Injectable therapies in type 2 diabetes

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Agenda

- Clinical inertia
- Barriers to insulin therapy
- Premix vs Basal Bollous
- FRC (GLP1 plus insulin)
- New concepts in insulin therapy:

Weekly insulins

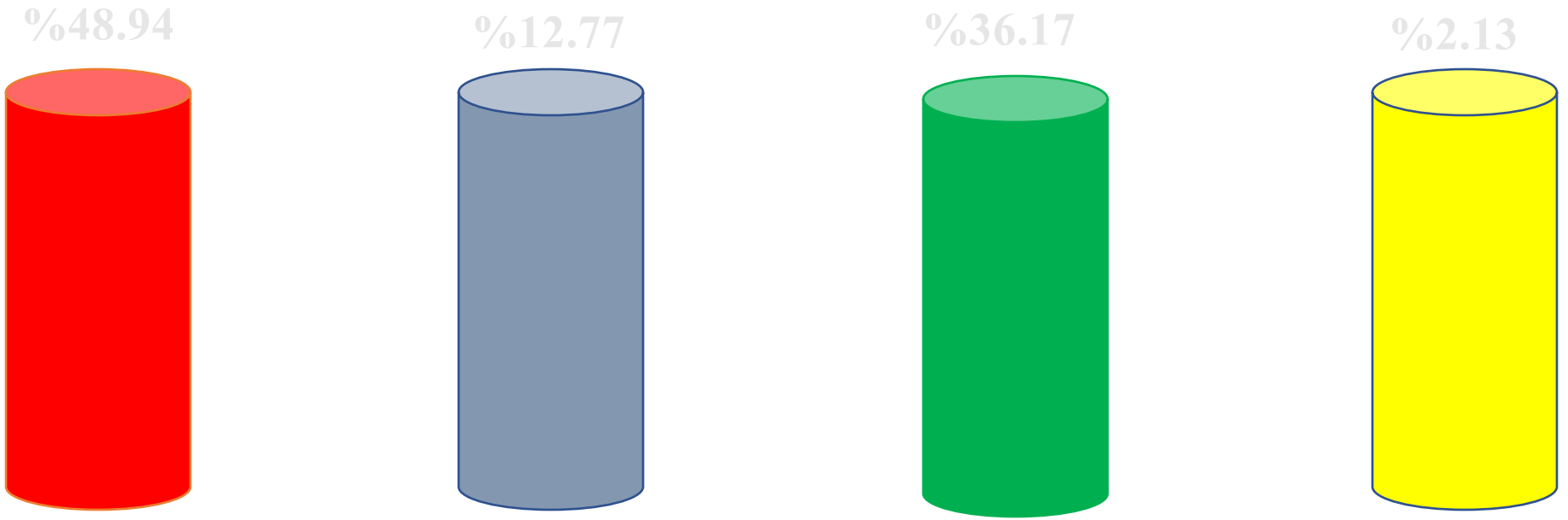
- BIF insulin trials
- Icodec insulin studies

Oral insulin

- Capsulin

Interactive Question

What is your opinion regarding Diabetes control in IRAN ?



HbA1c ≤ 7%

(A)

7< HbA1c ≤ 8%

(B)

8<HbA1c ≤ 9

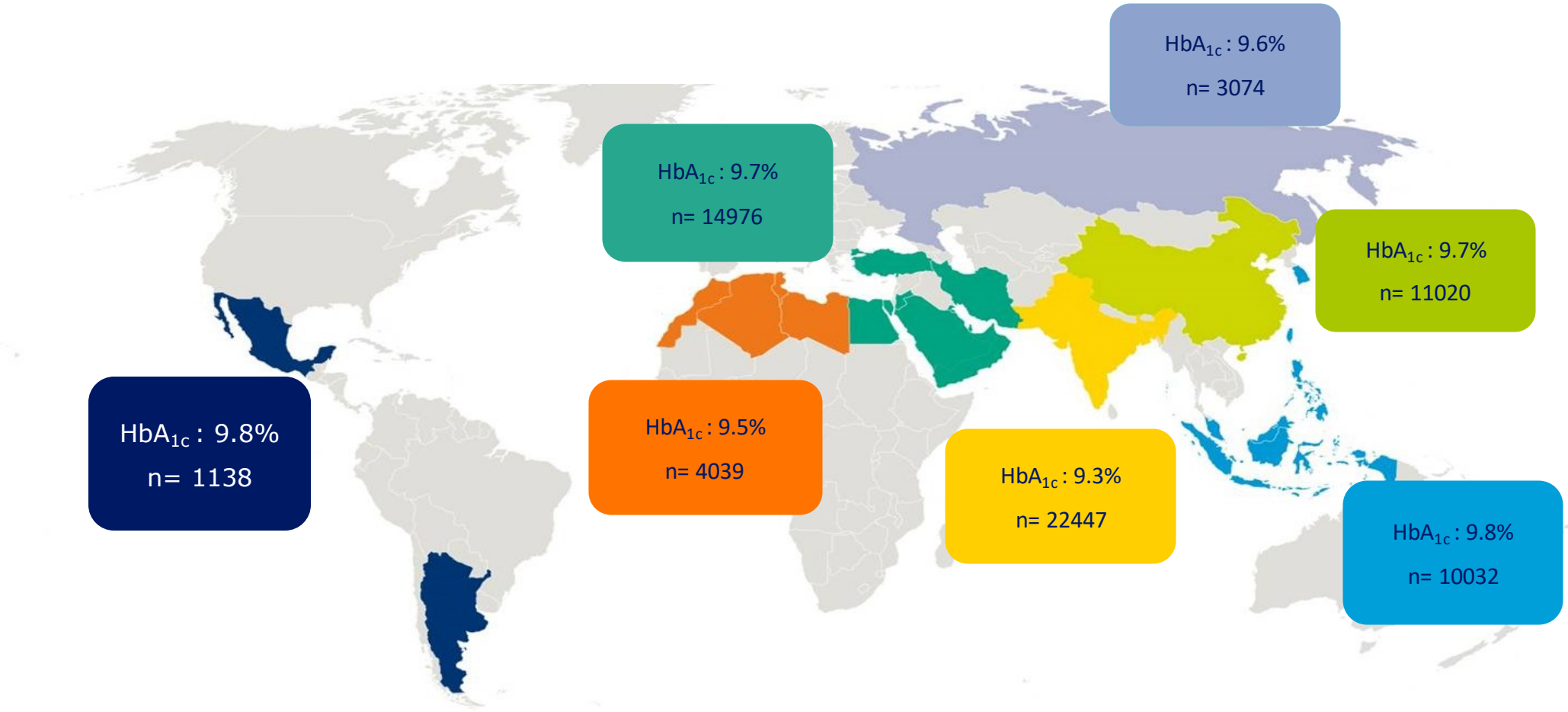
(C)

9<HbA1c

(D)

A_1chieve baseline results

Average HbA_{1c} 9.5 %



What are your A1C thresholds for intensifying drug therapy for diabetes?

… adding the first oral agent?
… adding a second oral agent?
… adding insulin?

1. > 6.5%
2. > 7%
3. > 8%
4. > 8.5%
5. > 9%

Managing Diabetes in Iran: Current status

35.1%

Increase in prevalence of T2DM over 6 y[1]

11.37%

Current Prevalence of T2DM in Iran[2]

60.5%

Patients on OADs[3,4]

36.6%

Patients on Insulin[3,4]

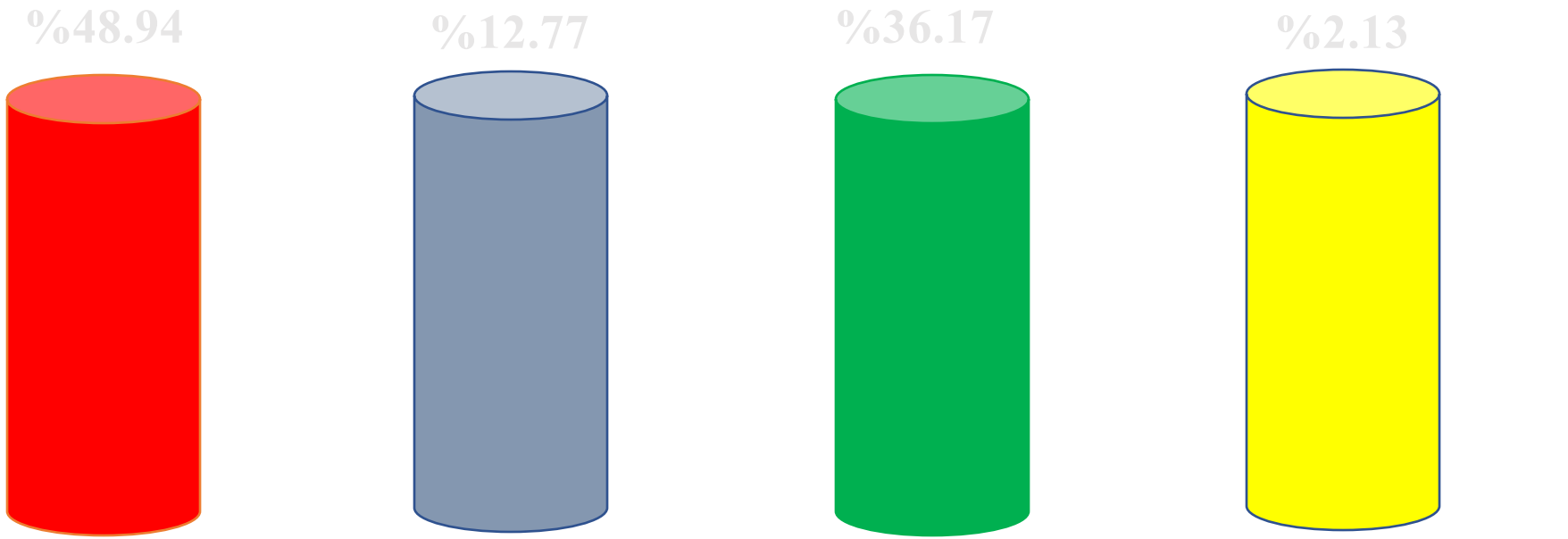
56.7%

Patients still have A1c > 7%[1]

