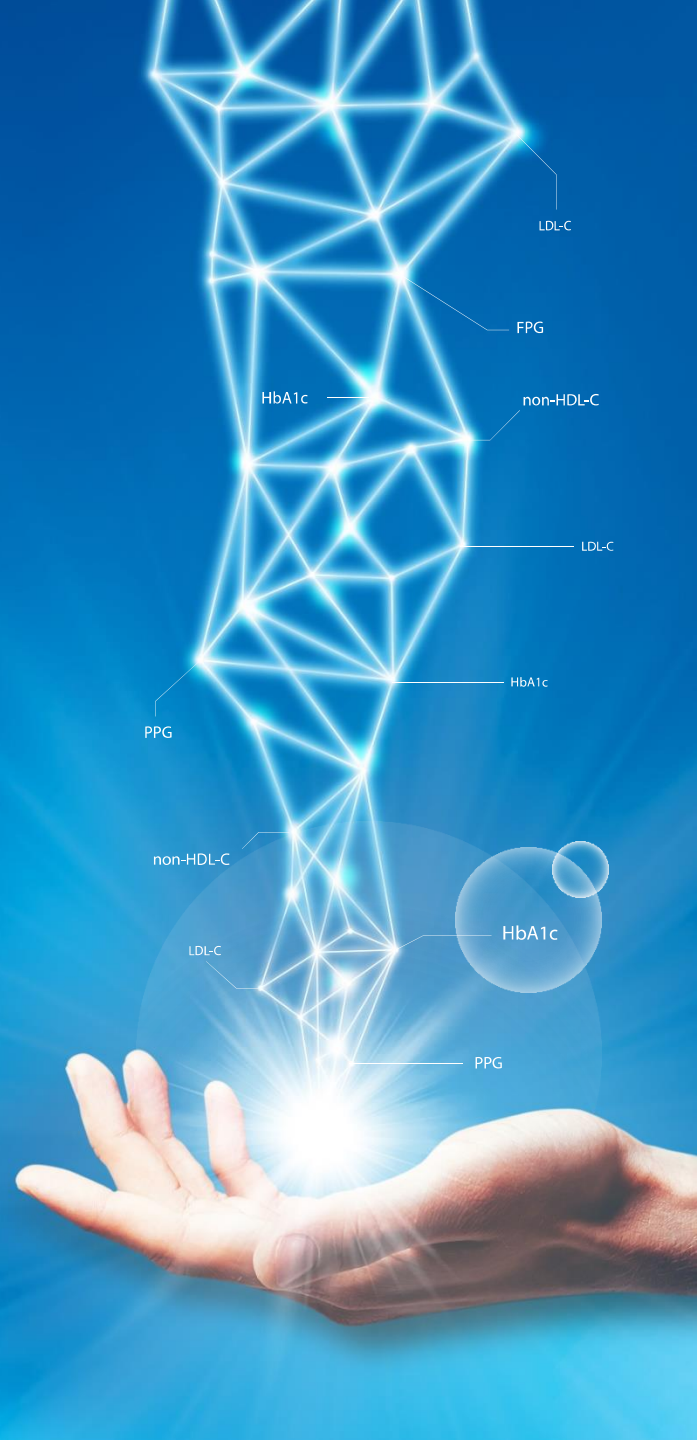
The Art of Fixed Ratio Combination In DM Treatment

謝安慈
中和班廷謝安慈診所



Outline

- Epidemiology of Type 2 Diabetes in Taiwan
- FPG and Insulin role in glycemic control
- When FPG control can not help patient to reach HbA1C goal
- Benefits of Basal Insulin and GLP-1 RA combination therapy
- Difference of short-acting GLP-1RA
- New option for optimal glycemic control: SOLIQUA (iGlarLixi)

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Current Disease Situation of Type 2 Diabetes in Taiwan

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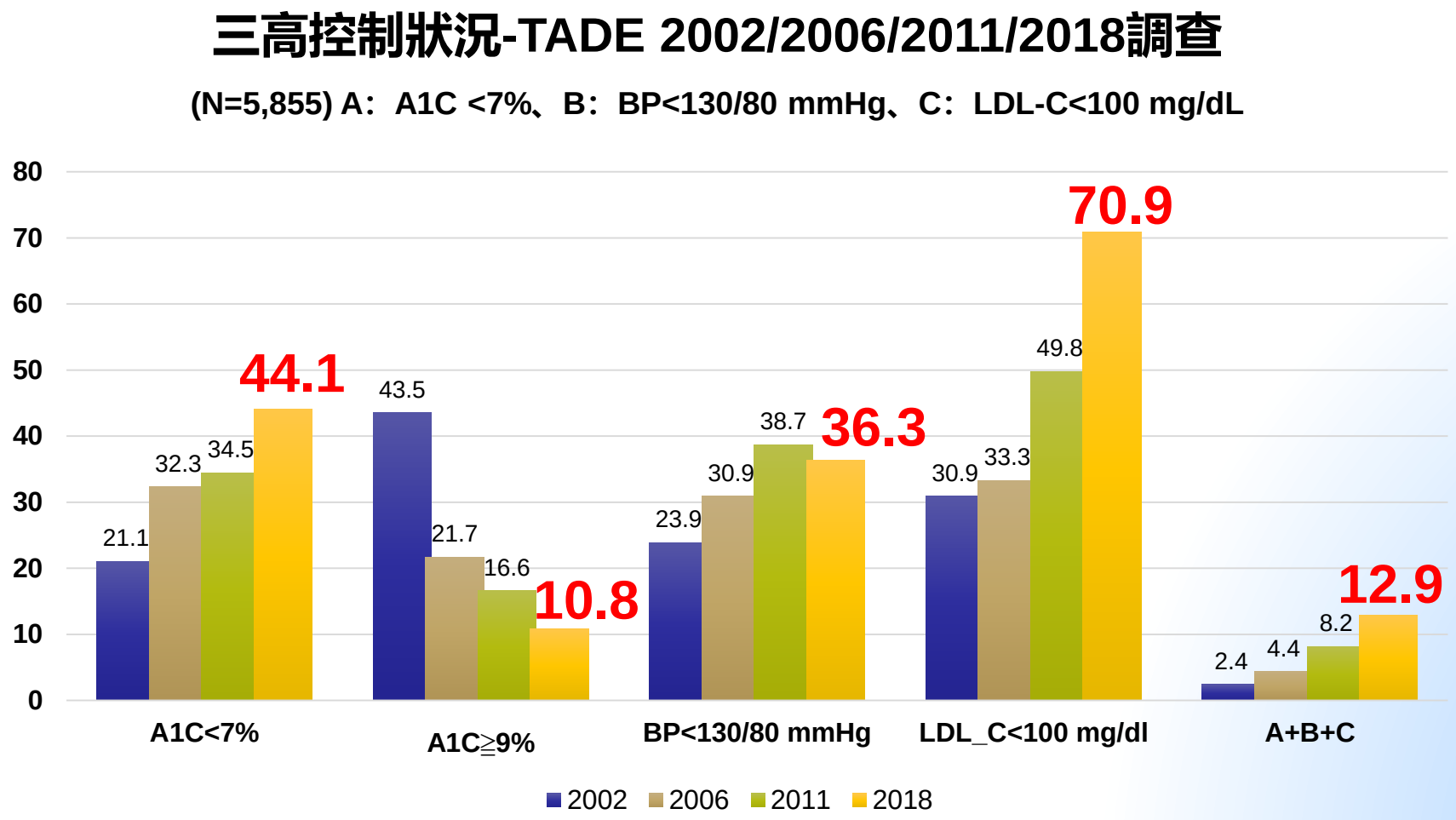

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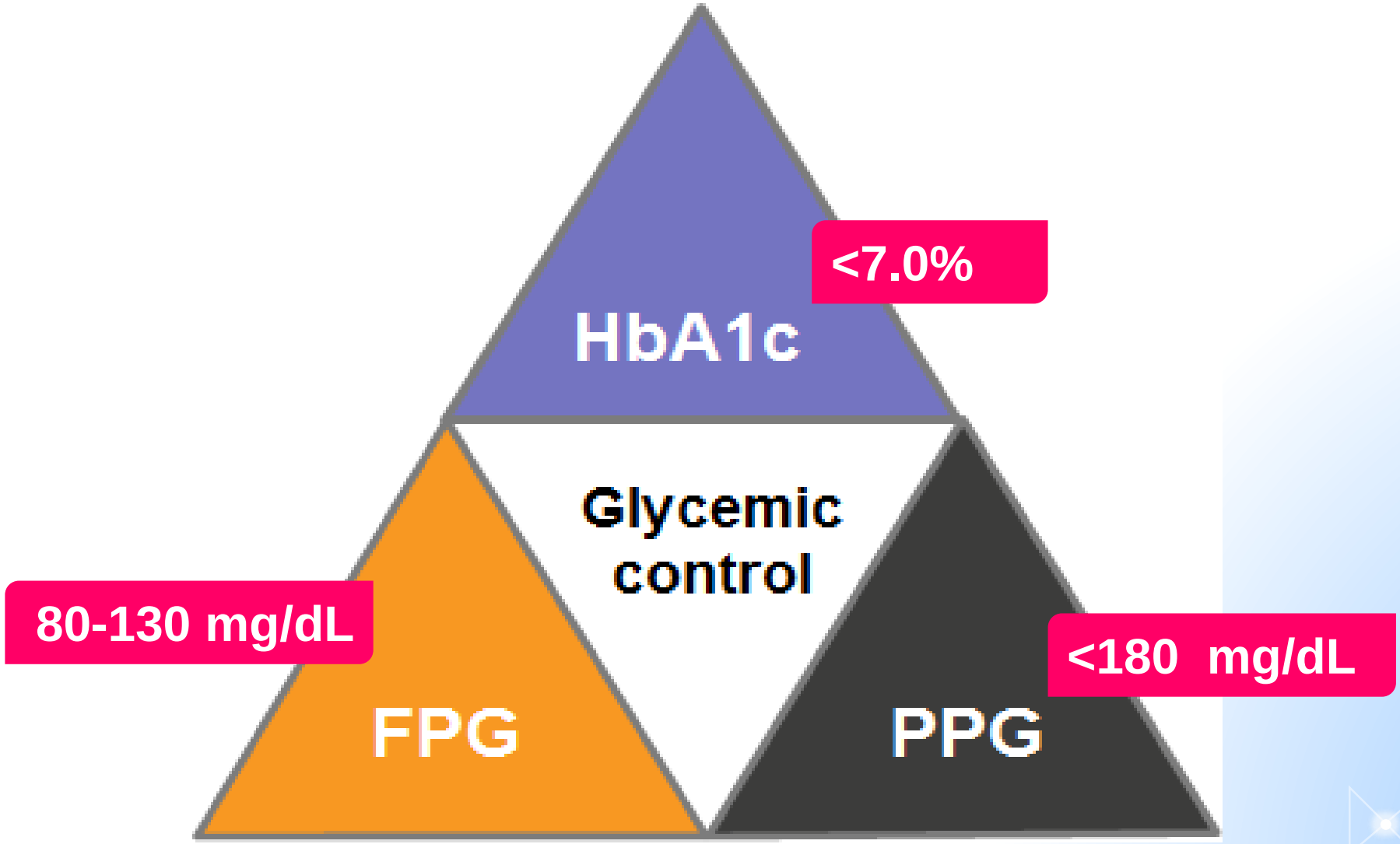
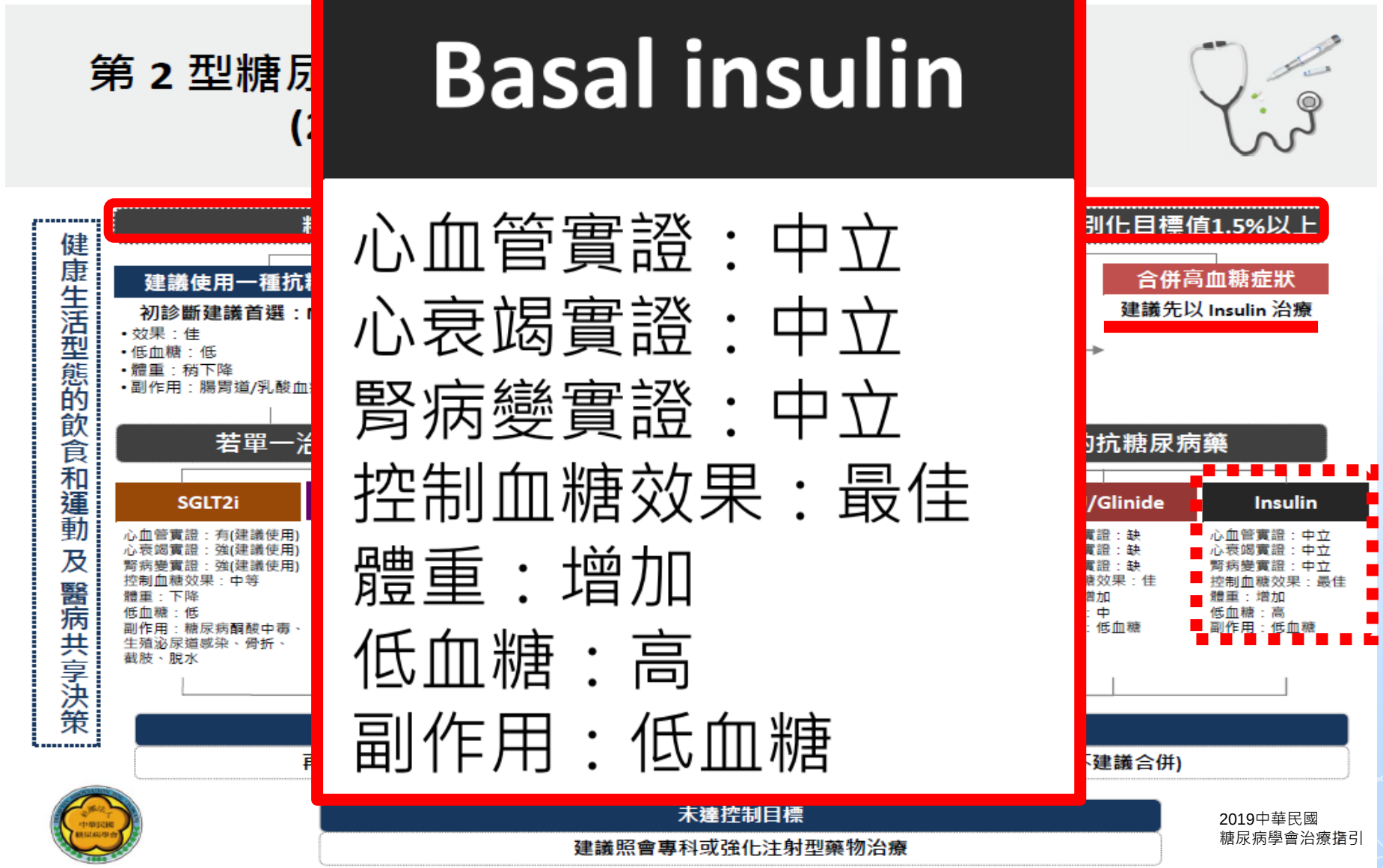
Achievement of glycaemic control is the primary goal of treatment for T2DM



The Role Of Insulin in in Glycaemic Control-Guideline



The Role Of Insulin in in Glycaemic Control

第二型糖尿病患者若在罹病第一年即搭配

胰島素

治療，和單用口服藥相較之下，可讓胰島細胞功能增加一倍，糖化血色素下降的幅度更多，加強胰島素治療更能有效控制糖尿病併發症風險。

2019糖尿病品質調查報告

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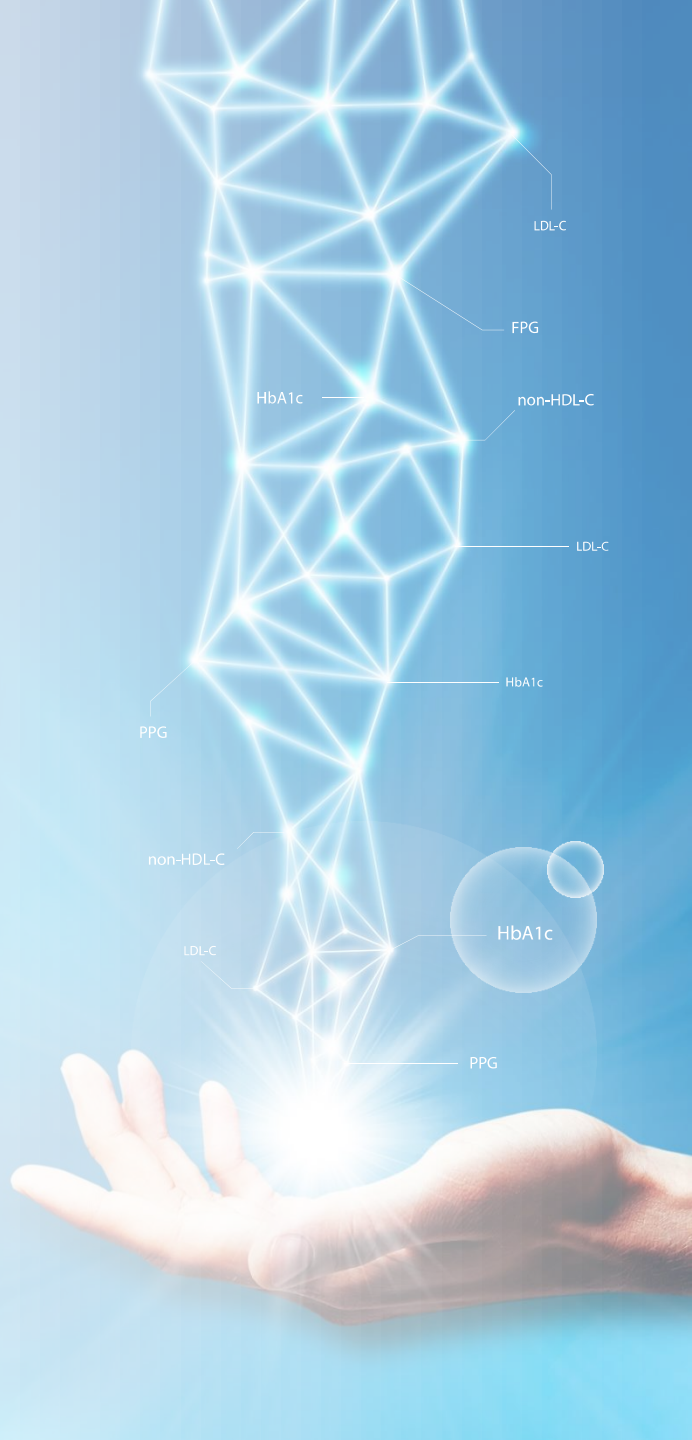
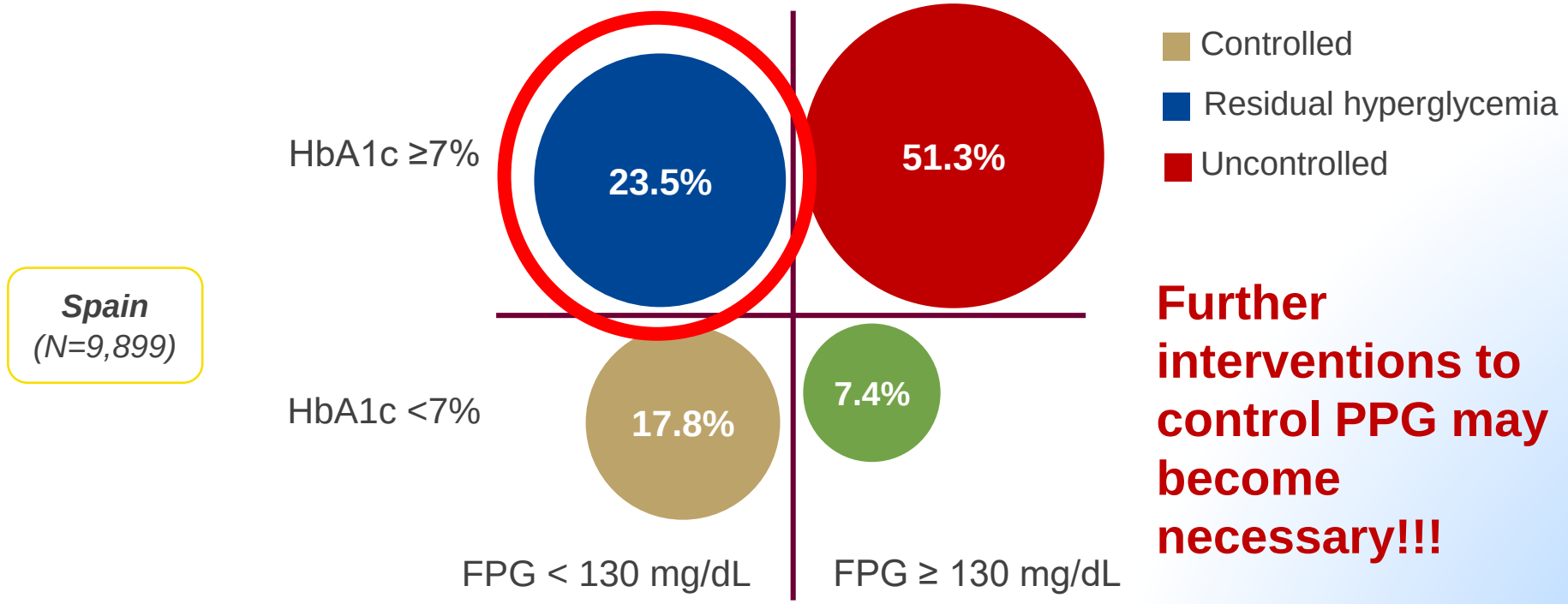


