새로나온 인슐린을 이용한 치료의 실제

성균관의대 삼성창원 병원
배지철

Progress of insulin

1. 동물(소, 돼지) 추출 인슐린→합성 인간 인슐린→유전자 재조합 insulin analogue

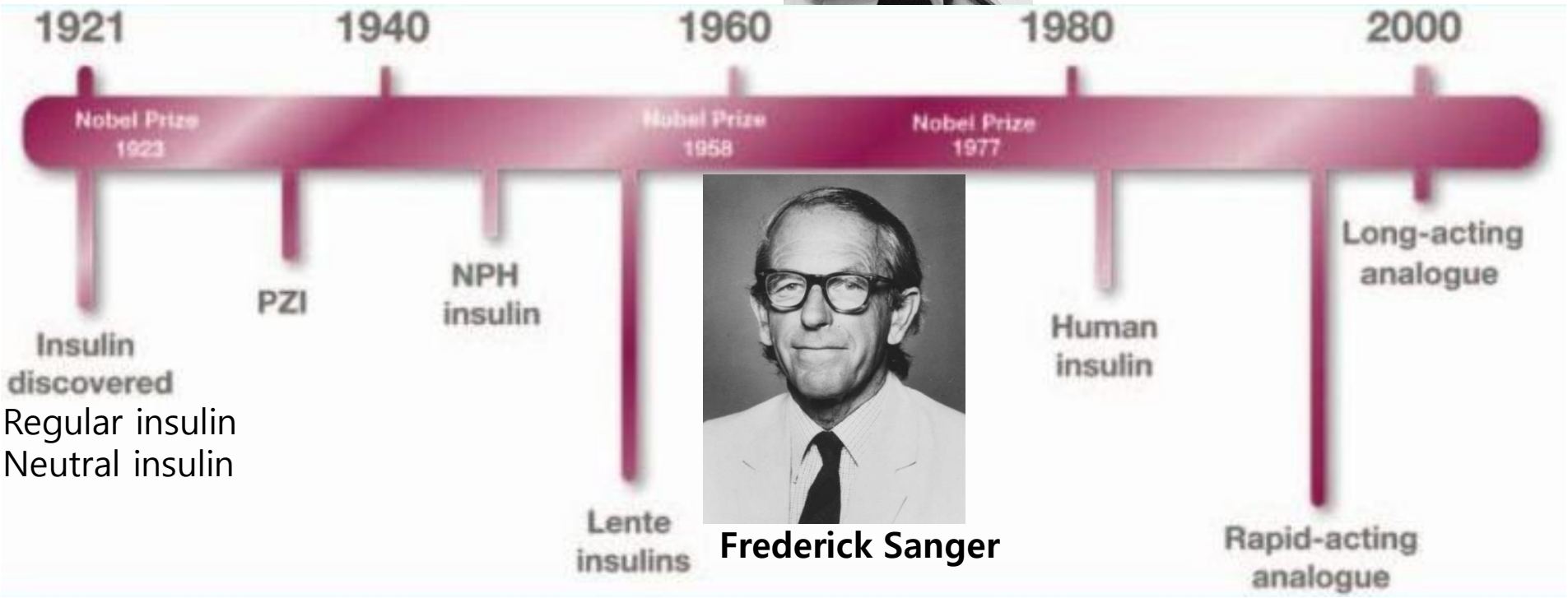
2. 인슐린 작용시간의 조정
   - 작용시간의 연장
   - 작용시간의 단축

Progress of insulin

Banting, Best

Eli Lilly
Nordisk

Rosalyn Yalow
Radioimmunoassay
(RIA) for insulin level

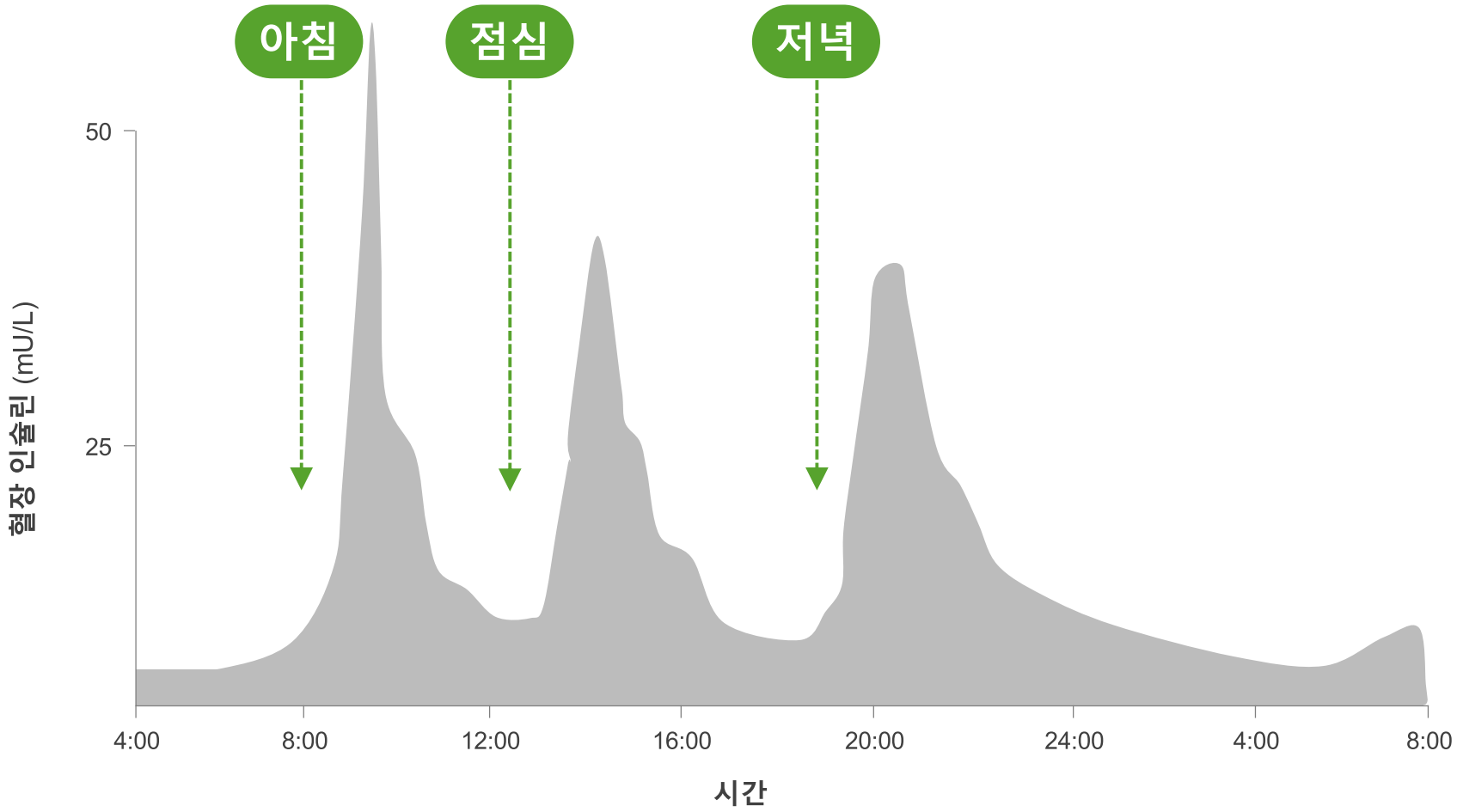


Regular insulin
Neutral insulin

Frederick Sanger

1. Amino acid sequence of bovine insulin
2. DNA sequencing

정상인의 인슐린 분비

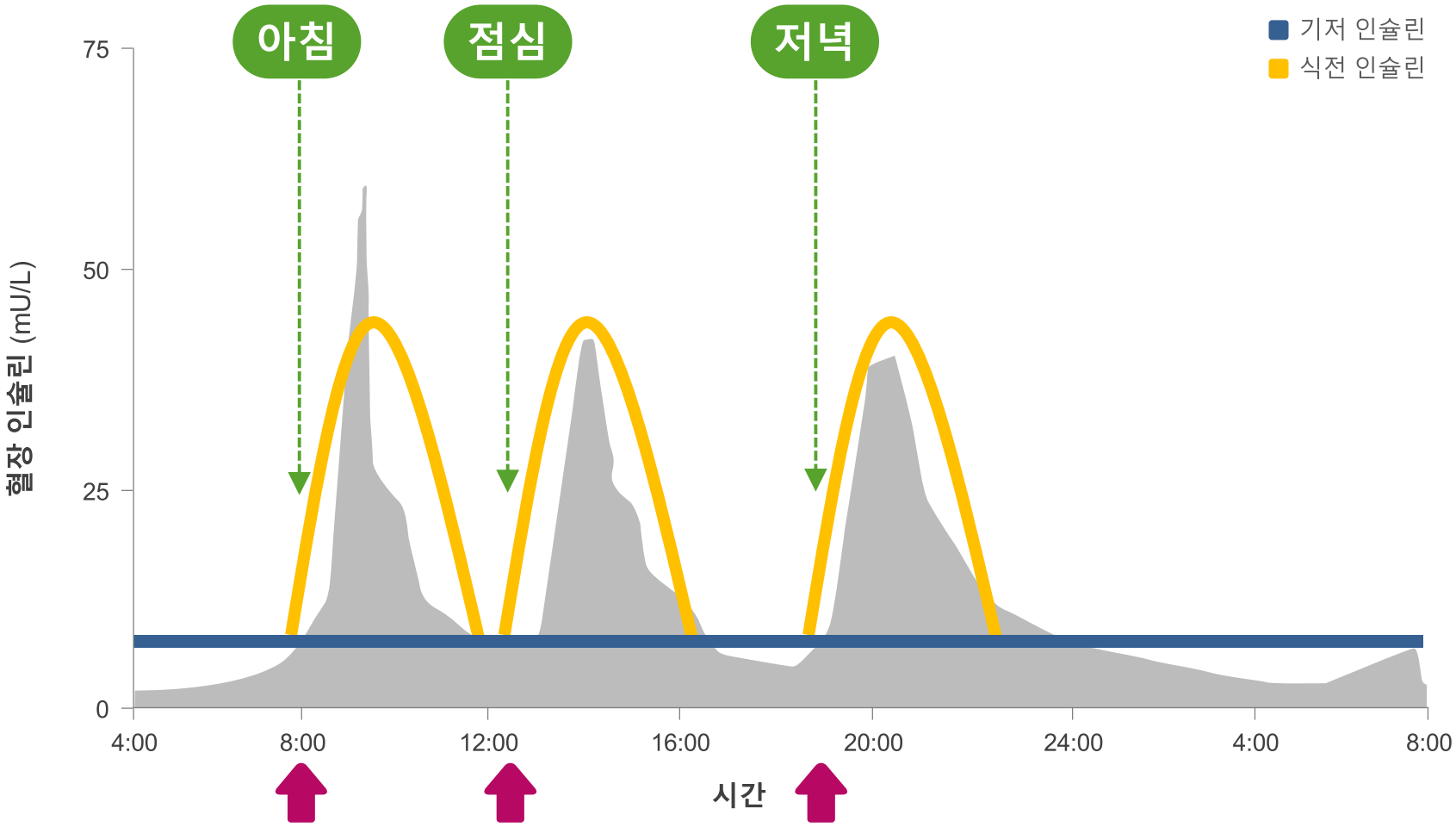


Thompson R *et al*. Curr Paed 2006;16:117-22.