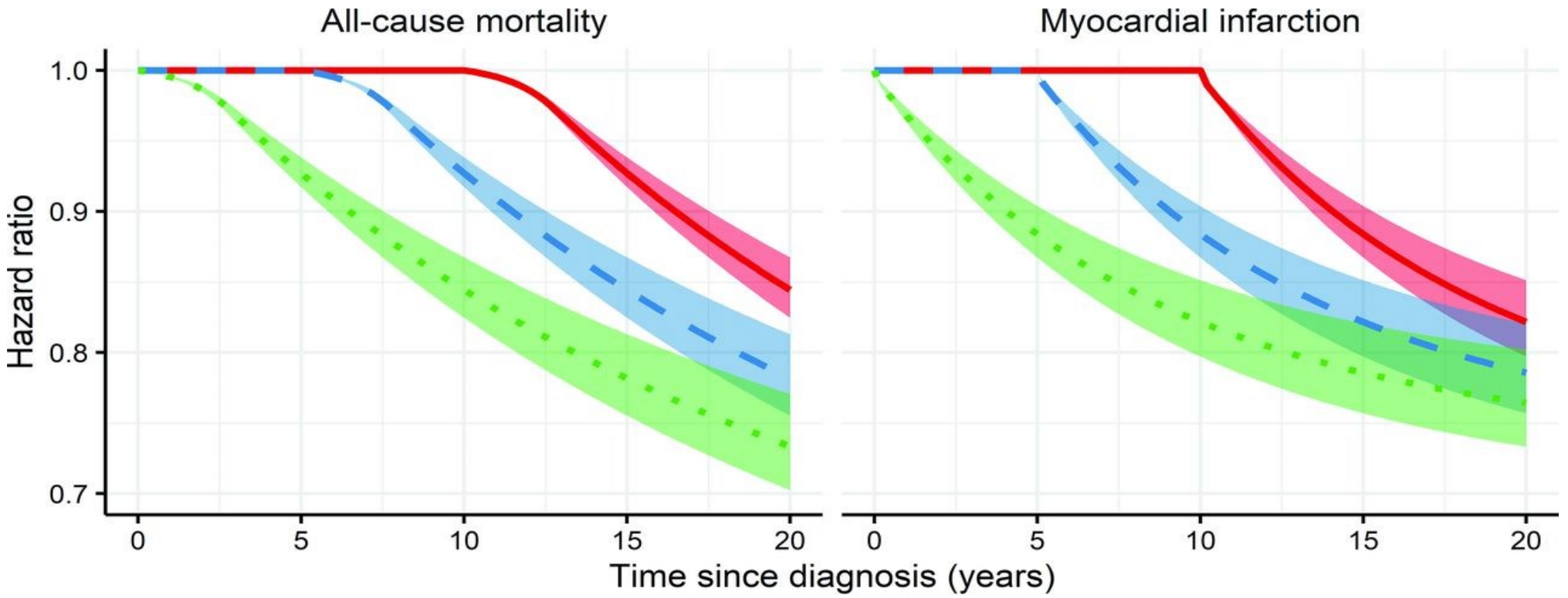
Thus there is a need for easily implementable insulin guidelines to assist clinicians in initiation and intensification with Insulin therapy.

Interactive Question

How long does it usually take from diagnosis to starting insulin in your T2D patients?



Delaying Control Increased All-Cause Mortality and MI Risk – Legacy Effect

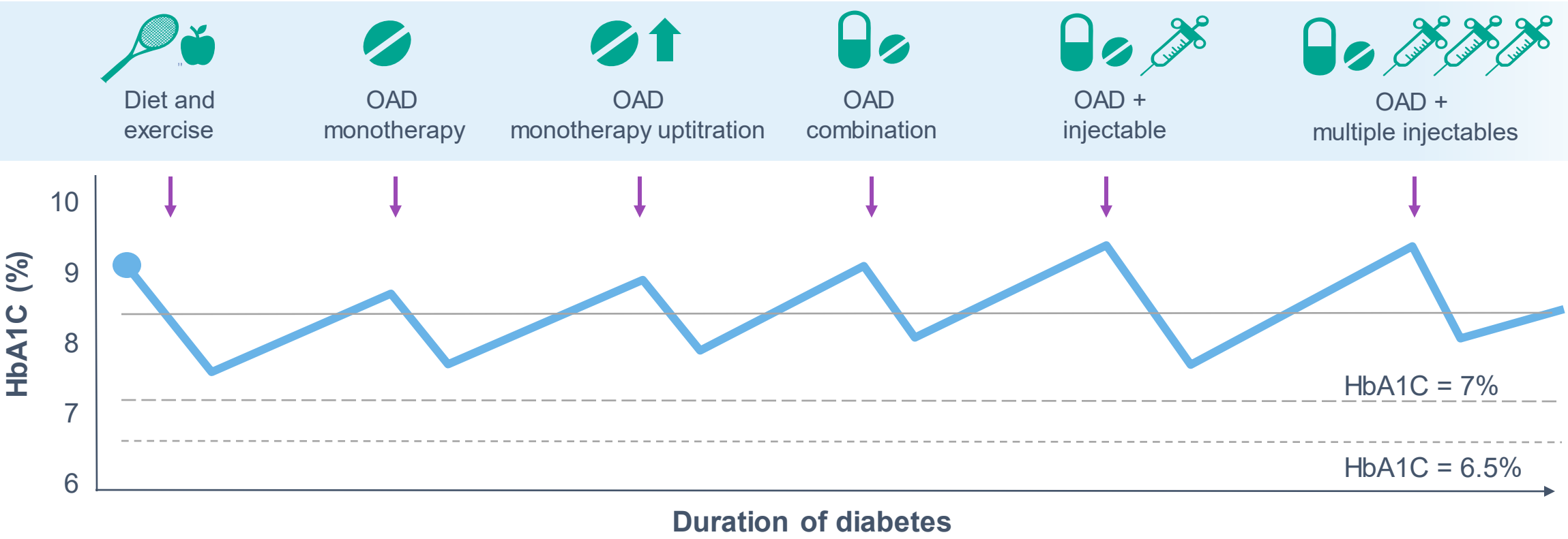


(Shaded area is 95%CI)

Lind M, Imberg H, Coleman RL, Nerman O, Holman RR. Historical HbA1c Values May Explain the Type 2 Diabetes Legacy Effect: UKPDS 88. *Diabetes Care*. 2021;44(10):2231-2237. doi:10.2337/dc20-2439

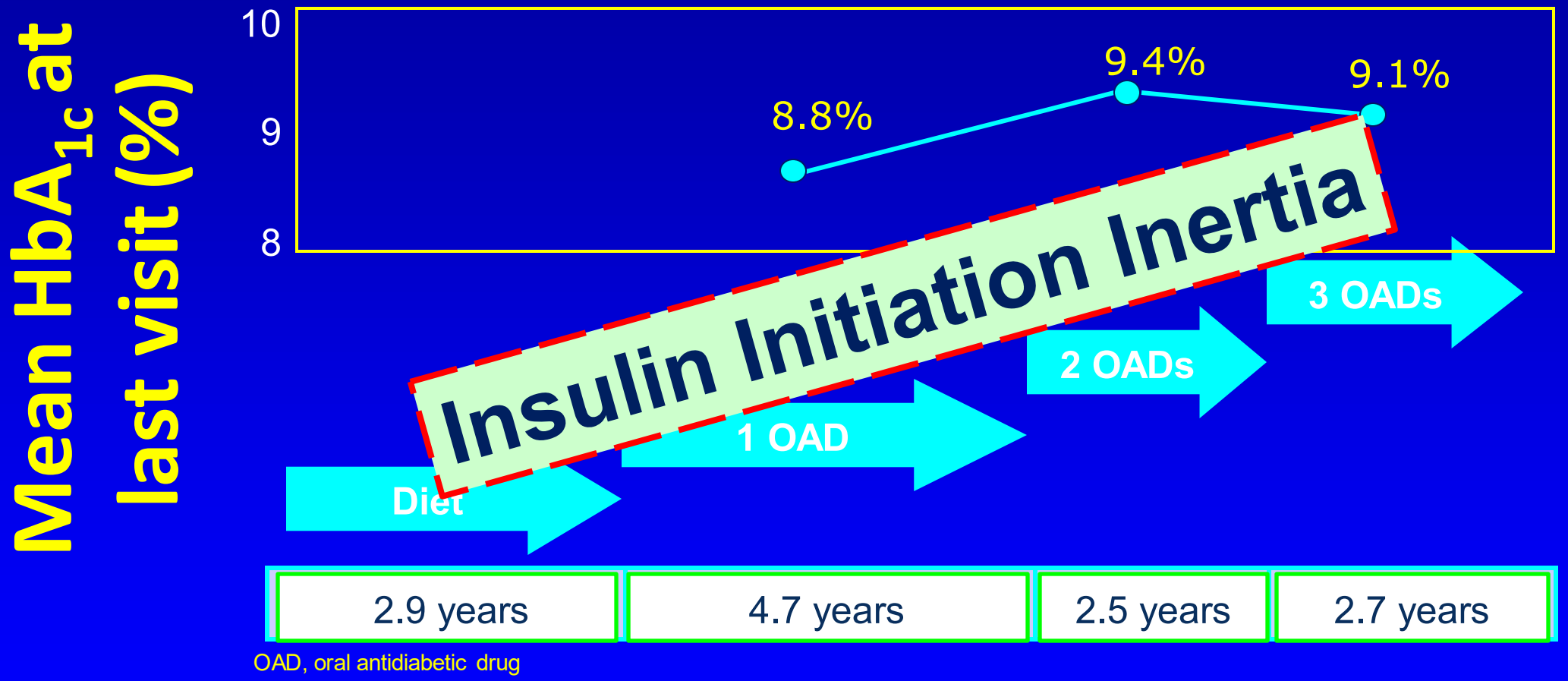
Sequential management of glycemia: Treatment to failure

Stepwise treatment intensification remains a common approach to T2D management; however, often results in clinical inertia



Schematic representation of a traditional stepwise approach to diabetes management based on Del Prato et al.
This stepwise approach often leads to unacceptable delays in achieving and maintain glycemic goals.
OAD, oral antidiabetic drug. Adapted from Del Prato S, et al. Int J Clin Pract 2005;59:1345–55.

