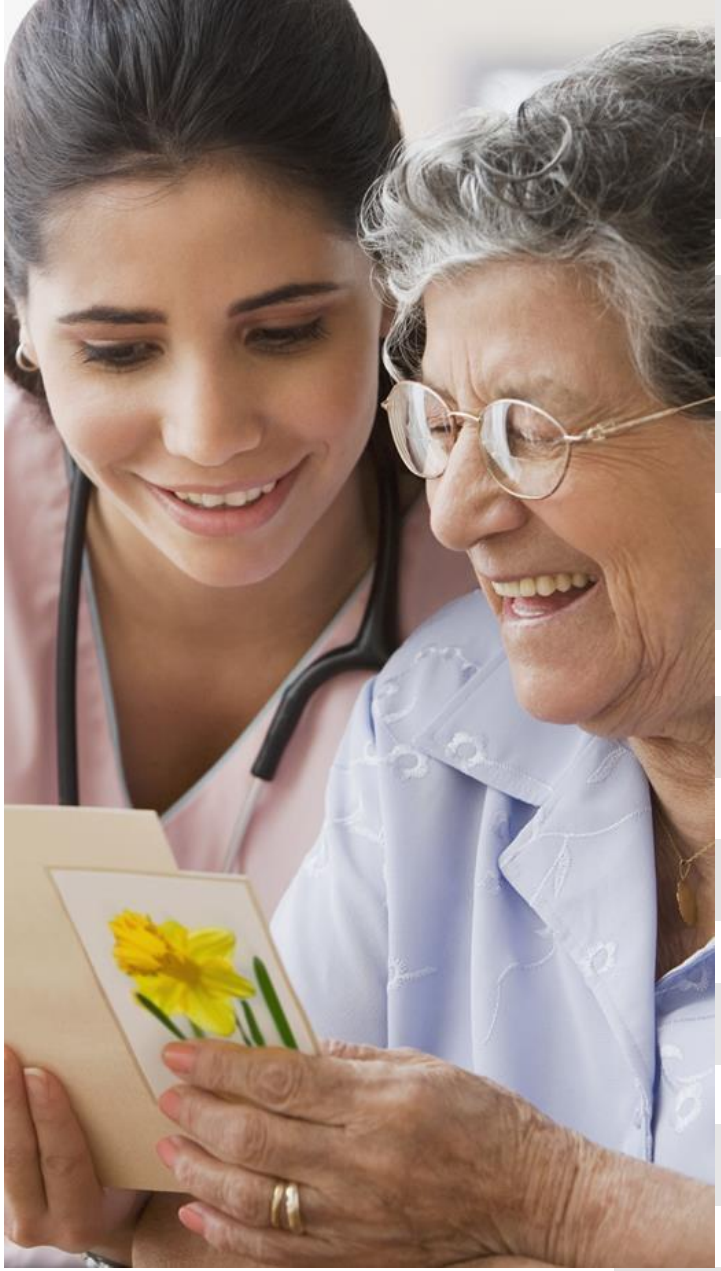
Update on New Basal Insulins and Combinations: Starting, Titrating and Adding to Therapy



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Discussion Points

- What new basal insulins and fixed-ratio combinations of basal insulin + GLP-1 receptor agonists (RA) are available?
- Why do we need them?
- How do we initiate, titrate and intensify them?
- What other drugs can we put with them to improve outcomes for type 2 diabetes?



Actions/Uses of Basal Insulin

Basal insulin (NPH, glargine [U-100 and U-300], detemir, degludec U-100, U-200)

- Controls fasting and preprandial glucose
- Titration is targeted at fasting plasma glucose (FPG)
- Released at nearly constant levels throughout the day

Common mistake: Using basal insulin to try and control postprandial glucose (PPG)

1. Insulin Therapy for Type 2 Diabetes: Making It Work. JFPONLINE.com Vol 59, Apr 2010
2. Insulin Regimens for Type 2 Diabetes Mellitus. JFPONLINE.com (December 2006-Supplement)

Brand Name	Generic
Novolin, Humulin	NPH
Levemir	Detemir
Lantus	Glargine 100 U/ml
Toujeo	Glargine 300 U/ml
Tresiba	Degludec
Novolog 70/30 Humalog 70/30	70% insulin aspart protamine suspension and 30% insulin aspart

Insulin Pharmacokinetics: Quick Summary

Insulin	Onset	Peak	Duration
NPH			
NPH	2-4 hours	4-10 hours	14-18 hours
Peakless Basal			
Glargine 100 U/ml	1-4 hours	Minimal	24 hours
Detemir	1-4 hours	Minimal	Up to 24 hours
Increased Duration Basal Insulins			
Glargine 300 U/ml	Develops over 6 hrs	None	> 30 hours (median)
Degludec 100 U/ml 200 U/ml	1-4 hours	None	Approx 42 hrs