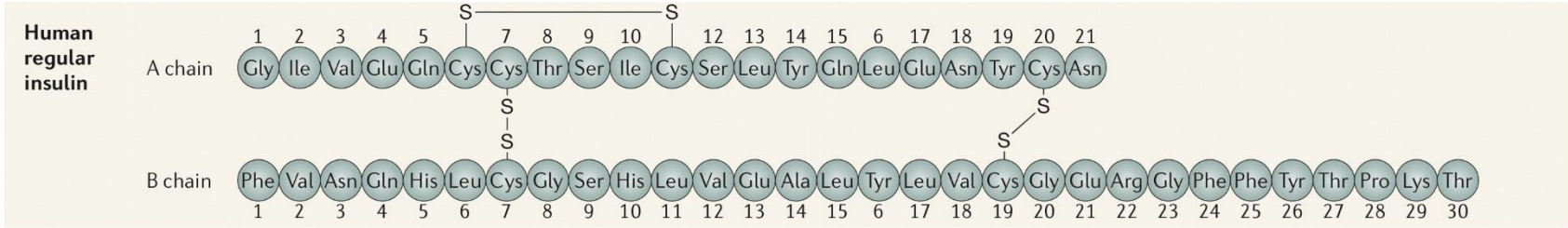
대한당뇨병학회 Korean Diabetes Association

EGDM

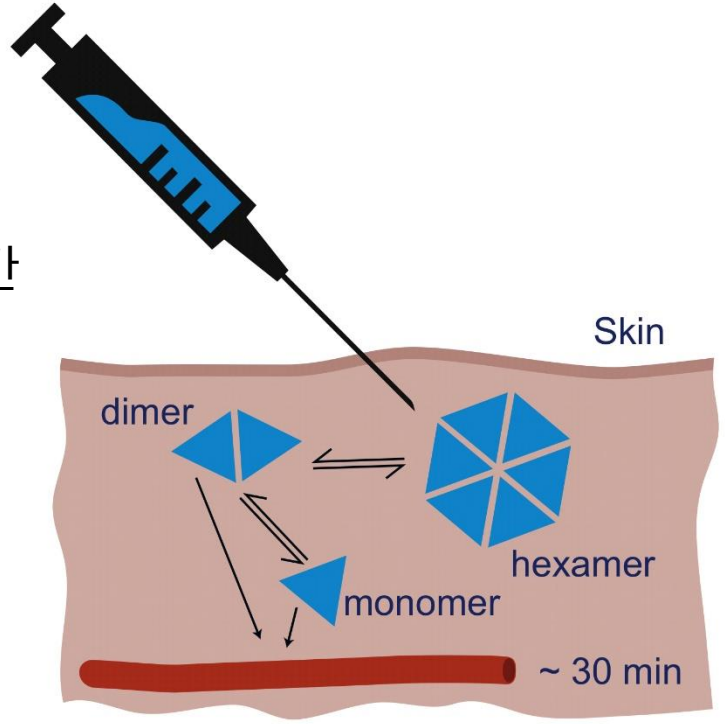
이상적인 인슐린 요법

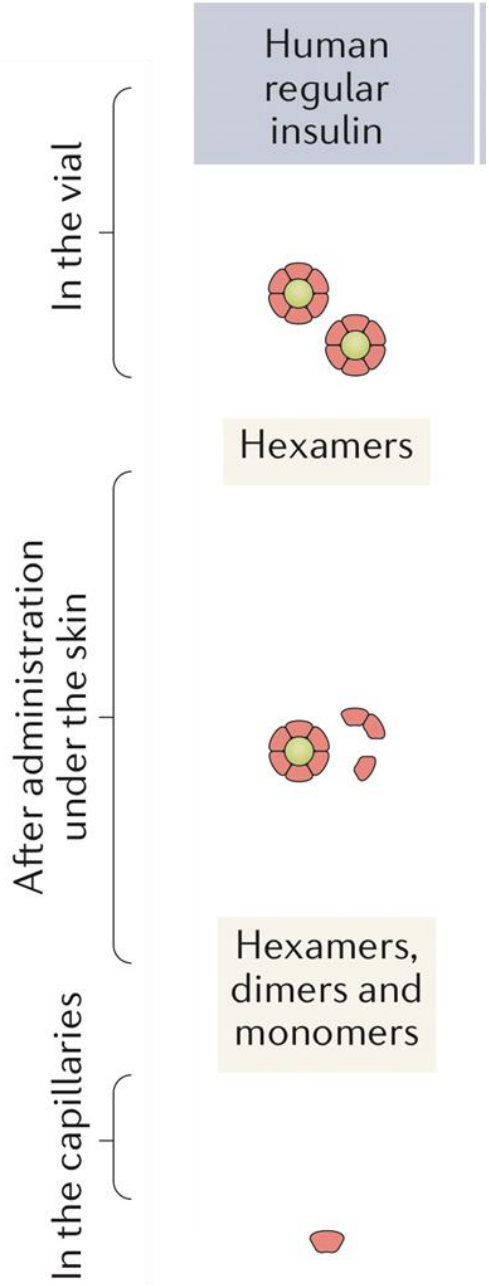


Huuman regular insulin



Peak effect: 2-4시간
Duration action:5~8시간





Senior, P. and I. Hramiak (2019). "Fast-Acting Insulin Aspart and the Need for New Mealtime Insulin Analogues in Adults With T1 and T2D" Can J Diabetes.
Mathieu, C., et al. (2017). "Insulin analogues in type 1 diabetes mellitus: getting better all the time." Nat Rev Endocrinol 13(7): 385-399.

Regular insulin

NPH

Insulin glargine
Insulin determir

Insulin degludec
Glargin U300

Insulin aspart
Insulin glurigin
Insulin lispro

Rapid acting-insulin aspart

NPH/RI
70/30
50/50

Insulin protamine aspart/aspart
Insulin protamine lispro/lispro
70/30, 75/25, 50/50

Insulin degludec/ insulin aspart
70/30

Progress of long-acting basal insulin

NPH

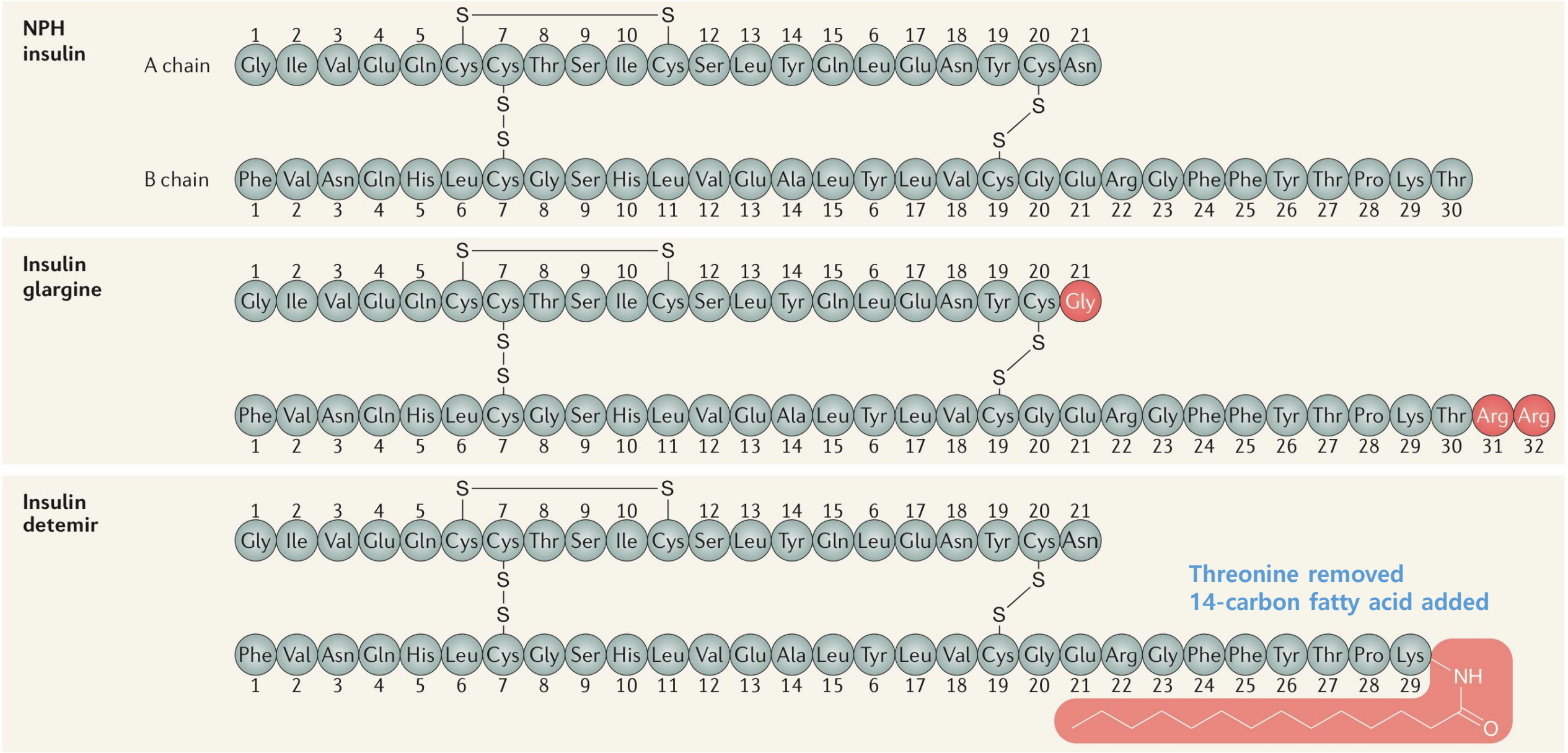
First generation basal insulin

Insulin glargine
Insulin detemir

Second generation basal insulin

Insulin degludec
Glargin U300

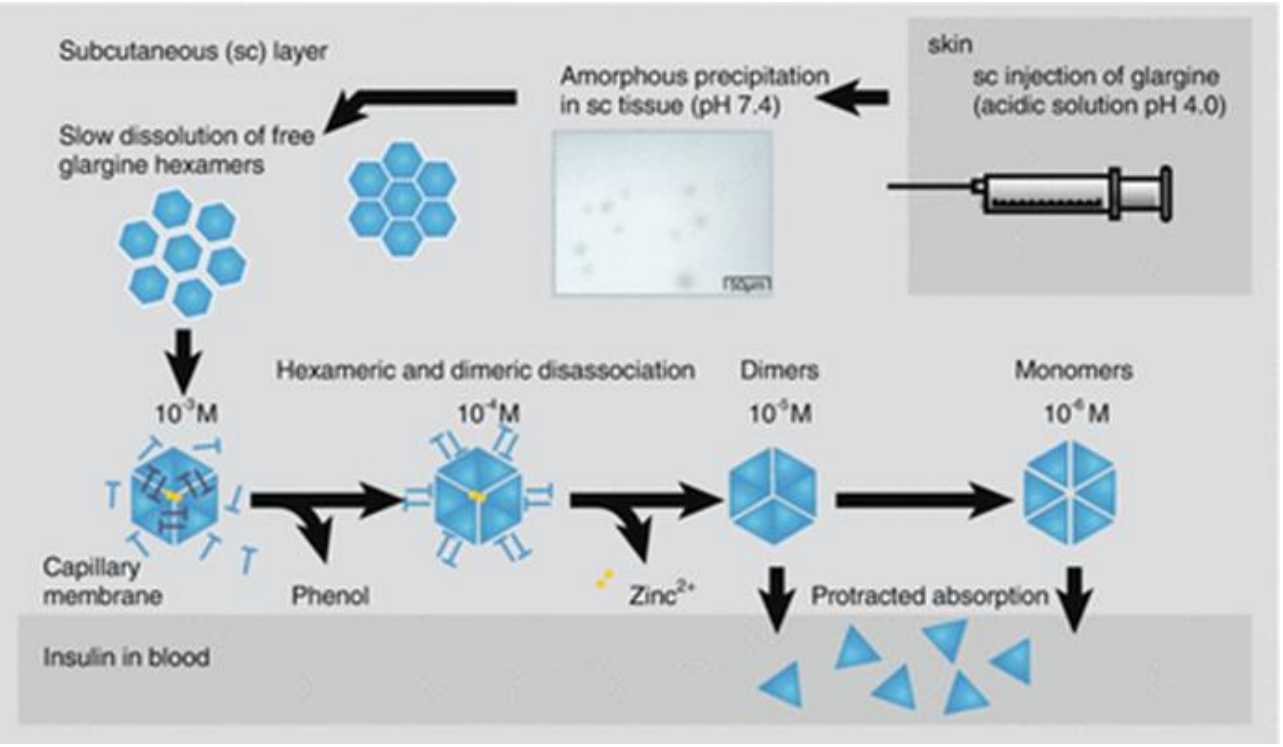
Amino acid structure of long-acting analogues



Mathieu, C., et al. (2017). "Insulin analogues in type 1 diabetes mellitus: getting better all the time." Nat Rev Endocrinol 13(7): 385-399.