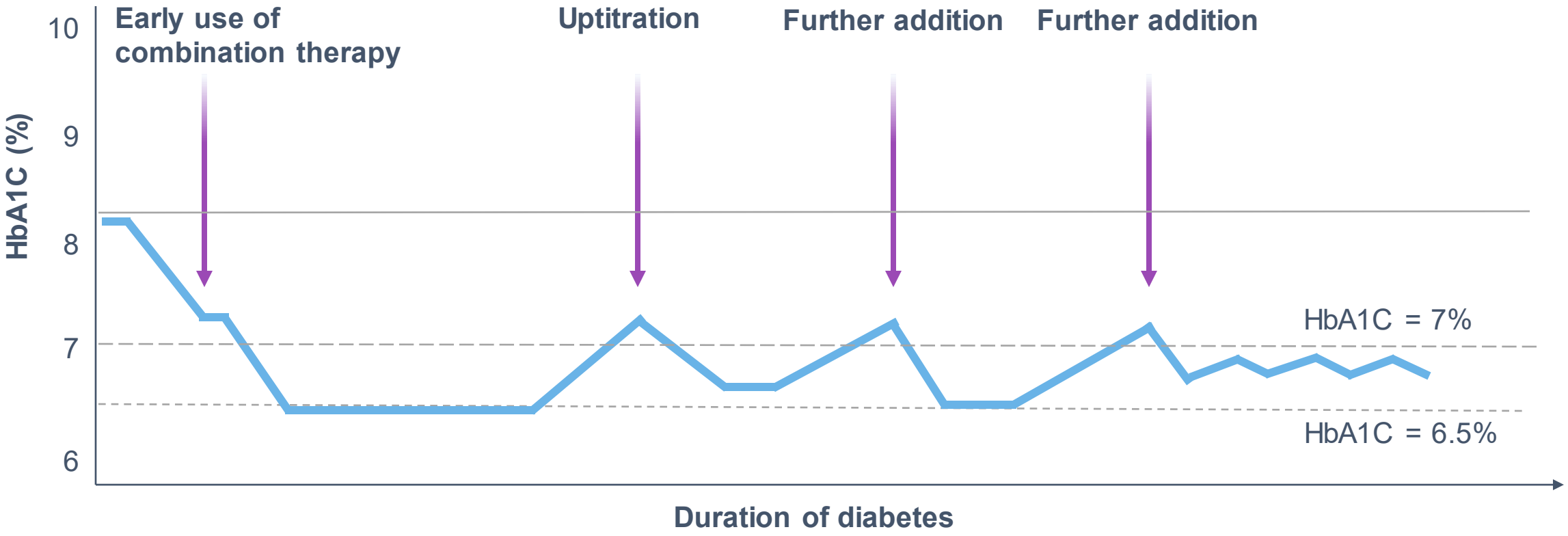
Insulin use is often delayed, despite poor glycaemic control



OAD, oral antidiabetic drug

Roper Starch US Study, 2000.

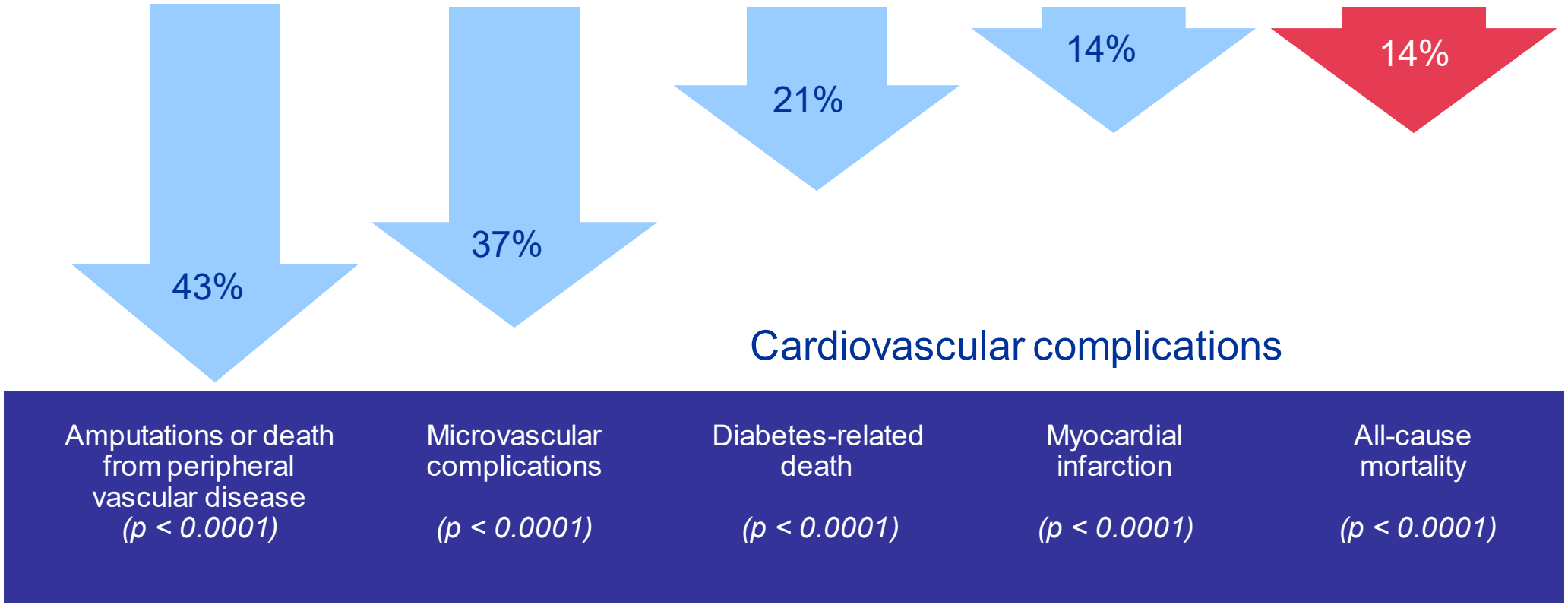
Early combination therapy for glycemic control: Treatment to target



Schematic representation of an early combination approach to diabetes management based on Del Prato et al.
This approach can be considered a 'proactive' approach versus the 'reactive' stepwise approach and is suggested to provide better and more rapid glycemic control.
Adapted from Del Prato S, et al. Int J Clin Pract 2005;59:1345–55.

Each 1% A_{1C} reduction decreases risk of complications

Correlation between a 1% A_{1C} decreas and reduced risk of complication



Stratton IM, *et al. BMJ*. 2000:321:405-412.

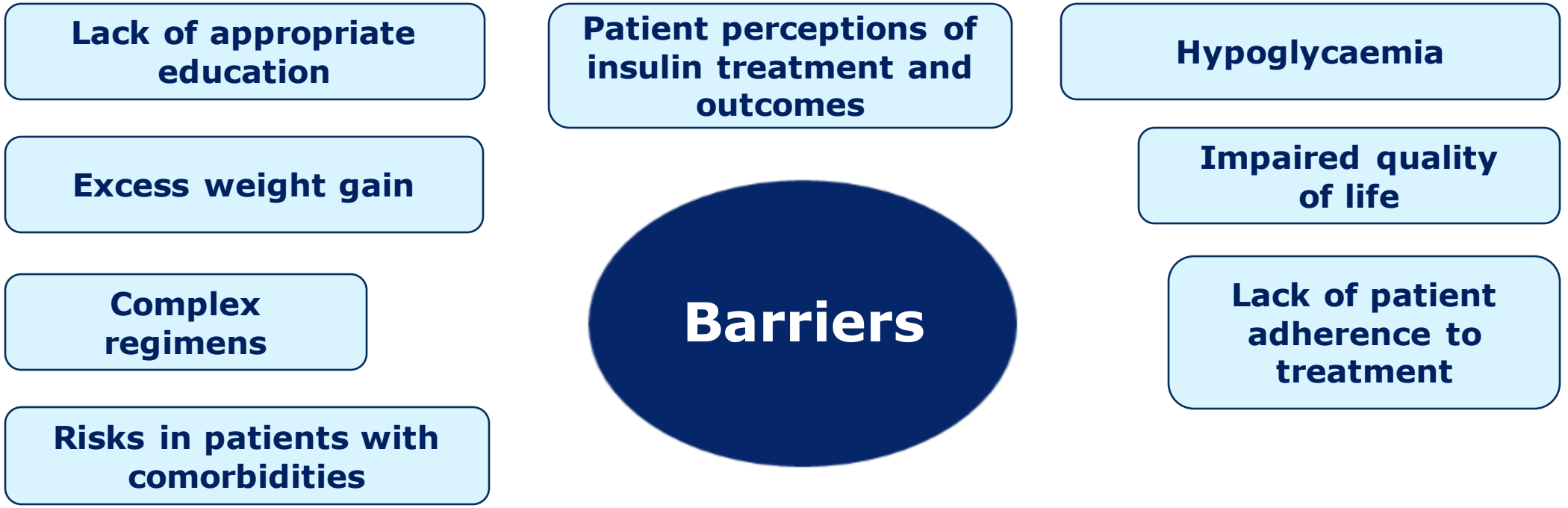
Multinational, observational study of T2DM (66,726) ACHIEVE study: Insulin therapy started in routine clinical care when HbA_{1c} 9.3–9.8%

	China	S. Asia	E. Asia	N. Africa	Mid East	Lat. Am.	Russia
n	9,493	21,107	9,062	3,623	11,971	1,032	2,954
Age (yrs)	55.7	51.7	56.5	58.3	52.8	59.6	59.2
T2DM (yrs)	7.9	6.7	12.5	11.4	10.2	15.5	9.6
Complications (%)	86.1	94.0	90.3	89.7	79.9	90.7	96.1
CV disease (%)	22.9	32.5	29.4	28.5	30.5	35.3	74.6
Renal disease (%)	26.1	28.7	34.6	36.5	43.6	41.8	41.7
Eye problems (%)	25.6	22.0	29.9	41.2	36.8	41.2	71.0
Foot ulcer (%)	2.5	6.5	5.8	3.5	8.7	7.7	5.1
Neuropathy (%)	33.7	29.4	40.1	38.9	56.0	47.6	84.4

- **Complications already present in people with T2DM when initiating insulin therapy**

Leon Litwak et al. Diabetol Metab Syndr. 2013.

