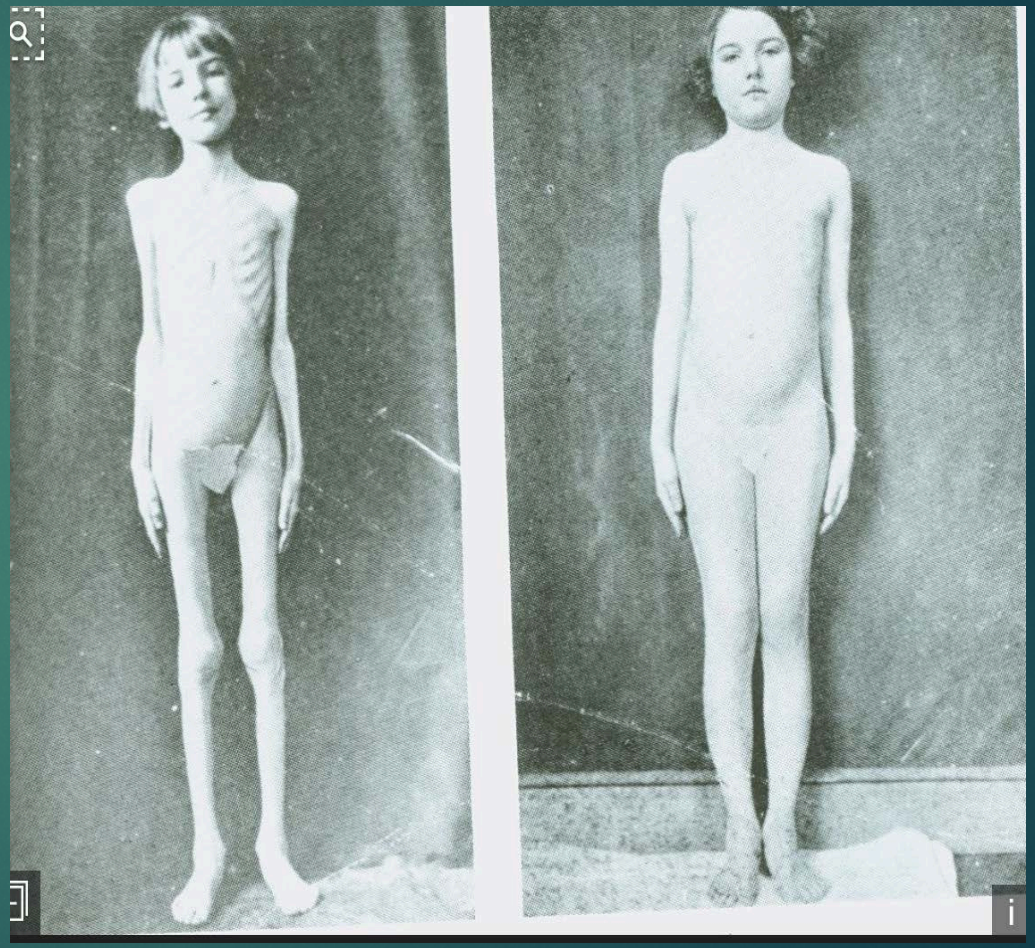
NEW INJECTABLE DIABETES MEDICATIONS

- DISCLOSURES: NONE

- OBJECTIVE: To describe new Insulins and Fixed Ratio Combinations that may enhance the care of people with diabetes

Insulin Chronology

- 1921: discovery of insulin
- 1922: first human treated with ox- derived insulin
- 1982: Human insulin
- 1996: first analog insulin: Humalog (lispro)
- 2001: first basal analog: glargine (Lantus)
- 2015: first concentrated basal insulin: U300 glargine(Toujeo)
- 2016: first “follow on” insulin: Basaglar
- 2017: first ultra-fast insulin: Fiasp



GLP-1 Chronology

- 1992: discovery of hormone in gila monster saliva: exendin-4
- 2005: approval of exenatide (Byetta)
- 2010: approval of liraglutide(Victoza)
- 2012: approval of first weekly GLP1(Bydureon)
- 2014: liraglutide approval for obesity
- 2017: liraglutide approval to reduce CV risk

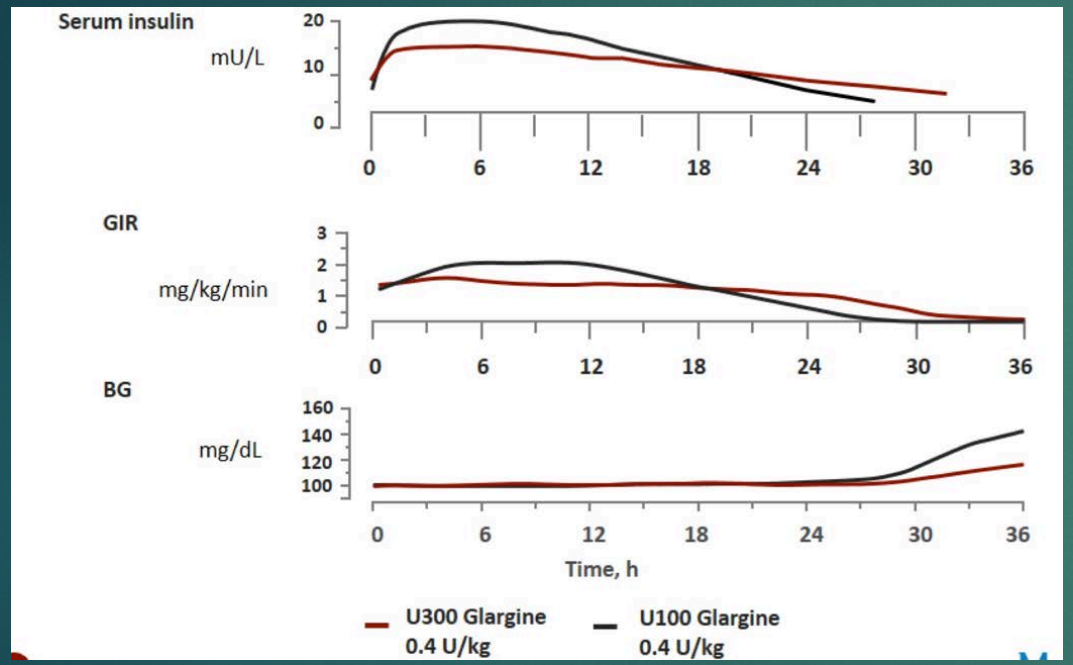
BASAGLAR® : insulin glargine (Lilly)