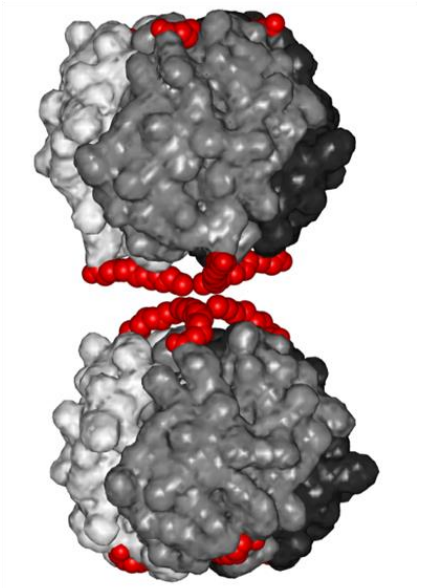
Mode of action: protraction principles

Insulin glargin

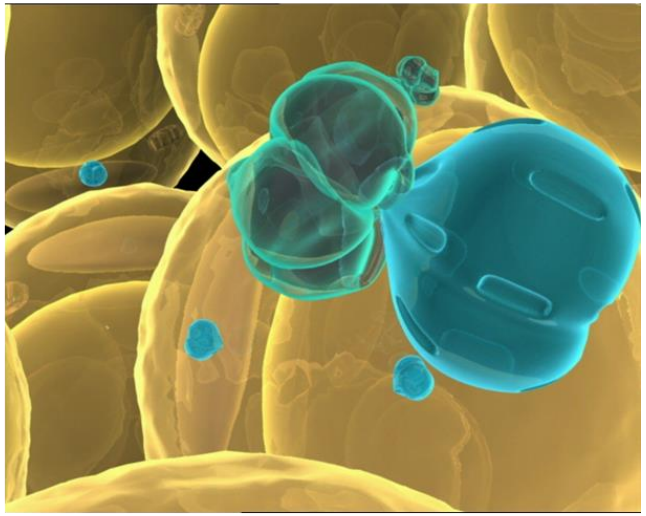


Insulin detemir

Protraction principle I: di-hexamerisation



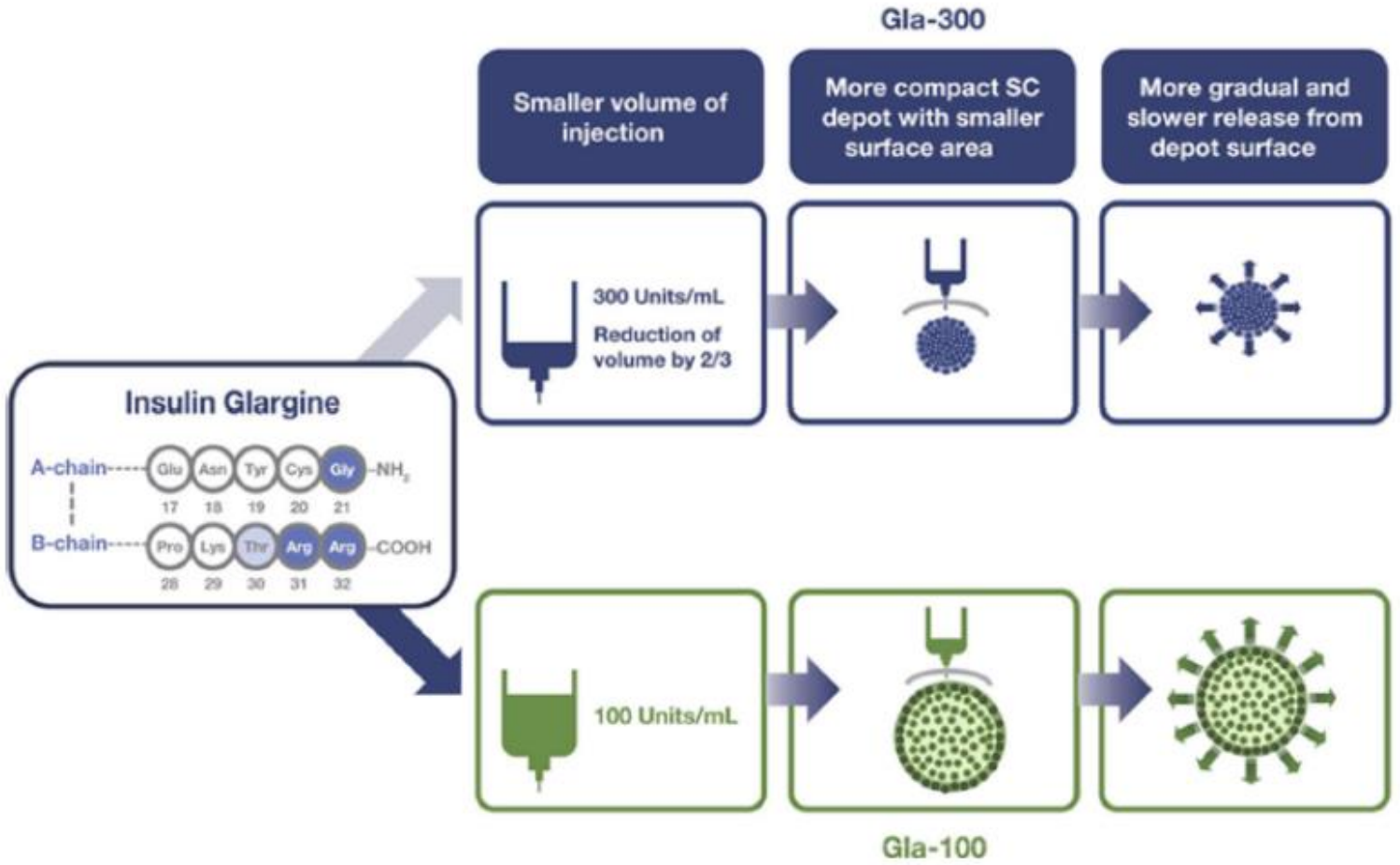
Protraction principle II: binding to albumin

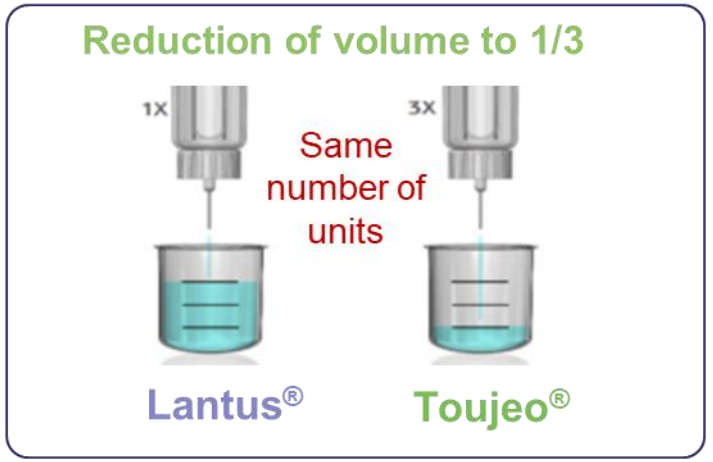


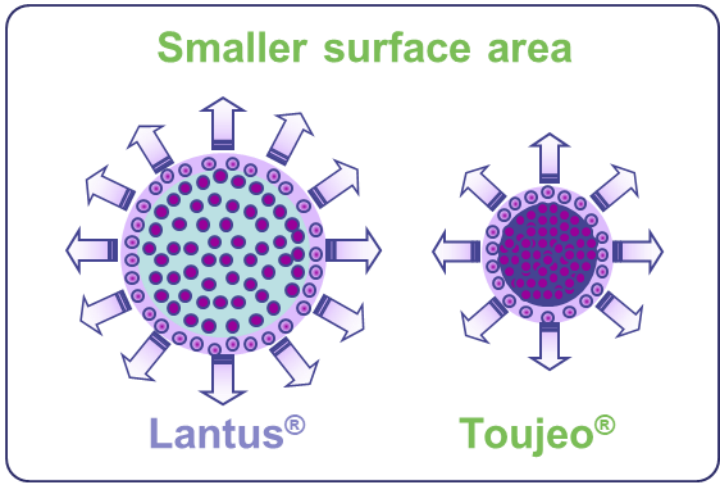
Handbook of Insulin Therapies pp 15-53

Whittingham *et al. Biochemistry* 1997;36:2826 Data on File at Novo Nordisk

Compact depot formation with Gla-300 results in more gradual insulin release as compared with Gla-100



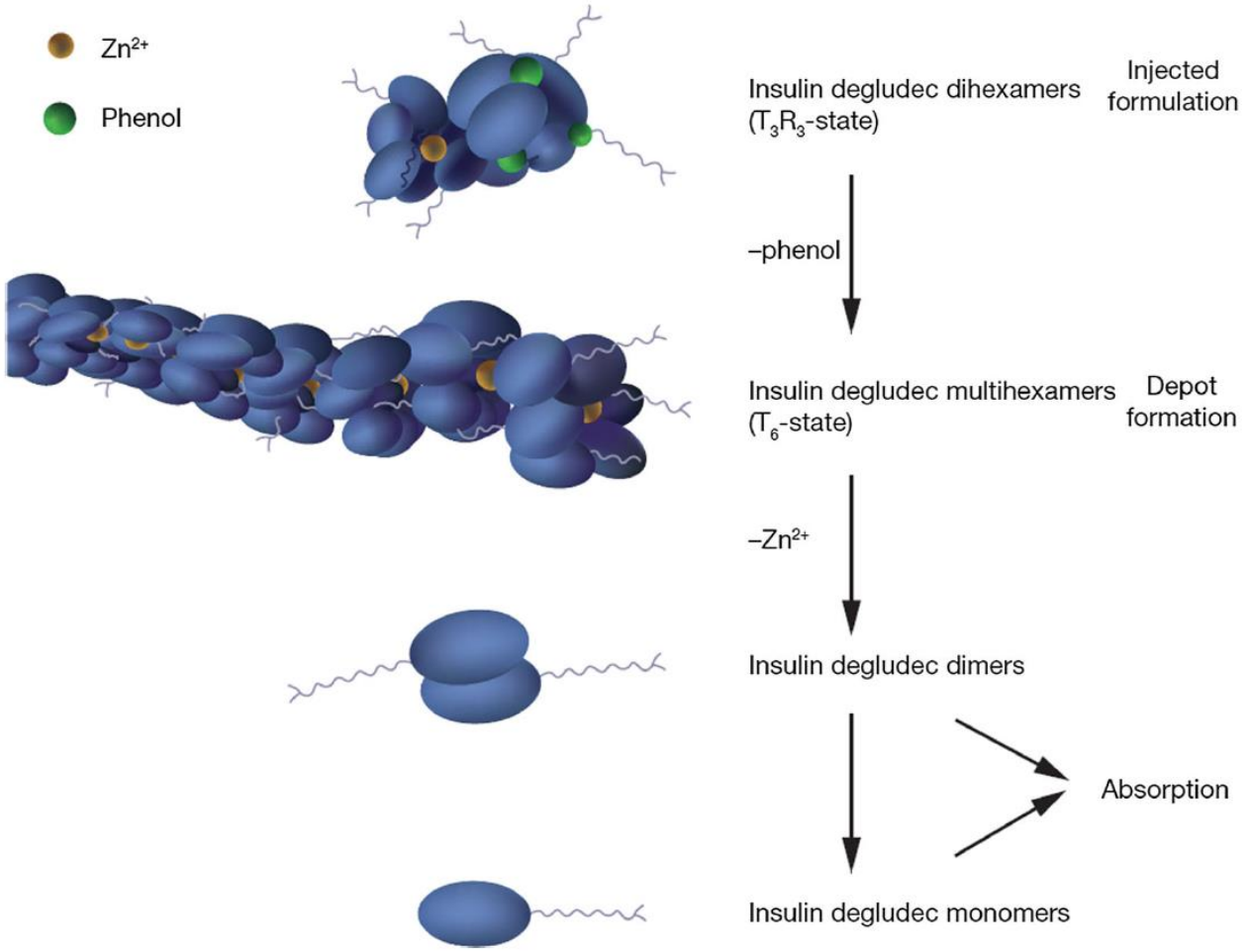


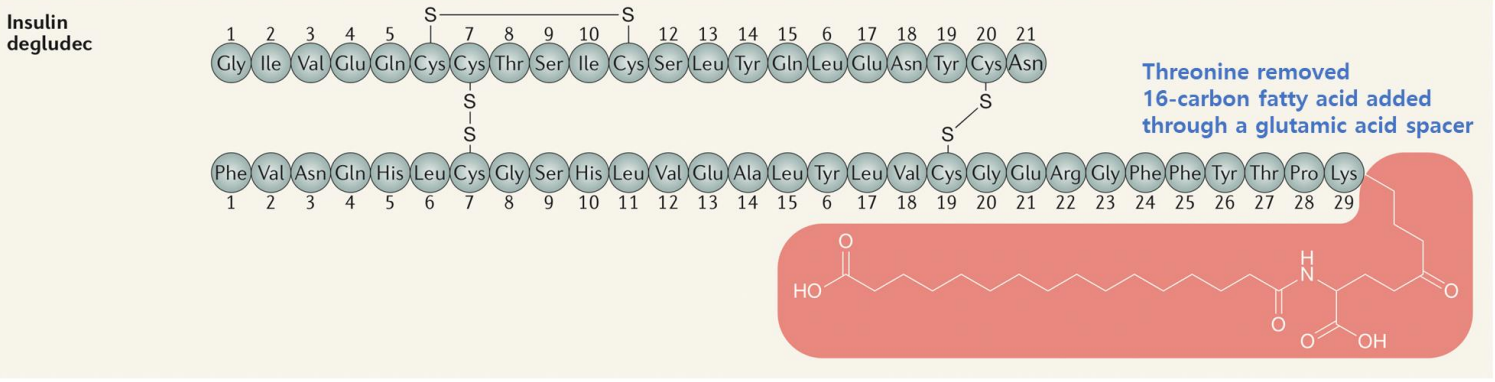


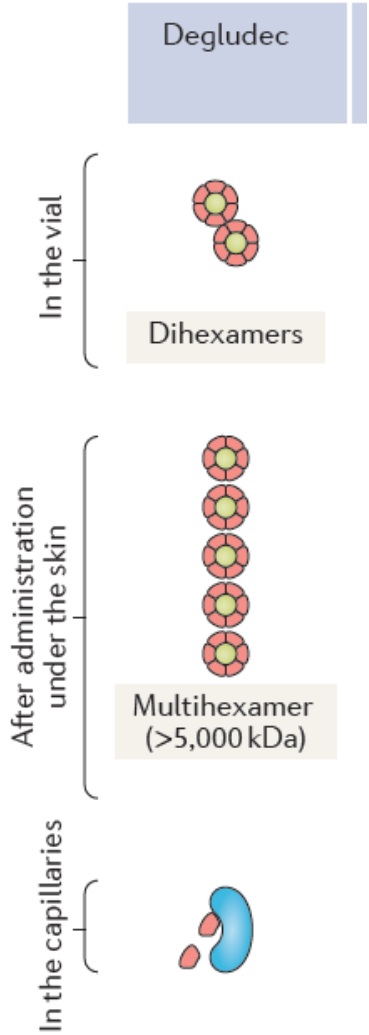
Adv Ther (2019) 36:1018–1030

Mathieu, C., et al. (2017). "Insulin analogues in type 1 diabetes mellitus: getting better all the time." Nat Rev Endocrinol 13(7): 385-399.