51% of T2DM patients on basal insulin have uncontrolled FPG and HbA1c, and 23.5% have residual hyperglycemia

Distribution of the overall population according to HbA1c and FPG levels. Of a population of 126,811 T2DM subjects, **9,899 were treated with basal insulin (NPH, detemir, or glargine)**

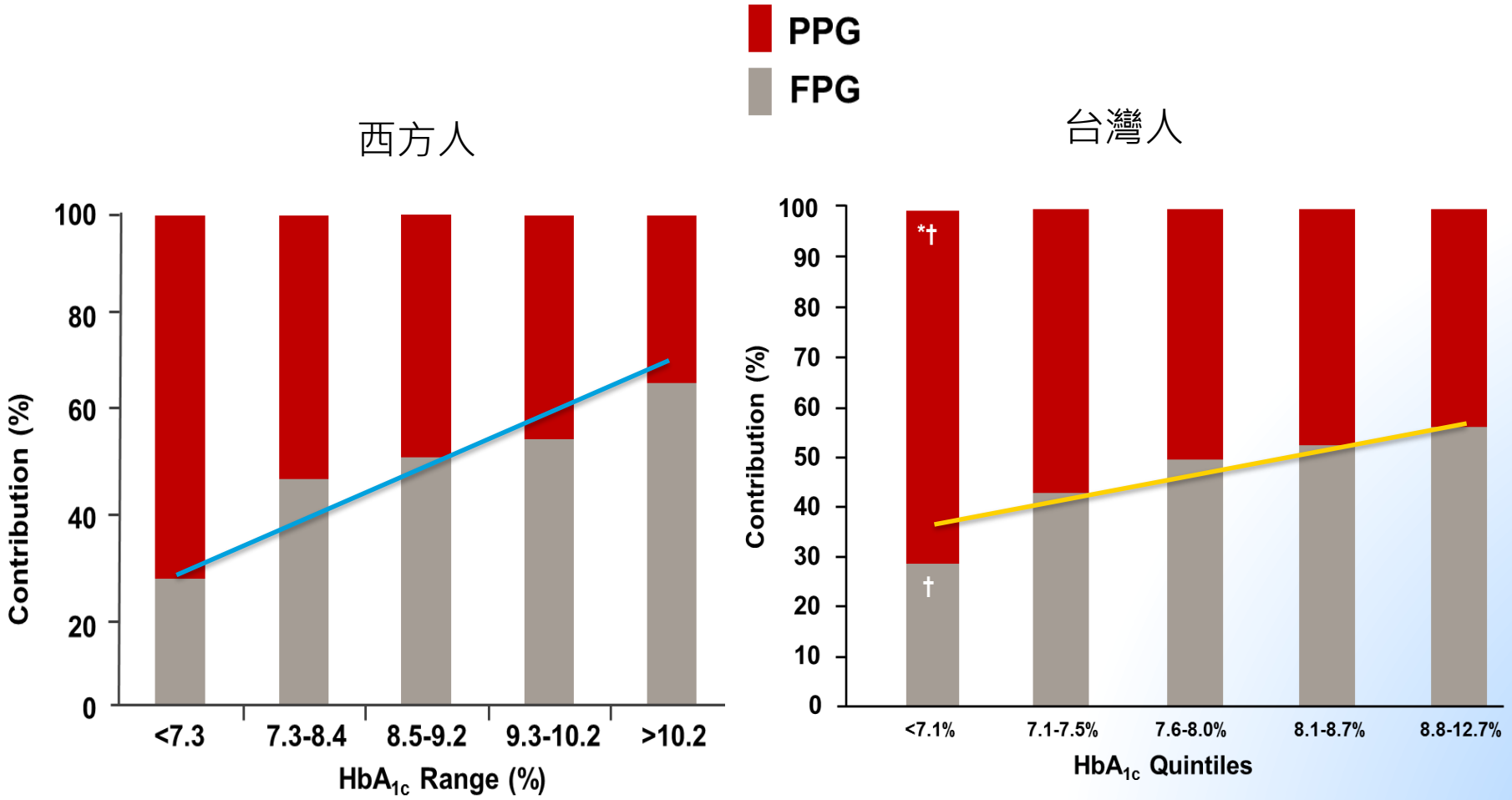


Further interventions to control PPG may become necessary!!!

Controlled *defined as HbA1c at target (HbA1c <7%);* ***Residual hyperglycemia*** *defined as HbA1c above target despite FPG at target (FPG <7.2/7.8 mmol/L [<130/140 mg/dL];* ***Uncontrolled*** *defined as neither HbA1c nor FPG at target*

A cross-sectional study on T2DM patients aged 31–90 years treated with basal insulin registered in the SIDIAPQ primary healthcare electronic database during 2010. Of a population of 126,811 T2DM subjects, 9,899 were treated with basal insulin (NPH, detemir, or glargine). Of these, 23.5% (n = 2322) achieved optimal FPG (<130 mg/dL) but an inadequate HbA1c target (>7%). Mean HbA1c values in the uncontrolled and controlled groups were 8.15% and 6.31%, respectively
Mata-Cases.M. et al, Journal of diabetes. 2016

Different between Caucasians and Asian Type 2 Diabetes

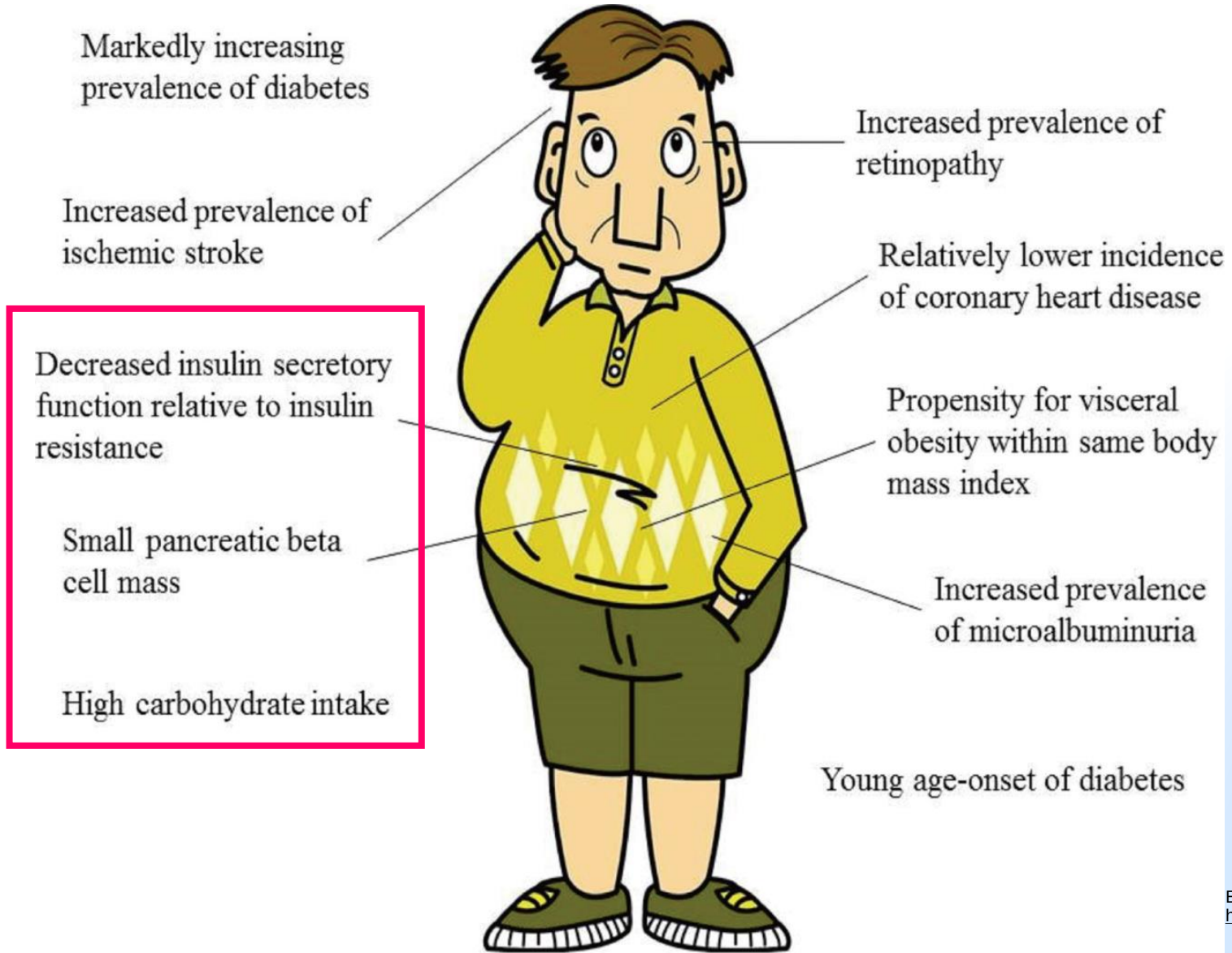


*Significant difference between FBG and PPG; †Significant difference from all other quintiles.

1. Monnier L, et al. *Diabetes Care*. 2003;26(3):881-885. 2.Wang JS, et al. *Diabetes Metab Res Rev*. 2011;27(1):79-84.

Wang, J.S., et al. *Diabetes Metab Res Rev.* 2011;27(1):79-84.

Characteristics of Asian patients with diabetes



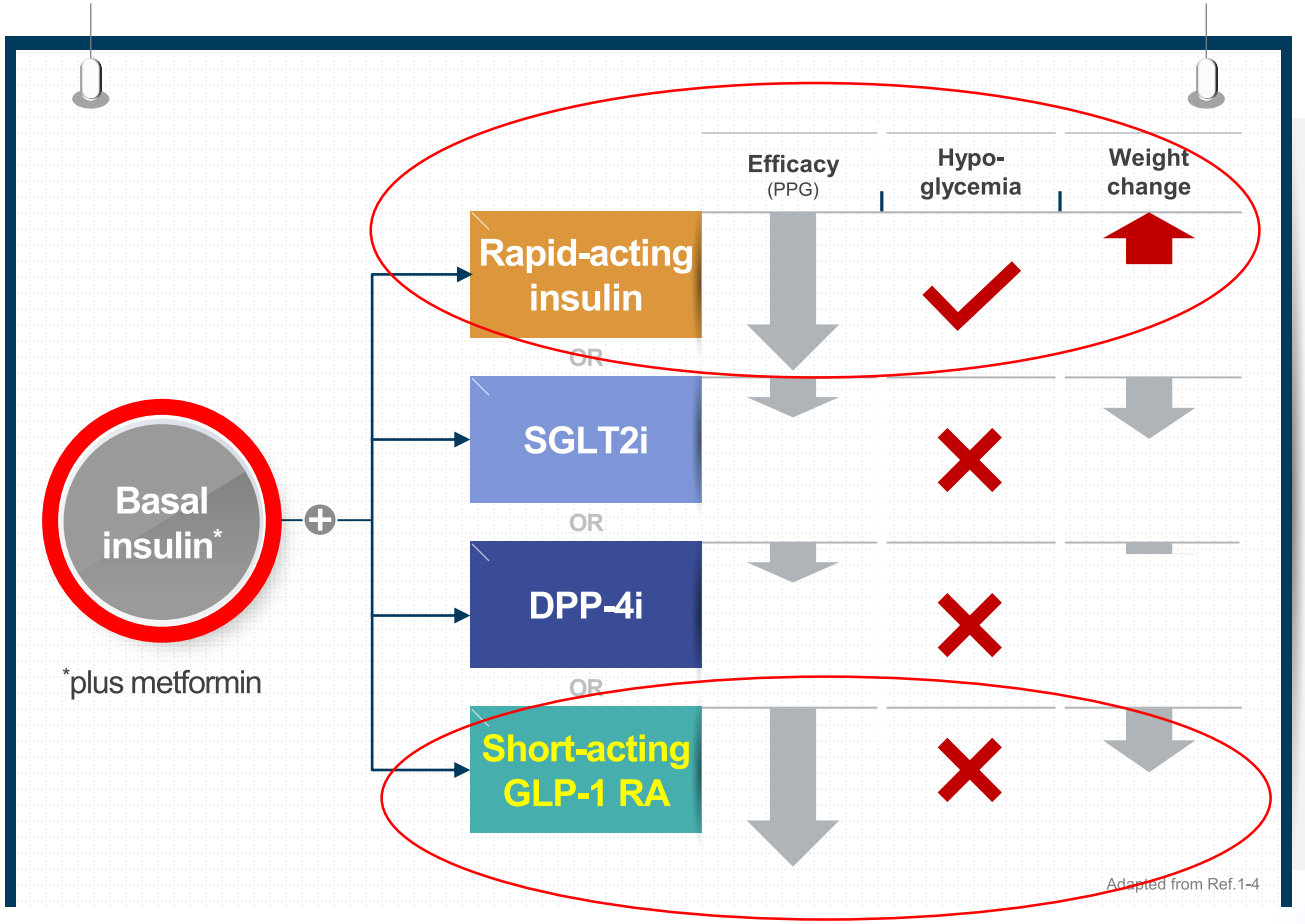
Endocrinol Metab. 2015 Sep;30(3):263-269.
http://dx.doi.org/10.3803/EnM.2015.30.3.263

Basal Glucose Can Be Controlled, but the Prandial Problem Persisted. It's the Next Target!

Matthew C. Riddle

Diabetes Care 2017;40:291–300 | DOI: 10.2337/dc16-2380

Comparison of available intensification options in patients sub-optimally controlled with basal insulin



- Traditional approach of adding **a prandial insulin increases the risk for hypoglycemia**[1,2]
- **GLP-1 RA more effective** than DPP-4i or SGLT-2i at HbA1c lowering in patients with long-standing T2DM not achieving glycemic targets[1]

1. Standard of Medical Care in Diabetes. 2018. Diabetes Care. 2018; 41(Suppl1):S1-S159 2. J Diabetes. 2016 Dec 15. [Epub ahead of print]
3. Clin Diabetes. 2015 Oct;33(4):175-80 4. J Korean Diabetes 2015;16:252-259