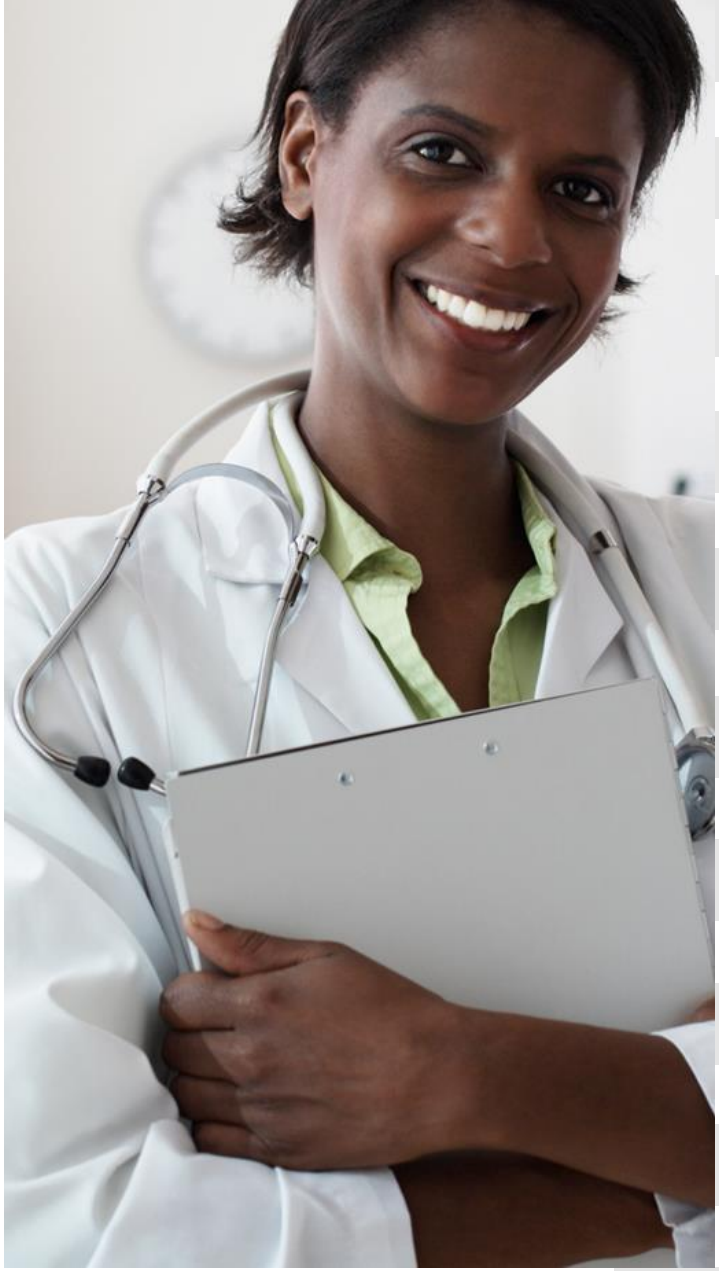
www.dlife.com/diabetes/insulin/about/insulin/insulin/chart accessed 5/1/2011

Why the Need for Newer Insulins?

NPH

- The same dose by the same person in the same site at the same time of day under the same conditions can vary up to 50% in absorption!

- NPH peaks in 4-6 hours, possibly resulting in nocturnal hypoglycemia





NPH Resurgence

- More people having to switch from basal insulin analogs due to cost
- Be prepared if switching from NPH insulin to go down in dose until glycemic control is established
- Patient demonstrates how to use vial and syringe
- Patient understands mixing (rolling technique)
- Help patients be more aware of activity levels, meals/snacks and possibly greater night time hypoglycemia

Why the Need for Newer Insulins?

Glargine and Detemir

- Still slight peak
- Some variability
- Hypoglycemia
- In some cases twice daily injections
- More injections, less adherence



Polling Question

Basaglar (insulin glargine 100 U/ml) is a generic version of Lantus and can be substituted for the brand name.

A) True

B) False

Basaglar (Insulin glargine 100 U/ml)

- Not a generic of Lantus
- Has similar properties
- Considered a follow-on biologic
- Identical amino acid sequence



Why the Need for Newer Basal Insulins?

Smoother, Flatter and More Constant Profiles

- Lower intra-patient variability
- Increased adherence
- Less hypoglycemia
- Less weight gain