Mode of protraction of insulin degludec

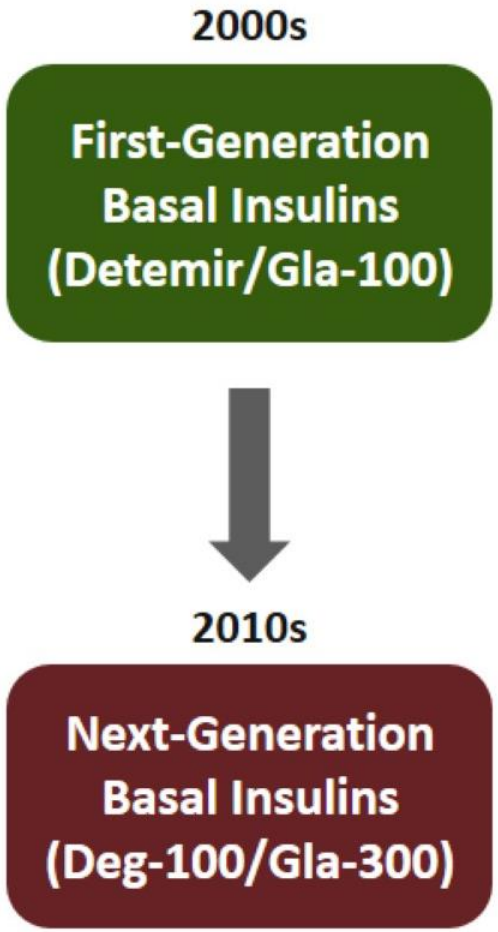






Adv Ther (2019) 36:1018–1030

First-generation 인슐린 대비 Second-generation basal insulin 의 특징



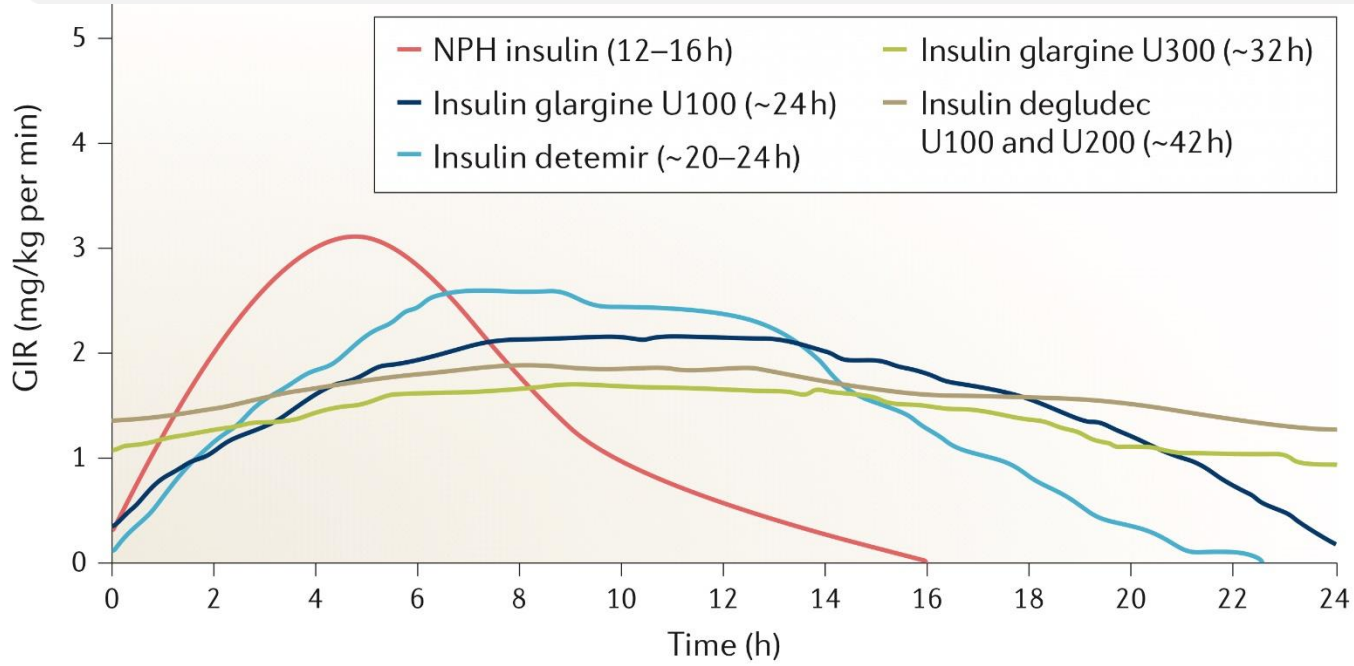
How next-generation basal insulins compare[a-c]

- Equally effective in lowering HbA1c
- Longer duration of action: ≥24 hours coverage
- Even flatter action profile - less variability
- Safer - lower risk for hypoglycemia, especially nocturnal

a. Borgoño, CA, et al. *Endocrin Metab Clin North Am.* 2012;41:1-24; b. Hermansen K, et al. *Diabetes Obes Metab.* 2007;9:209-217; c. Owens DR, et al. *Diabetes Metab Res Rev.* 2014;30:104-119.

Pharmacodynamic action profiles of long-acting insulins

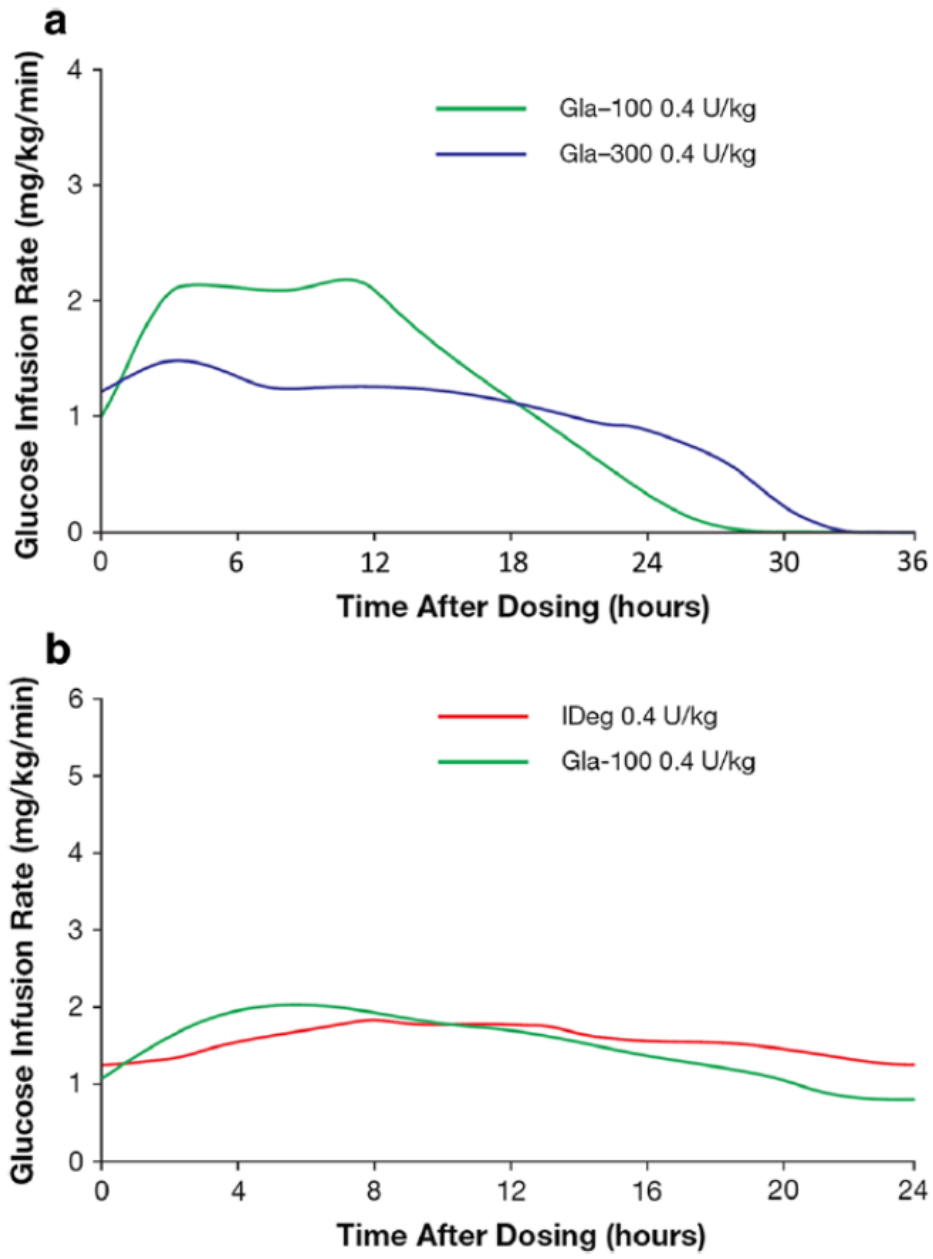
인슐린 종류 (상품명)	작용 시작	최고 작용	작용 시간
기저인슐린			
장시간형 기저인슐린 (투명)			
인슐린 디터머 (Levemir)	90분	없음	24 시간
인슐린 글라르진 (Lantus, Basaglar)			24 시간
인슐린 글라-300 (Toujeo)	6시간		36시간 이상
인슐린 데글루덱 (Tresiba)	60-90 분		42시간 이상
중간형 인슐린 휴물린 N (혼탁)	1-3시간	5-8 시간	18 시간까지



Mathieu, C., et al. (2017). "Insulin analogues in type 1 diabetes mellitus: getting better all the time." Nat Rev Endocrinol 13(7): 385-399.

Glucose infusion rate profile of Gla-300 and IDeg compared with Gla-100

When compared with Gla-100, Gla-300 and Insulin degludec are associated with a flatter and more consistent glucose-lowering effect, with more evenly distributed PK/PD profiles



Adv Ther (2019) 36:1018–1030

EDITION T2DM Trials Meta-Analysis:
Glargine U300 vs Glargine U100

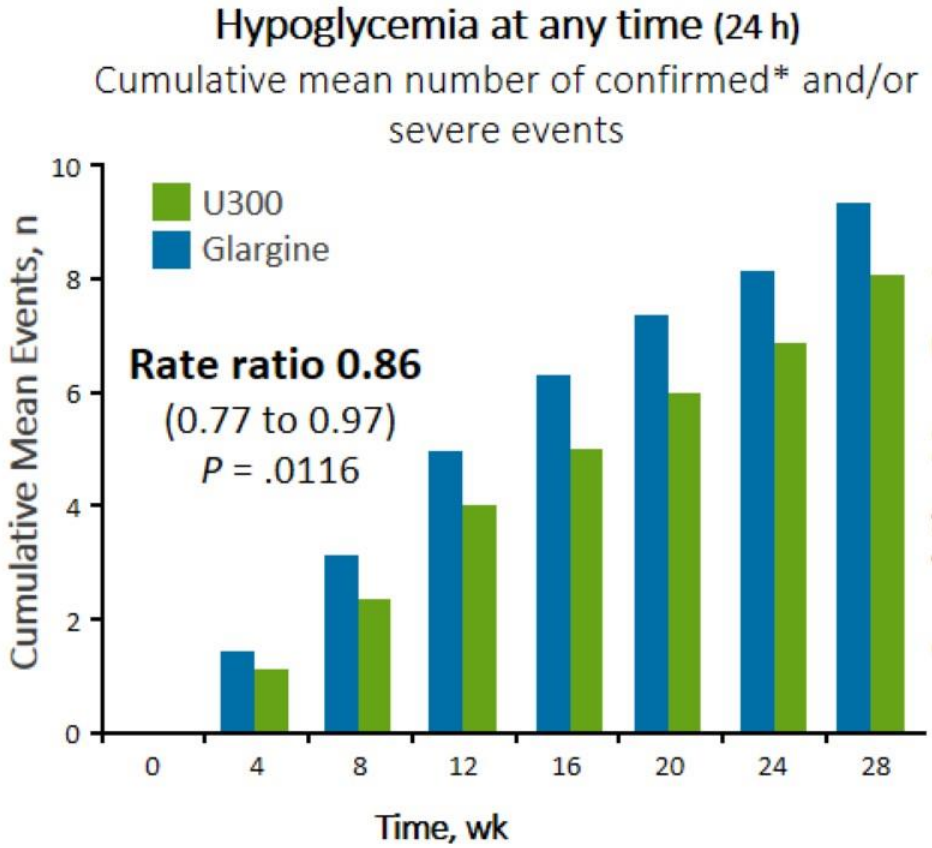
	EDITION 1	EDITION 2	EDITION 3
Population	Basal-Bolus	OAD + >42 units BI	OAD
N	807	811	878
HbA1c (primary outcome)	NS	NS	NS
U300 Insulin dose	≈10% higher	≈10% higher	≈15% higher

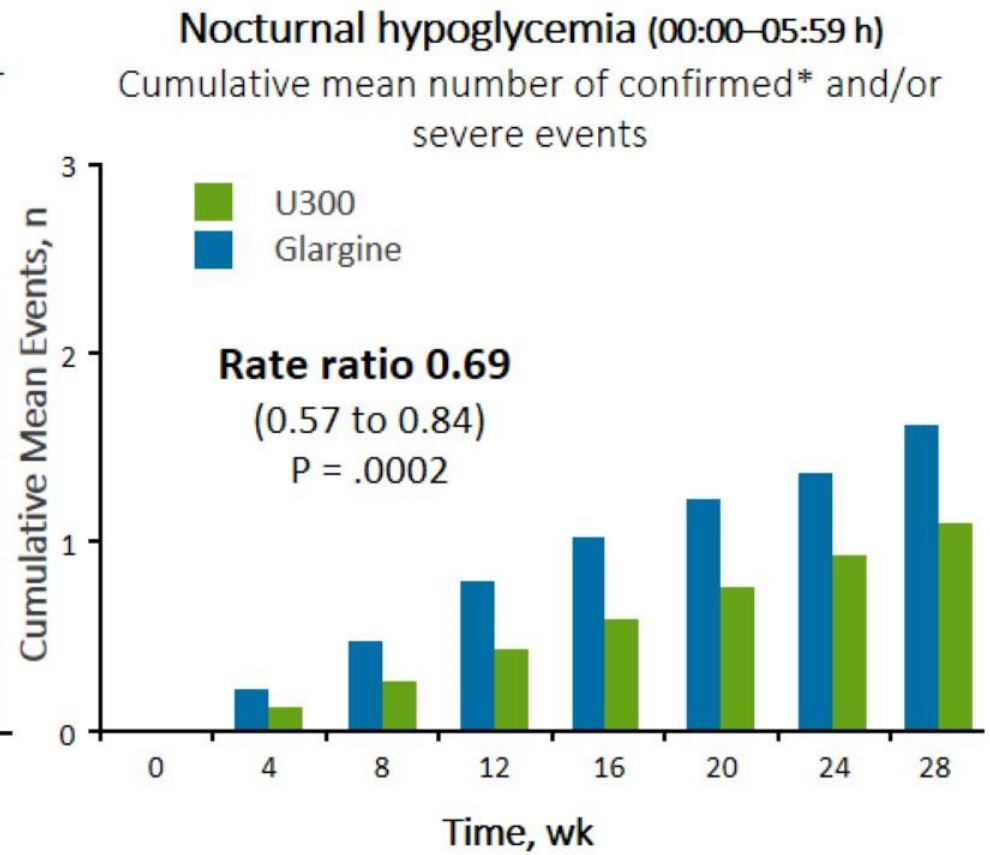
같은 혈당 목표에 도달하기 위해서는 인슐린 글라진 대비 10~15% 정도
더 많은 U300의 용량이 필요하였다

Ritzel R, et al. *Diabetes Obes Metabol.* 2015;17:859–867.

EDITION T2DM Trials Meta-Analysis:

Lower Confirmed/Severe and Nocturnal Hypoglycemia With Glargine U300 vs U100





*Confirmed events based on plasma glucose ≤70 mg/dL (3.9 mmol/L)

Ritzel R, et al. *Diabetes Obes Metabol*. 2015;17:859-867.