Clinical inertia: Patient and physician barriers

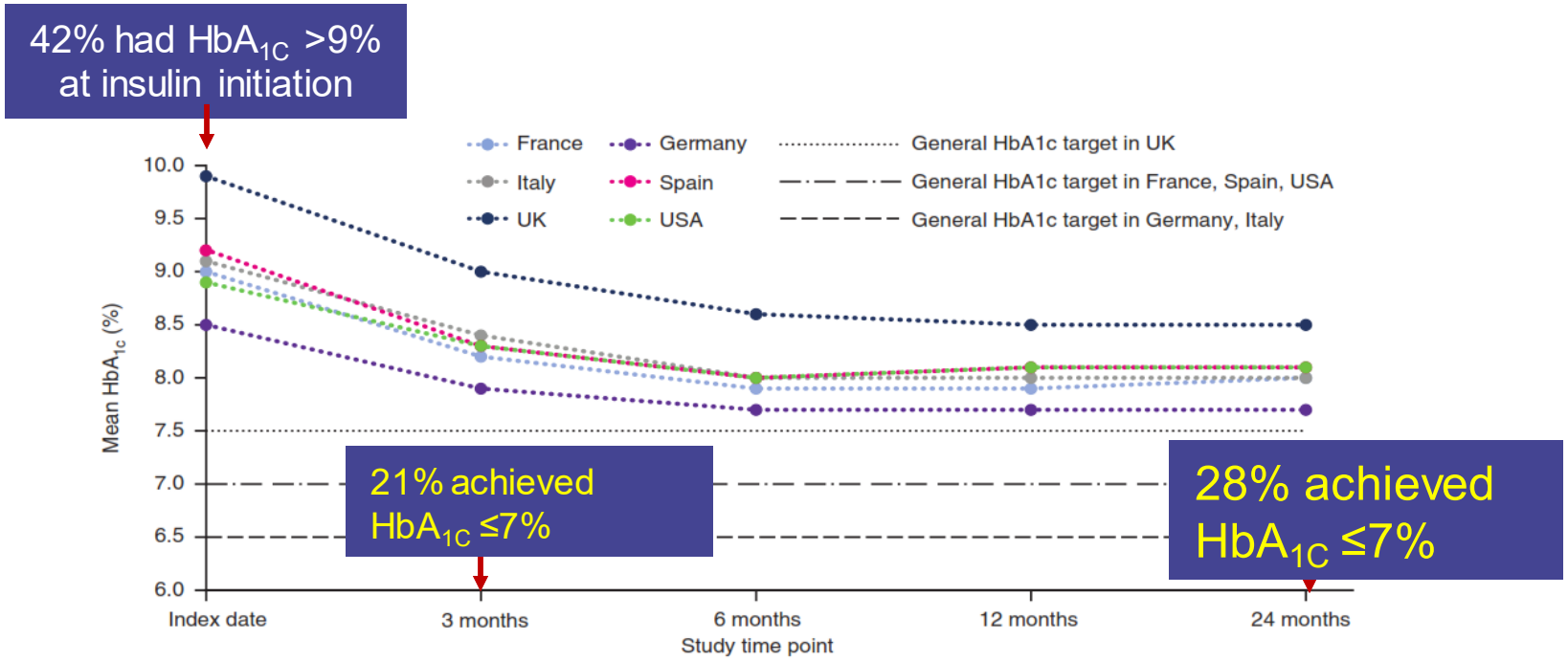


Many barriers to overcoming Clinical Inertia

Peyrot *et al. Diabetes Care* 2005;28:2673–9; Elgrably *et al. Diabet Med* 1991;8:773–7; Wallace and Matthews. *Q J Med* 2000;93:369–74; Kunt and Snoek. *Int J Clin Pract* 2009;63(Suppl. 164):6–10

Many patients do not achieve glycemic targets

- Many patients start insulin with HbA_{1C} >9% = delayed intensification
- Few patients achieve HbA_{1C} ≤7% after insulin initiation

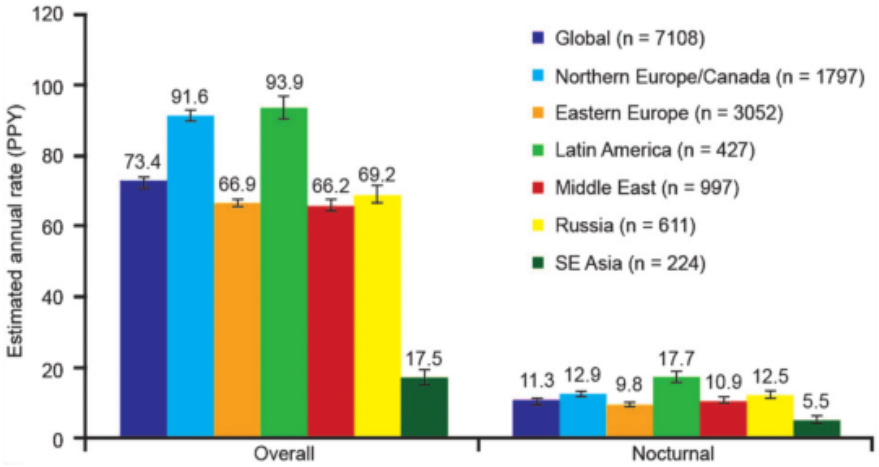


Observational retrospective analysis of Cegedim Strategic Data from 40,627 patients with T2DM ± OADs/GLP-1RA initiating basal insulin from France, Germany, Italy, Spain, UK and USA (2008–2012)

BI, basal insulin; OADs, oral antihyperglycemic drugs
Mauricio D et al. Diabetes Obes Metab. 2017;19:1155-1164

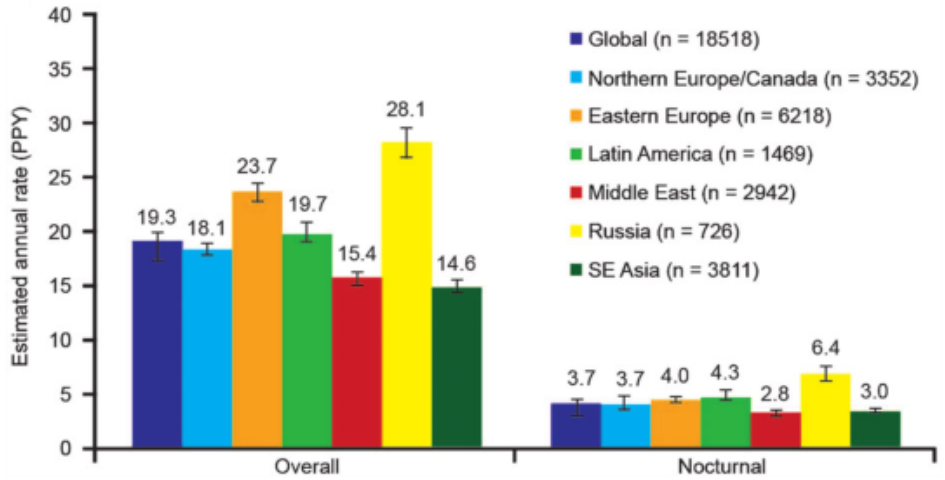
High hypoglycemia rates with insulin therapy and adverse impact

T1DM*



Overall: 73.4 events/patient-year
14.4% reported a severe event

T2DM*



Overall: 19.3 events/patient-year
8.9% reported a severe event

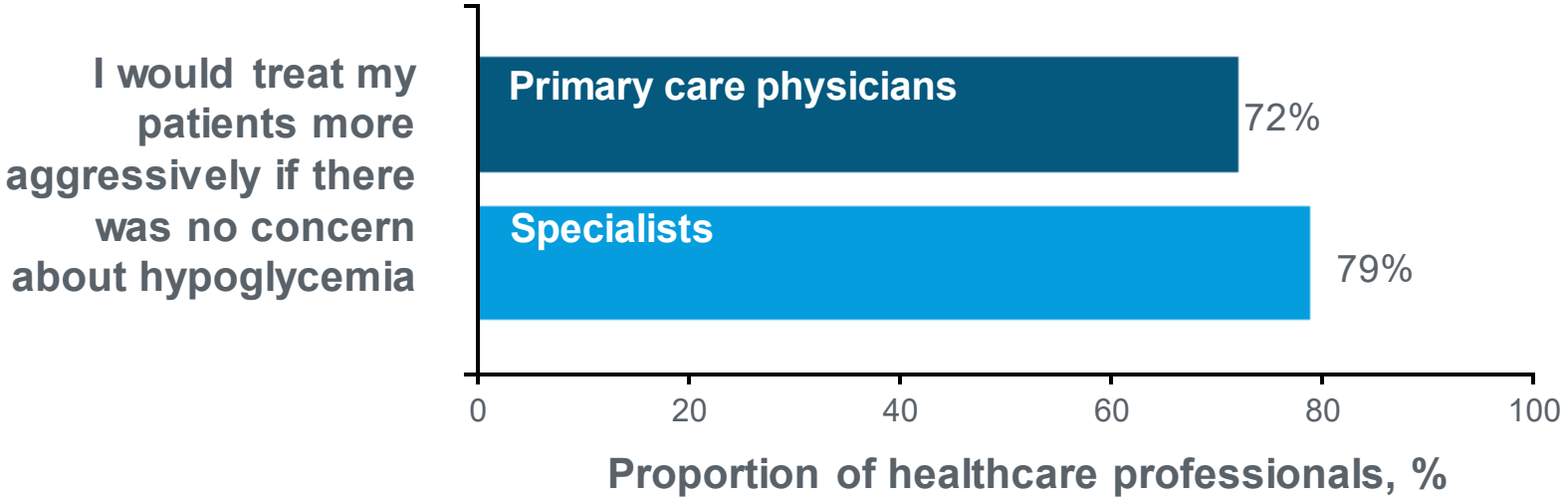
- Hypoglycemia incurs morbidity and increased health care utilization
- Hypoglycemia is a limiting factor in achieving good glycemic control