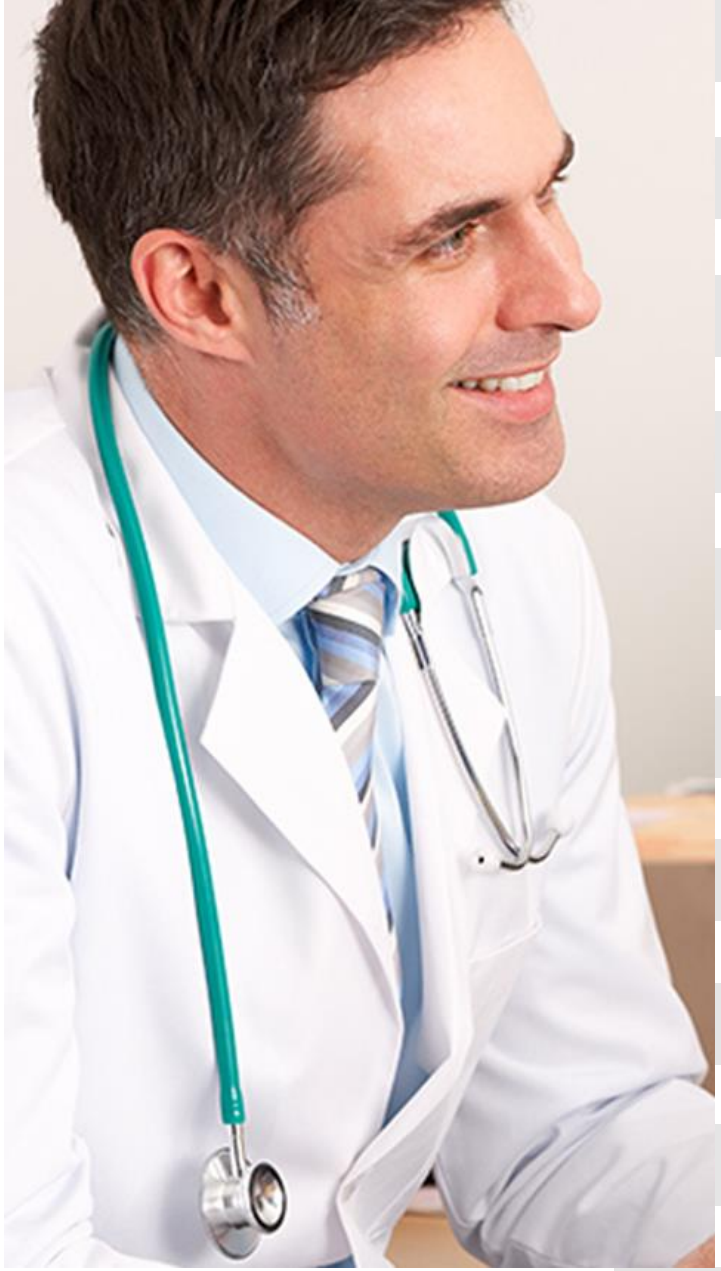


Newer Insulin Starts

- Single insulin
- Easy education (insulin pen only)
- Clear and defined glucose target (FPG)
- Once daily injection
- Straightforward titration
- Low dose initiation
- Low incidence of hypoglycemia



Newest Insulins are "Forgiving" Leading to Greater Adherence



Glargine 300 U/ml

- Dose is given once daily but can be administered within a 3 hour window either way[1]

Degludec 100 U/mL and 200 U/mL

- If dose is missed may be given the next day as long as there is 8 hours before next dose[2]

1. Type 1 diabetes mellitus in adults: high-strength insulin glargine 300 units/ml (Toujeo) NICE Advice, published Oct 2015. Accessed Mar 24, 2016
2. Tresiba [package insert]. Bagsvaerd, Denmark: Novo Nordisk; 2015.

Decreased Hypoglycemia

Both degludec and glargine 300 U/ml were associated with 25% less nocturnal hypoglycemia (vs NPH)

Fear of hypoglycemia

- Less adherence
- Suboptimal control



Birkeland KI, Home PD, Wendisch U, et.al. Diabetes Care. 2011;34:661–665
Accessed 3/24/0216
Reuter's, Sat Jun 14, 2014 Sanofi Reports Positive Phase 3 Results for Toujeo
Accessed 3/26/2016

Other Considerations

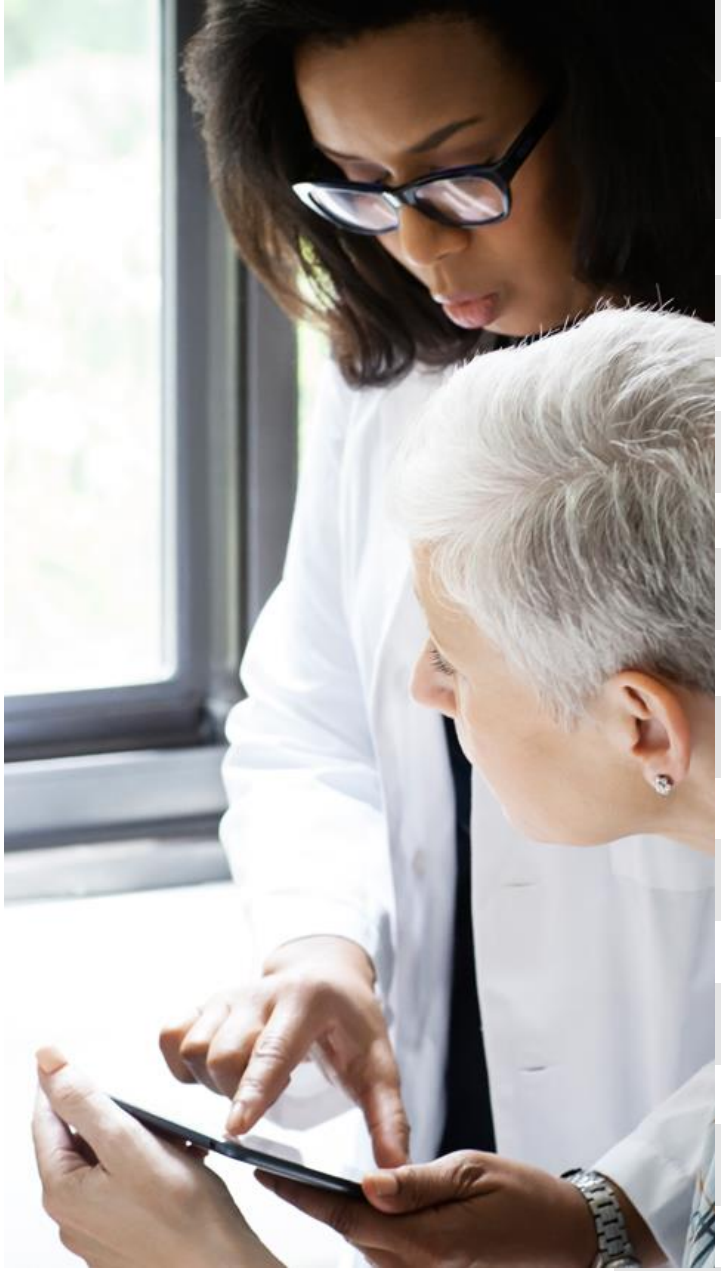
Degludec

- Comes as 100 U/ml and 200 U/ml
- Pharmacodynamics are similar and flat
- U-200 pen delivers up to 160 units per injection