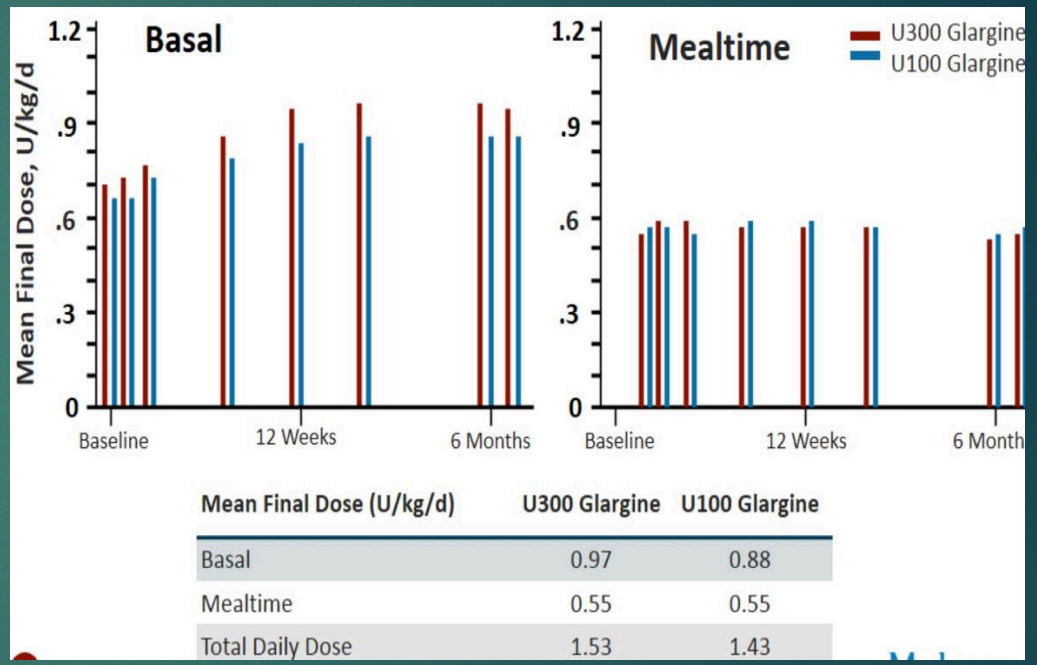
- FDA approval 12/15; marketed 12/16
- Chemical structure identical to Lantus®
- Abbreviated approval process based on studies demonstrating similar action to Lantus®
- Considered interchangeable not “biosimilar” by FDA
- Available only in prefilled KwikPen
- Switch from Lantus: same dose
- Switch from Toujeo: use 80% of Toujeo dose
- List price 15% below Lantus

Toujeo®: U300 insulin glargine

- U300 insulin glargine (Toujeo®)offers a smaller depot surface area leading to a reduced rate of absorption
- Flat prolonged pharmacodynamic profile
- Half-life is ~23 hours; duration of action ≤36 hours
- Less potent than U100 glargine

U300 Glargine vs U100 Glargine





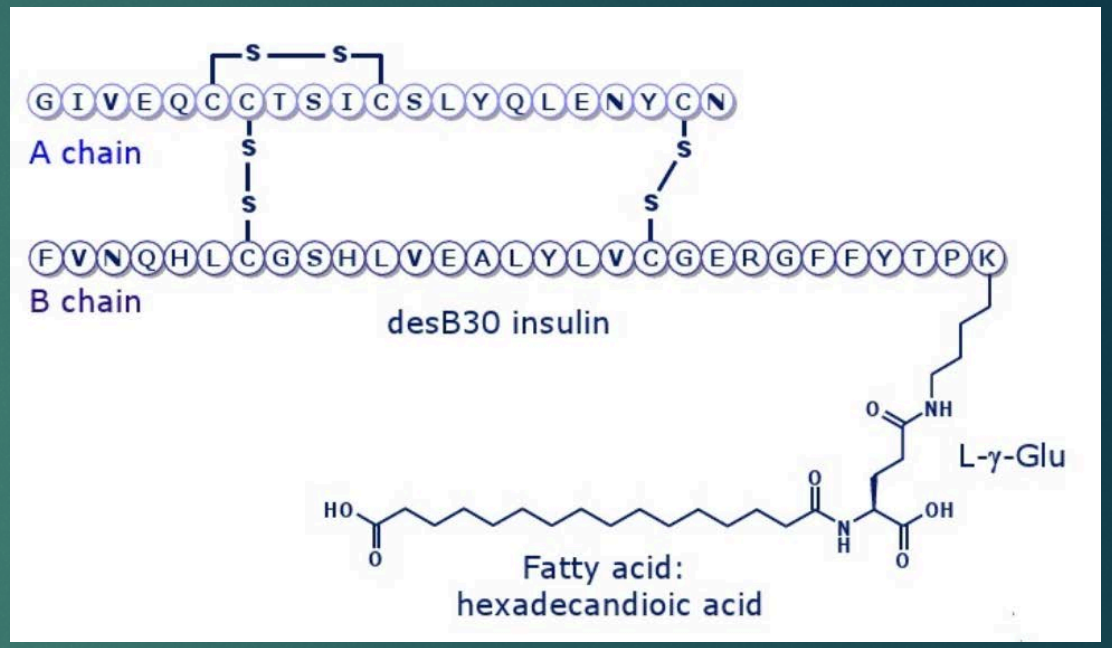
Mean Final Dose (U/kg/d)	U300 Glargine	U100 Glargine
Basal	0.97	0.88
Mealtime	0.55	0.55
Total Daily Dose	1.53	1.43