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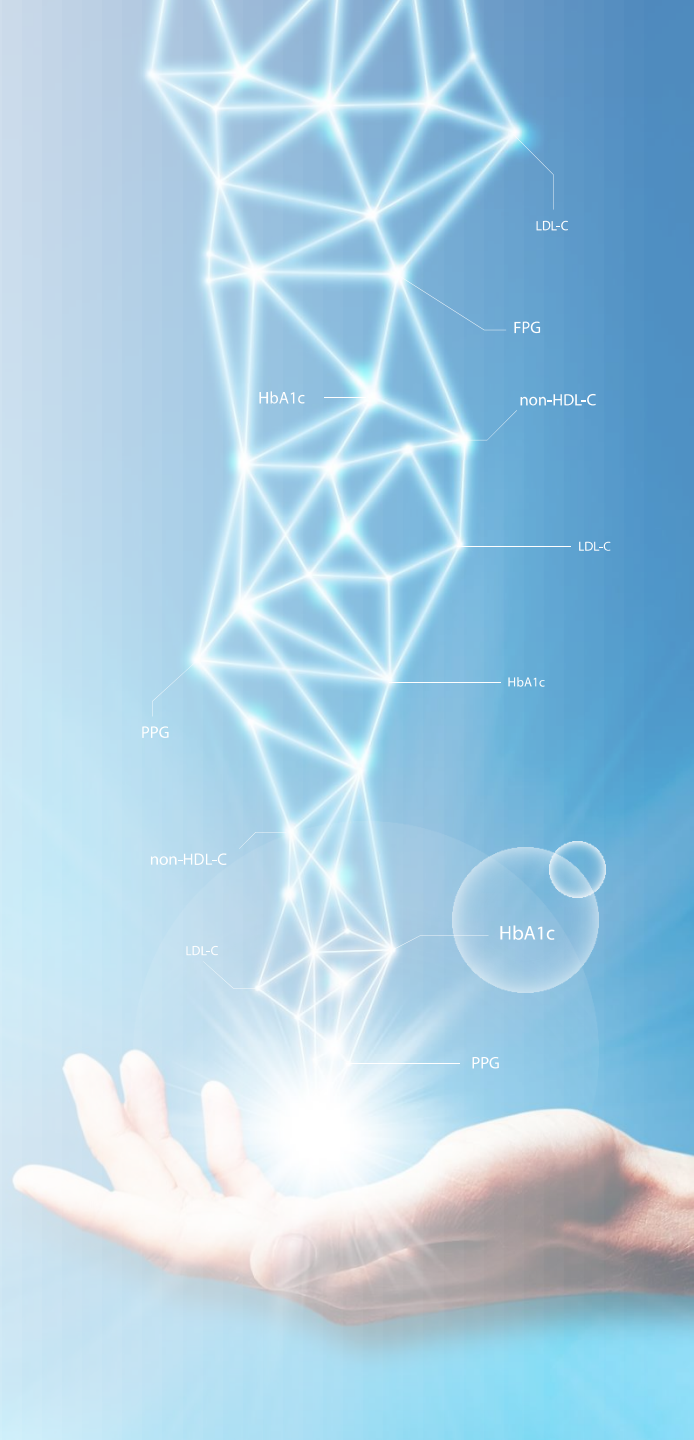
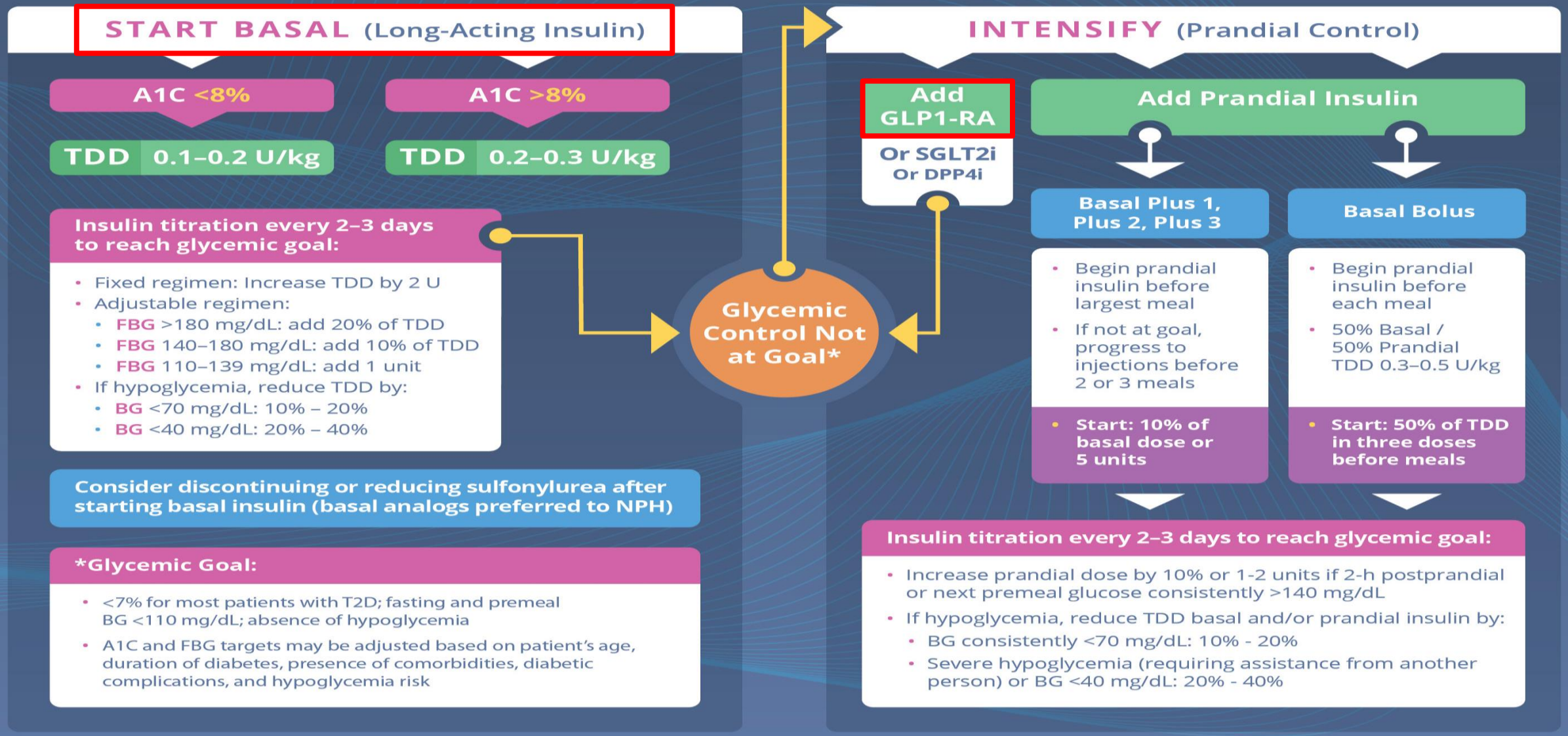
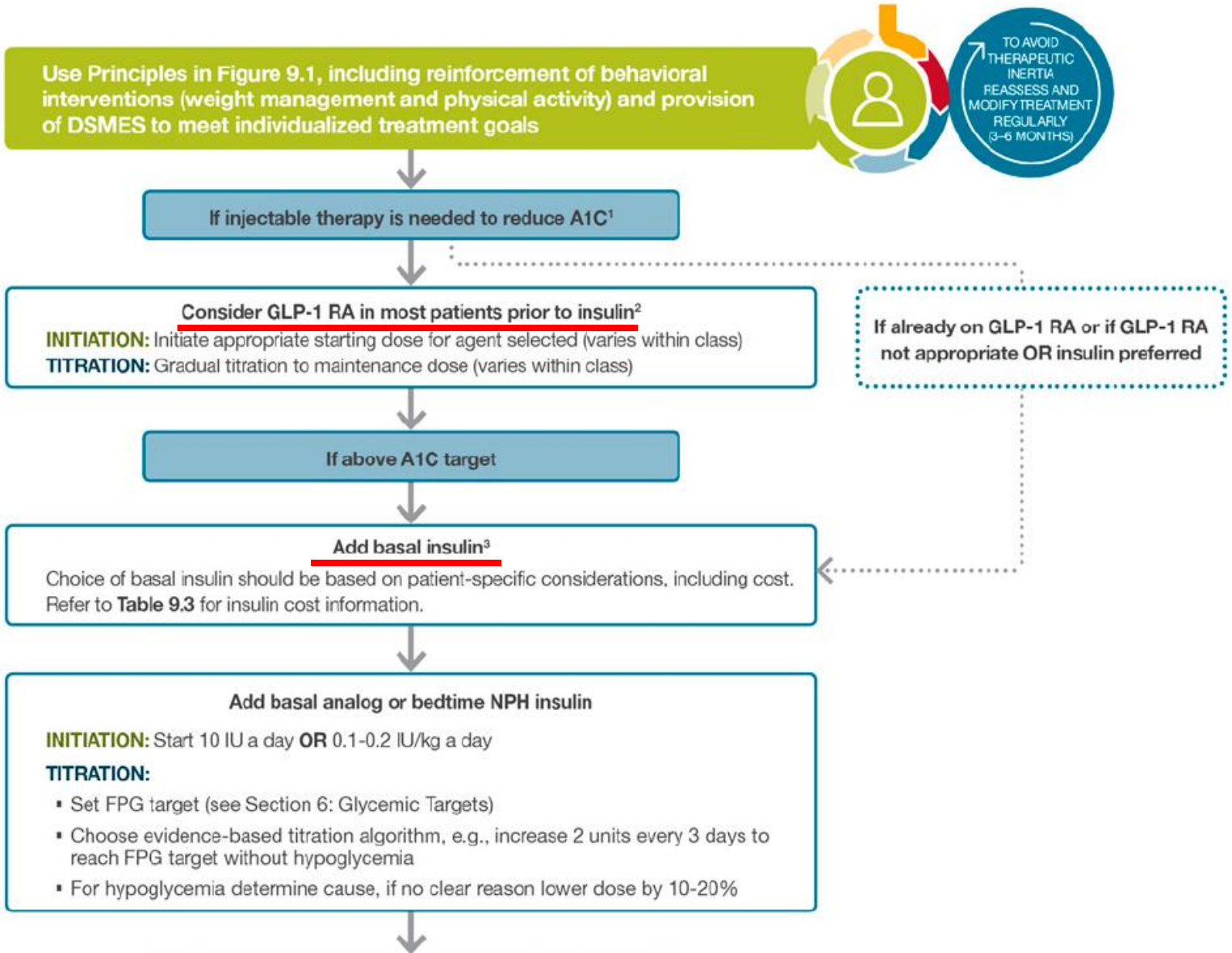


Algorithm for Insulin Intensification - AACE

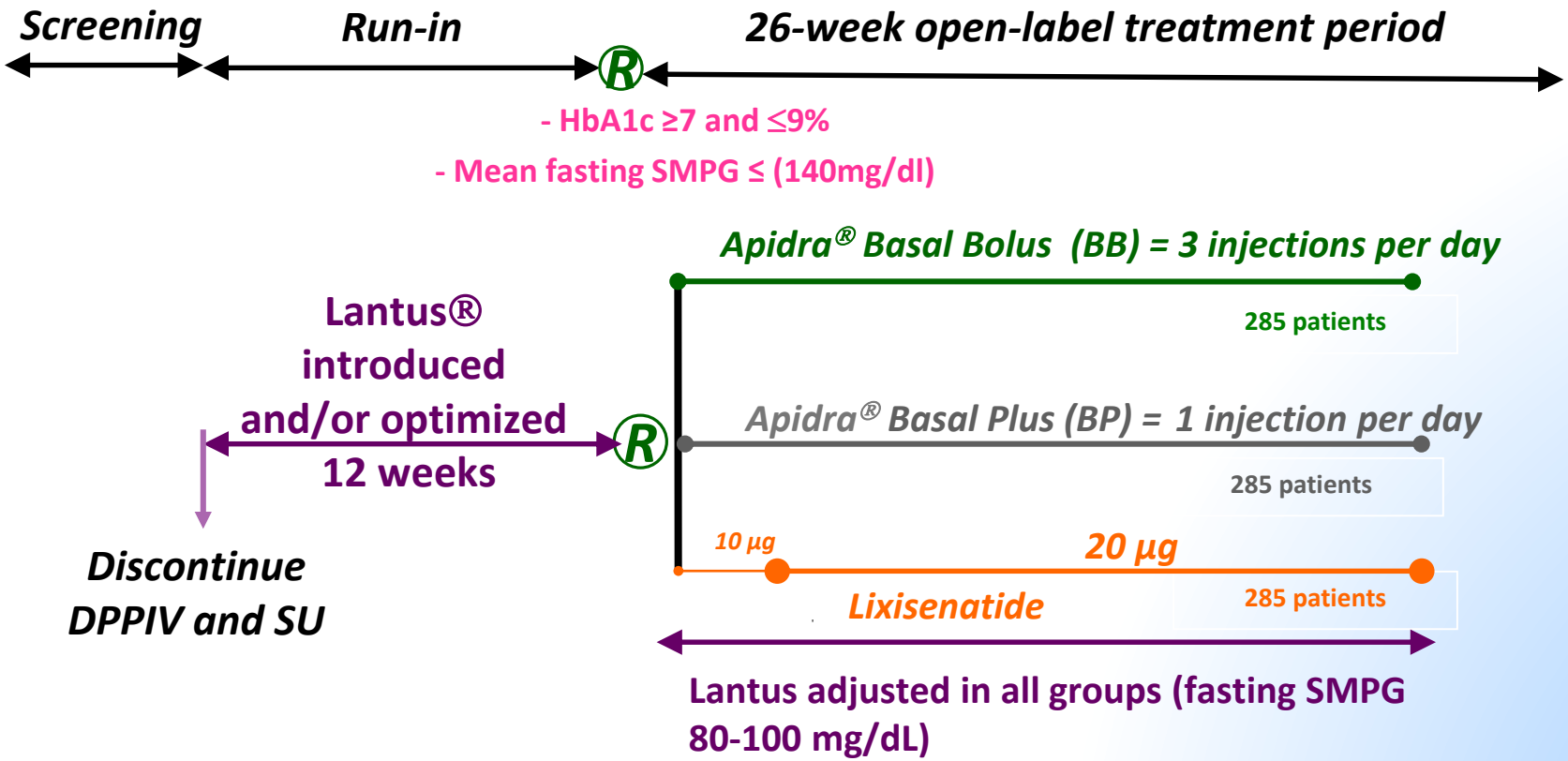



Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
If injectable therapy is needed to reduce A1C[1]
Consider GLP-1 RA in most patients prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Gradual titration to maintenance dose (varies within class)
If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred
If above A1C target
Add basal insulin[3]
Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to Table 9.3 for insulin cost information.
Add basal analog or bedtime NPH insulin
INITIATION: Start 10 IU a day OR 0.1-0.2 IU/kg a day
TITRATION:
▪ Set FPG target (see Section 6: Glycemic Targets)
▪ Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
▪ For hypoglycemia determine cause, if no clear reason lower dose by 10-20%

GetGoal-Duo 2
Free combination V.S BB/BP

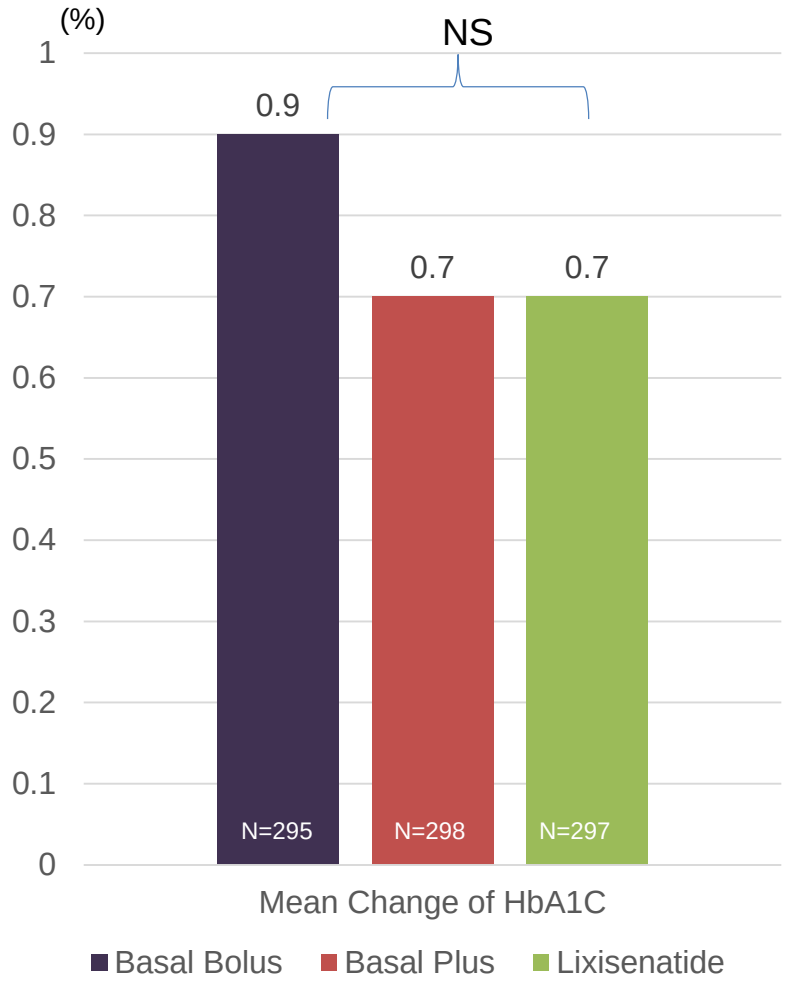
-T2D patients

- Basal insulin ± OADs



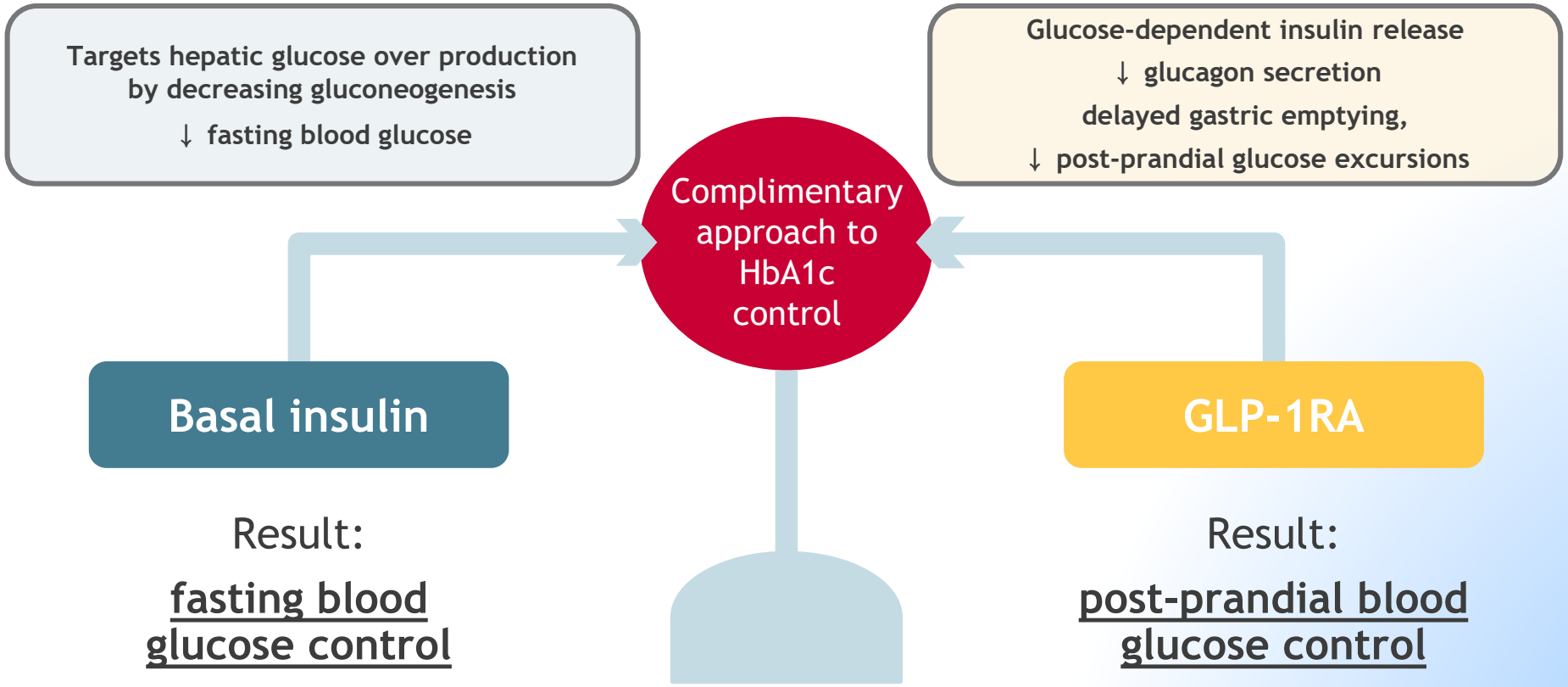
RAI: rapid acting insulin; SMBG: self-monitored blood glucose; T2DM: type 2 diabetes mellitus;
OADs: oral antidiabetic drugs; R: randomisation; DPP4: di-peptidyl peptidase 4; SU: sulphonylurea.