Glargine 300 U/ml

- When converting from glargine U-100 is unit for unit but studies show that dose may need to be titrated up by 10-18%
- Pen delivers 80 units max

Titrate both insulins in 3-4 day increments to FPG target



Initiation

Titration

Intensification

Various Basal Insulin Starts For Glargine 100 U/ml

Treat to Target Trial "2-4-6-8" algorithm

- Add 2,4, 6,or 8 units of glargine weekly until mean FPG=100 mg/dl (5.6 mmol/L)

ATLANTUS Study "3-2-1" algorithm

- Add 2 units glargine every 3 days until mean FPG=100 mg/dl (5.6 mmol/L)

No compromise in safety

Straightforward and standardized approach

Example: Once-Daily Dosing for Glargine

Start with 10 units once daily and adjust weekly

Self-monitored FPG from preceding 7 days with no episodes of severe hypo or prandial glucose ≤ 72 mg/dL (4.0 mmol/L)	Titration: Increase in insulin dose (units/day)
100–120 mg/dL (5.6-6.7 mmol/L)	**2**
120–140 mg/dL (6.7-7.8 mmol/L)	**4**
140–180 mg/dL (7.8-10 mmol/L)	**6**
≥ 180 mg/dL (10 mmol/L)	**8**

Riddle M, et al. Diabetes Care 2003;26:3080–3086.

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dl, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY[a]	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS[b]	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY[a]	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS[b]	low	low	high	high	high	high

If A1C target not achieved after approximately 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- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

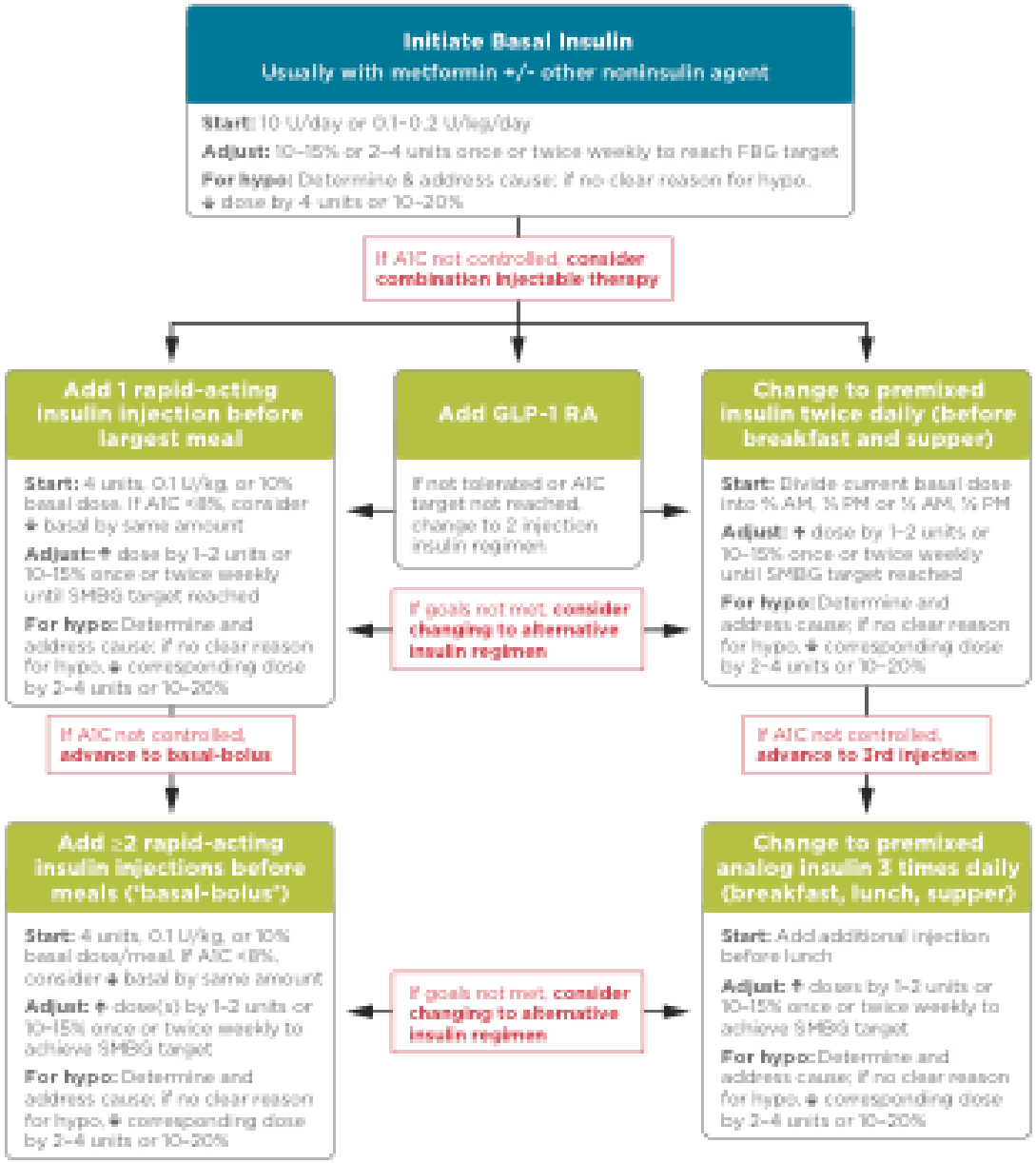
Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[c]	or GLP-1-RA	or Insulin[c]	or GLP-1-RA
or Insulin[c]	or Insulin[c]		or Insulin[c]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA. (2) on GLP-1 RA, add basal insulin or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e. adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 3)