Becker. DiabCare2015

Riddle.EASD2013

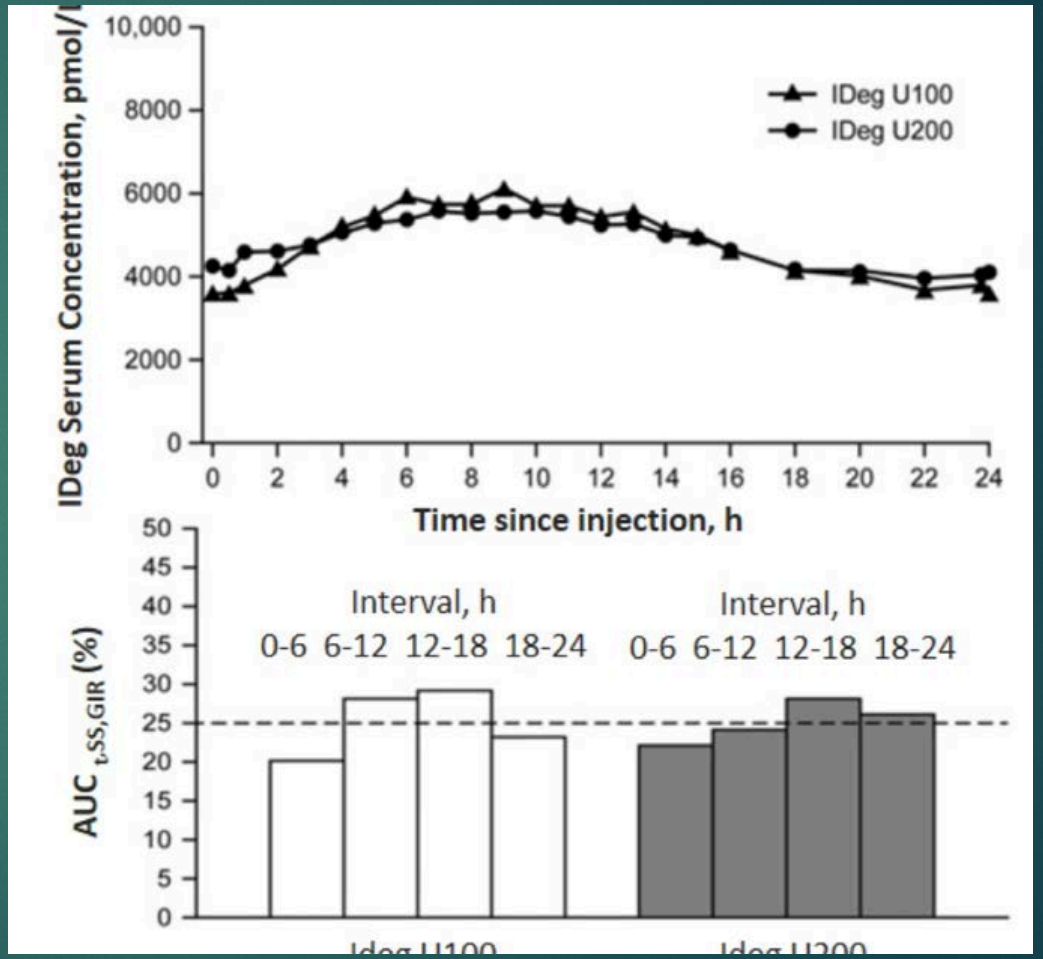
INSULIN DEGLUDEC: TRESIBA® (Novo Nordisk)

- FDA approval 9/2015;marketing 1/16
- Fatty acid sidechain/zinc results in hexamer and slow absorption
- Flat prolonged pharmacodynamic profile
- Half life ~25 hrs: duration ~42 hrs
- Steady state achieved in 3-4 days