Degludec vs Glargine U100: BEGIN Trials

Meta-Analysis of Patients With T2DM on High Doses of Insulin

HbA1c was reduced by the same extent with insulin degludec and glargine U100

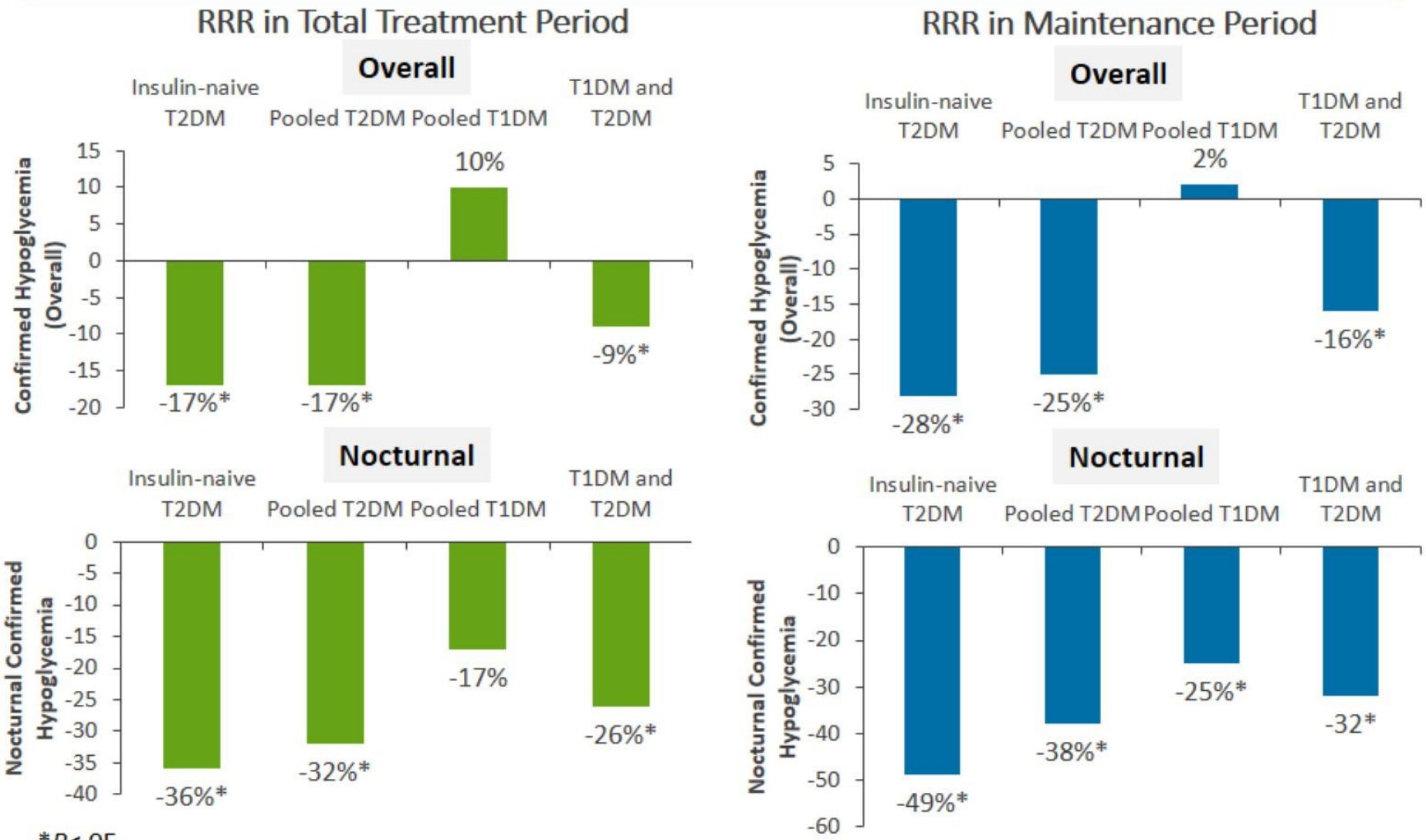
Lower Rates of Hypoglycemia With Degludec

Less overall hypoglycemia (P = .02)

Less nocturnal hypoglycemia (P = < .01)

Rodbard HW, et al. *Endo Pract.* 2013;18:285-292.

Hypoglycemia Rates With Novel Basal Analogues Meta-Analysis: Insulin Degludec vs Glargine



*$P<.05$

Ratner RE, et al. *Diabetes Obes Metab*. 2013;15:175-184.

Patients who Will Benefit Most from Second-Generation basal insulin

- All patients who need insulin, in particular those:[a-i]
  - Using basal insulin, but experiencing hypoglycemia
  - Currently using twice-daily basal insulin
  - Starting insulin
  - Vulnerable patients who may have a higher risk for hypoglycemia

기존 glargine, detemir 대비
Same efficacy
Long duration
Less hypoglycemia

a. Garber AJ, et al. *Lancet*. 2012;379:1498-507; b. Zinman B, et al. *Diabetes Care*. 2012;35:2464-2471; c. Gough SC, et al. *Diabetes Care*. 2013;36:2536-2542; d. Meneghini L, et al. *Diabetes Care*. 2013;36:858-864; e. Onishi Y, et al. *J Diabetes Invest*. 2013;4:605-612; f. Riddle MC, et al. *Diabetes Care*. 2014;37:2755-2762; g. Yki-Järvinen H, et al. *Diabetes Care*. 2014;37:3235-3243; h. Bolli GB, et al. *Diabetes Obes Metab*. 2015;17:386-394; i. Terauchi Y, et al. *Diabetes Obes Metab*. 2016;18:366-374.

Insulin degludec Vs Glargine U300

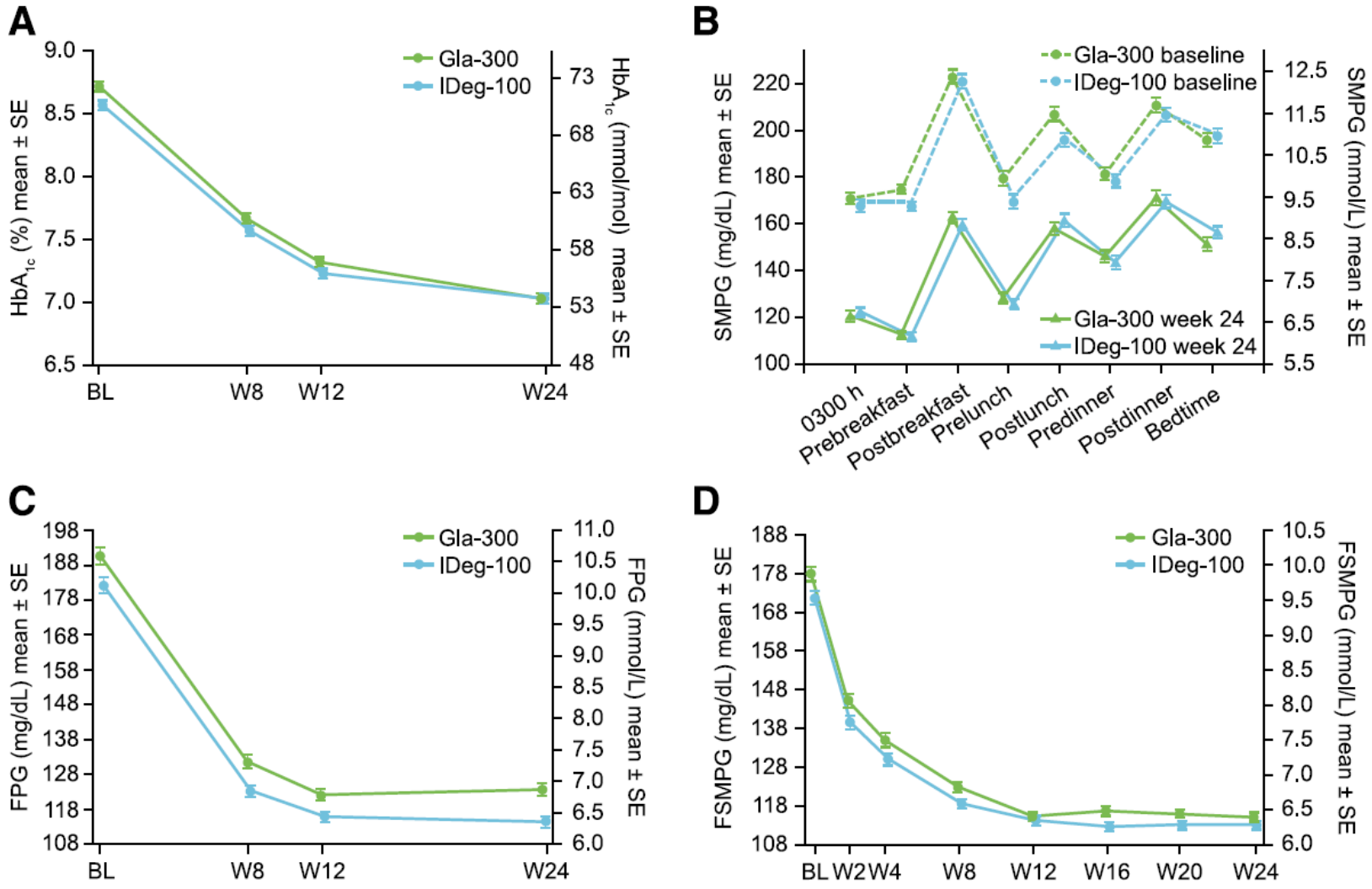
Diabetes Care Volume 41, October 2018

More Similarities Than Differences Testing Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL in Insulin-Naive Type 2 Diabetes: The Randomized Head-to-Head BRIGHT Trial

Julio Rosenstock,[1] Alice Cheng,[2] Robert Ritzel,[3] Zsolt Bosnyak,[4] Christine Devisme,[5] Anna M.G. Cali,[6] Jochen Sieber,[7] Peter Stella,[8] Xiangling Wang,[9] Juan P. Frías,[10] Ronan Roussel,[11,12,13] and Geremia B. Bolli[14]

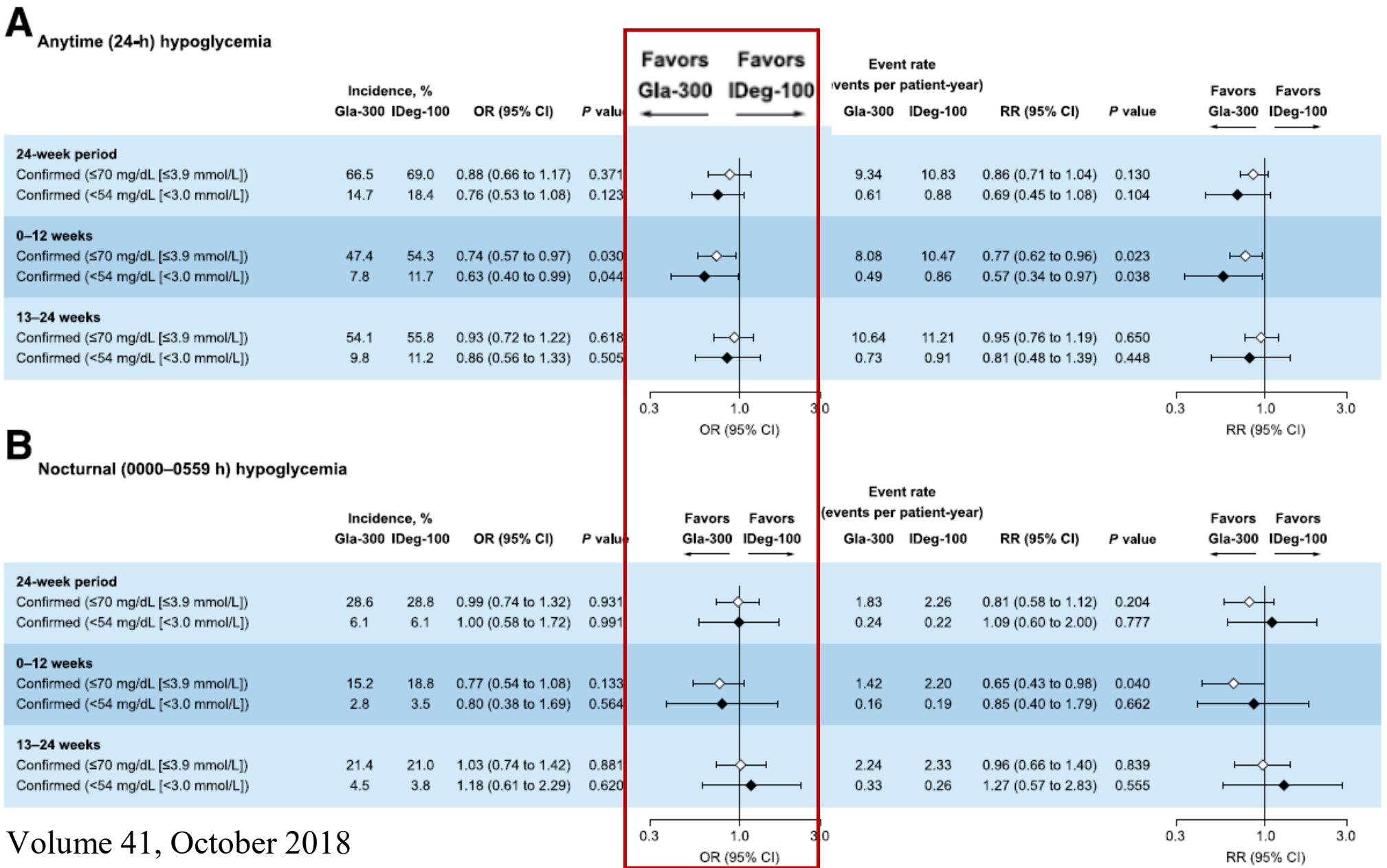
Diabetes Care 2018;41:2147–2154 | https://doi.org/10.2337/dc18-0559

Insulin degludec Vs Glargine U300
The Bright study



Diabetes Care Volume 41, October 2018

Insulin degludec Vs Glargine U300. The Bright study



Diabetes Care Volume 41, October 2018

Bright Study: Results summary

- Similar glycemic control improvements with Ideg-100 and Gla-300
- Similar variability with Ideg-100 and Gla-300
- A higher mean daily insulin dose for Gla-300 at study end
- Hypoglycemia incidence and rates were comparable with both insulins during the full study period but lower in favor of Gla-300 during the titration period.