American Diabetes Association Standards of Medical Care in Diabetes 2017. Diabetes Care 2017;40(Suppl. 1):S54.

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American Diabetes Association Standards of Medical Care in Diabetes 2017. Diabetes Care 2017;40(Suppl. 1):S54.

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Degludec Start and Titration (Type 2)

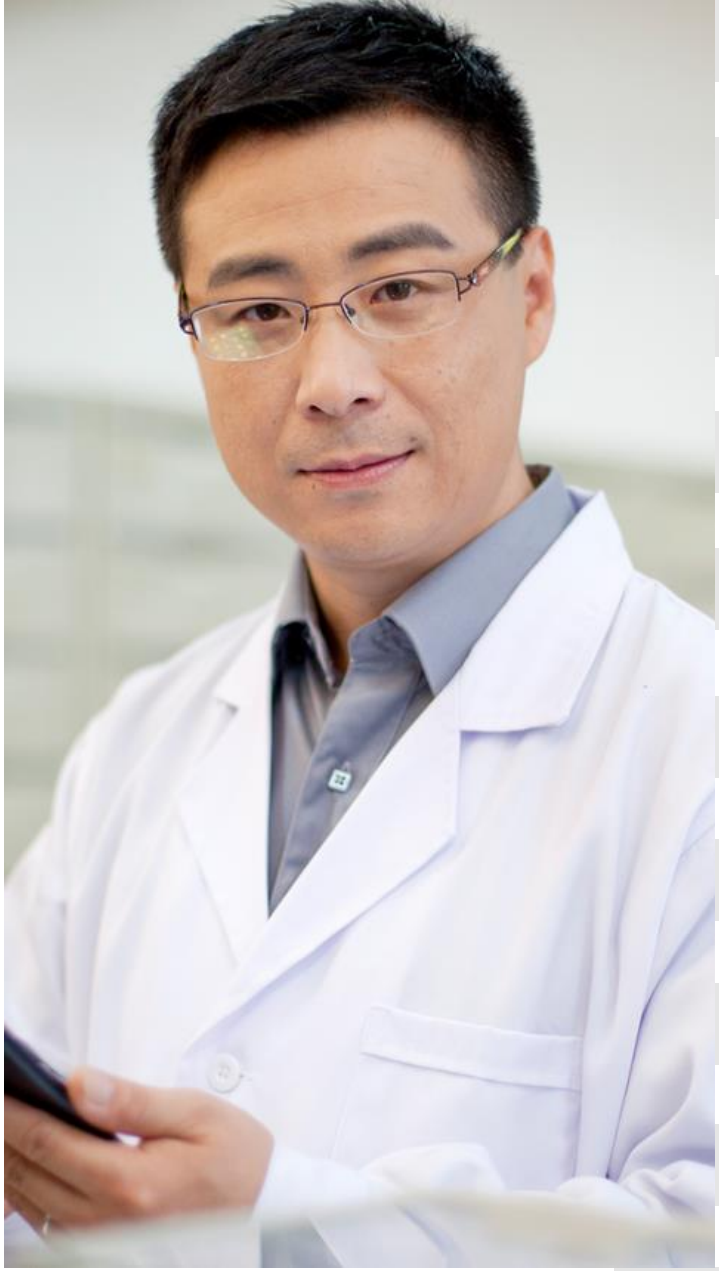
Insulin naïve

- Start 10 units daily

If converting from long-acting or intermediate acting insulin is 1:1

Titration

- Every 3-4 days according to BG and glycemic control



Polling Question

The suggested starting dose for a person with type 2 diabetes for insulin glargine 300 units/ml is:

A) 0.5 units per kilogram

B) 0.2 units per kilogram

C) 10 units for all patients

D) Either 10 units or 0.2 units per kilogram is correct

Insulin Glargine 300 U/ml: Start and Titration (Type 2)