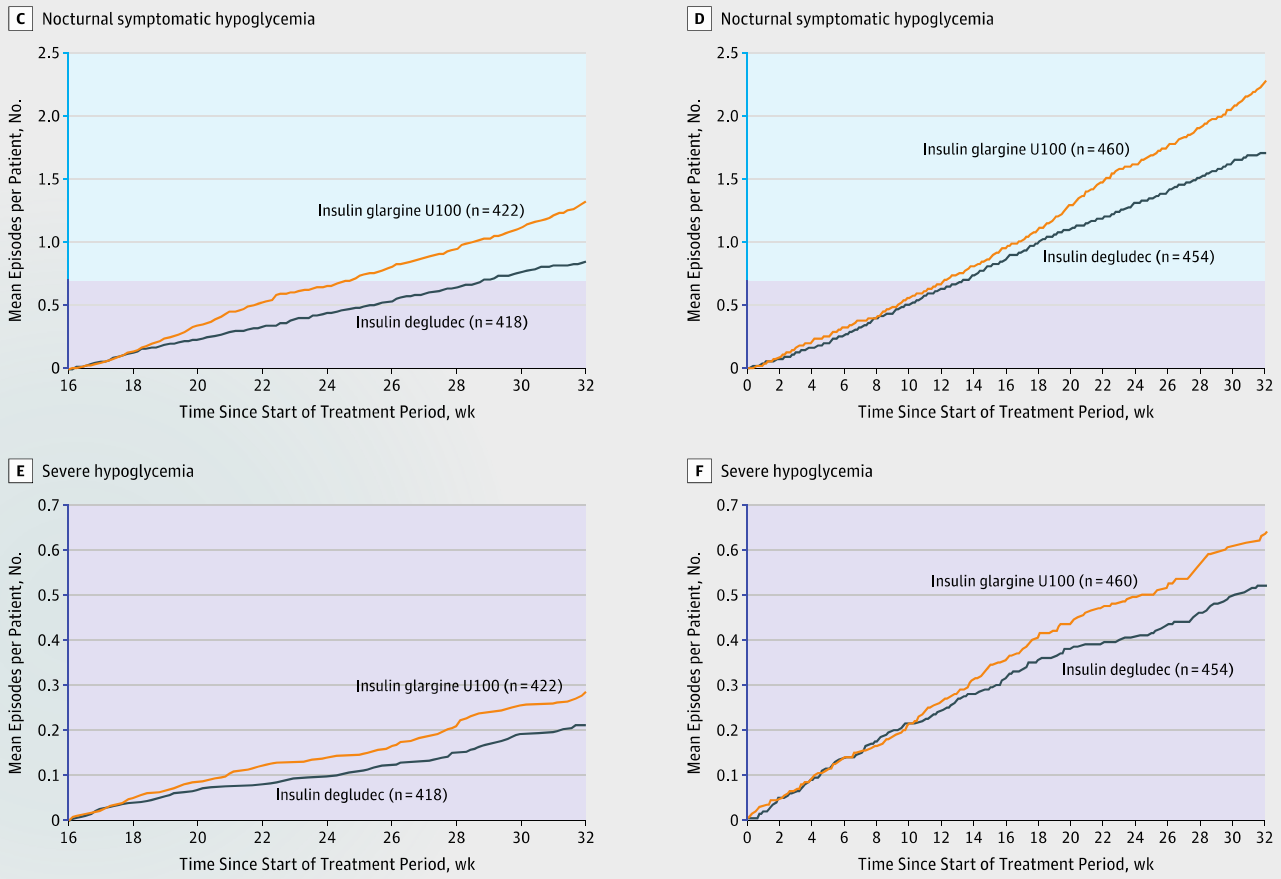
INSULIN DEGLUDEC: TRESIBA® (Novo Nordisk)

- Available as U100 or U200 which have identical PK/PD
- Available only in Flextouch pen
- U100 and U200 pens are color-coded
- Max dose per injection is 80 or 160



Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes
The SWITCH 1 Randomized Clinical Trial

Wendy Lane, MD; Timothy S. Bailey, MD; Gregg Gerety, MD; Janusz Gumprecht, MD, PhD; Athena Philis-Tsimikas, MD; Charlotte Thim Hansen, MD, PhD; Thor S. S. Nielsen, MS; Mark Warren, MD

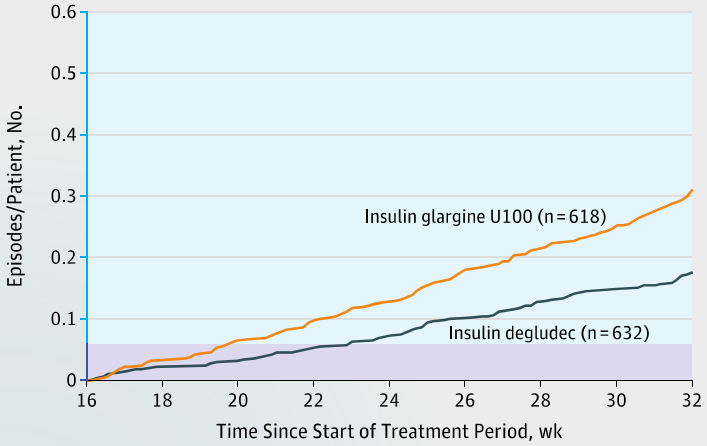


Data are based on safety analysis set. The tinted region in blue indicates the range from y = 0.7 to 2.5, the mean cumulative number of episodes per person; the tinted region in purple, y = 0 to 0.7, the mean cumulative number of episodes per person.