Diabetes Care Volume 41, October 2018

RWE for Second-Generation Basal Insulins

Insulin-naive patients with T2DM

- **LIGHTNING -** lower rates of severe hypoglycemia when using Gla-300 vs Deg-100[a]
- **CONFIRM -** lower rates of hypoglycemia in those using Deg-100 than with Gla-300[b]

Patients with T2DM switching basal insulin

- **LIGHTNING -** comparable rates of severe hypoglycemia when switching to either Gla-300 or Deg-100[a]
- **DELIVER -** less hypoglycemia in patients switching to Gla-300 than other basal insulins[c, d]

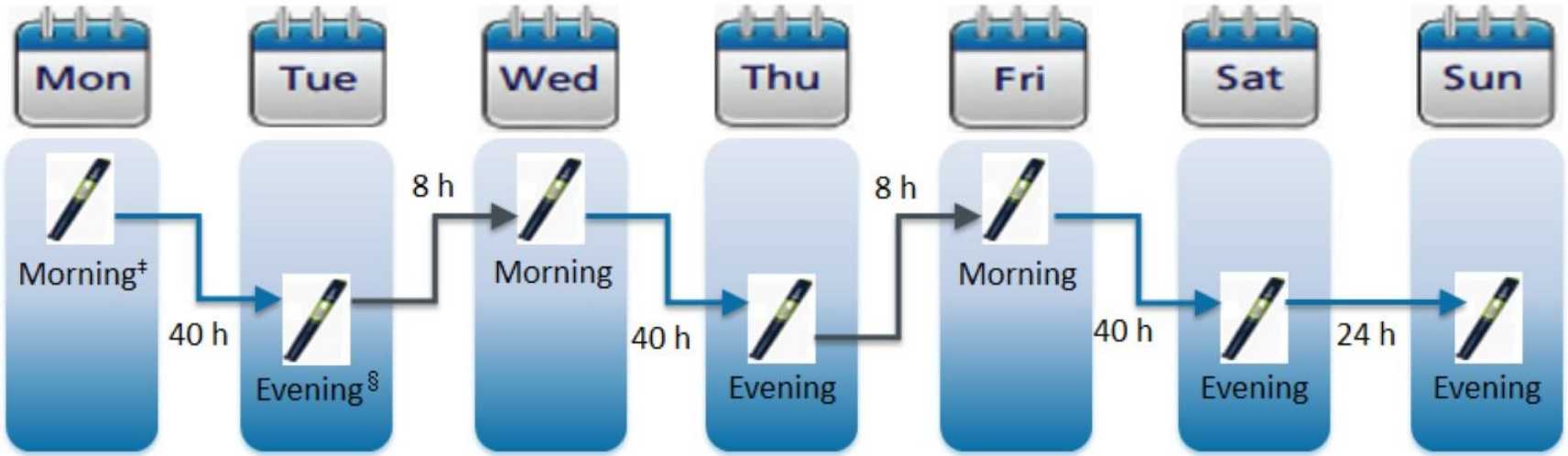
a. Pettus J, et al. ADA 2018. Abstract 2289-PUB; b. Tibaldi J, et al. ADA 2018. Abstract 98-LB; c. Ye F, et al. ADA 2016. Abstract 943-P; d. Zhou FL, et al. ENDO 2017. Poster LB SUN 81.

New long-acting insulin analogue 의 사용

- Insulin naïve patients
  - Type 2 DM
    - 시작 용량은 10단위 또는 0.2unit /kg. 환자 혈당의 정도에 따라 adjust
    - 용량의 titration 은 3-4일 간격으로
  - Type 1 DM: multi dose injection이 필요
    - Total dose 는 0.2~0.4 unit /kg
    - Total dose 의 1/3 ~ 1/2 을 basal insulin 으로

- Switching from Gla-100 or Detemir
  - 기존의 Insulin analogue 를 안정적으로 사용하던 경우는 변경할 필요가 없음
  - 변경한다면 동일 용량으로 시작.

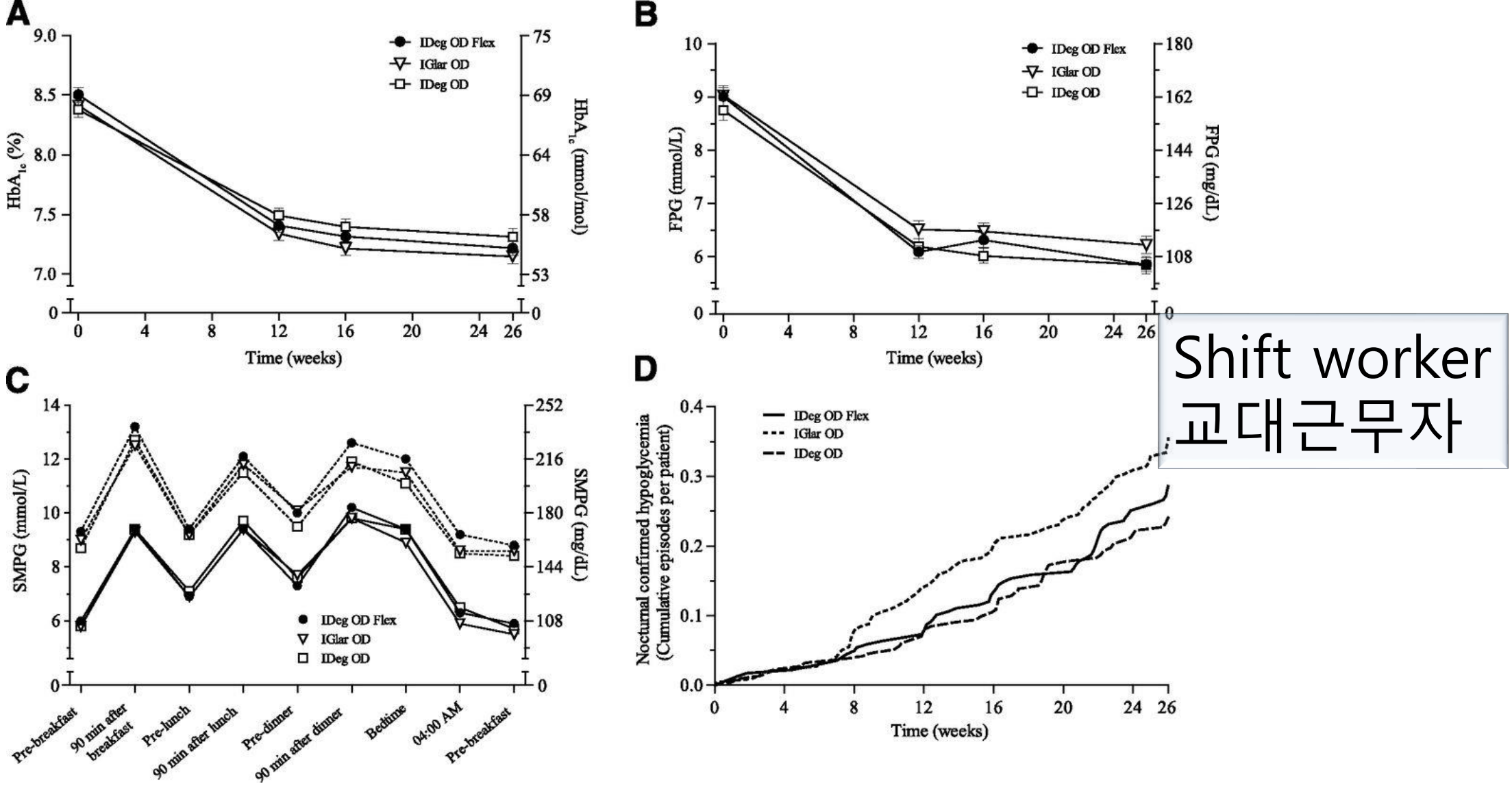
Degludec Variable Dosing† vs Glargine U100 or Degludec Dosed Regularly*



Variable dosing with degludec had similar efficacy and similar hypoglycemia compared with either regular dosing regimen

*687 patients with T2D in a 26-wk, randomized, open-label, parallel-group, treat-to-target trial; †Dosing schedule provided for a maximum dosing interval of 40 h and a minimum dosing interval of 8 h; ‡Morning defined as time period from waking up to first meal of day; §Evening defined as time period from start of evening meal to bedtime.

Meneghini L, et al. *Diabetes Care.* 2013;36:858-864.



Shift worker
교대근무자

The use of extreme dosing intervals of 8–40 h demonstrates that the daily injection time of IDeg can be varied without compromising glycemic control or safety

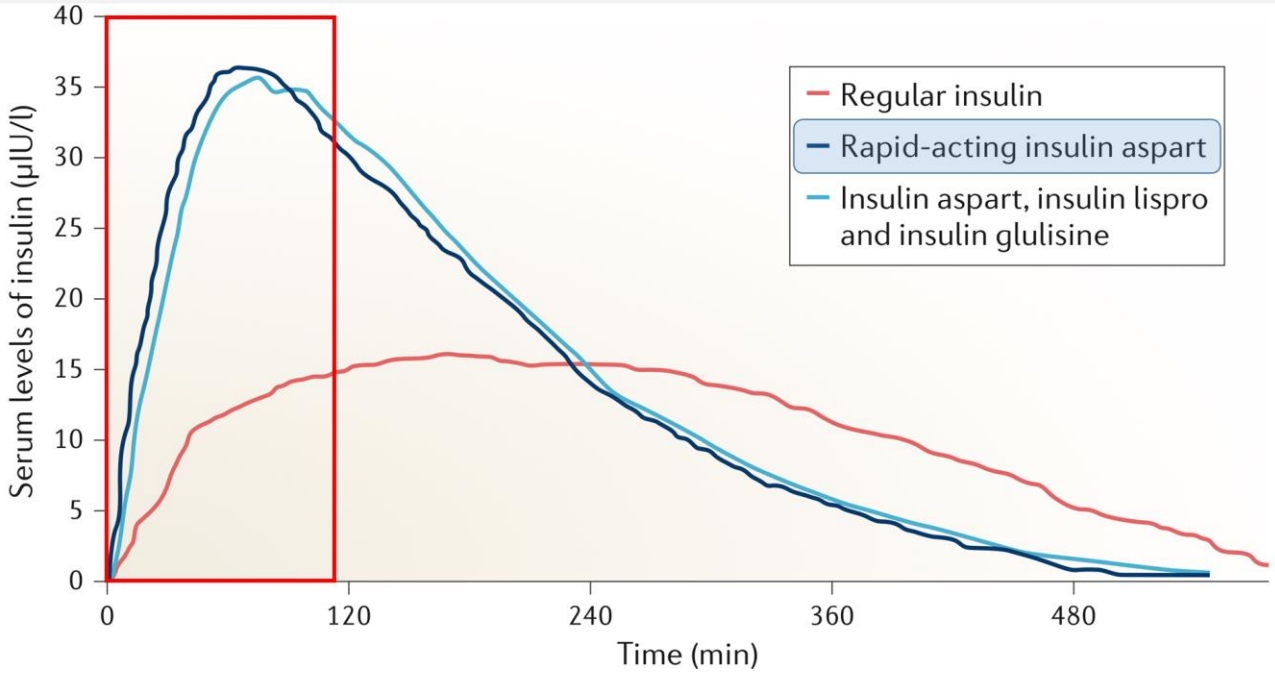
Diabetes Care 2013 Apr; 36(4): 858-864

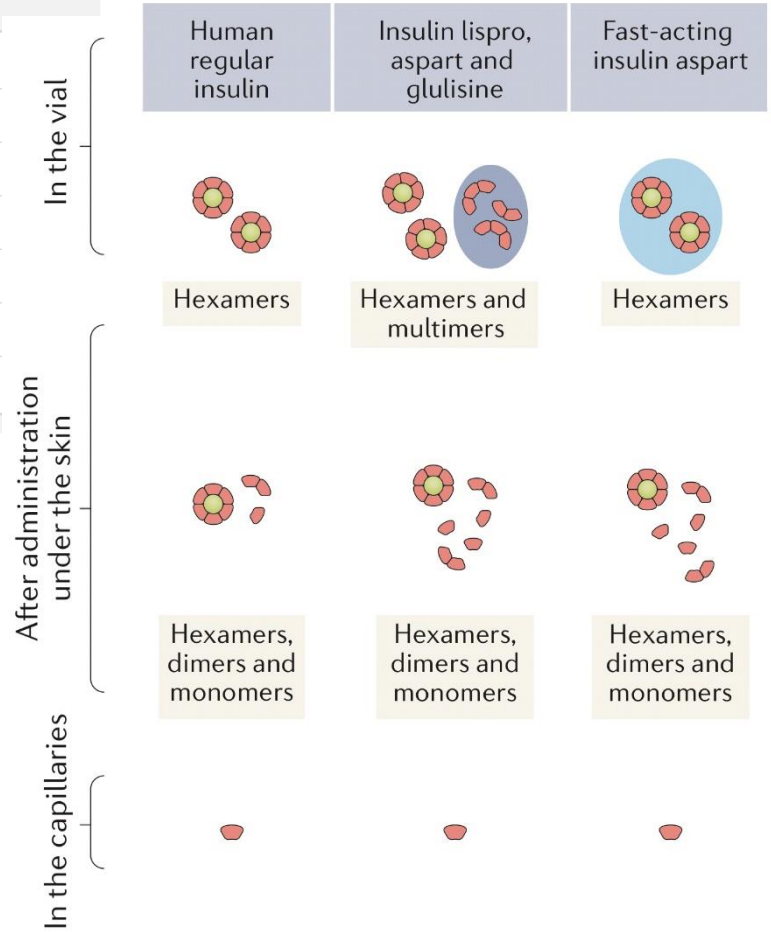
Progress of rapid-acting insulin

Regular insulin → Insulin aspart, Insulin glurigin, Insulin lispro → Rapid acting-insulin aspart

Pharmacokinetic action profiles of rapid-acting insulins

인슐린 종류 (상품명)	작용 시작	최고 작용	작용 시간
식전 인슐린			
속효성 인슐린 (투명)			
휴물린R	30 분	2-3 시간	6.5 시간
속효성 인슐린 유사체 (투명)			
인슐린 리스프로 (Humalog)	10-15 분	1-2 시간	3.5-4.75 시간
인슐린 글루리진 (Apidra)		1-1.5 시간	3-5 시간
인슐린 아스파르트 (NovoRapid)		1-1.5 시간	3-5 시간
Faster 아스파르트 (Flasp)	5 분	1 시간	3-4 시간





Mathieu, C., et al. (2017). "Insulin analogues in type 1 diabetes mellitus: getting better all the time." Nat Rev Endocrinol 13(7): 385-399.