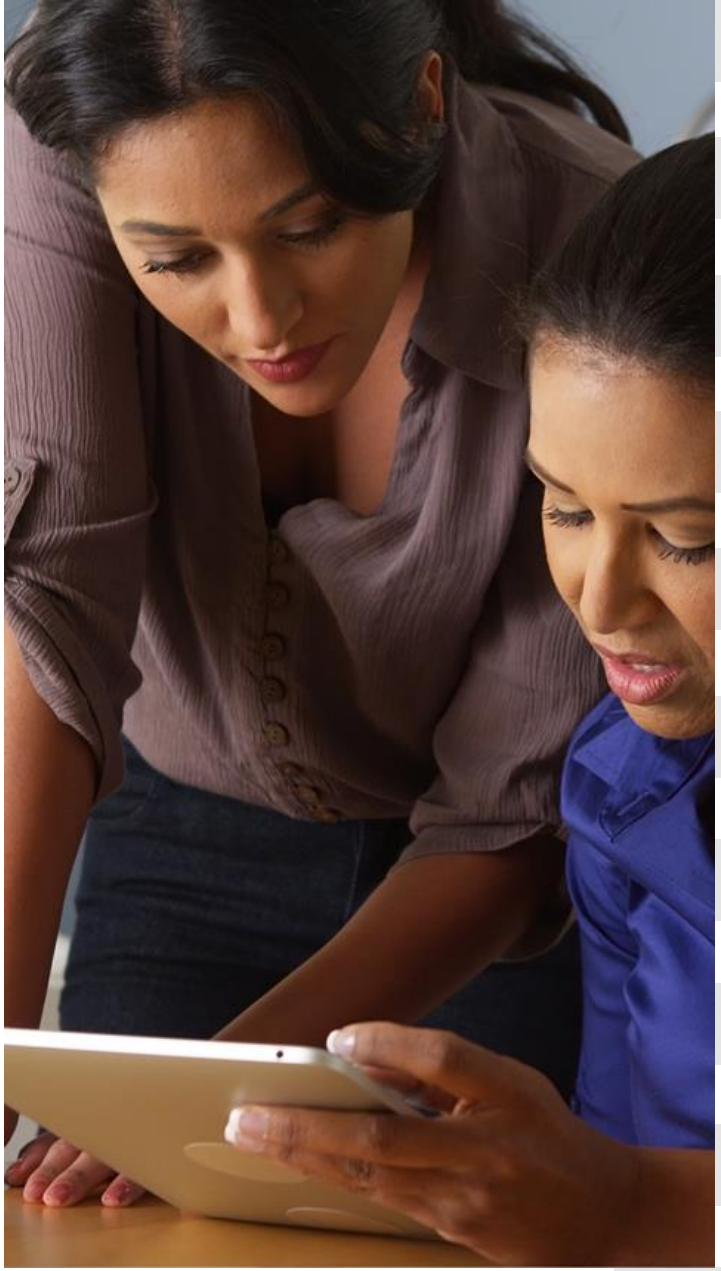
0.2 units/kg

- If converting from long-acting or intermediate acting insulin once daily is 1:1

For twice daily NPH start at 80% of TDD

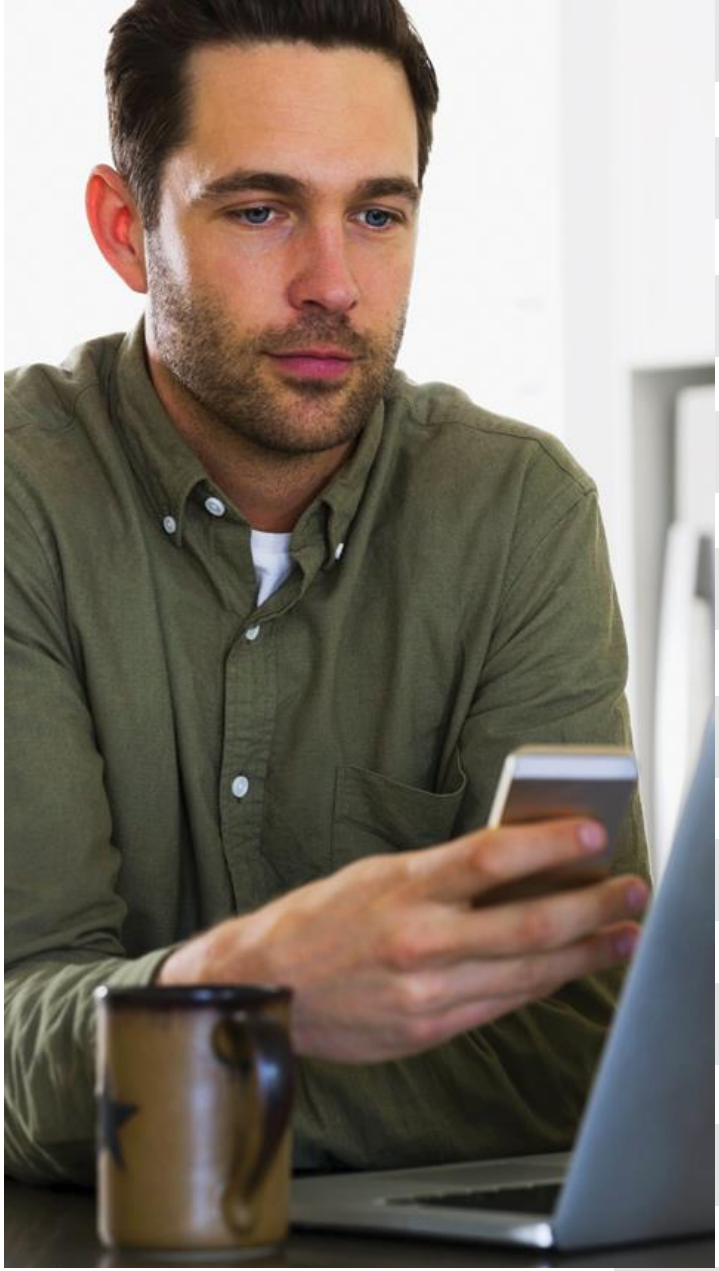
Titration

- No more often than every 3-4 days according to BG and glycemic control



Insulin Intensification

- Basal plus one (prandial insulin after largest meal)
- Basal/bolus (2-3 prandial doses)
- Switch to insulin pre-mix twice daily (70/30, 50/50)
- Add GLP-1 RA once daily