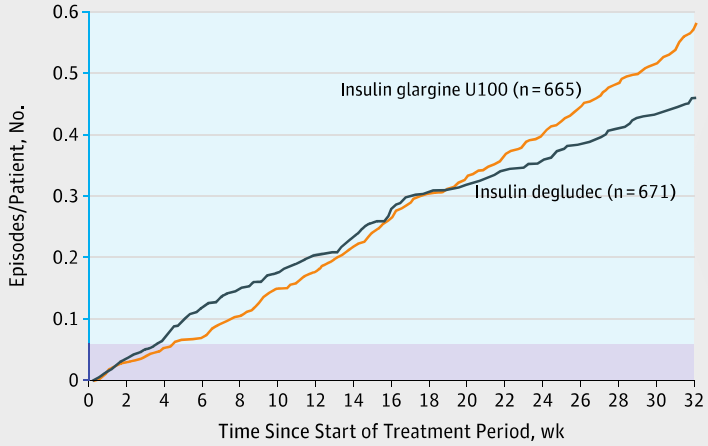
Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes
The SWITCH 2 Randomized Clinical Trial

Carol Wysham, MD; Anuj Bhargava, MD; Louis Chaykin, MD; Raymond de la Rosa, MD; Yehuda Handelsman, MD; Lone N. Troelsen, MD, PhD; Kajsa Kvist, MSc, PhD; Paul Norwood, MD

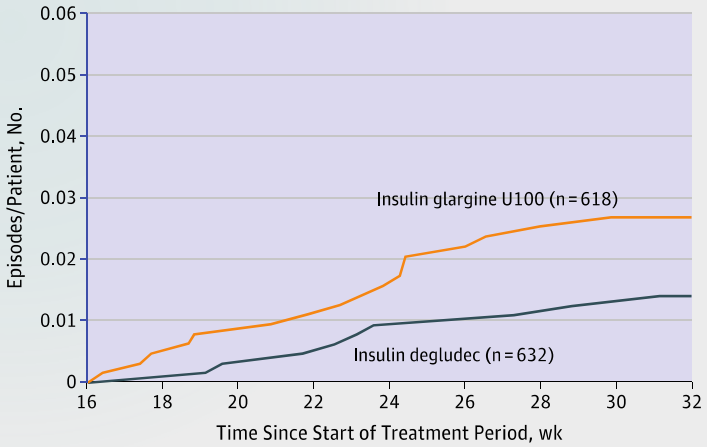
C Nocturnal symptomatic hypoglycemia



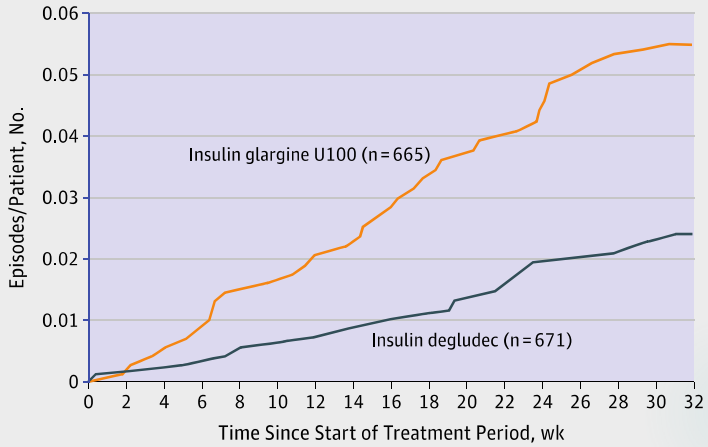
D Nocturnal symptomatic hypoglycemia



E Severe hypoglycemia

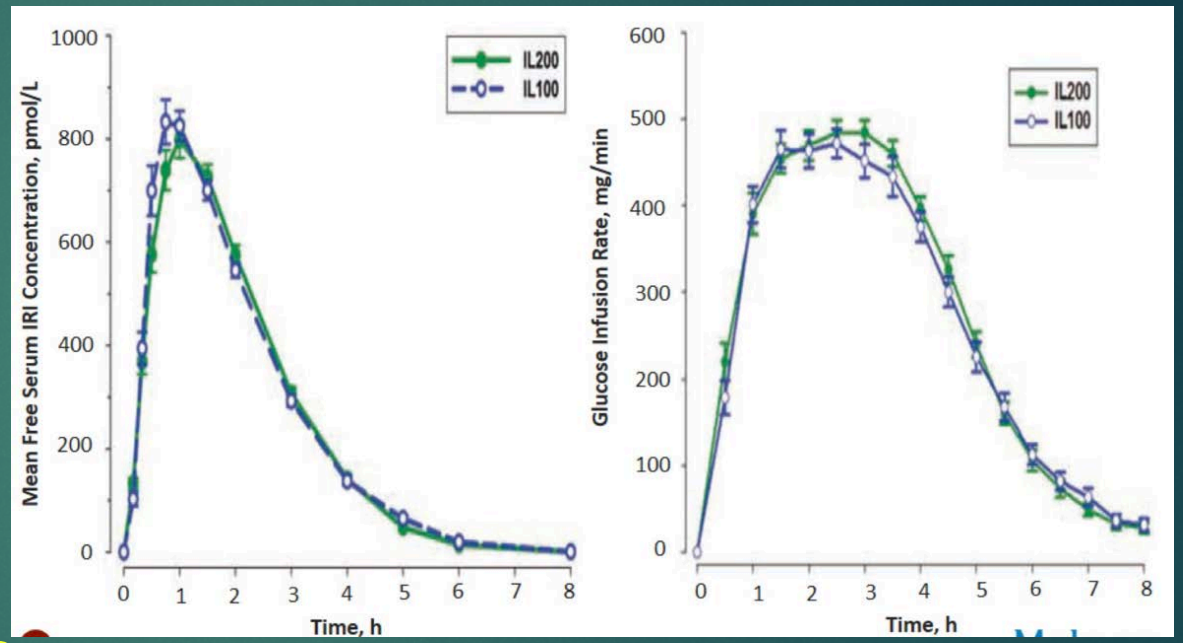


F Severe hypoglycemia



U200 Lispro (Humalog®)