Combination of Basal Insulin/Lixisenatide provide similar HbA1C control with less weight gain



Diabetes Care Publish Ahead of Print, published online May 23, 2016

The complementary modes of action of basal insulins and GLP-1 RAs provide control of both FPG and PPG



1. Balena R, et al. Diab Obes Metab 2013;15:485–502; 2. Baggio LL and Drucker DJ. Gastroenterol 2007;132: 2131–57
3. Wang Z, et al. Diab Care 2010;33:1555–60; 4. Holst JJ, et al. Physiol Rev 2007;87:1409–39

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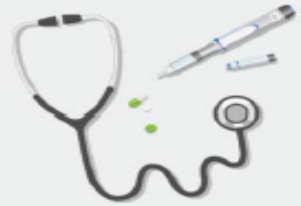
類升糖素肽-1 受體促效劑的作用*



類升糖素肽-1 受體促效劑 (GLP1-RA) 的作用

1. 促進胰島素的釋出
   抑制升糖素的分泌
   → 降低血糖

2. 減緩胃的排空：
   •減少餐後血糖的上升
   •減少飢餓感、增加飽足感
   → 減重效果

短效型 GLP1-RA 製劑

- Exenatide：作用時間短，需一日注射二次
- Lixisenatide：一日注射一次

長效型 GLP1-RA 製劑

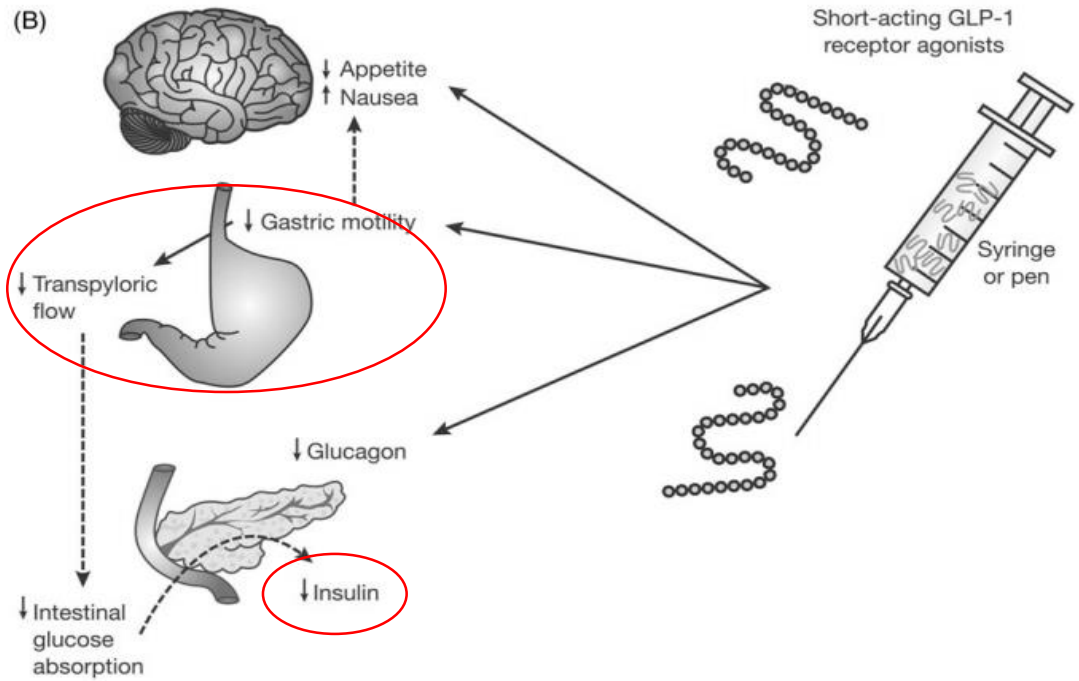
- Liraglutide：一日注射一次
- Exenatide 的長效懸液注射劑 Bydureon，dulaglutide 及 semaglutide：每週注射一次

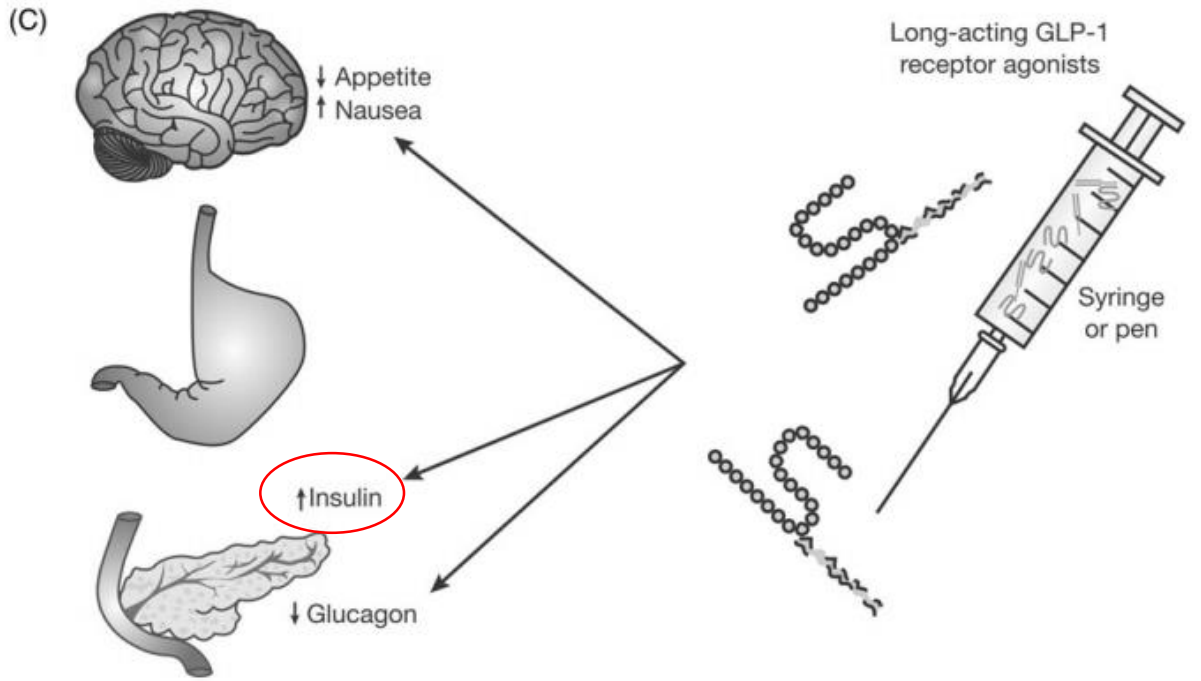
*全球未上市之Albuglutide及二年內台灣不會上市之口服Sema不在本指引此次討論之內故不列入

Difference Mechanisms of GLP-1 RA

Short-acting GLP-1RA

Long-acting GLP-1RA





Curr Med Res Opin. 2019 May;35(5):793-804.

類升糖素肽-1 受體促效劑的成分
-GLP-1 analogues

Liraglutide[1]

97%
amino acid homology
to human GLP-1

Native human GLP-1

Dulaglutide[2]

90% amino acid homology
to human GLP-1

Semaglutide[3]

94%
amino acid homology
to human GLP-1

GLP-1, glucagon-like peptide-1; **GLP-1RA**, glucagon-like peptide-1 receptor agonist; **IgG**, immunoglobulin G; **rH**, recombinant human

1. Victoza SmPC. July 2016; 2. Kuritzky L et al. *Postgrad Med* 2014;126:60–72; 3. Kapitza C et al. *J Clin Pharmacol* 2015;55:497–504

類升糖素肽-1 受體促效劑的成分
- Exendin-4-based peptides

Exenatide BID[1,2]

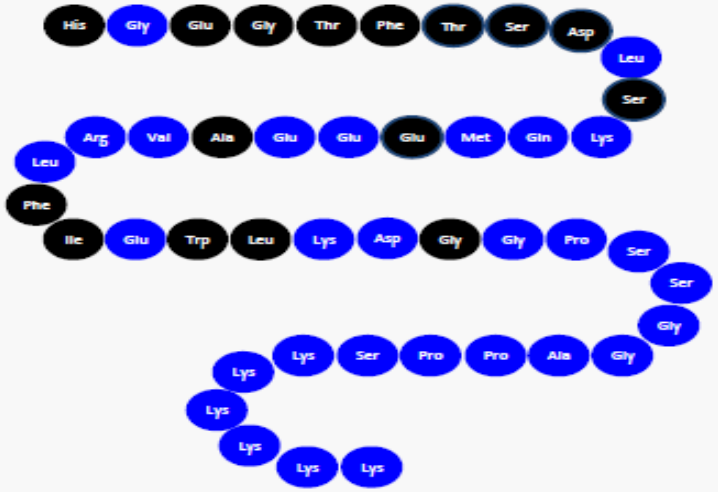
~50%
amino acid homology
to human GLP-1

Native human GLP-1

Exenatide QW[1,2]

Exenatide molecules in a
biodegradable
polylactide-co-glycolide
polymer matrix

Lixisenatide[3,4]

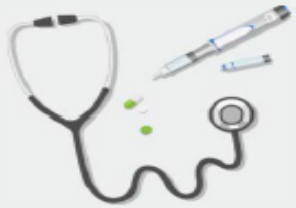


~50%
amino acid homology
to human GLP-1

BID, twice daily; **GLP-1**, glucagon-like peptide-1; **GLP-1RA**, glucagon-like peptide-1 receptor agonist; **QW**, once weekly

1. De Young MB et al. *Diab Technol Ther* 2011;13:1145–1154; 2. Fineman M et al. *Clin Pharmacokinet* 2011;50:65–74; 3. Christensen M et al. *IDrugs* 212:503–513; 4. Brown DX et al. *Drug Des Devel Ther* 2014;8:25–38

類升糖素肽-1 受體促效劑的比較



	Pharmacokinetics		Structure		Size	
	Short-acting	Long-acting	Exendin-4-based	GLP-1-based	Small	Large
GLP-1 RA	• Exenatide BID • Lixisenatide	• Exenatide QW • Liraglutide • Semaglutide • Dulaglutide	• Exenatide BID • Exenatide QW • Lixisenatide	• Liraglutide • Semaglutide • Dulaglutide	• Exenatide BID • Exenatide QW • Liraglutide • Lixisenatide • Semaglutide	• Dulaglutide
Effect	Gastric emptying PPG	FPG	May produce antibodies		Better penetration in the brain Better effect on appetite suppression	Smaller effect on body weight

FDA-approved pharmacological interventions that target postprandial hyperglycemia* (~2017 Feb)

Agent	A1C Reduction, %	PPG Reduction, mmol/L (mg/dL)	CV Benefit
AGIs			
Acarbose	0.4–0.8	4.0 (72)	
Miglitol	0.2–0.8	1.5–3.5 (27–63)	
Glinides			
Repaglinide	0.6–1.5	2.6 (47)	
Nateglinide	0.5–0.8	2.6 (47)	
Insulin			
Rapid-acting	1.5–2.5	No limit	
SGLT2 inhibitors			
Canagliflozin	0.8–1.0	2.4–3.3 (43–59)	
Dapagliflozin	0.6–1.0	3.6–3.8 (65–68)	V
Empagliflozin	0.7–0.8	2.0–2.6 (36–47)	

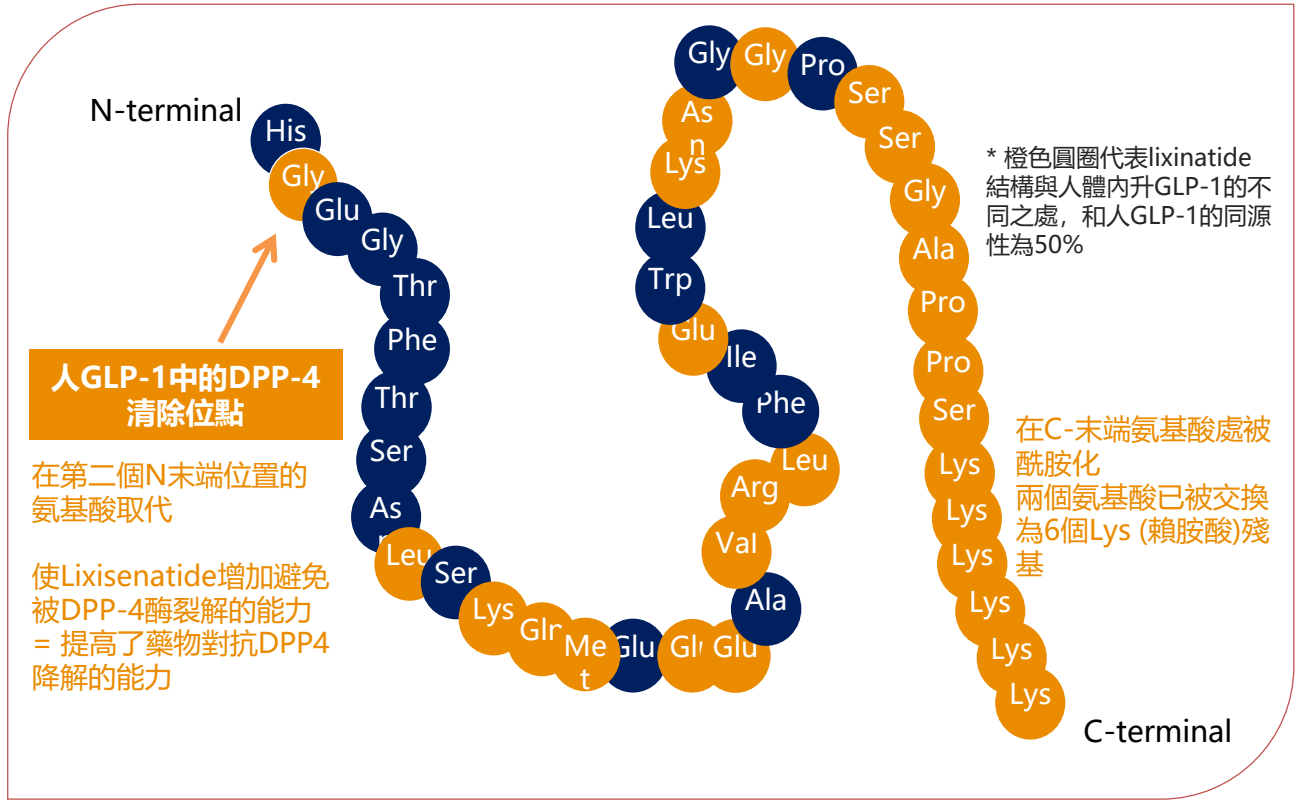
Agent	A1C Reduction, %	PPG Reduction, mmol/L (mg/dL)	CV Benefit
GLP-1 RA			
Exenatide	0.5–1.0†	3.6 (65)	
Liraglutide	1.0–1.5†	1.7–2.7 (31–49)	V
Lixisenatide	**0.5–0.9**	**3.1–5.9 (56–106)**	
DPP-4 inhibitors			
Sitagliptin	0.6–0.8	2.8 (50)	
Saxagliptin	0.6–0.8	2.8 (50)	
Combo agents			
iDegLira	0.8–1.9	Not reported	
iGlarLixi	**1.1–1.6**	**4.7–5.7 9 (85–103)**	

**Used as monotherapy or in combination with other antidiabetic agents.*
†Assuming starting value ≥8%.

相較於長效 GLP-1 RA， Lixisenatide有額外的延緩胃排空以及抑制食慾的效果，並且有很好的降PPG能力

Hrshon et al .Clinical Diabetes 2019 Jul; 37(3): 250-259.

Lixisenatide is a selective short-acting GLP-1 RA



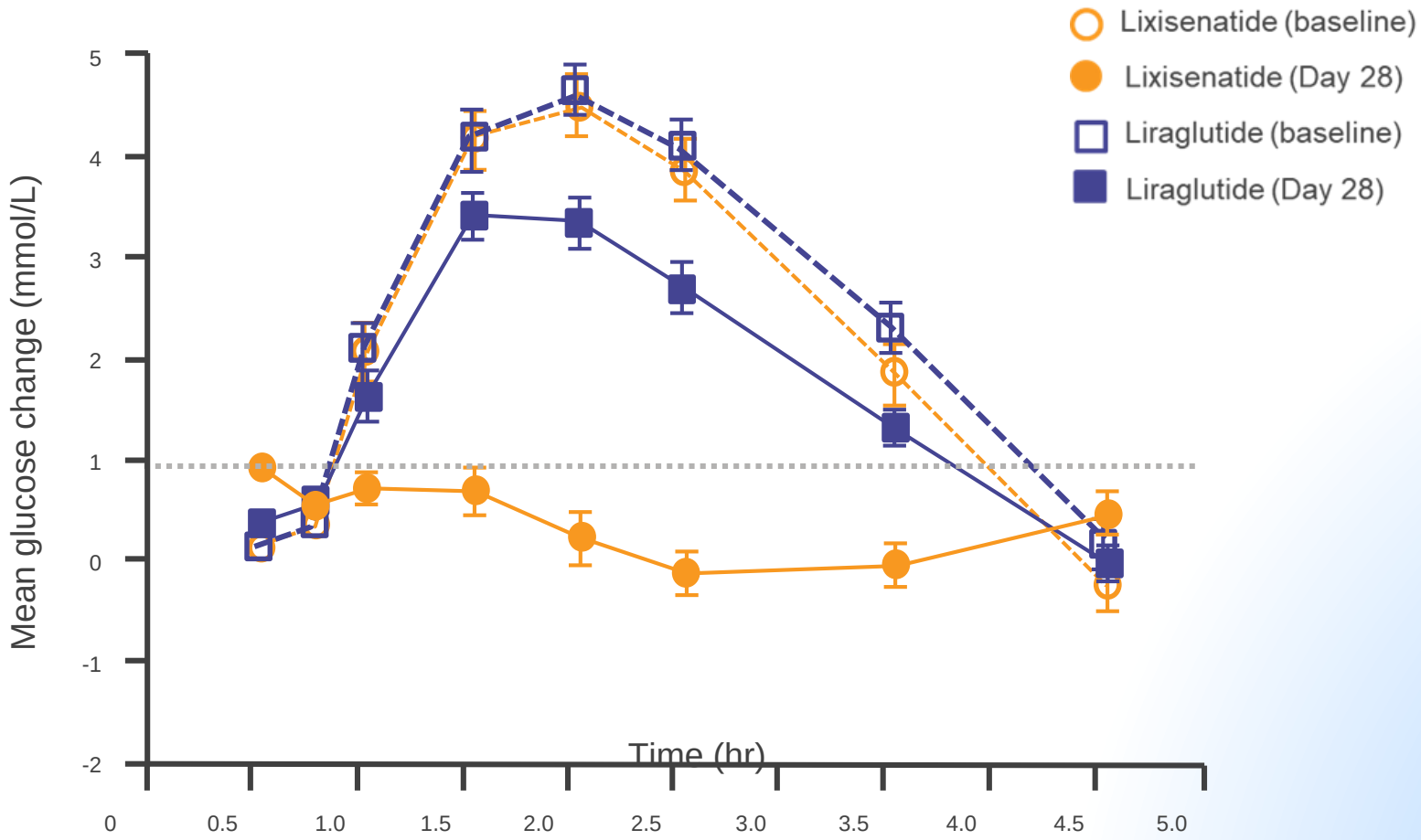
- Lixisenatide可抵抗DPP-4快速降解以長久維持體內活性
- 血漿半衰期約1.5-4.5h
- 親和力相對於人體GLP-1的倍數:

親和力相對於人體GLP-1的倍數	
Lixisenatide	**4x**
Exenatide	0.64x
Liraglutide	3x

相較於內生性GLP-1，Lixisenatide對於GLP-1 receptor具有4倍的高親和性，進而減緩半衰期，因此只需要一天一次給藥

Werner U, et al. Regul Pept 2010;164:58–64
Thorkildsen C, et al. J Pharmacol Exp Ther 2003;307:490–6

Lixisenatide shows better postprandial glucose-lowering effects than Liraglutide



148 adults with T2DM insufficiently controlled (A1C 6.5−9.0%) on ≥1.5 g/day of metformin

Kapitza C, et al. *Diabetes Obes Metab* 2013;15:642-649

Overview of short and long acting GLP-1 RA

Parameters	Short-acting GLP-1 RAs	Long-acting GLP-1 RAs
Compounds	Exenatide, Lixisenatide	Albiglutide, Dulaglutide, Exenatide-LAR, Liraglutide
Half-life	2-5 h	12 h - several days
FPG levels	Modest reduction	**Strong reduction**
PPG levels	**Strong reduction**	Modest reduction
Glucagon secretion	Reduction	Reduction
Blood pressure	Reduction	Reduction
Heart rate	**No effect or small increase** (0-2 bpm)	**Moderate increase** (2-5 bpm)
Body weight reduction	1-5 Kg	2-5 Kg
Induction of nausea	20-50%, attenuates slowly (weeks to many months)	20-40%, attenuates quickly (~4-8 weeks)

Meier, JJ. *Nat Rev Endocrinol*. 2012;8(12):728-42.