Polling Question

The main side effect of GLP-1 RA and insulin combinations is listed as:

A) Gastrointestinal upset

B) Hypoglycemia

C) Cough

D) Jimmy legs

Why Combine GLP-1 RA with Basal Insulin?



- Improved A1C (comparable to adding prandial insulin)
- Added lowering of FPG
- Beneficial effects on PPG
- Lowers risk of hypoglycemia compared to increased basal insulin alone or adding prandial insulin
- Less weight gain

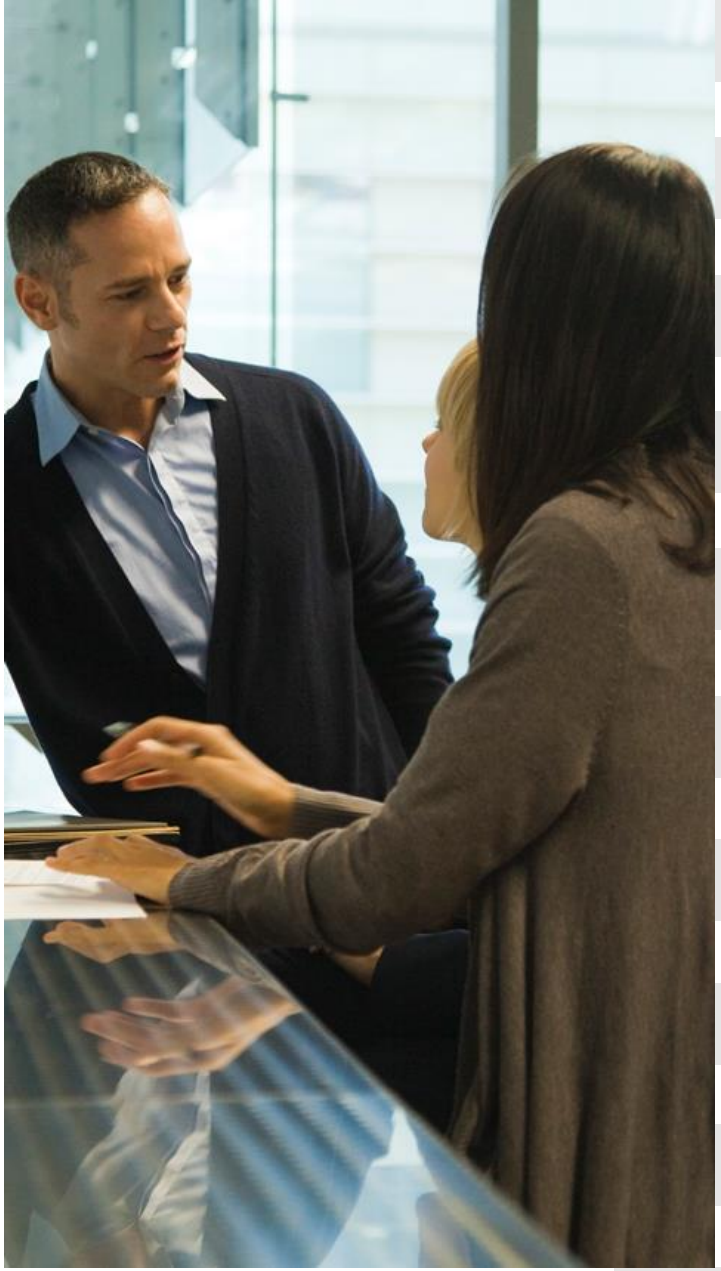
GLP-1 RA Plus Basal and Vice Versa

If adding GLP-1 RA to basal insulin, a downward titration of basal insulin is suggested

- Reduction of basal insulin dose reduces risk of hypo and weight gain

Adding basal insulin to GLP-1 RA obviates need for downward titration of basal

Both provide safer and easier way to achieving control



Riddle M, Metformin+exenatide+basal insulin vs metformin+placebo+basal insulin: reaching A1c <6.5% without weight-gain or serious hypoglycemia Diabetes 2010;**57**(Suppl. 1)

DeVries JH, Bain SC, Rodbard HW, et al., Liraglutide-Detemir Study Group Diabetes Care2012;**35**:1446–1454

US Indications for iGlarLixi and IDegLira



SOLIQUA™ 100/33 (insulin glargine and lixisenatide injection). Prescribing Information, Sanofi-Aventis U.S. November 2016.

INDICATION AND USAGE:

SOLIQUA 100/33 is a combination of a long-acting human insulin analog with a glucagon-like paptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide



XULTOPHY® 100/3.6 (insulin degludec and liraglutide injection). Prescribing Information, Novo Nordisk. November 2016.