- FDA approval May 2015
- Available only in Kwikpen
- Maximum dose 60 units per injection
- PK/PD same as U100 lispro
- Pen holds 600 units as opposed to 300 units in U100 pen



GLP-1 agonist and basal insulin combination: a meta-analysis

- 15 studies, 4300 subjects
- Greater reductions in A1c than other combinations
- No increased risk of hypoglycemia
- Mean weight reduction of 3.2kg
- Compared to basal/bolus insulin: greater A1c reduction, less hypoglycemia and mean weight reduction of 5.6 kg

- *Lancet Sept 2014*

Basal Insulin/GLP-1 FRC

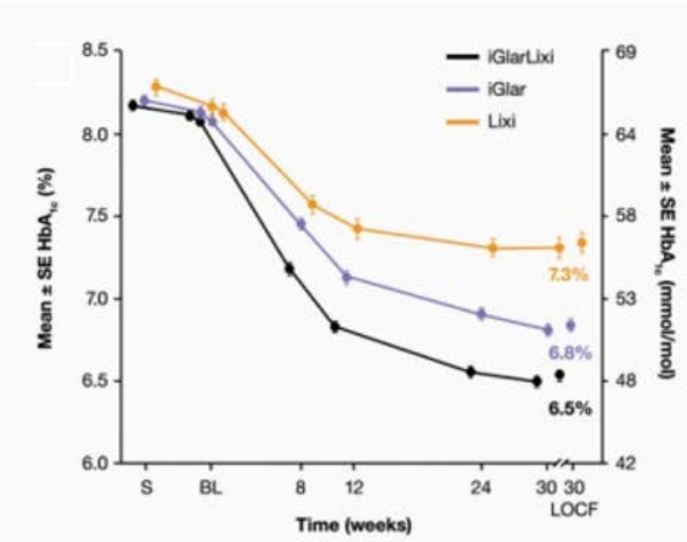
IDegLira and IGlarLixi

	IDegLira[a]	IGlarLixi[b]
Ratio	1 dosing unit = degludec U-100 1 unit/ liraglutide 0.036 mg	1 dosing unit = glargine U-100 1 unit/ lixisenatide 0.33 µg
Maximum dose	50 units	60 units
Starting dose	Start at 16 units for all conversions (IDegLira and IGlarLixi should prime pen device on use)	15 units if: < 30 units basal insulin Conversion from lixisenatide 30 units if: Convert from 30-60 units basal insulin
Not recommended	Basal insulin dose > 50 units	Basal insulin dose > 60 units
Delivery/adjust	Pen device daily dosing/ 3-4 d	Pen device daily dosing/ weekly

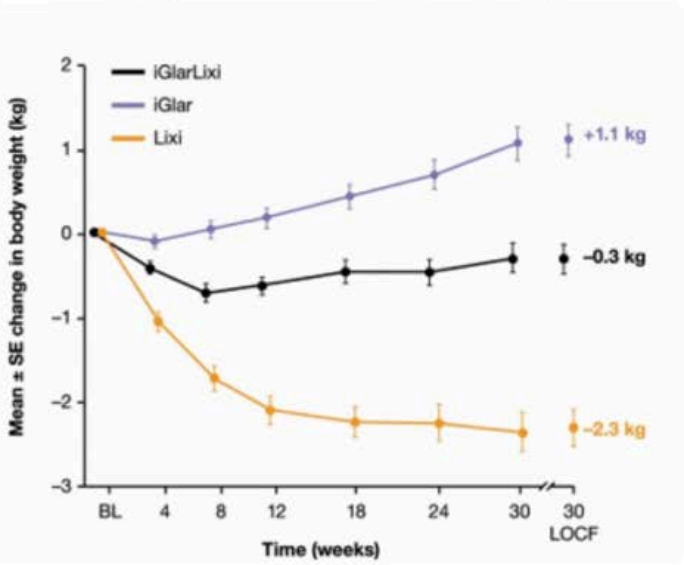
a. Xultophy® PI 2016.
b. Soliqua™ PI 2016.

GLP-1 vs Basal Insulin vs FRC

Change in HbA_{1c}



Change in Weight (kg)



Hypoglycem Events (PP

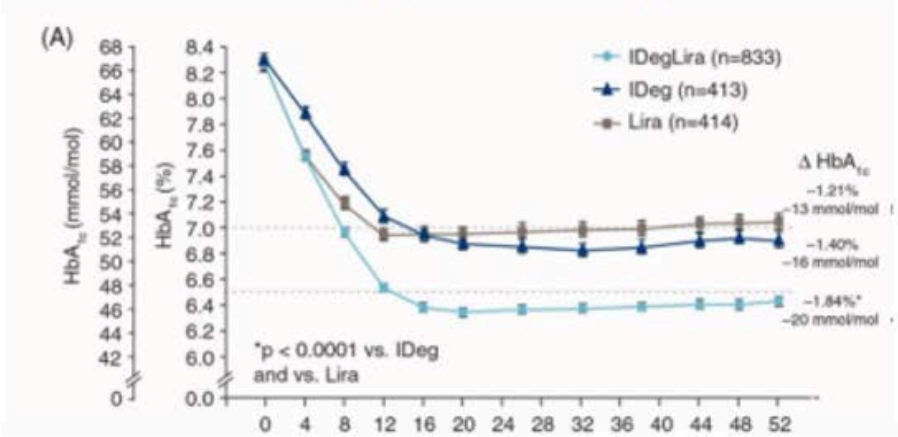
	0.3
	0.5
	0.1

*≤60 mg/dL.