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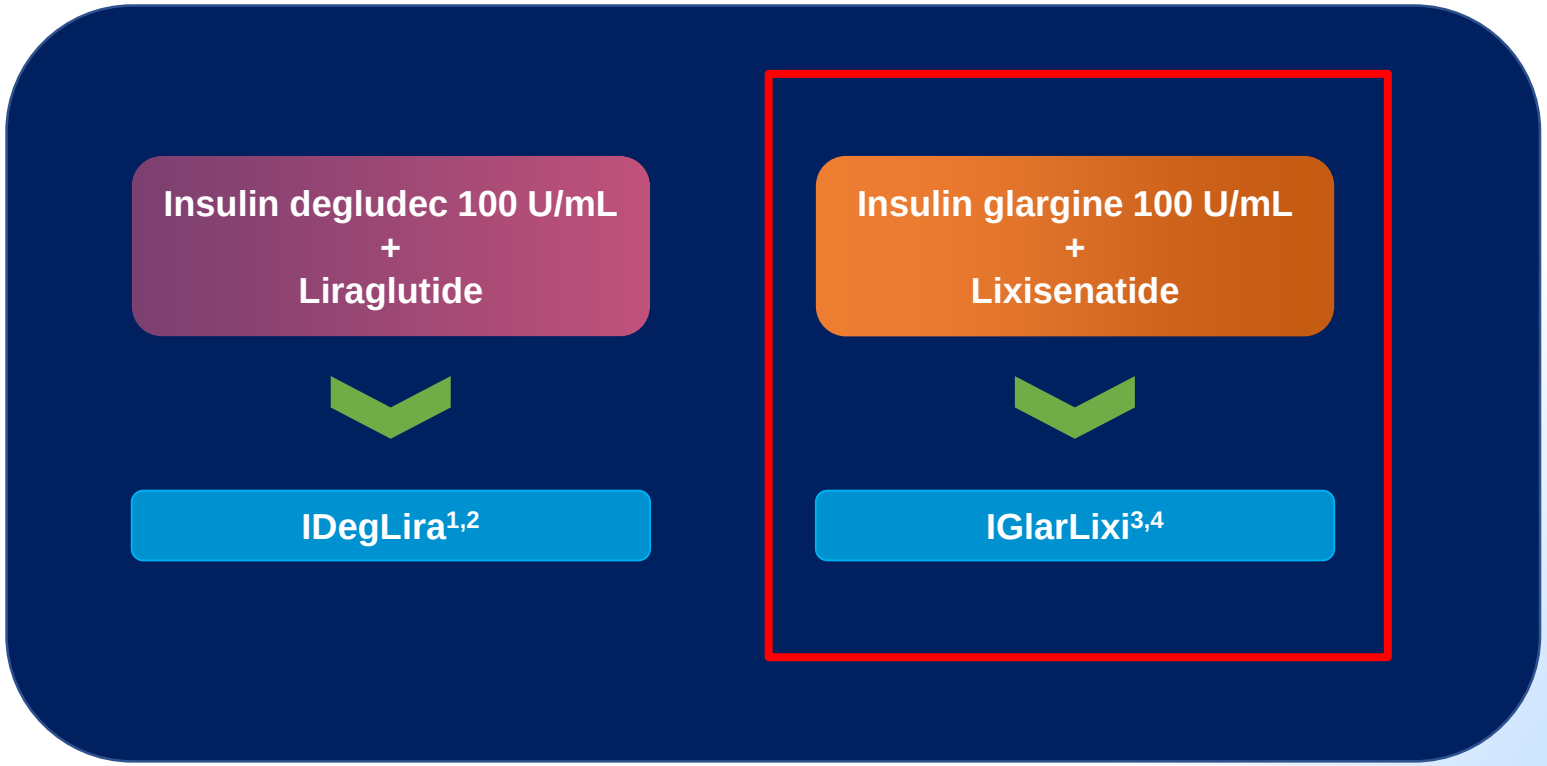
Two basal insulin / GLP-1 RA fixed-ratio combination therapies developed to date



1. Gough S, et al. *Lancet Diab Endocrinol* 2014;2:885–9
2. Buse JB, et al. *Diabetes Care* 2014;37:2926–33
3. Rosenstock J, et al. *Diabetes Care* 2016;39:2026–35
4. Aroda VR, et al. *Diabetes Care* 2016;39:1972–80

Soliqua (iGlarLixi) dosing

Composition

- Similar physicochemical features allow mixing in a defined fixed ratio for delivery as a single daily injection

Complementary actions

- Fixed-ratio combination (FRC) delivers iGlar 100 U/mL over a range of 10–60 U/day in steps of 1 U, providing different dosing options:
  - → iGlarLixi (10–40) pen (2:1 dose ratio iGlar:Lixi)
  - → iGlarLixi (30–60) pen (3:1 dose ratio iGlar:Lixi)
- FRC limits lixisenatide to 20 µg max daily dose

Complementary actions

- Stepwise dosing (60 dose steps) allows:
  - → dose to be individualized based on clinical response (titrated based in insulin need)
  - → a slow increase in lixisenatide dose that follows basal insulin titration (mitigating GI effects)

Flexible, step-wise dose titration allows effective treatment individualization

Sanofi-Aventis Deutschland GmbH. Suliqua™ Summary of Product Characteristics, 2017. Available from http://www.ema.europa.eu/ Accessed July 2017;
Rosenstock J, et al. Diabetes Care 2016;39:2026–35.

Soliqua®

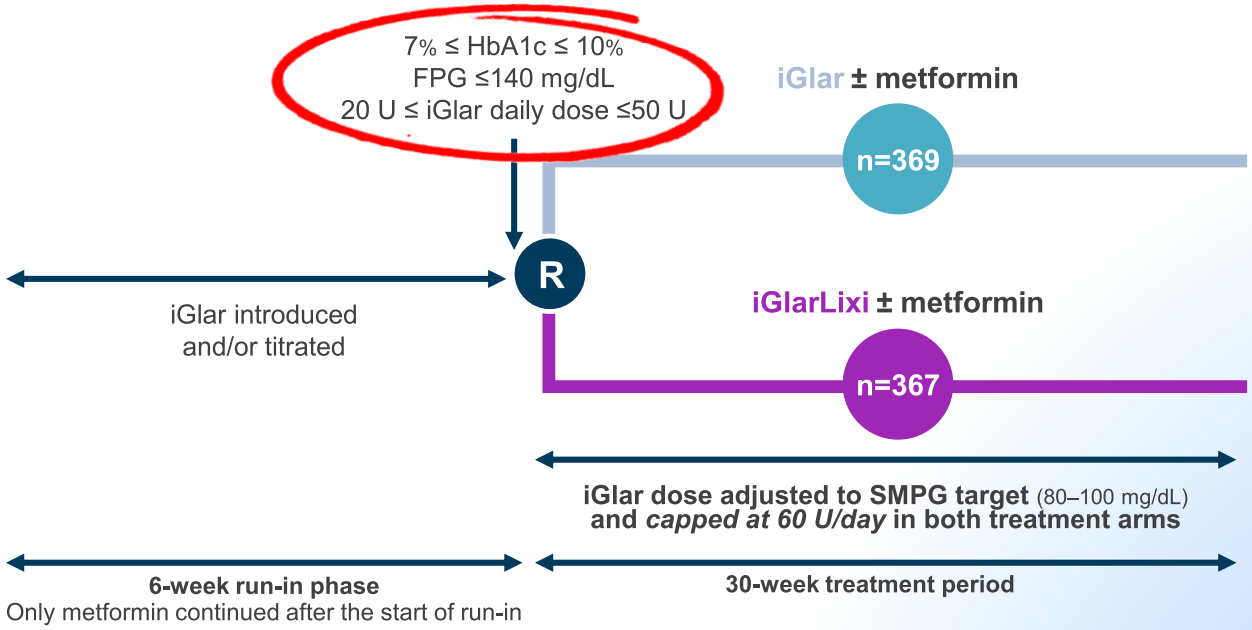
	 **Soliqua® (10–40)**
Composition	Soliqua SoloStar® 300 units of insulin glargine and 150 µg lixisenatide in **3 mL** solution **(100 units/mL + 50 µg/mL)**
Lixisenatide concentration	50 µg/mL
Ratio Glargine: lixisenatide	2 IU : 1 µg
Dose range	10 IU to 40 IU insulin glargine **10-40 units** 合併 lixisenatide **5-20 µg**
Color	**Peach 黃桃色**

Highlights from the TW SmPC are provided here; please refer to the SmPC for more detailed information.

LixiLan-L:
Patients with T2DM not controlled on basal insulin ± OADs

DESIGN: Randomized, open-label, parallel-group, 30-week treatment study

- T2DM patients with:
- Basal insulin >6 months
- Stable dose 15–40 U/day ± OADs
- HbA1c ≥7.5%–10%
- FPG ≤180–200 mg/dL



Primary objective:
Superiority of iGlarLixi over iGlar in HbA1c change at Week 30

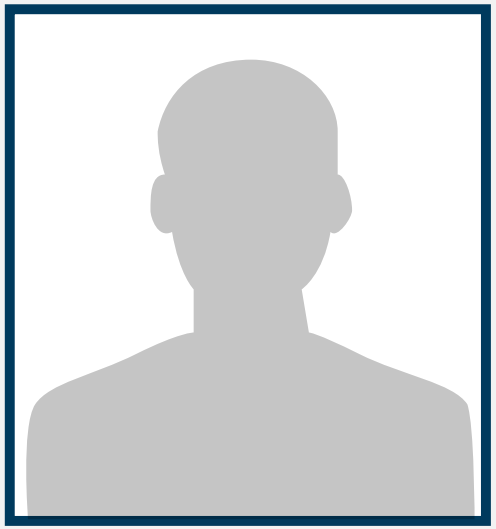
Two fixed ratio pens (10–40 Pen and 30–60 Pen) allow titration of iGlar from 10–60 U/day, with lixisenatide daily dose capped at 20 µg once daily; iGlar: Insulin Glargine 100 Units/mL

Aroda VR *et al*. Diabetes Care. 2016;39(11):1972-1980

LixiLan-L:
Enrolled patients uncontrolled on basal insulin[1,2]

iGlarLixi was studied in patients with T2DM uncontrolled despite several years on basal insulin and up to 2 OADs

Average Patient at Baseline*



Age
59.6 years

BMI
31.3 kg/m^2
(**57.5%** of patients had a BMI of ≥30 kg/m2)

Diabetes duration
12 years

Duration of basal insulin
3.1 years

A1c at baseline
8.1%

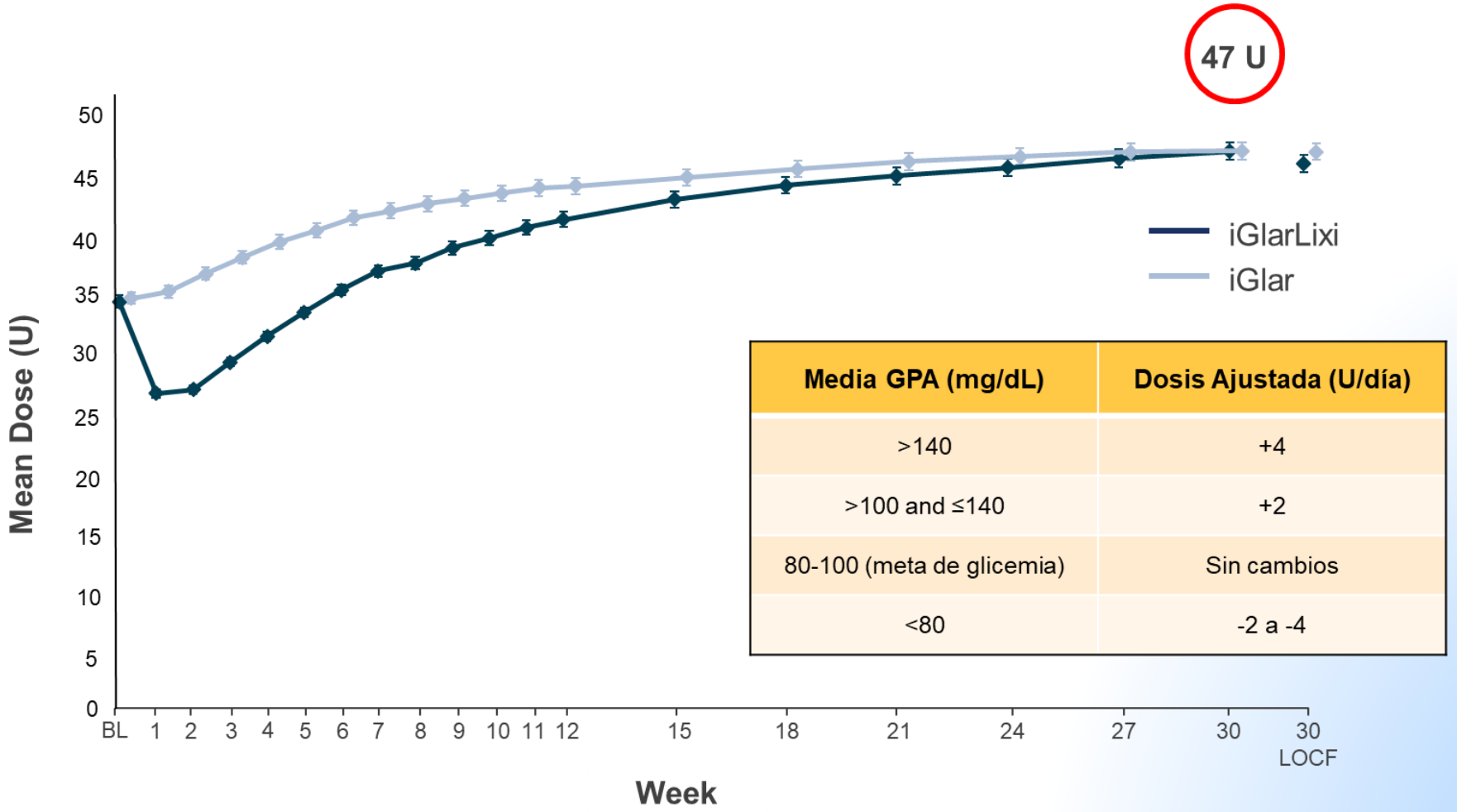
FPG at baseline
132 mg/dL

*Data are presented as the mean ± SD, or as indicated. A1c: glycated hemoglobin; BMI: body mass index; FPG: fasting plasma glucose; OAD: oral antidiabetic; T2DM: type 2 diabetes mellitus.

1. Aroda VR et al. *Diabetes Care*. 2016;39:1972-1980. Study sponsored by Sanofi. 2. Sanofi. Data on file. 2015.

LixiLan-L:

Insulin titration algorithm and mean daily insulin glargine dose

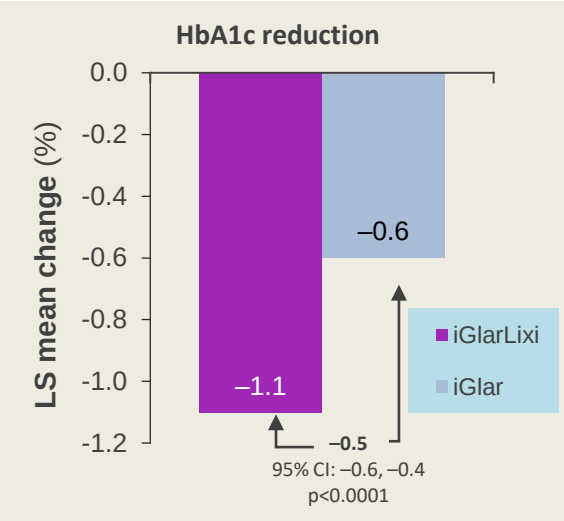


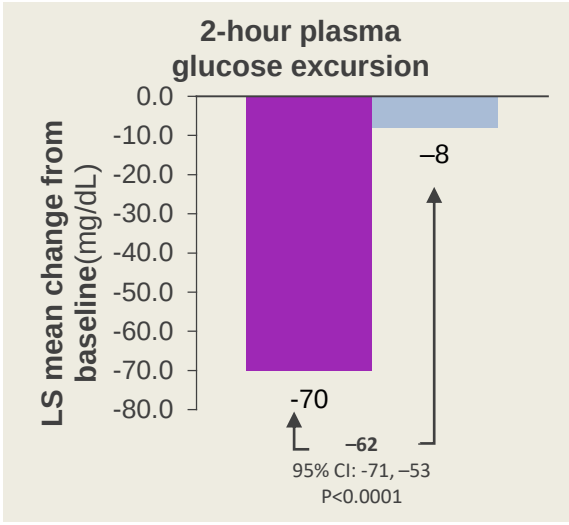
Media GPA (mg/dL)	Dosis Ajustada (U/día)
>140	+4
>100 and ≤140	+2
80-100 (meta de glicemia)	Sin cambios
<80	-2 a -4

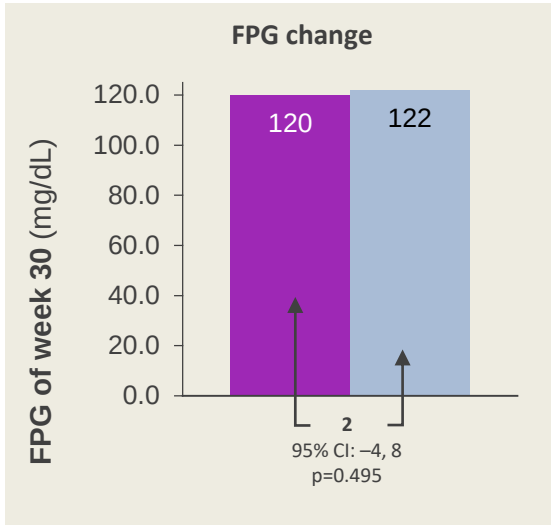
Aroda VR, et al. *Diabetes Care* 2016;39:1972–80

LixiLan-L:

Key Results – Glycemic control





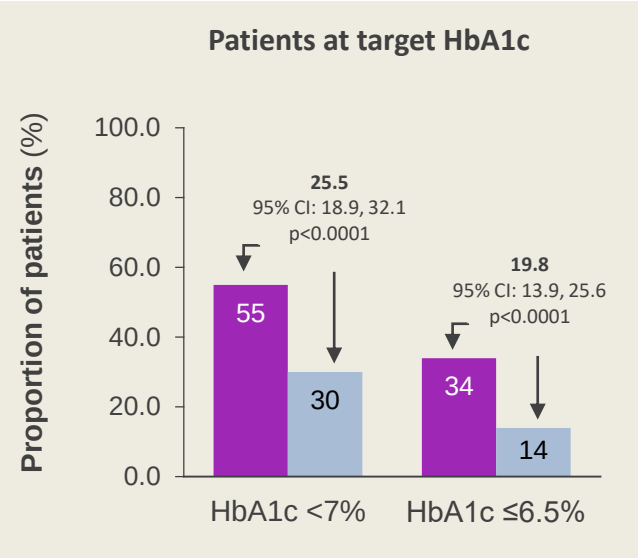


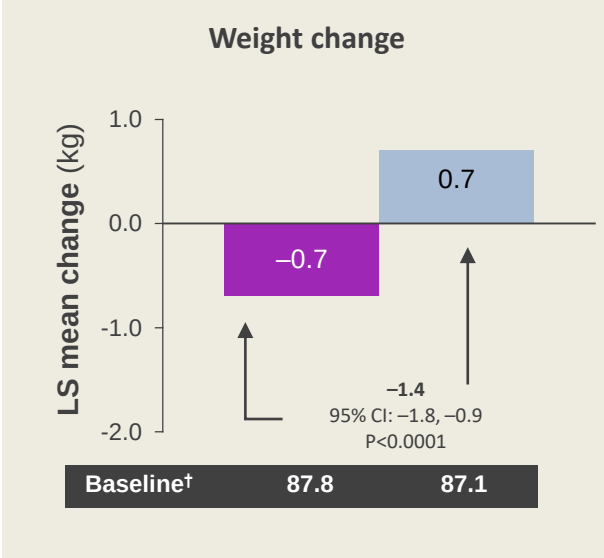
† Mean body weight (kg) at baseline; ‡Documented symptomatic hypoglycemia, defined as plasma glucose ≤70 mg/dL
§ Severe hypoglycemia was reported in 4 (1.1%) patients in the iGlarLixi group and 1 (0.3%) patient in the iGlar group

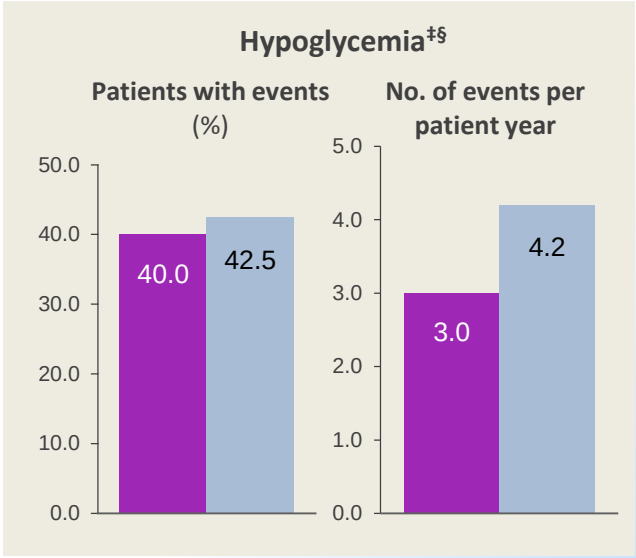
Aroda V, *et al*. Diabetes Care. 2016;39:1972-1980.