Non-interventional 6-month retrospective and 4-week prospective global HAT study of 27,585 patients with T1DM or T2DM treated with insulin for <12 months from 24 countries

*During the prospective period

Khunti K et al. Diabetes Obes Metab. 2016;18:907-15

The possibility of hypoglycemia may limit treatment intensification



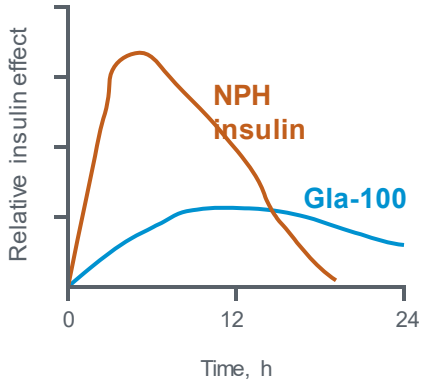
- Insulin regimens with lower risk of hypoglycemia may potentially lead to improvements in glycemic control

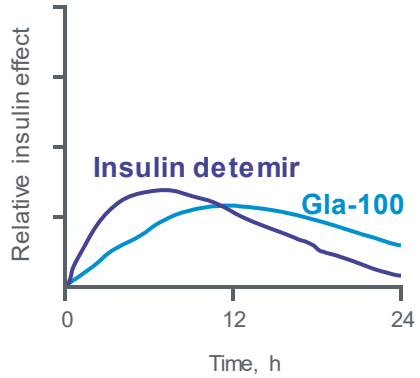
International Global Attitudes of Patients and Physicians in Insulin Therapy internet survey: 1,250 physicians who treat patients with T1DM and T2DM

Adapted from Peyrot M et al. Diabet Med. 2012;29:682-689

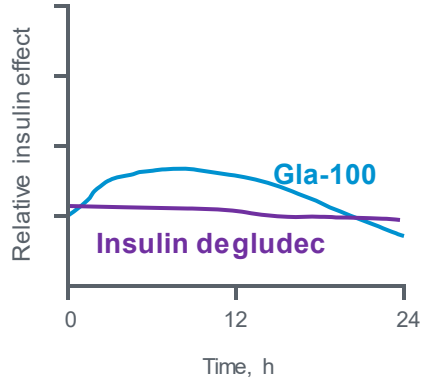
Evolution of basal insulin development: Overcoming limitations

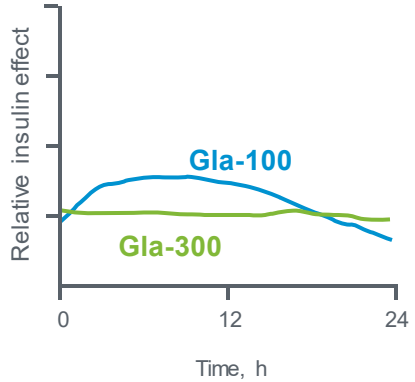
- Insulin glargine 100 U/mL (Gla-100) and insulin detemir were developed to overcome some limitations of early basal insulins such as NPH insulin, with less variable absorption and longer duration of action[1,2]





- Longer-acting basal insulins, insulin glargine 300 U/mL (Gla-300) and insulin degludec, have since been developed with less variability and more prolonged durations of action (>24 h)[1,2]

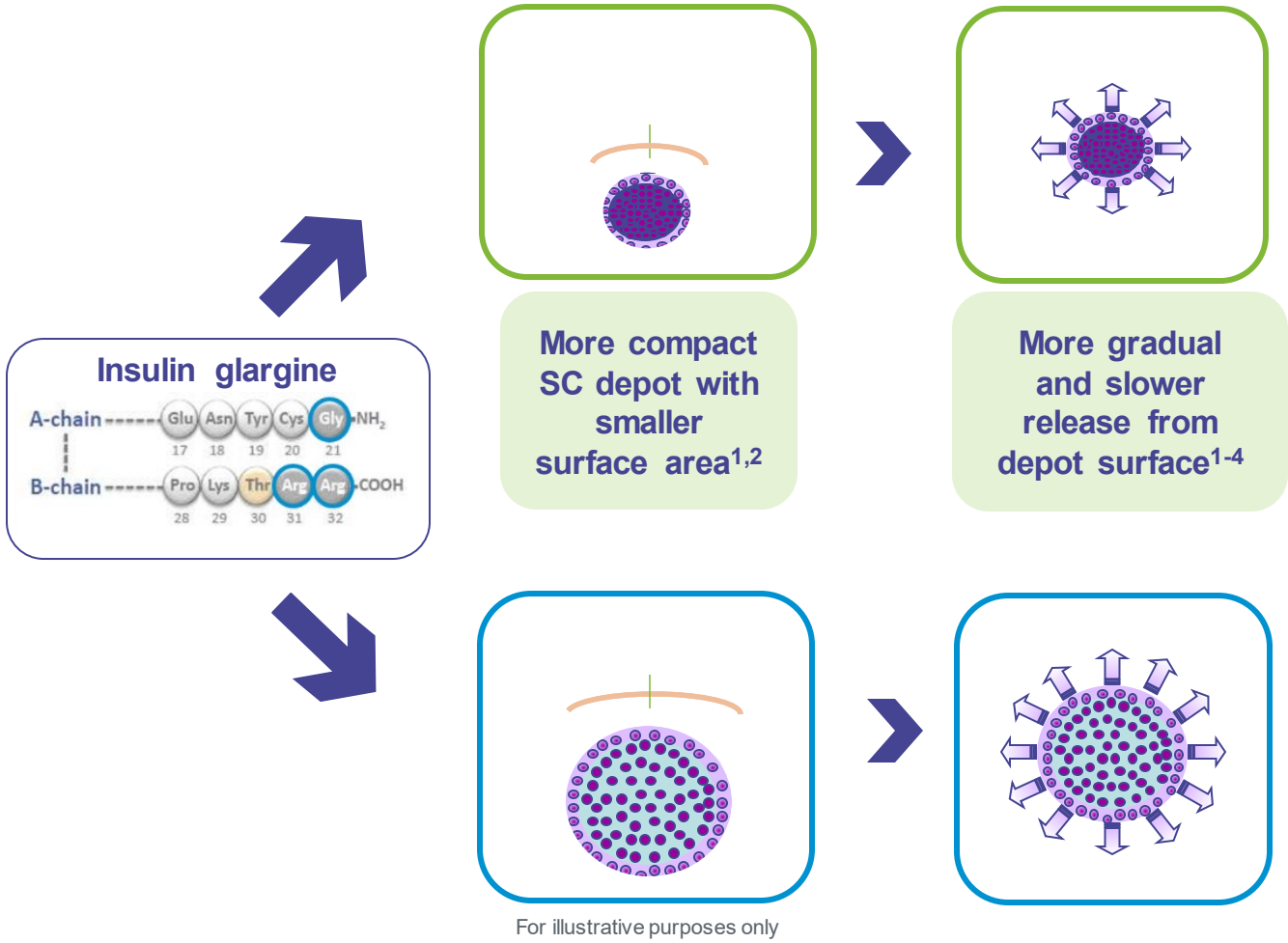




Comparison of action after a single dose for NPH and Gla-100 and for Gla-100 and insulin detemir; comparison at steady state for Gla-100 and Gla-300 and for Gla-100 and insulin degludec
NPH, neutral protamine Hagedorn

1. Eliaschewitz FG, Barreto T. Diabetol Metab Syndr. 2016;8:2; 2. Adapted from Pettus J et al. Diabetes Metab Res Rev. 2016;32:478-96

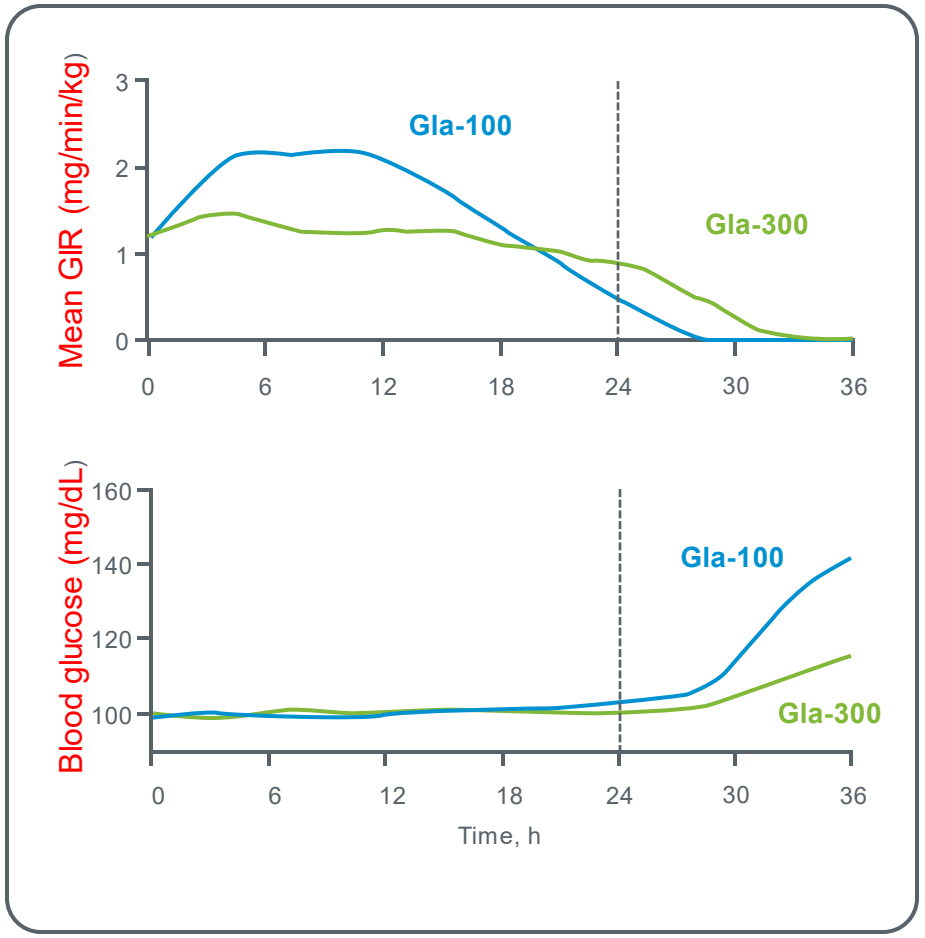
Compact depot formation results in more gradual insulin release