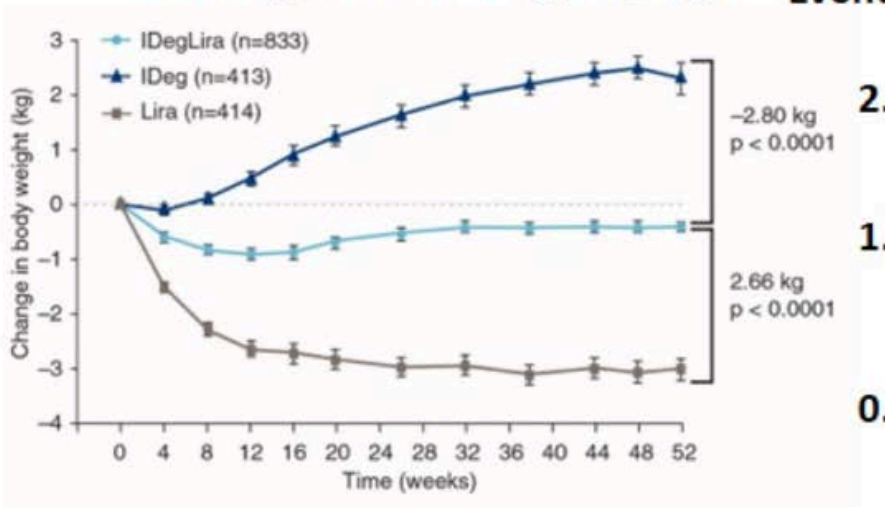
Rosenstock J, et al. *Diabetes Care*. 2016;39:2026-2035.

GLP-1 vs Basal Insulin vs FRC

Change in HbA_{1c}



Change in Weight, kg



Hypoglycemic Events (PYE)

2.79

1.77

0.19

Gough SC, et al. *Diabetes Obes Metab.* 2015;17:965-973.

Basal Insulin/GLP-1 FRC Considerations

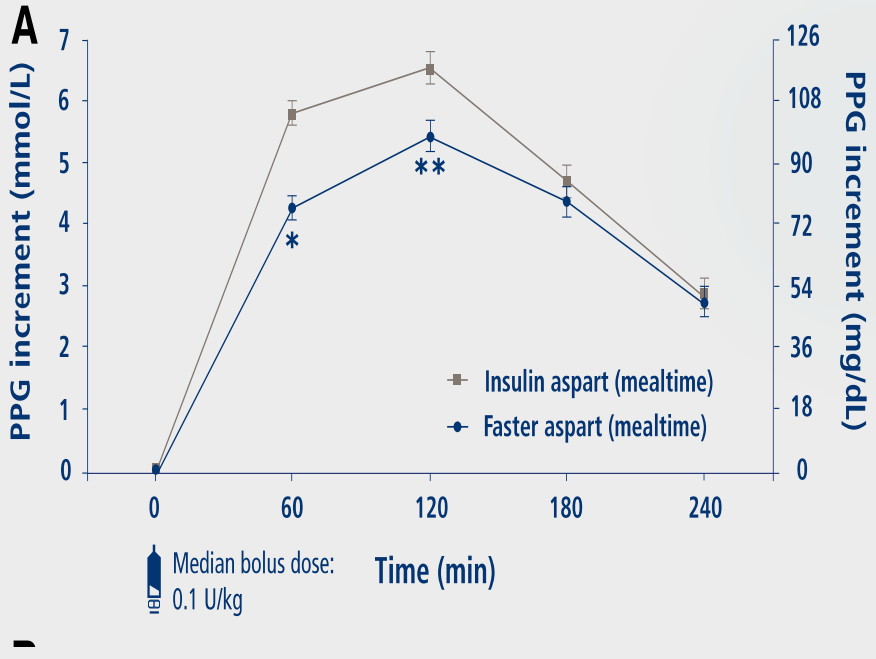
Pros	Cons
• Convenient: once-daily injection • More HbA_{1c} reduction vs either agent alone • More patients to goal • Lessen GI AEs vs GLP-1 RA alone • Hypoglycemia comparable to basal insulin • Less costly than individual agents • Potentially improved adherence	• Less weight loss vs GLP-1 RA therapy alone • Hypoglycemia risk not abated • GI-related AEs still present • Not all can get to goal with top allowed dose • Cost/coverage issues remain

Moghissi ES. *J Am Osteopath Assoc*. 2014;114(suppl 2):S22-S29.