LixiLan-L:

Key Results – HbA1C achieve rate/BW/Hypoglycemia

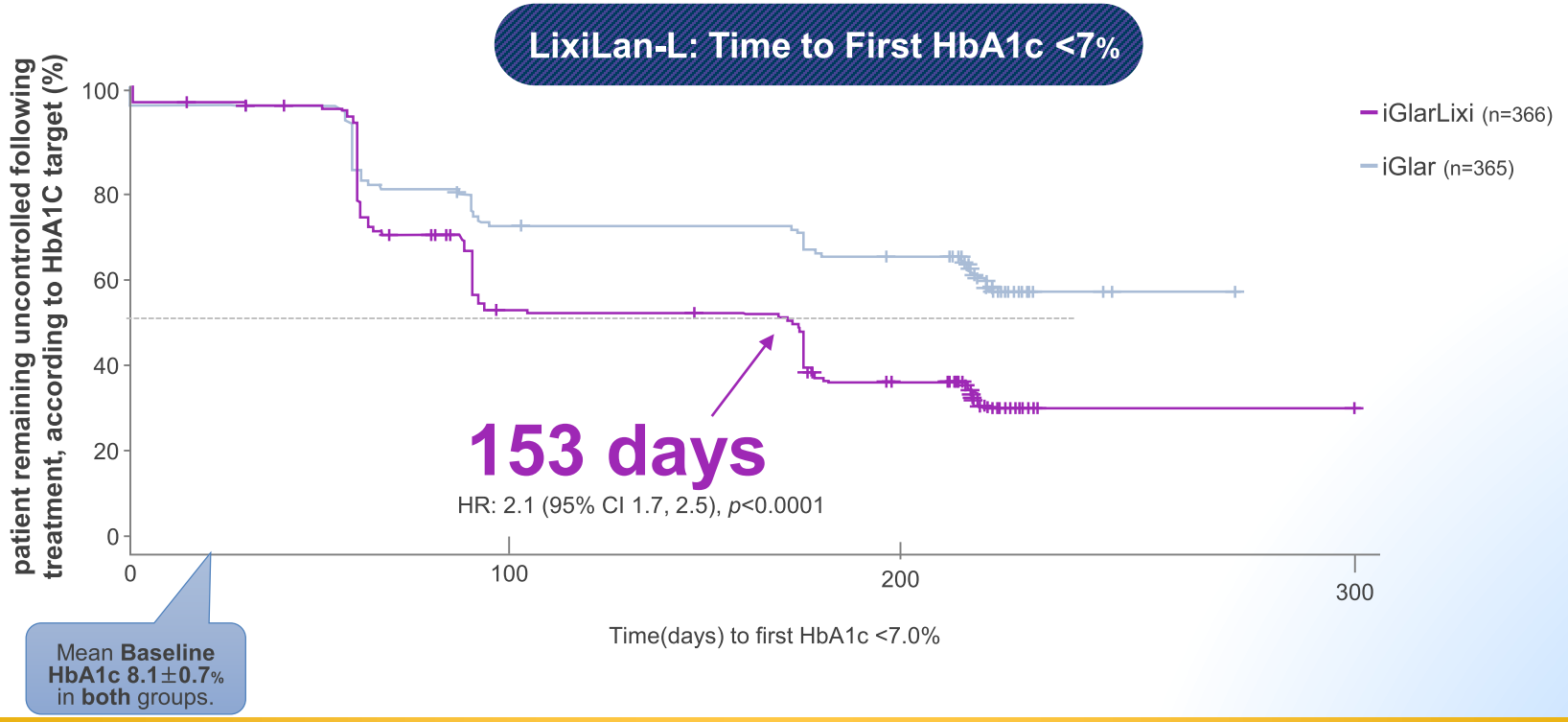






† Mean body weight (kg) at baseline; ‡Documented symptomatic hypoglycemia, defined as plasma glucose ≤70 mg/dL
§ Severe hypoglycemia was reported in 4 (1.1%) patients in the iGlarLixi group and 1 (0.3%) patient in the iGlar group

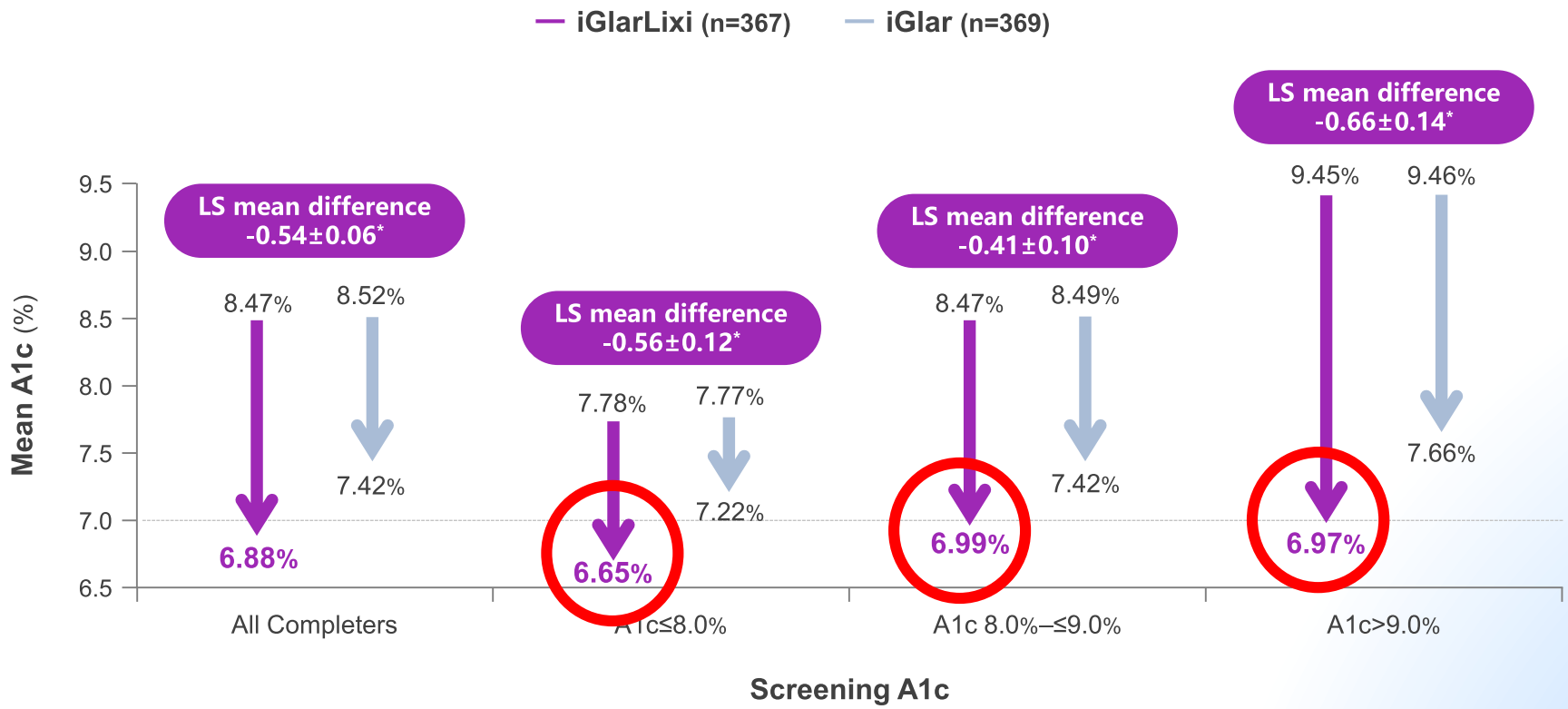
Shorter time to glycemic control with iGlarLixi vs. iGlar alone



Median time to target HbA1c was 153 days with iGlarLixi, while target HbA1c was never reached by 50% of patients with iGlar.

iGlar: Insulin Glargine 100 Units/mL, HR: hazard ratio,

iGlarLixi helps T2DM patients reach HbA1C goal even patients are under pool control (HbA1C>9%)



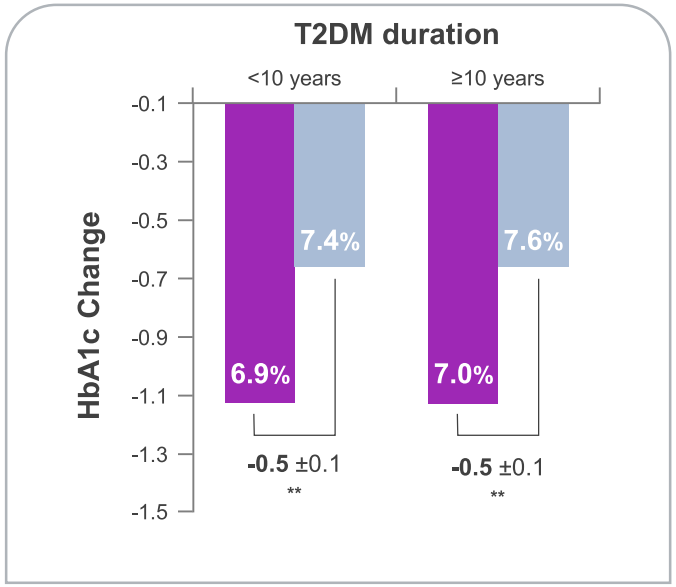
Consistent superiority of iGlarLixi vs. iGlar in HbA1c change irrespective of initial HbA1c level

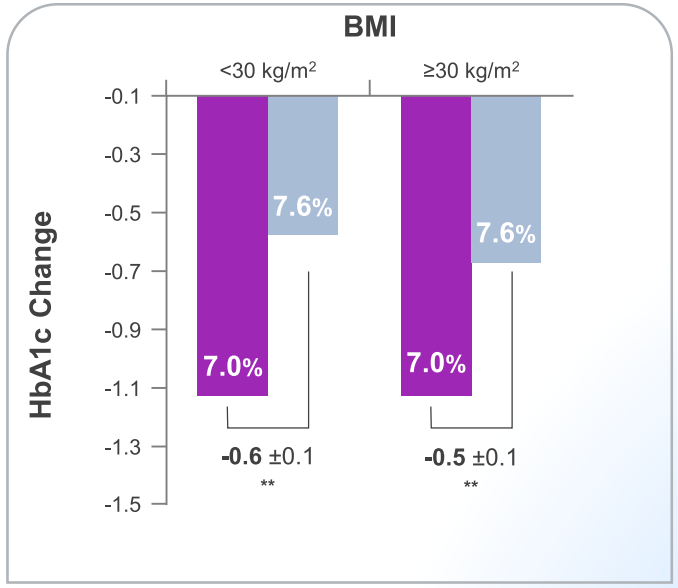
Modified intent-to-treat population. *P<0.0001 for difference in LS mean ± SE from screening to Week 30 for SOLIQUA 100/33 vs insulin glargine 100 Units/mL.
A1c: glycated hemoglobin; LS: least squares; SE: standard error; iGlar: Insulin Glargine 100 Units/mL

Niemoeller E *et al*. Diabetes Ther. 2018 Feb;9(1):373-382

iGlarLixi provides similar treatment response irrespective of T2DM duration and BMI

Similar treatment response irrespective of T2DM duration and BMI





iGlarLixi significantly reduced HbA1c vs. iGlar regardless of T2DM duration or BMI

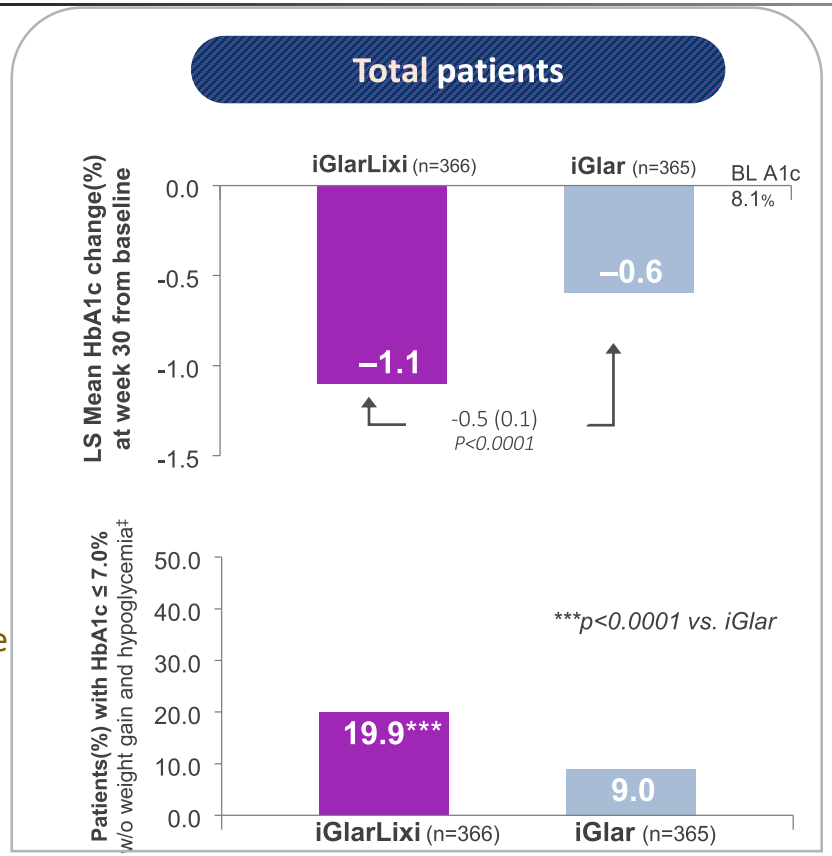
Data are mean ± SE. Treatment comparison *p*-values based on two-factor ANOVA (with last observation carried forward) compared with iGlarLixi
**p*=0.001, ***p*<0.0001 for iGlarLixi vs iGlar (indicated by arrows and asterisks)
†Between-subpopulation comparison *p*<0.0001; heterogeneity was assessed and all *p*-values for heterogeneity were not significant ANOVA, analysis of variance; BMI, body mass index; HbA1c, glycated hemoglobin;
SE, standard error; T2DM, type 2 diabetes mellitus; iGlar: Insulin Glargine 100 Units/mL

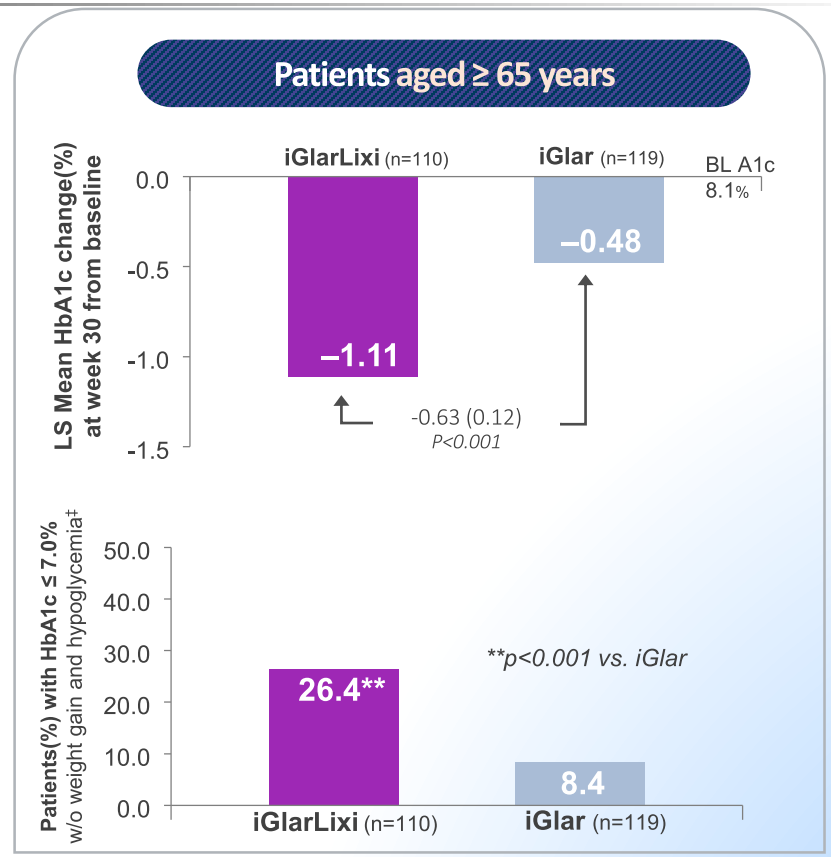
Wysham C *et al.* Diabetes Obes Metab. 2017;19:1408-1415

iGlarLixi provides similar treatment response for elderly patients

HbA1c reduction

Composite achieved rate*





Consistent superiority of iGlarLixi vs. iGlar **in patients(%) reached target A1c w/o weight gain and hypoglycemia in elderly**

iGlar: Insulin Glargine 100 Units/mL
*Composite of A1c <7.0% + no weight gain + no documented symptomatic hypoglyce mia.)

Handelsman Y et al. ADA 2016, Poster 954. Availablte at https://ada.scientificposters.com/epsAbstractADA.cfm?id=1 (as of 2018-07-20)

LixiLan-L:

Adverse events

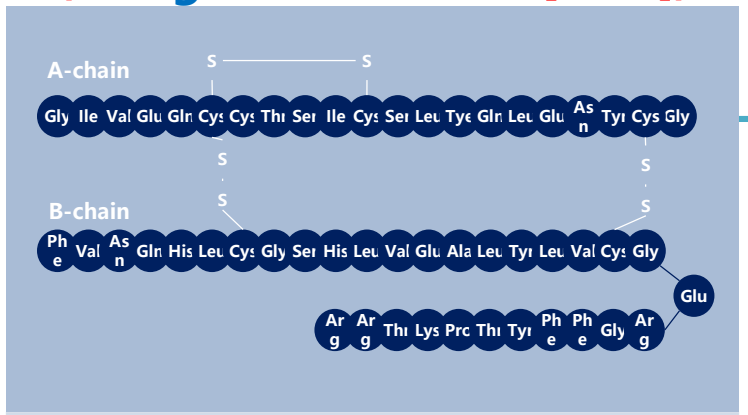
- Both treatments were well tolerated
- Safety profile of iGlarLixi generally reflected the established safety profiles of its components
- GI disorders were more common with iGlarLixi, were generally mild to moderate, and led to very few discontinuations (1.1%)

Patients with:	iGlarLixi (n=365)	iGlar (n=365)
Nausea	10.7%	0.5%
Vomiting	3.6%	0.5%
Diarrhea	4.4%	2.7%

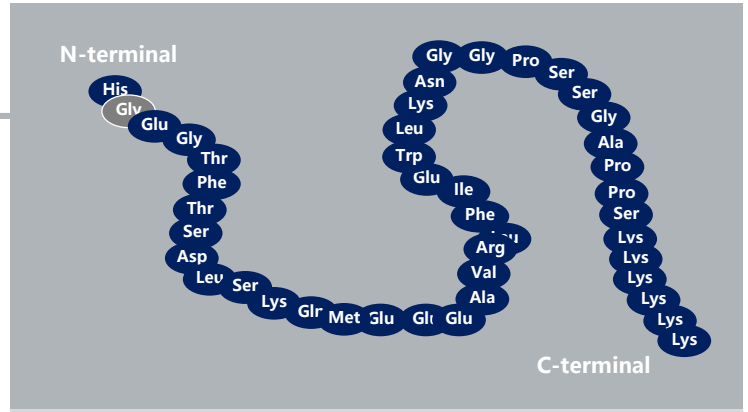
Aroda VR, et al. *Diabetes Care* 2016;39:1972–80

iGlarLixi: Complementary mechanisms of action of iGlar and lixisenatide in a single daily injection

Basal insulin
(Glargine 100 U/mL [iGlar])