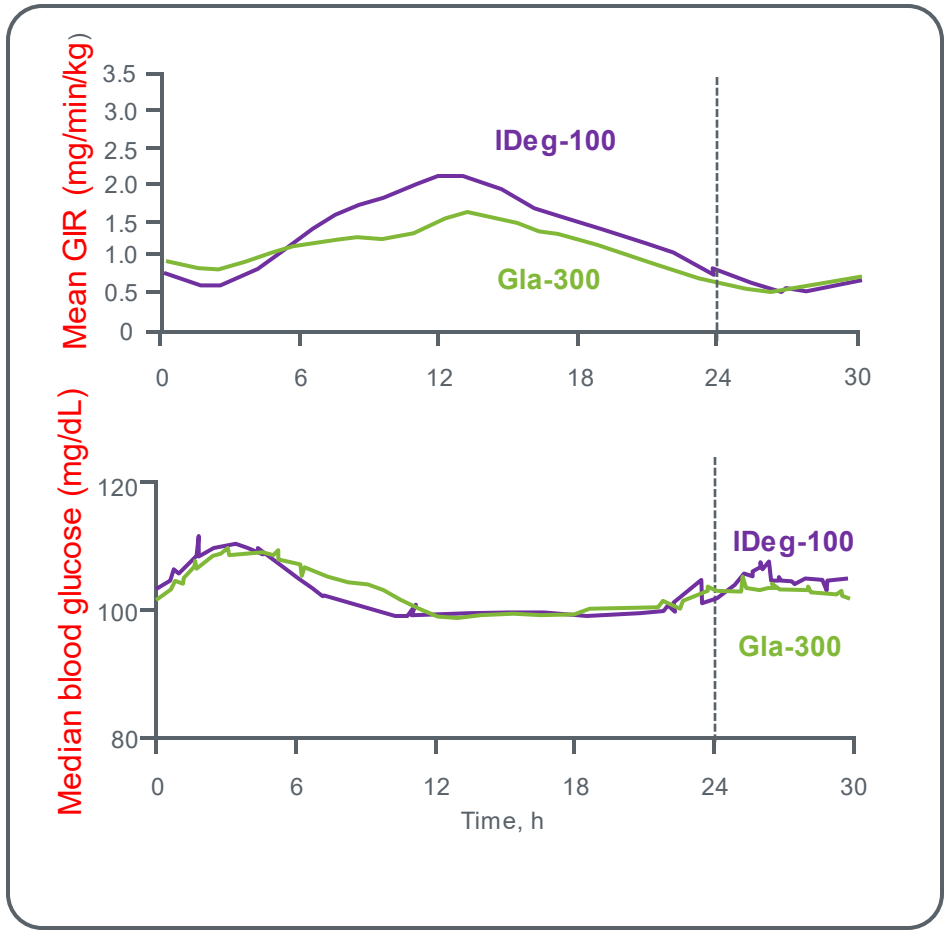


For illustrative purposes only

1. Pettus J et al. Diabetes Metab Res Rev. 2016;32:478-96; 2. Adapted from Sutton G et al. Expert Opin Biol Ther. 2014;14:1849-60;
3. Steinstraesser A et al. Diabetes Obes Metab. 2014;16:873-6; 4. Becker RH et al. Diabetes Care. 2015;38:637-43

More stable glucose-lowering (PD) profile with Gla-300 vs Gla-100 and Gla-300 vs IDeg-100





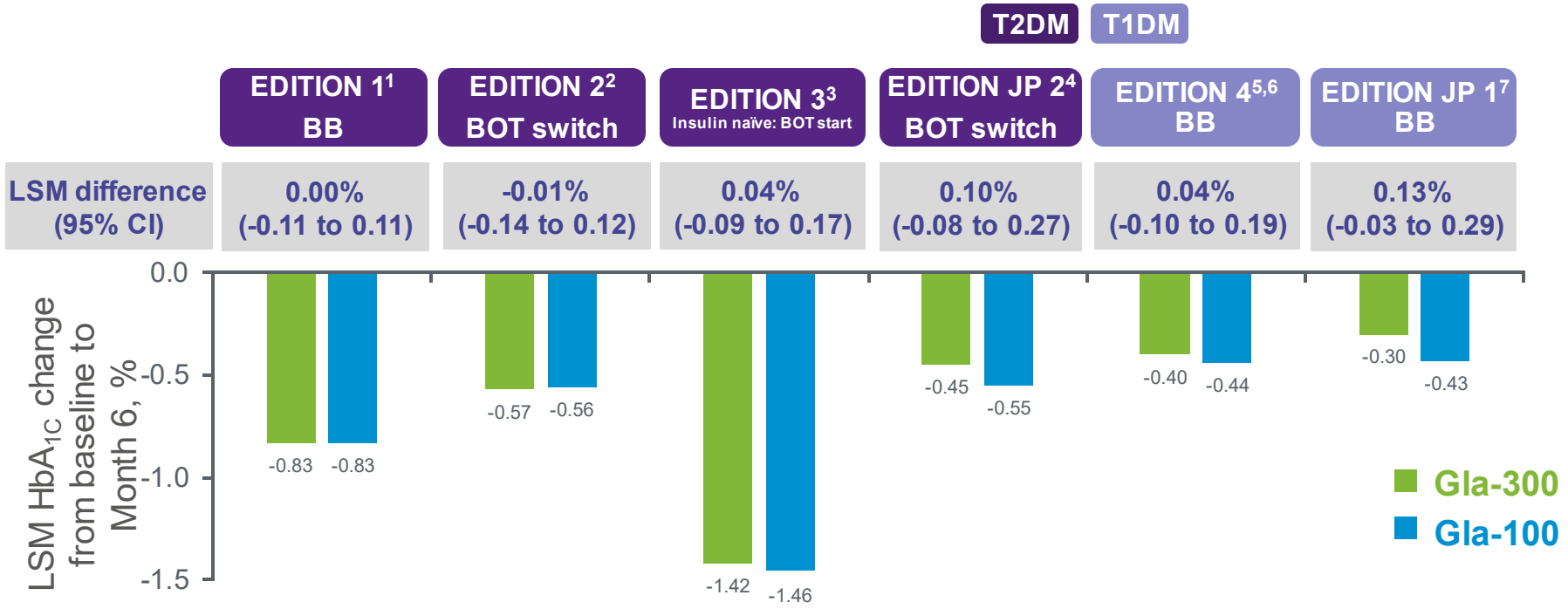
20 % lesser Within-day variability with Gla-300 vs Degludec

GIR, glucose infusion rate

Adapted from Becker RH et al. Diabetes Care. 2015;38:637-43; Bailey TS et al. Diabetes Metab. 2017 Nov 16. pii: S1262-3636(17)30538-4. doi: 10.1016/j.diabet.2017.10.001. [Epub ahead of print]

Consistently effective glycemic control

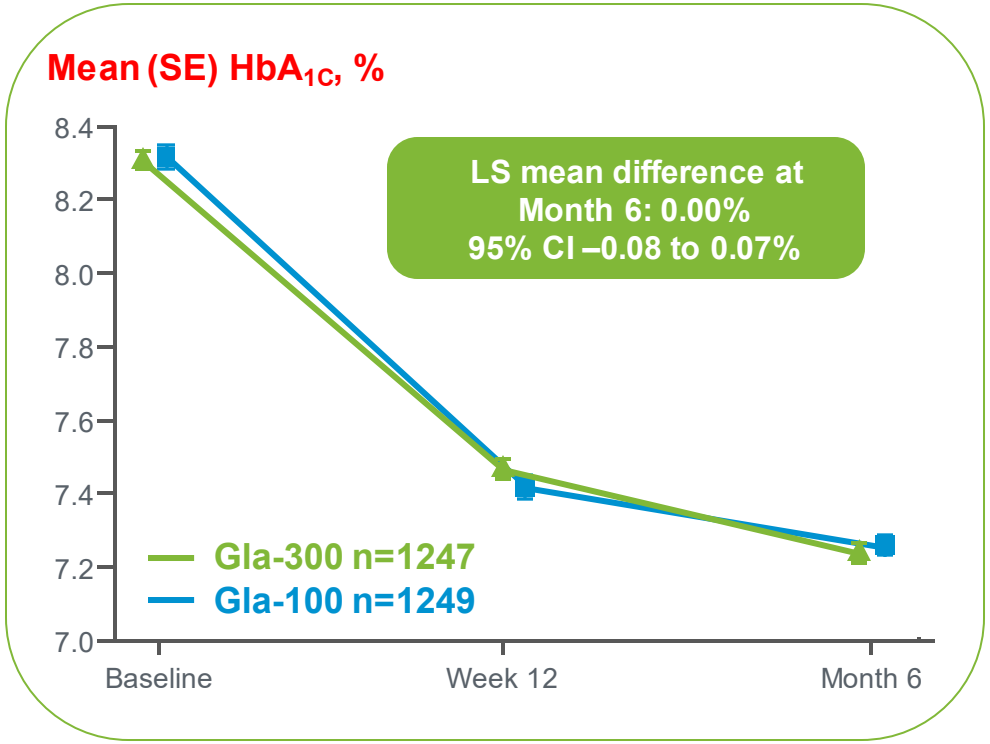
Non-inferior change in HbA_{1C} for Gla-300 vs Gla-100 at Month 6 in the EDITION program