INDICATION AND USAGE:

Xultophy 100/3.6 is a combination insulin degludec, a long-acting human insulin analog, and liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily)

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EU Indications for iGlarLixi and IDegLira

SULIQUA is indicated in combination with metformin for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or with basal insulin.

Xultophy is indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycaemic control

Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA), Suliqua Summary of Opinion 2016, Xultophy Summary of Opinion 2016

Fixed-Ratio Combinations of GLP-1 RAs and Basal Insulin

IdegLira (Xultophy 100/3.6) (administered once daily via pen)

- Liraglutide-Lira (GLP-1 RA)
- Degludec (insulin U-100)

Fixed-Ratio Combination

- 1 mL of IDegLira contains 100 units degludec and 3.6 mg Lira
- Max dose 50 units
  - 50 units degludec
  - 1.8mg liraglutide
- Slow titration=greater tolerability

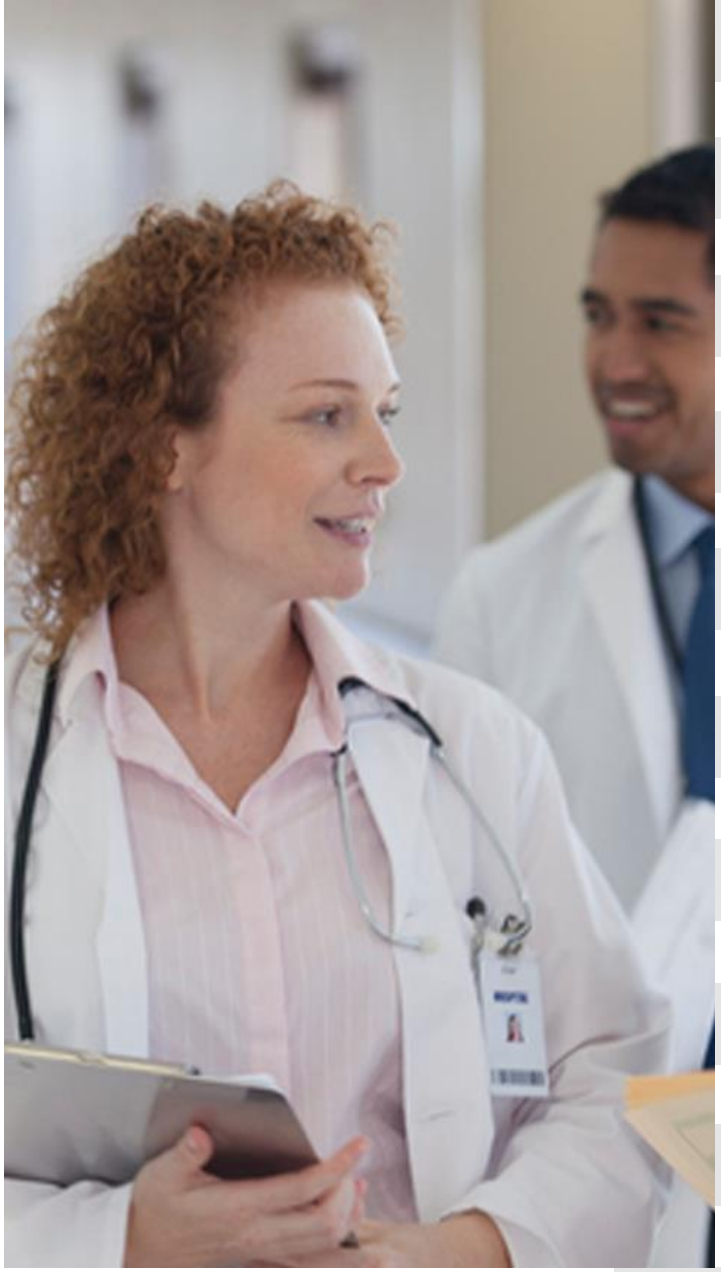


IDegLira 100/3.6 Titration

Starting dose:

- Previously treated with GLP-1 RA or insulin:
  - 16 units
    - 16 units delgludec
    - 0.6 mg liraglutide

- Titrate by 2 units every 3-4 days



Fixed-Ratio Combinations of GLP-1 RAs and Basal Insulin

iGlarLixi

- Lixisenatide (GLP-1 RA)
- Glargine U-100 insulin

Fixed Ratio

- Dose range 15-60 units
- Maximum dose: 60 units of insulin glargine and 20 mcg lixisenatide



Soliqua 100/33 Titration

Starting dose:

- TDD of insulin < 30 units/day
  - Start at 15 units
- If TDD of insulin ≥30 units/day
  - Start at 30 units
- Titrate 2-4 units weekly until target FPG is reached



Overall Results of Fixed Combo GLP-1 RA/Basal



- Robust lowering of A1c
- Well tolerated
- Less weight gain versus basal insulin alone
- Possible lower (only one) co-pay
- Single injection daily
- Less burdensome to patients
- Consider using with patient above goal requiring basal insulin in place of insulin alone
- No increased risk of hypo versus basal insulin alone

Conclusions

- The new basal insulin formulations have considerable advantages over earlier insulins such as decreased hypoglycemia and increased adherence rates
- Earlier insulin initiation along with proper titration and intensification is essential to help patients get to goal and remain there
- Fixed ratio GLP-1 RA and insulin combinations offer greater flexibility and tolerability as well as decreased hypoglycemic events and weight gain

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