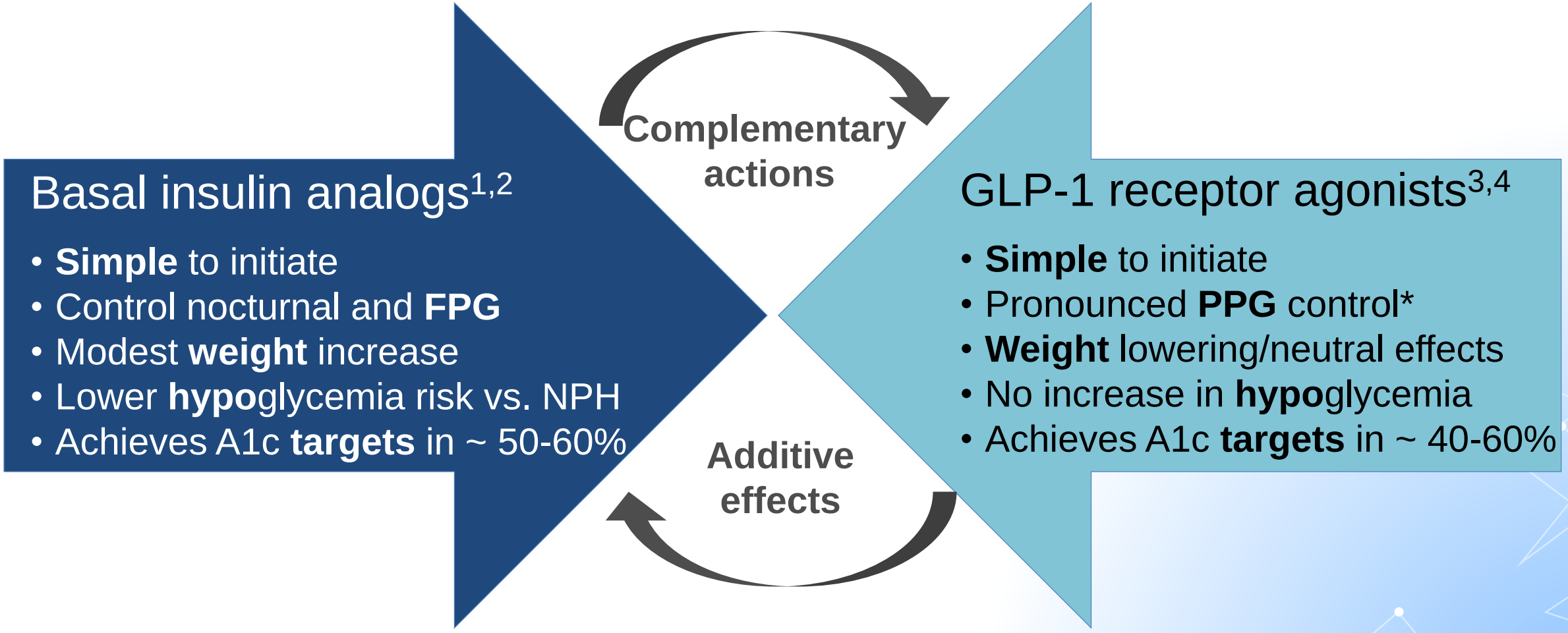
GLP-1RA
(lixisenatide)



Expected advantages of iGlarLixi

- ✓ 同時控制飯前及飯後血糖
- ✓ 有效降低HbA1c
- ✓ 幫助更多病人達到血糖控制目標
- ✓ 減少因為basal insulin增的體重
- ✓ 不增加低血糖發生 vs. basal insulin
- ✓ 減少腸胃道副作用發生 vs. GLP-1RAs

Scientific Rationale for Combining Basal Insulin with a GLP-1 RA

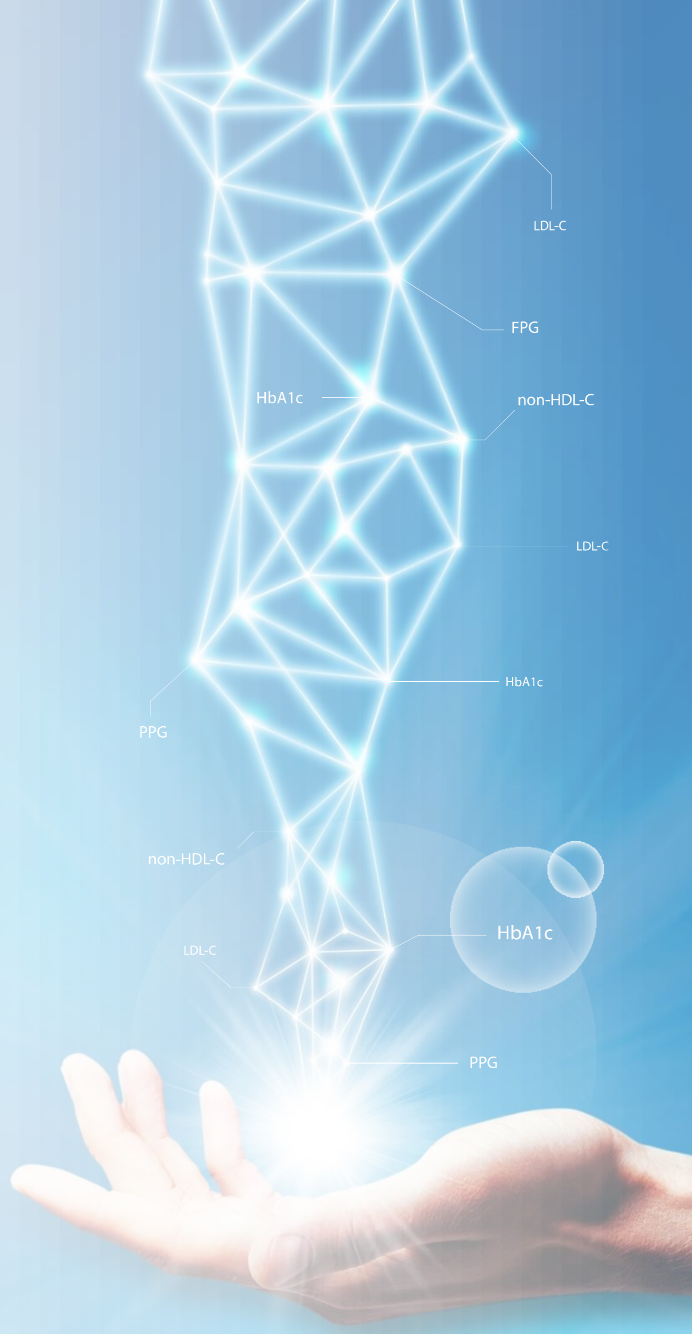


Adapted from figure courtesy of J. Rosenstock, MD.

*Relative impact on FPG /PPG varies (depending on specific agent)

1- Liebl A. Curr Med Res Opin. 2007; 23:129-32. 2- Rosetti P. Arch Physiol Biochem. 2008; 114:3-10.
3- Holst JJ, et al. Mol Cell Endocrinol. 2009; 297:127-36. 4- Calabrese D. Am J Managed Care. 2011; S52-S58.

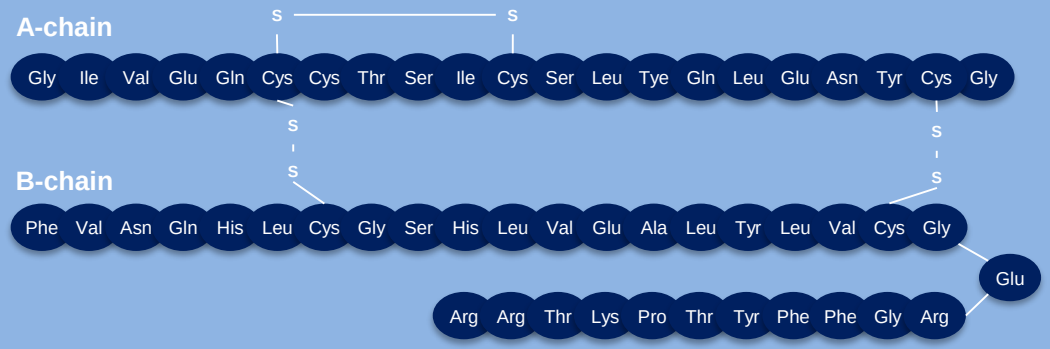
thank you
gracias
danke
謝謝
ngiyabonga
teşekkür ederim
рахмат
Баярлалаа
спасибо
dank je
tapadh leat
mochchakkeram
go raibh maith agat
bedankt
dziękuję
hvala
mauruuru
obrigado
sukriya
kop khun krap
terima kasih
arigatō
takk
dakujem
мерси
grazie
감사합니다
ευχαριστώ
merci
ありがとう



LDL-C
FPG
HbA1c
non-HDL-C
LDL-C
HbA1c
PPG
non-HDL-C
HbA1c
LDL-C
PPG

iGlarLixi: Component characteristics

Basal insulin (glargine 100 U/mL [iGlar])



Micro-precipitates slowly dissociate into dimers and monomers, which are absorbed across into blood capillaries

Once-daily subcutaneous injections result in a prolonged insulin action

Targets hepatic glucose overproduction by decreasing gluconeogenesis

Reduces fasting blood glucose

GLP-1RA (lixisenatide)

Once-daily SC injection results in:

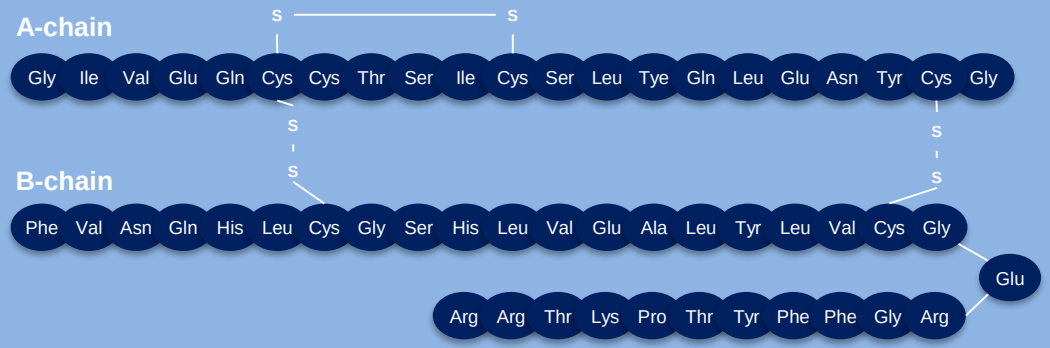
- Glucose-dependent insulin release
- Suppressed glucagon secretion
- Delayed gastric emptying

Reduces post-prandial blood glucose

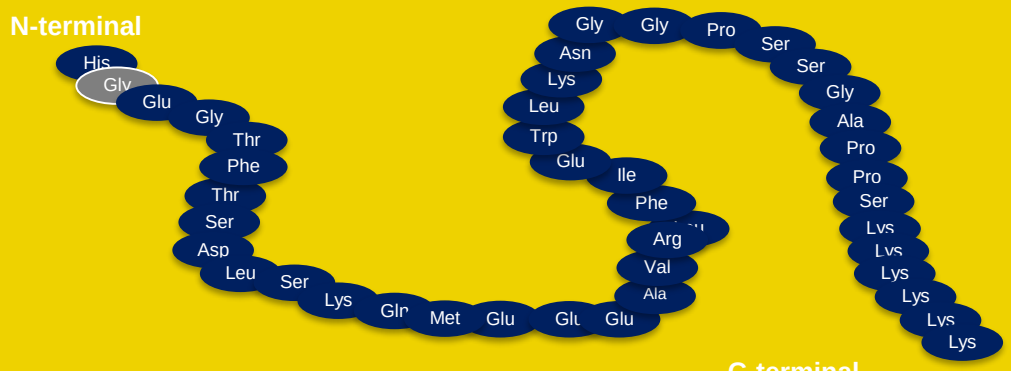
1. Kramer W. Exp Clin Endocrinol Diabetes 1999;107(suppl 2):S52–61 . 2. Werner U, et al. Regul Pept 2010;164:58–64; 3. Thorkildsen C, et al. J Pharmacol Exp Ther 2003;307:490–6

iGlarLixi: Component characteristics

Basal insulin (glargine 100 U/mL [iGlar])



GLP-1RA (lixisenatide)



Micro-pr
monom
capillaries

Onc

Targets he

ayed gastric
emptying

ose

Expected effects of FRC

1. **Fasting + post-prandial glucose control**
2. **Effective HbA1c reduction**
3. **More patients achieving glycemic targets**
4. **Mitigating weight increase of basal insulin**
5. **No additional risk of hypoglycemia vs. basal insulin**
6. **Improved GI tolerability vs. GLP-1RAs**

1. Kramer W. Exp Clin Endocrinol Diabetes 1999;107(suppl 2):S52–61 . 2. Werner U, et al. Regul Pept 2010;164:58–64; 3. Thorkildsen C, et al. J Pharmacol Exp Ther 2003;307:490–6

iGlarLixi dosing in patients switching from previous basal insulin (<30 U)

10–40 Pen
(2 U:1 µg ratio)

10 U	5 ug
11	5.5
12	6
13	6.5
14	7
15	7.5
16	8
17	8.5
18	9
19	9.5
20	10
21	10.5
22	11
23	11.5
24	12
25	12.5
26	13
27	13.5
28	14
29	14.5
30	15
31	15.5
32	16
33	16.5
34	17
35	17.5
36	18
37	18.5
38	19
39	19.5
40	20

Starting Dose*

Switching from <30 U

20

Mean FPG (mg/dL)	Dose adjustment (U/day)
>140	+4
>100 and ≤140	+2
80-100 (glucosa target)	No change
<80	-2 to -4

*iGlar Weekly Titration Algorithm
Aroda V, et al. Diabetes Care 2016;39:1972−80

iGlarLixi dosing in patients switching from previous basal insulin (≥30 U to 40 U)

30 U	10 ug
31	10.3
32	10.7
33	11
34	11.3
35	11.7
36	12
37	12.3
38	12.7
39	13
40	13.3
41	13.7
42	14
43	14.3
44	14.7
45	15
46	15.3
47	15.7
48	16
49	16.3
50	16.7
51	17
52	17.3
53	17.7
54	18
55	18.3
56	18.7
57	19
58	19.3
59	19.7
60	20

Starting Dose*

30

Switching from 30–40 U

30–60 Pen

(3 U:1 µg ratio)

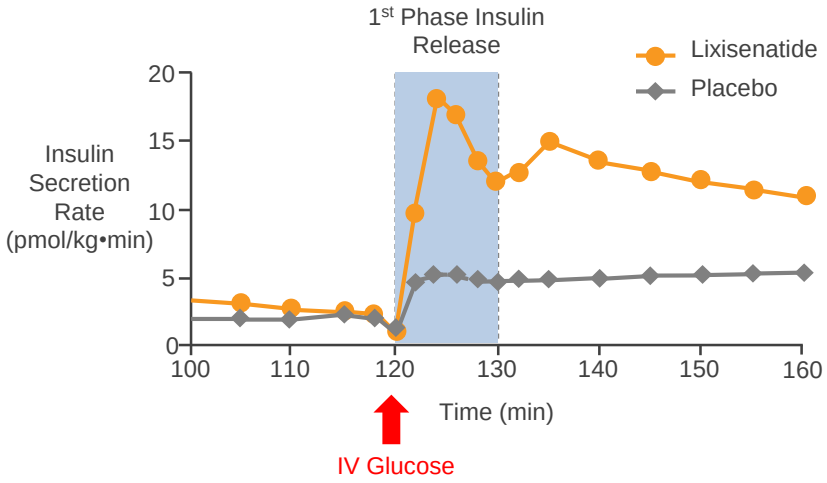
Mean FPG (mg/dL)	Dose adjustment (U/day)
>140	+4
>100 and ≤140	+2
80-100 (glucosa target)	No change
<80	-2 to -4

30-60 Pen: 台灣並未販售

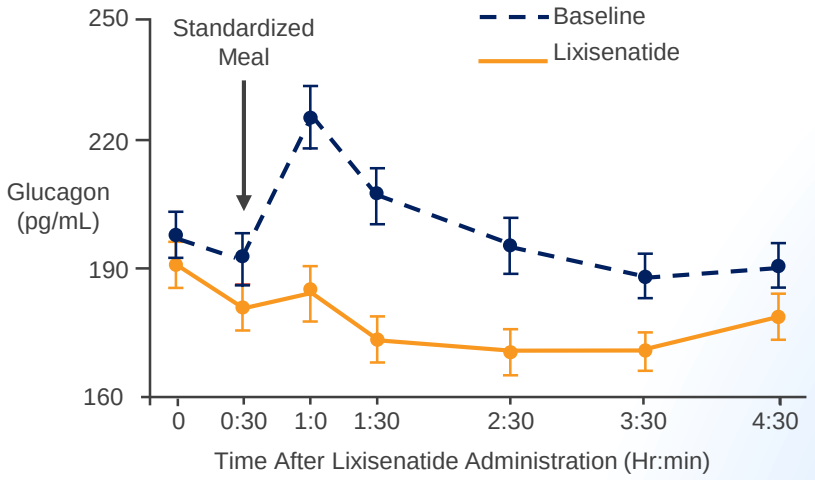
*iGlar Weekly Titration Algorithm
Aroda V, et al. Diabetes Care 2016;39:1972−80

Lixisenatide: Key mechanisms of action leading to lowering of postprandial glucose

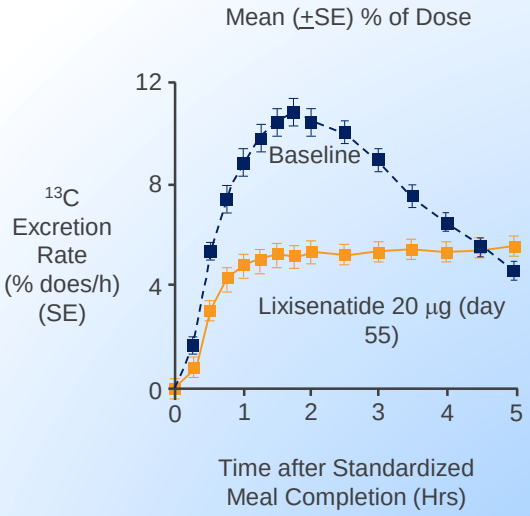
Enhances glucose-stimulated insulin secretion[1]



Reduces glucagon secretion

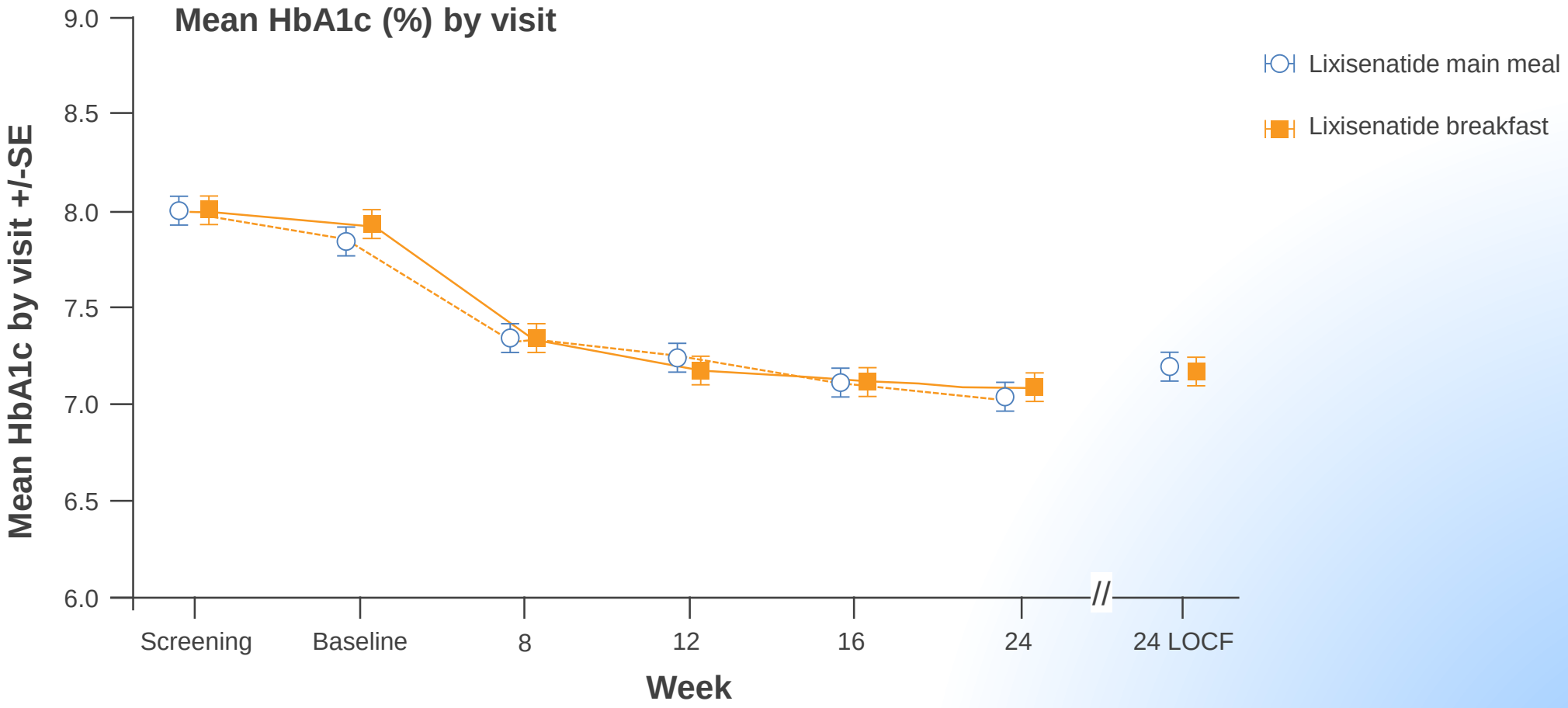


Slows gastric emptying



1. Becker RH, et al. Diabetes Obes Metab. 2014;16:793-800.

Lixisenatide is equally effective when given before breakfast or the main meal of the day