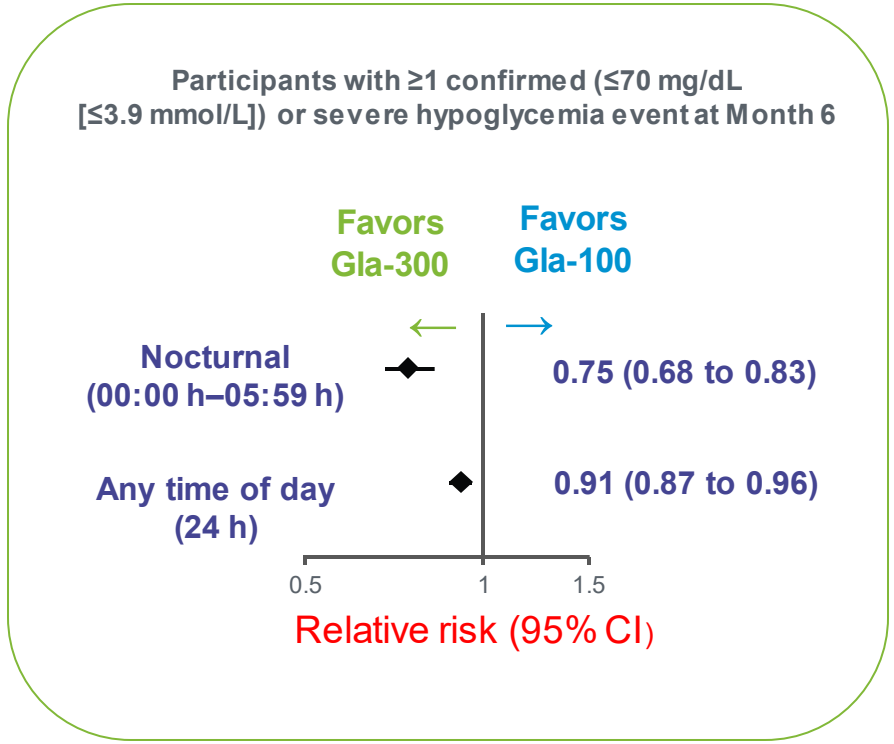


Modified intention-to-treat population; BB, basal-bolus therapy; BOT, basal-oral therapy; CI, confidence interval; LSM, least squares mean

1. Riddle MC et al. Diabetes Care. 2014;37:2755-62; 2. Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; 3. Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94;
4. Terauchi Y et al. Diabetes Obes Metab. 2016;18:366-74 (main article and Supplementary Table 2); 5. Home PD et al. Diabetes Care. 2015;38:2217-25;
6. Data on file, EDITION 4 CSR (6 months) pg 88; 7. Matsuhisa M et al. Diabetes Obes Metab. 2016;18:375-83 (main article and Supplementary Table 1)

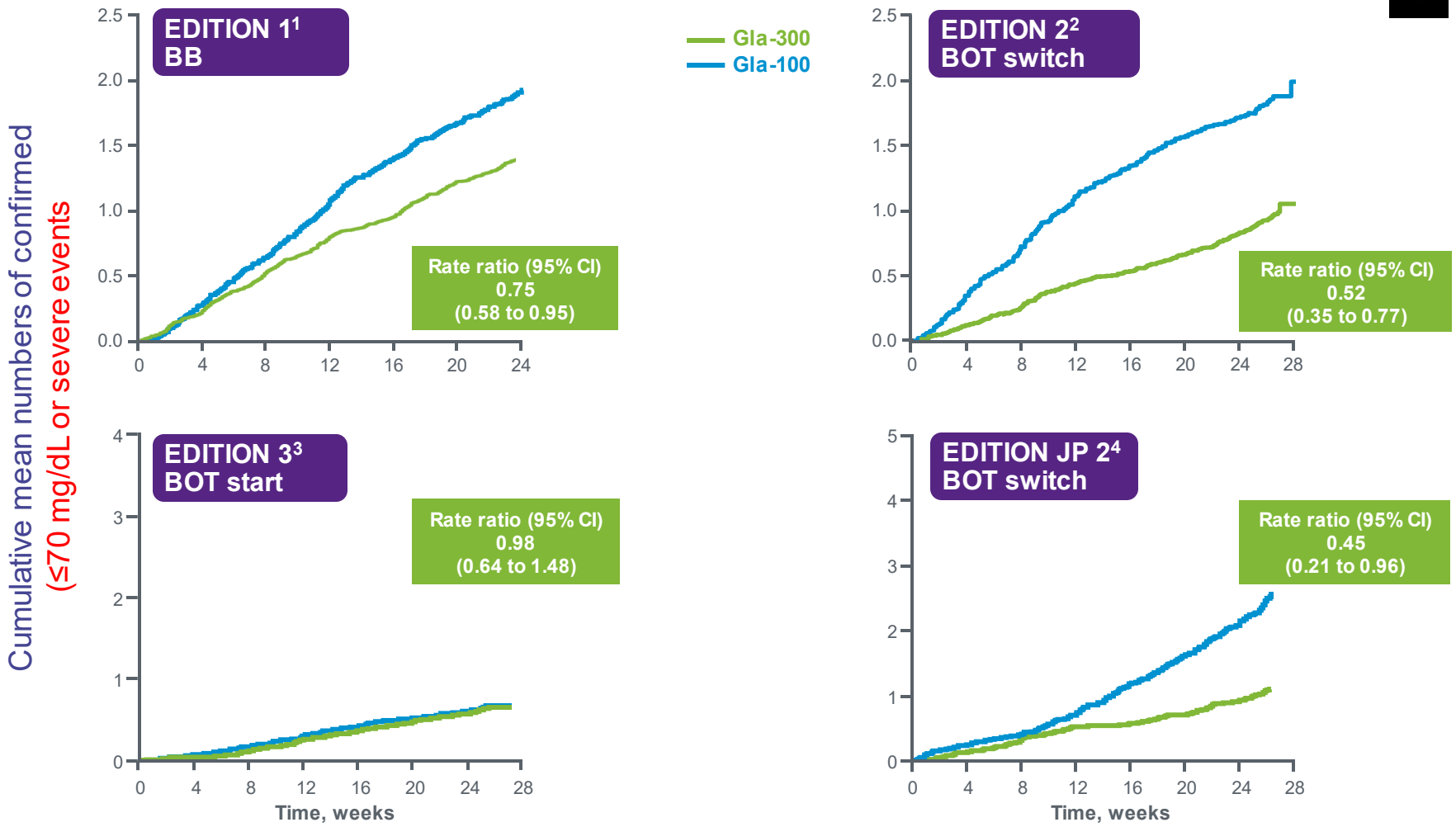
Similar HbA_{1C} reduction with lower incidence of hypoglycemia Gla-300 vs Gla-100 in EDITION T2DM studies* to Month 6





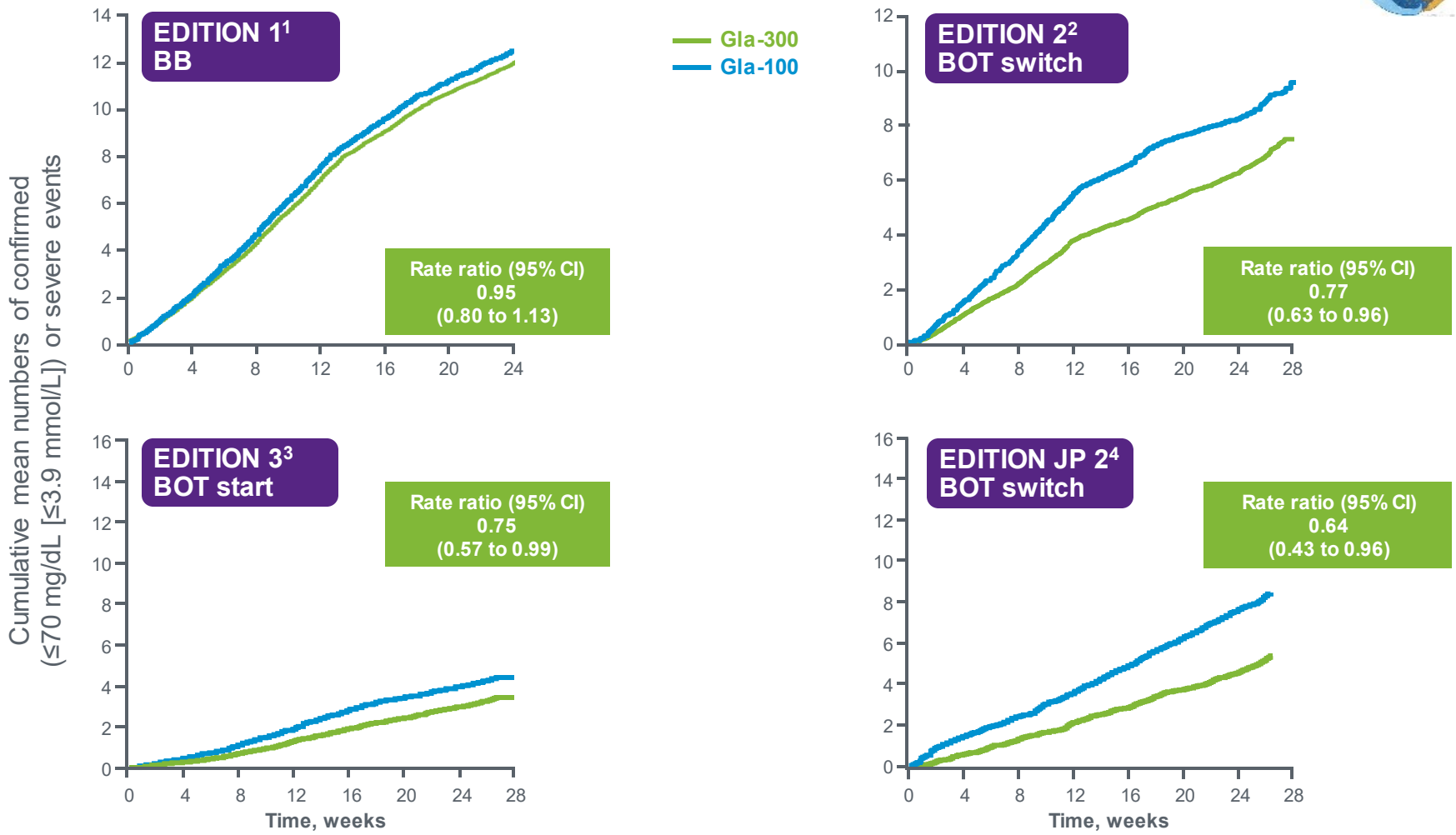
*Patient-level meta-analysis of EDITION 1 (BB), EDITION 2 (BOT switch) and EDITION 3 (BOT start) studies in a broad population of patients with T2DM
SE, standard error
Adapted from Ritzel R et al. Diabetes Obes Metab. 2015;17:859-67