- Basal insulin combination with a GLP-1 RA can address many pathophysiologic abnormalities
- Combination therapy:
  - Increases number of patients to goal HbA_{1c}
  - Lessens weight gain associated with insulin therapy
  - Provides comparable hypoglycemia risk to basal insulin component
  - GI AEs from GLP-1 RA therapy
  - Cost may continue to be prohibitive
- May lessen confusion for varied dosing with GLP-1 RA as dosed in units
- Adherence may be improved by decreasing complexity of regimen

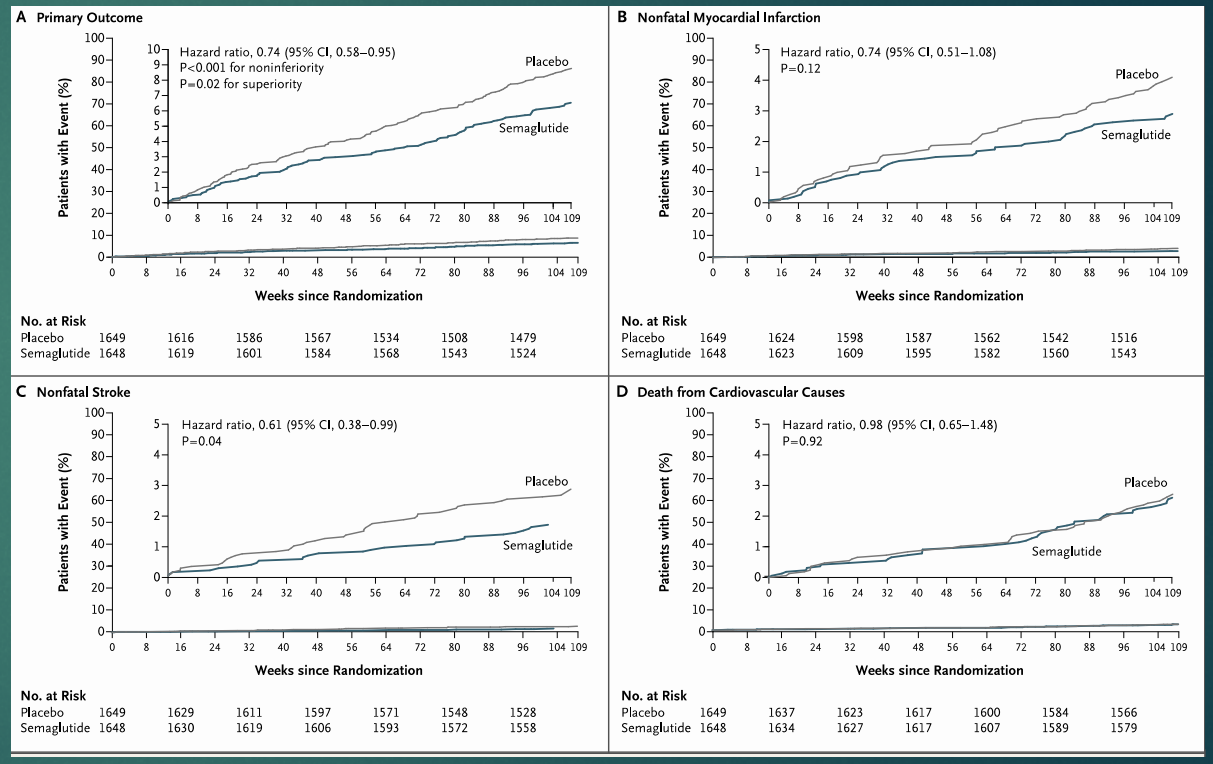
Fiasp: new ultra-fast insulin approved by FDA 09/2017

- *Fiasp*: new formulation of NovoLog; niacinamide (Vitamin B3) has been added to speed absorption
- Fiasp levels increase within 2.5 minutes of injection
- Postprandial glucose levels are lower at 1 and 2 hrs compared to standard aspart in type 1 and type 2 DM patients
- HbA1c levels lower in Fiasp group
- Overall rate of hypoglycemia similar, but more events at 1 hr postprandial
- Not approved for insulin pumps in US



New injectables on horizon

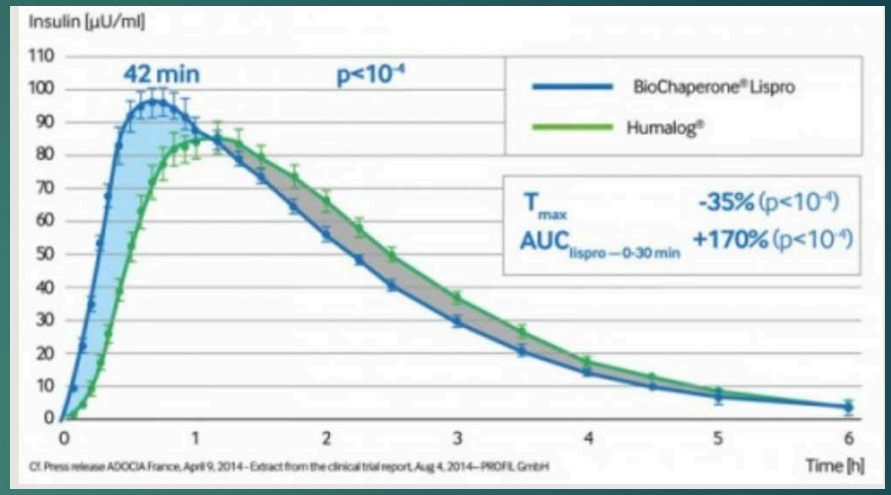
- Semaglutide(NovoNordisk) : potent weekly (and oral form) has demonstrated superior efficacy in reducing A1c and weight
- CV safety study showed significant reductions in CV events in high risk pts



Marso.NEJM.2016

New injectables on horizon

- BioChaperone lispro(Adocia): ultra-fasting acting insulin in late stage trials, but recent collaboration with Lilly was terminated
- Ryzodeg(ideglu/aspart 75/25)NovoNordisk: approved by FDA; not yet marketed in US



Conclusion

- Newer and emerging insulins and GLP-1 RAs provide advantages over previous therapies and deserve greater application in the management of people with diabetes