Rapid-acting insulins aspart

In a pharmacokinetic study

- A faster onset of action than insulin aspart (4.9 min versus 11.2 min) and reached the 50% maximum concentration more quickly (20.7 min versus 31.6 min)
- The greatest difference occurred during the first 15 min, when the area under the curve was 4.5-fold greater with fast-acting insulin aspart

In a pharmacodynamic analysis

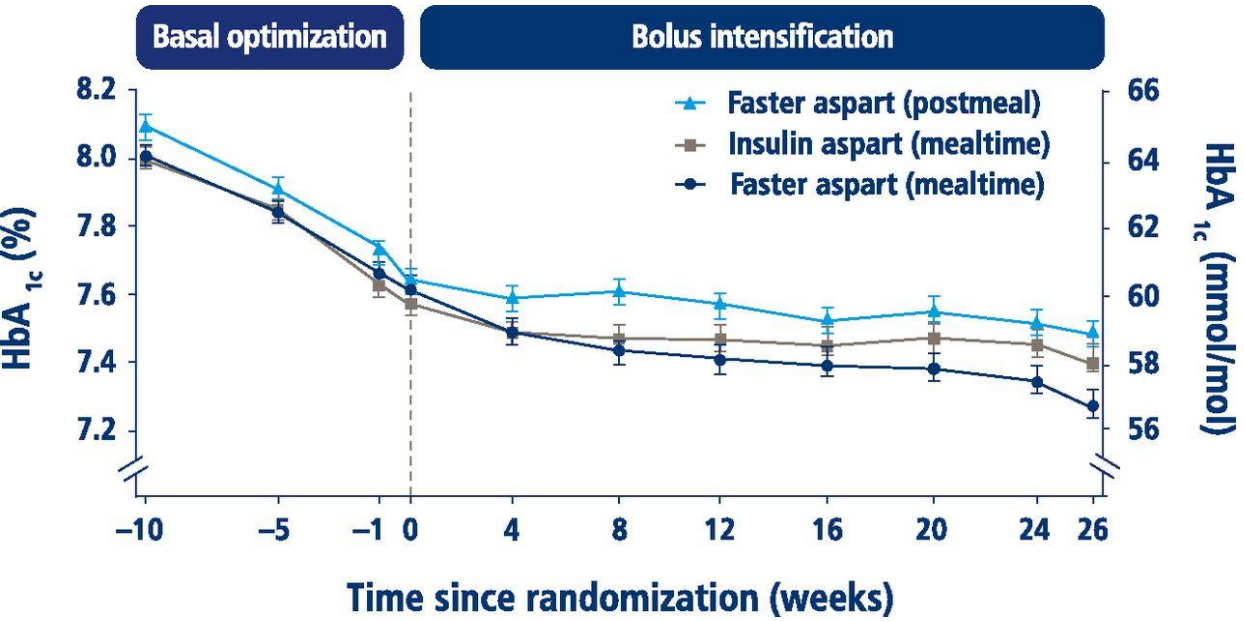
- A greater glucose-lowering effect within 90 min after dosing than insulin aspart
- Similar overall potency but that a shift of action to earlier time

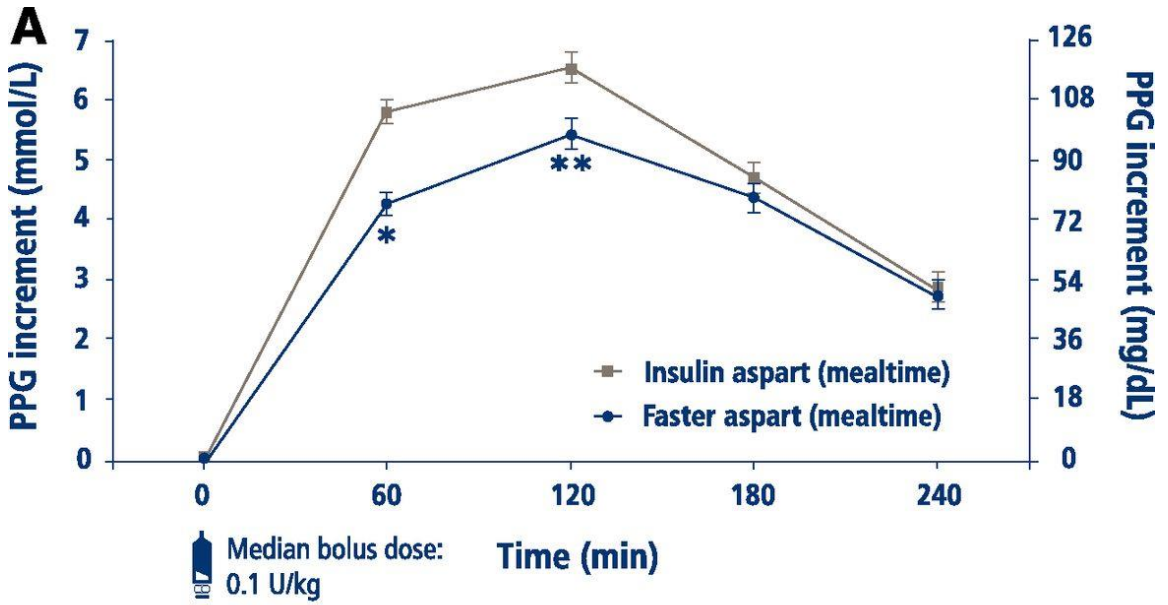
Mathieu, C., et al. (2017). "Insulin analogues in type 1 diabetes mellitus: getting better all the time." Nat Rev Endocrinol 13(7): 385-399.

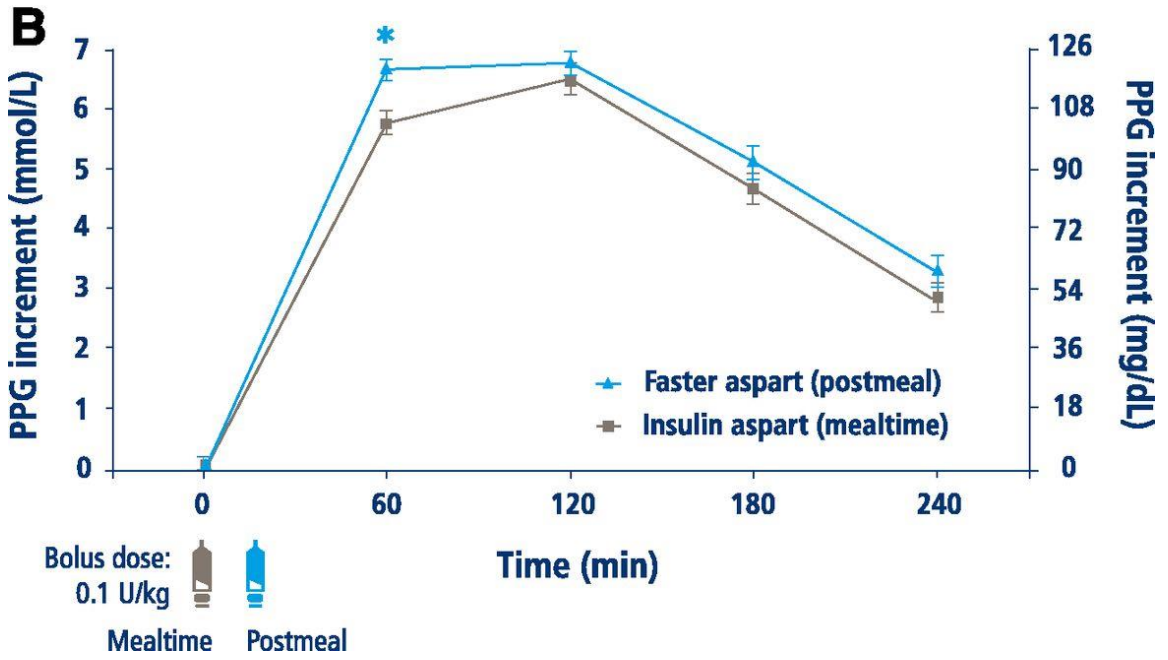
Diabetes Care Volume 40, July 2017

Fast-Acting Insulin Aspart Improves Glycemic Control in Basal-Bolus Treatment for Type 1 Diabetes: Results of a 26-Week Multicenter, Active-Controlled, Treat-to-Target, Randomized, Parallel-Group Trial (onset 1)

Diabetes Care 2017;40:943–950 | https://doi.org/10.2337/dc16-1771







20 min after

Rapid-acting insulins aspart

- In real-life settings,

  These few minutes make a considerable difference to the lives of people with diabetes

  Type 1 DM

  Type 2 DM ?

  Gaining another 4–5 min in speed of onset of insulin action will contribute to more flexibility in people's lives without compromising efficacy or safety of the insulin regimens

Mathieu, C., et al. (2017). Nat Rev Endocrinol 13(7): 385-399.

Progress of premixed formulations

Regular insulin

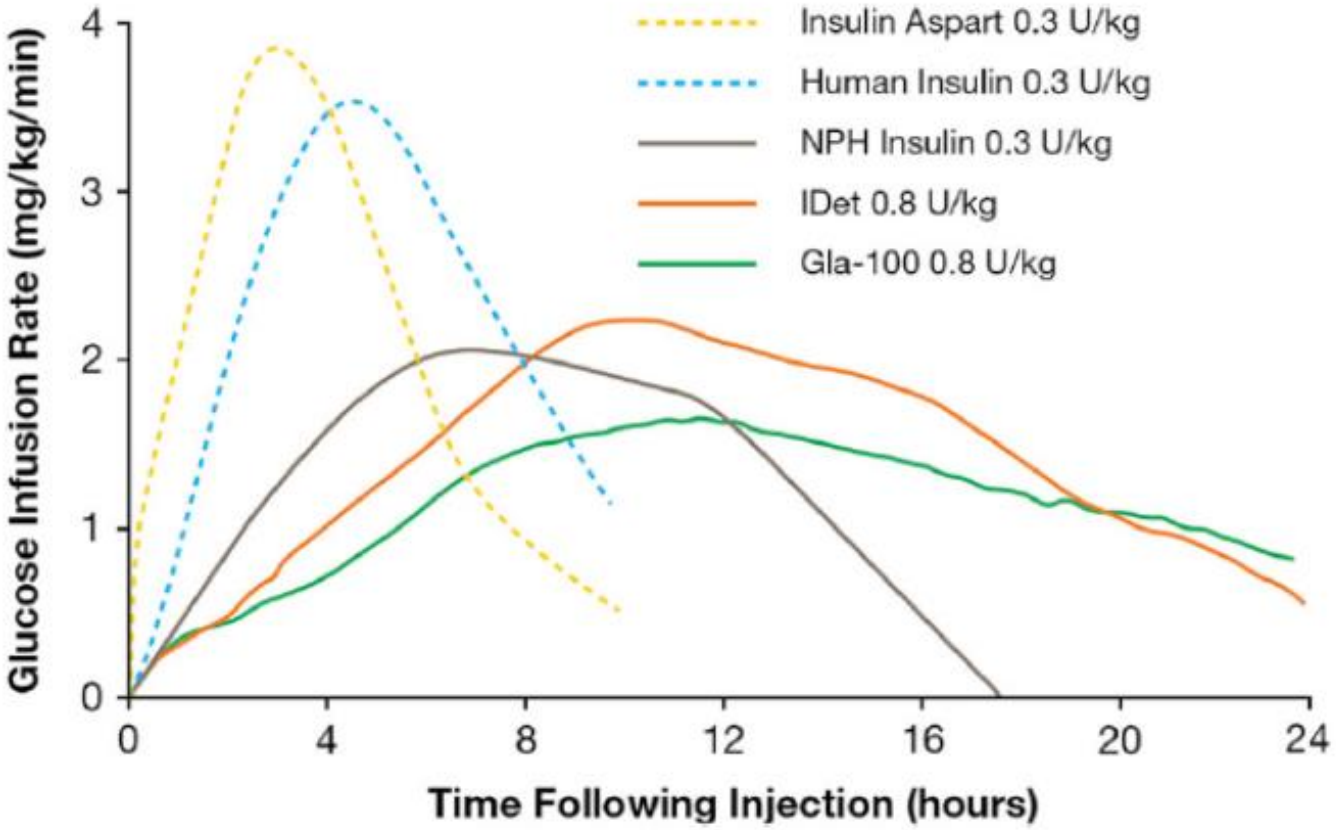
NPH/RI
70/30
50/50

Insulin protamine aspart/aspart
Insulin protamine lispro/lispro
70/30, 75/25, 50/50

Insulin degludec/
insulin aspart
70/30

Pre-mixed formulations

Insulins	Compounds
Premixed insulin products	• NPH/Regular 70/30
	• Lispro 50/50
	• Lispro 75/25
	• Aspart 70/30