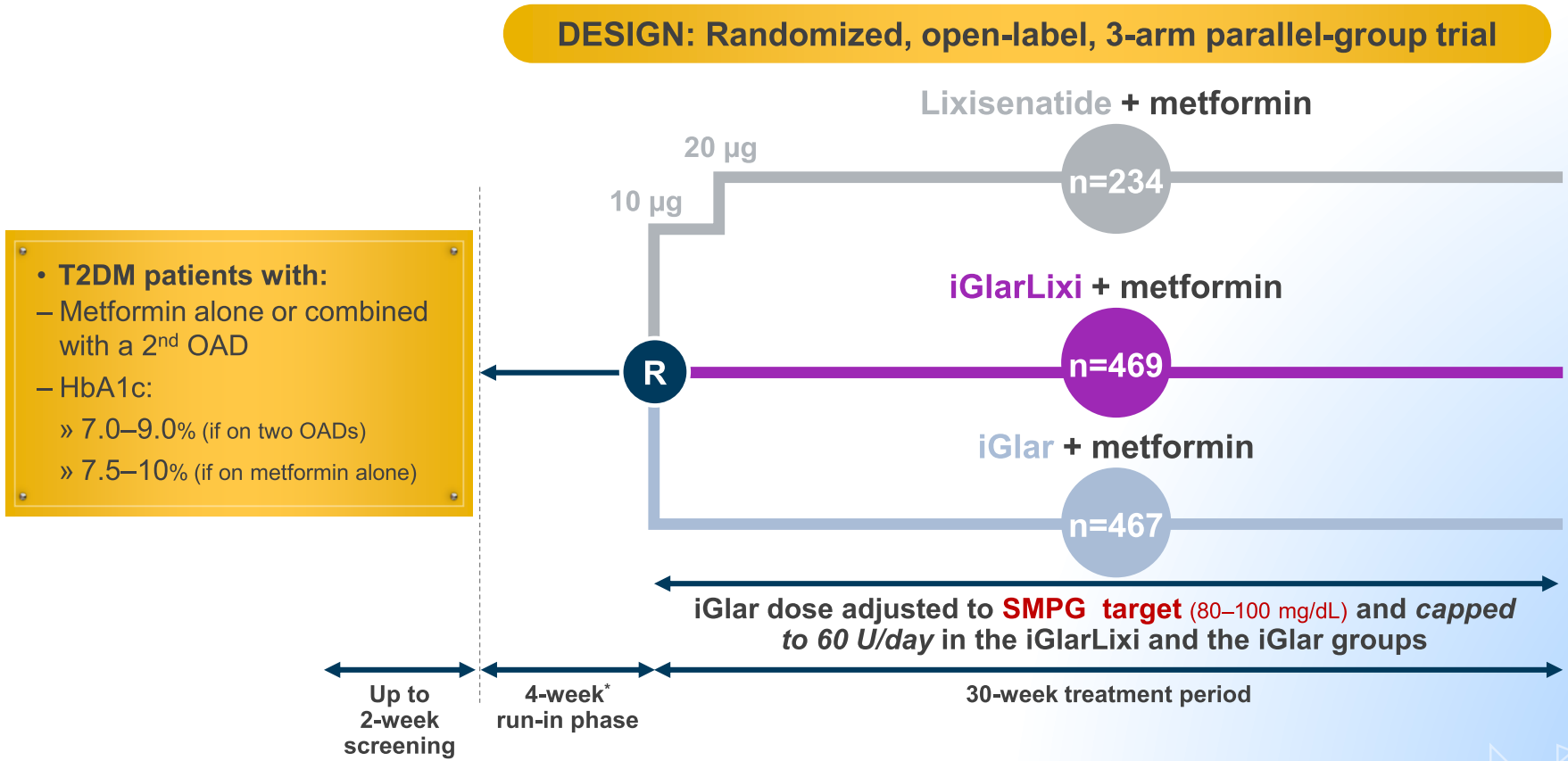


Lixisenatide treatment allows flexibility in administration timing

mITT population. The plot included measurements obtained up to 14 days after the last injection of the investigational medicinal product. LOCF, last observation carried forward; SE, standard error.
Ahrén B, et al. J Diabetes Complications. 2014; 28:735-41.

LixiLan-O:
Patients with T2DM not controlled on OADs

- **Primary objective:** : superiority of iGlarLixi over lixisenatide and non-inferiority of iGlarLixi over iGlar (pre-specified sequential non-inferiority then superiority tested) in HbA1c change at Week 30

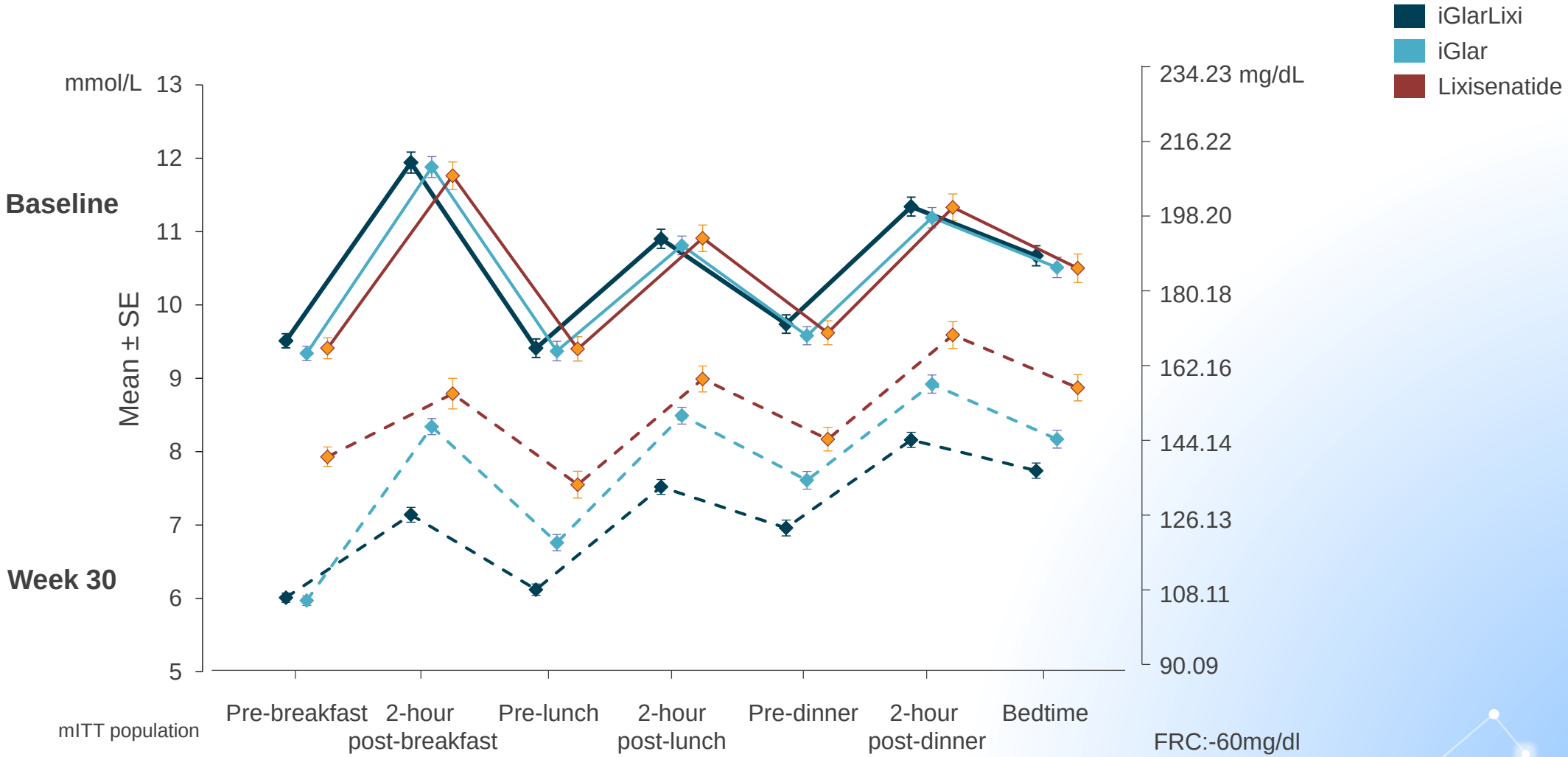


*Stop 2nd OAD, and titrate metformin up to ≥2,000 mg/d or maximal tolerated dose (≥1,500 mg/d to allow randomization)

Two fixed ratio pens (10–40 Pen and 30–60 Pen) allow titration of iGlar from 10–60 U/day, with lixisenatide daily dose capped at 20 µg once daily iGlar: Insulin Glargine 100 Units/mL

Rosenstock J, et al. *Diabetes Care* 2016;39:2026–35

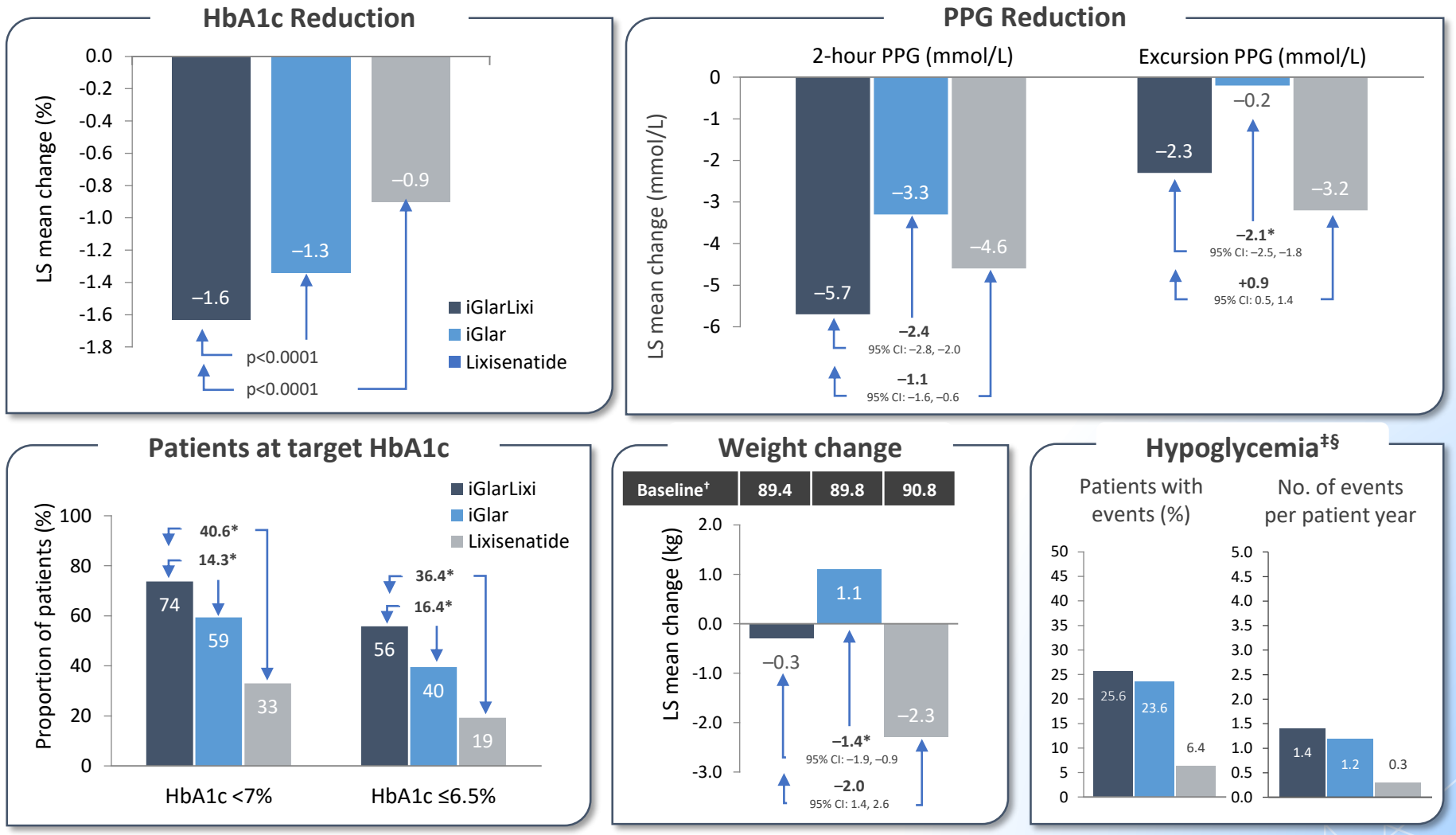
LixiLan-O: 7-point self-measured glucose profiles



FRC:-60mg/dl
Lantus:-48mg/dl
Lixi: -35m/dl

Rosenstock J et al. Diabetes Care. 2016; August 15 [Epub ahead of print]. DOI 10.2337/dc16-0917.

LixiLan-O: Key Results

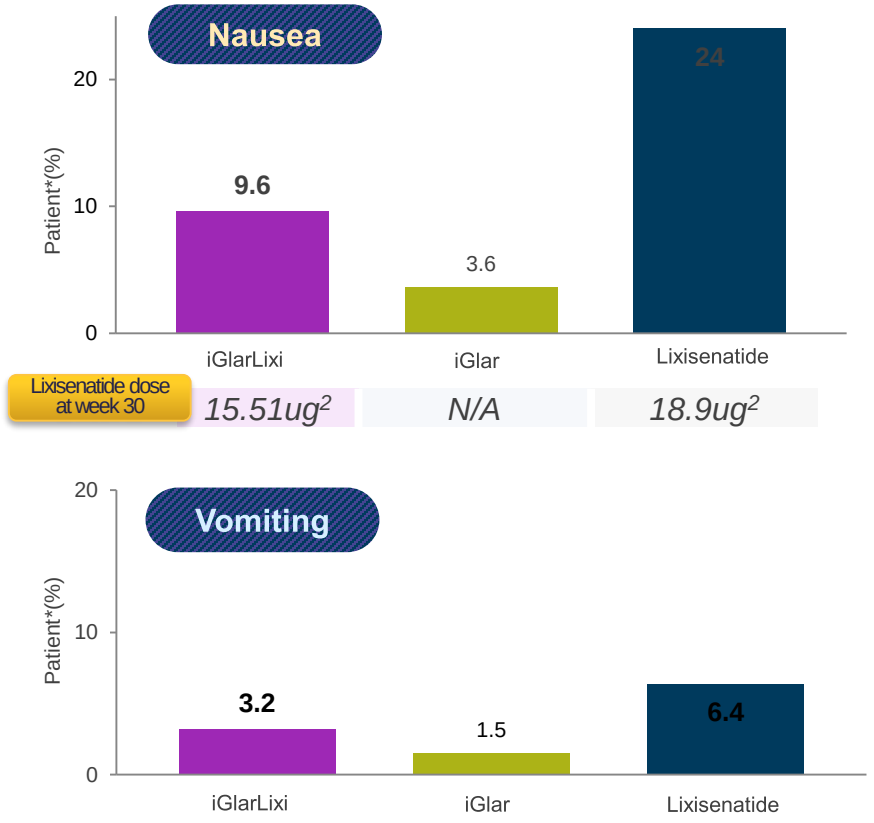


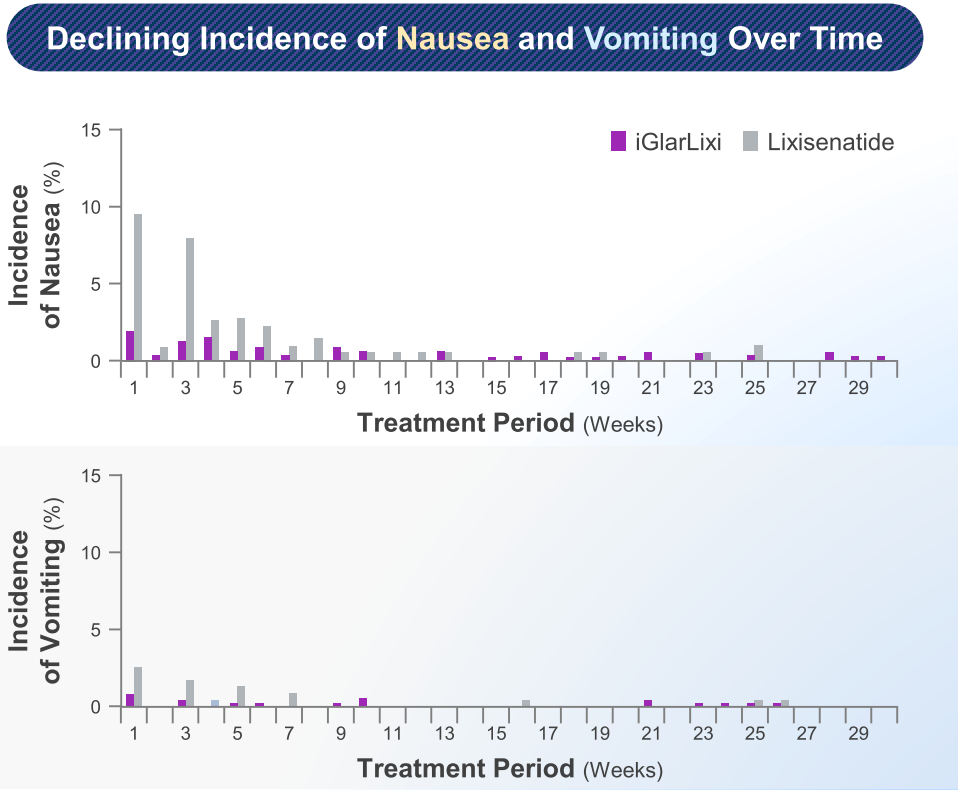
*p<0.0001; †Mean body weight (kg) at baseline; ‡Documented symptomatic hypoglycemia, defined as plasma glucose ≤70 mg/dL

§One event of severe hypoglycemia was reported during the study and occurred in the iGlar group; Sanofi data on file – LixiLan-O CSR pages 86-115, 124-127

Rosenstock J, et al. Diabetes Care 2016;39:2026–35.

LixiLan-O: Effect of iGlarLixi on GI adverse events





The incidence of GI adverse events were lower compared to lixisenatide group

Gradual up-titration of lixisenatide component is possible with iGlarLixi (Every 1 Unit has 0.5 mcg of lixisenatide)**

Rosenstock J, et al. Diabetes Care 2016;39:2026−35.