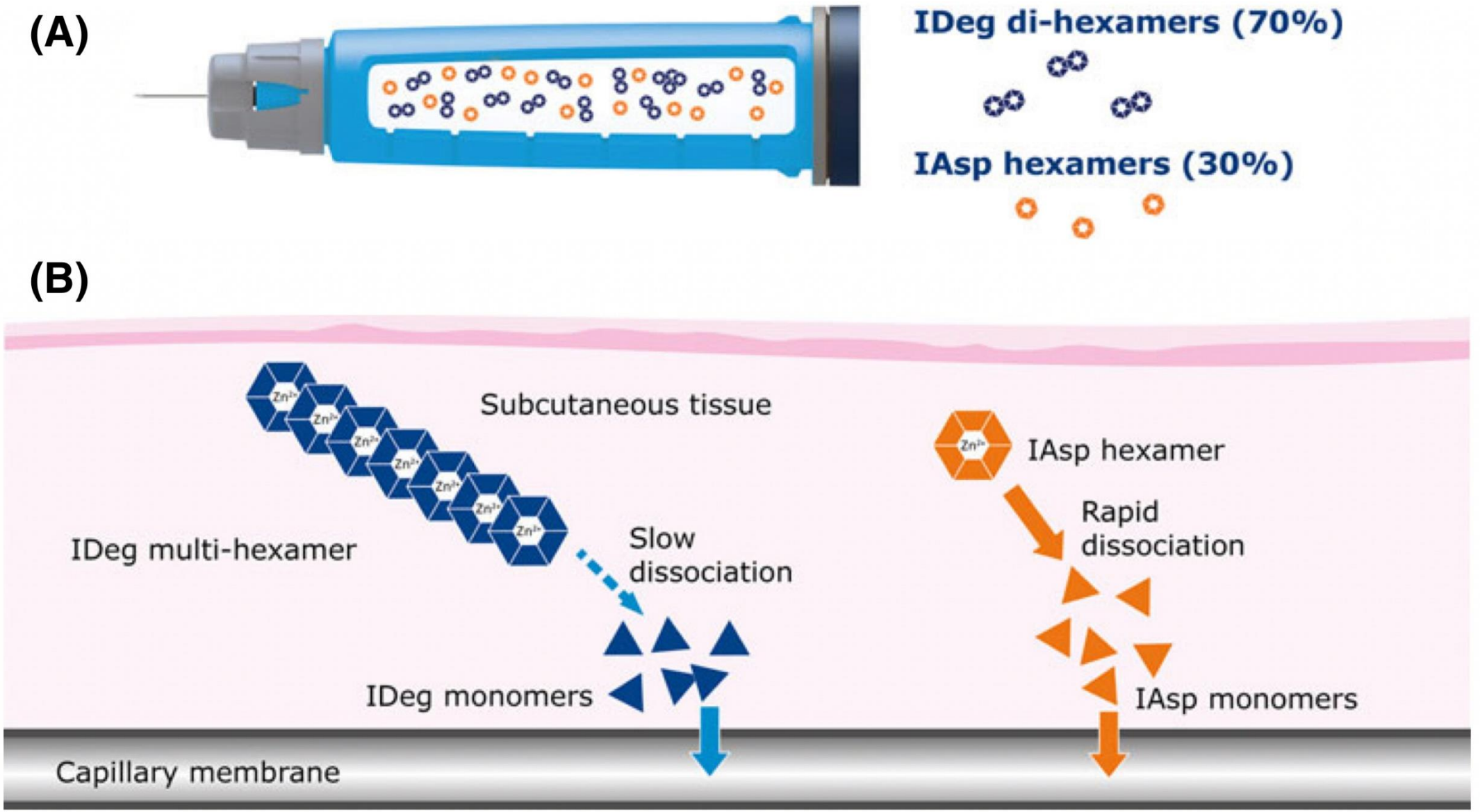


아침 점심 저녁 아침

Lispro protamine
Aspart protamine

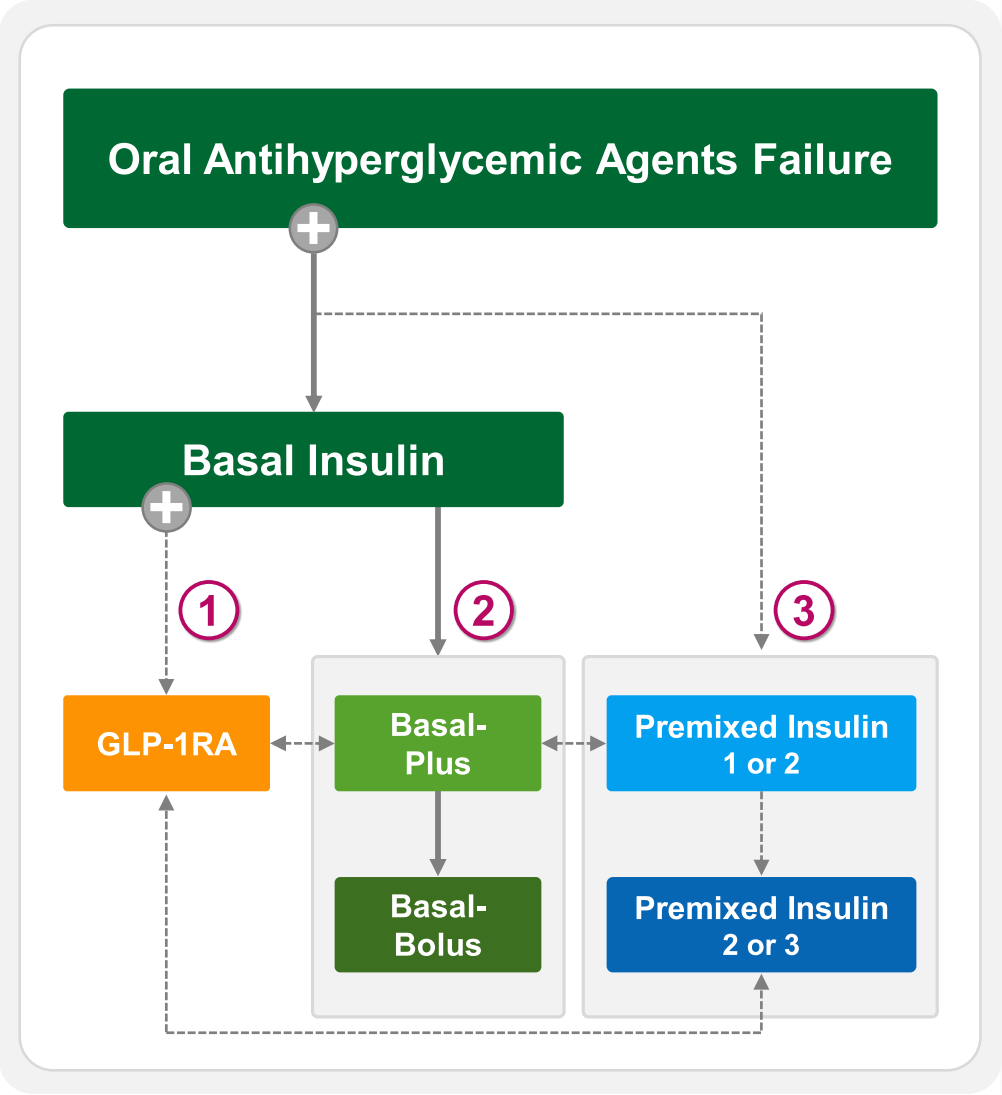
ADA. (2019). "9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019." Diabetes Care 42(Suppl 1): S90-S102.

Pre-mixed insulin: IDegAsp (Ryzodeg®)



Kumar, A., et al. (2016). "Clinical use of the co-formulation of insulin degludec and insulin aspart." Int J Clin Pract 70(8): 657-667.

기저인슐린 치료로 혈당 조절 실패 시 강화 주사제 치료의 선택



1. GLP-1 수용체작용제 추가
(DPP-4 억제제는 중단)

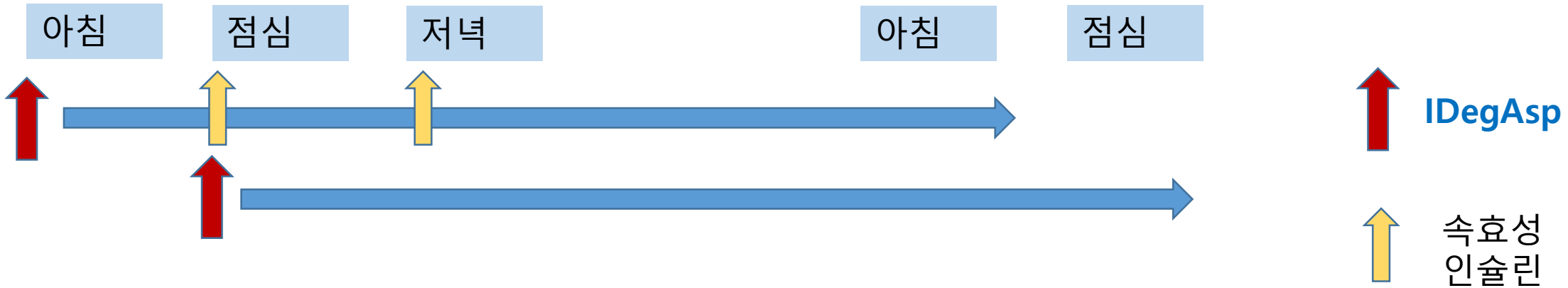
2. 기저-플러스 인슐린 요법
(1회/일 식전 인슐린 추가)
➡ 기저-식전 인슐린 요법으로
(2~3회/일 식전 인슐린 추가) 진행 가능

3. 혼합형 인슐린 요법 1일 2회 이상으로 전환

3제 병합요법에도 HbA1c ≥ 10%
➡ 처음부터 강화 인슐린 치료 고려

대한당뇨병학회. 당뇨병 진료 지침. 2017.

Pre-mixed insulin: IDegAsp

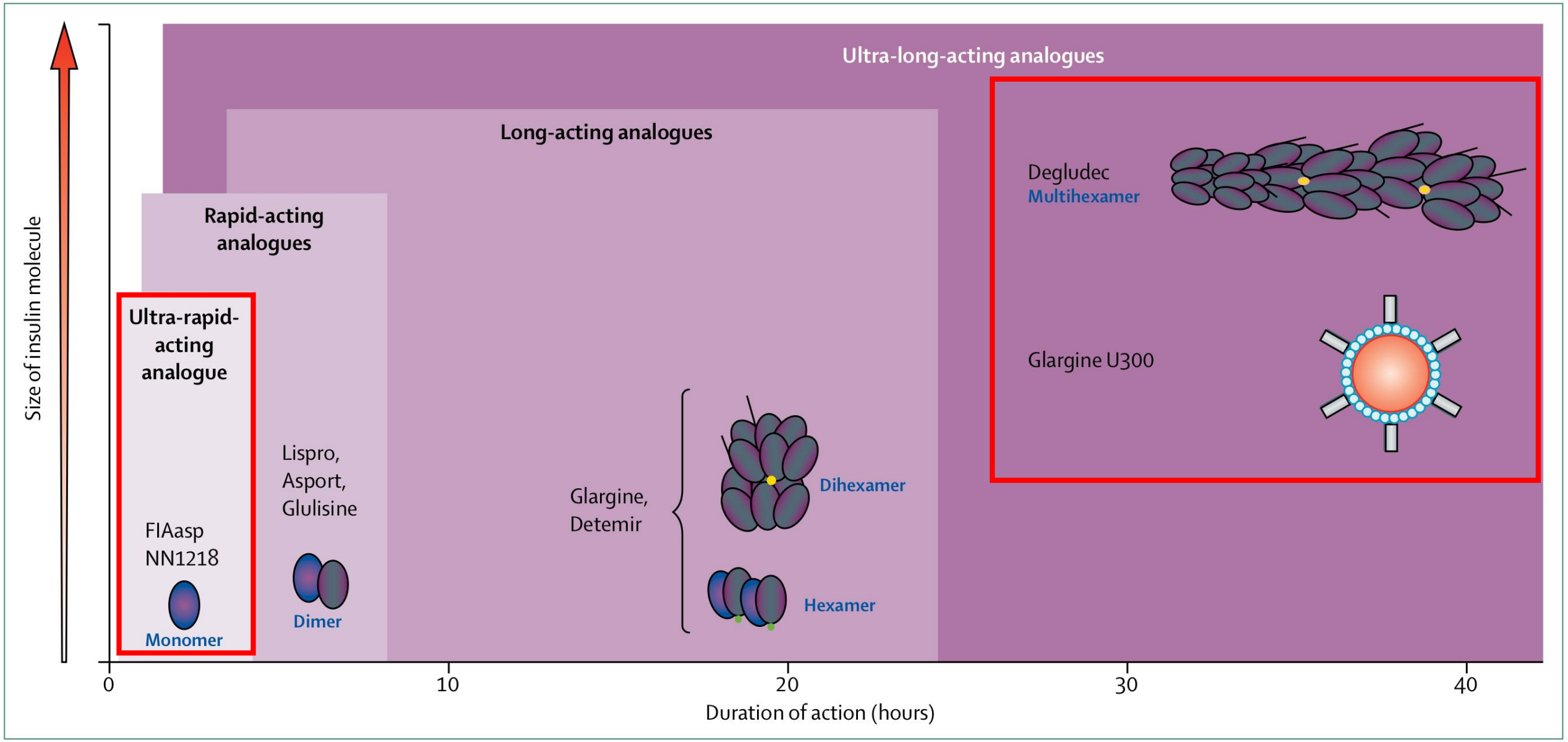


사용 예

Basal insulin 과 2가지 경구약제를 사용함에도 당화혈색소가 8.7% 정도로 높고 공복혈당은 90-110 mg/dl 정도로 유지되나 식후 혈당이 250-280 mg/dl 정도로 높은 52세 남자환자

→ 하루 중 식사량이 가장 많은 끼니 전에 속효성 인슐린 한번을 투여하려고 한다.

Insulin analog formulations with duration of action



Chatterjee, S., et al. (2017). "Type 2 diabetes." Lancet 389(10085): 2239-2251.

Summary

- 1. Insulin degludec, Glargin U300
  - Same efficacy
  - Longer duration→ better flexibility (Degl>U300)
  - Less hypoglycemia
  - U300의 경우 부피가 작기때문에 고용량 사용하는 환자에 편리성
- 2. Faster aspart
  - 작용시간이 5~10분 더 빠르다
  - Type 1 DM 환자.
  - 식후에 주사를 맞아야 하는 경우(more flexibility)
- 3. Pre-mixed insulin: Insulin degludec/Aspart
  - Basal-plus 방법을 1번 주사 투여로 주사횟수를 줄임
  - 기존의 Pre-mixed insulin 보다 flexibility 가 높다