Rate of nocturnal (00:00–05:59 h) confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia in T2DM studies at Month 6



Safety population; rate ratio and 95% CI are based on annualized rates per patient-year for confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia
BB, basal-bolus therapy; BOT, basal-oral therapy; CI, confidence interval; T2DM, type 2 diabetes mellitus
1. Adapted from Riddle MC et al. Diabetes Care. 2014;37:2755-62; 2. Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; 3. Bolli GB et al. Diabetes Obes Metab 2015;17:386-394 (main article and Supplementary Figure 3); 4. Terauchi Y et al. Diabetes Obes Metab. 2016;18:366-74

Rate of confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia at any time of day (24 h) in T2DM studies at Month 6



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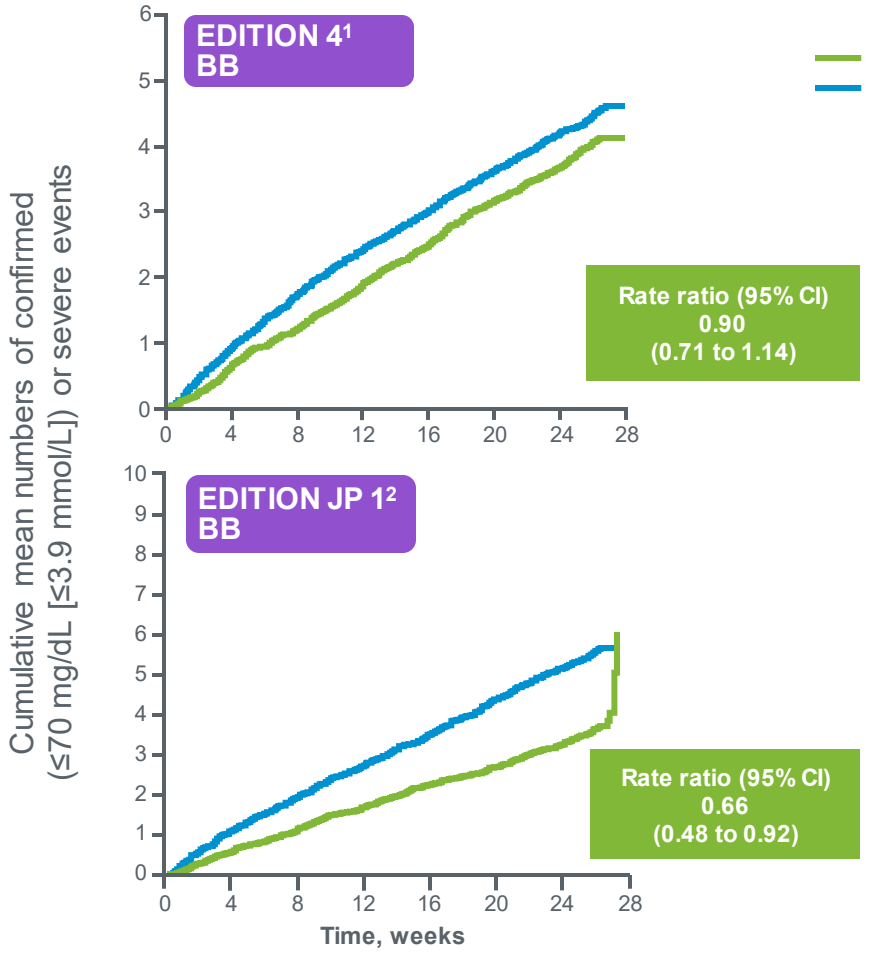
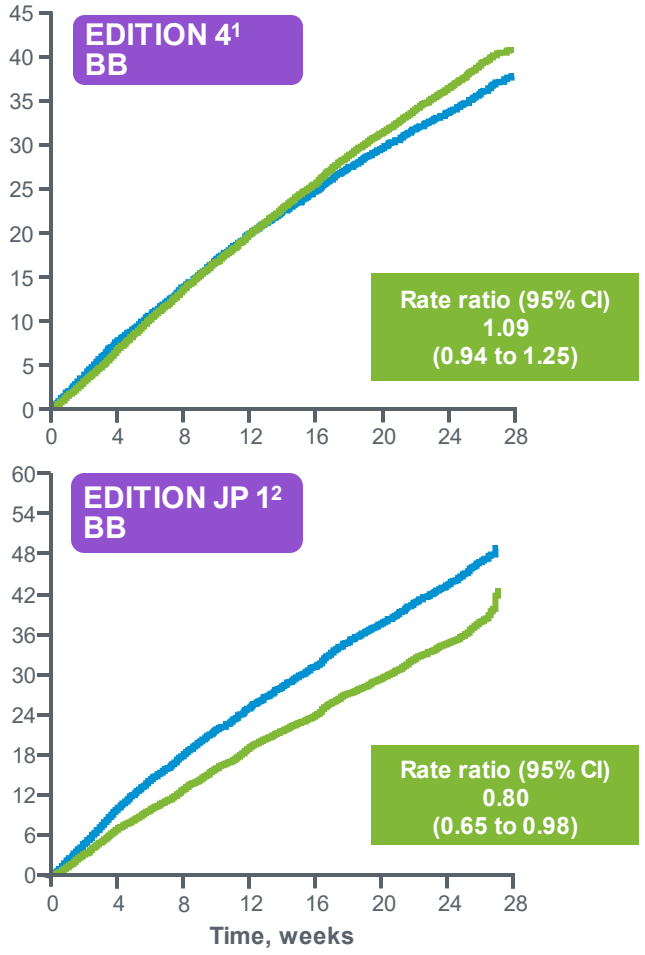
1. Adapted from Riddle MC et al. Diabetes Care. 2014;37:2755-62; 2. Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; 3. Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94 (main article and Supplementary Figure 3); 4. Terauchi Y et al. Diabetes Obes Metab. 2016;18:366-74

Rate of confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia in T1DM studies at Month 6

Nocturnal (00:00–05:59 h)



Any time of day (24 h)



Safety population; rate ratio and 95% CI are based on annualized rates per patient-year for confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia
BB, basal-bolus therapy; CI, confidence interval; T1DM, type 1 diabetes mellitus
The steep increase in the Gla-300 group during the last 8 days of the main 6-month treatment period in EDITION JP 1 is explained by the very low number of patients exposed to treatment during this time who experienced only 1 event on each of Day 187, Day 189 and Day 190
1. Adapted from Home PD et al. Diabetes Care. 2015;38:2217-25 (main article and Supplementary Figure 3); 2. Matsuhisa M et al. Diabetes Obes Metab. 2016;18:375-83

Gla-300 clinical profile: Conclusions

- **Comparable HbA_{1C} reductions** to Gla-100, but with **lower risk** of confirmed or severe hypoglycemia, also during the titration period
- Smoother PK/PD profiles of Gla-300 associated with **reduced daily glycemic variability and lower risk for hypoglycemia**
- **Less glycemic variability** with Gla-300 when administered in the morning or evening
- **Flexibility** to select the timing of injections to either am or pm dosing and within a ± 3 hours window when needed
- Comparable glycemic control and similar hypoglycemia benefits in **special populations**
- **Convenient** administration with the easy-to-use TOUJEO™ SoloSTAR® pen

1. Riddle MC et al. Diabetes Care. 2014;37:2755-62; 2. Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; 3. Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94; 4. Terauchi Y et al. Diabetes Obes Metab. 2016;18:366-74; 5. Ritzel R et al. Diabetes Obes Metab. 2015;17:859-67; 6. Home PD et al. Diabetes Care. 2015;38:2217-25; 7. Matsuhisa M et al. Diabetes Obes Metab. 2016;18:375-83; 8, Kovatchev B et al. Oral presentation at EASD 2017; abstract OP-78; 9. Bergenstal RM et al. Diabetes Care. 2017;40:554-560; 10. Riddle M et al. Diabetes Technol Ther. 2016;18:252-7; 11. Klonoff D et al. J Diabetes Sci Technol. 2015;10:125-30;12. Ritzel R et al. Poster presentation at Abstract 469; 12. Halimi S et al. Poster presentation at ATTD 2017; 13. Bertolini M et al. Poster presentation at EASD 2017; abstract 937

Insulin + GLP-1 RA

Basal insulin is the most effective agent to lower fasting glucose but it is associated with hypoglycemia and weight gain

GLP-1 agonists lowers both **fasting** and **post-prandial** glucose without causing an intrinsic effect to cause hypoglycemia while promoting weight loss

Rationale: Combine two powerful glucose-lowering agents to get even better efficacy
Clinical trial date: Robust efficacy while mitigating the adverse effects of both agents (weight, hypoglycemia, nausea)

Buse JB, et al. Diabetes Obes Metab 2015;17:145–151
Balena R, et al. Diabetes Obes Metab 2013;15:485–502

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

Insulin glargine 100 U/mL
+
Lixisenatide

iGlarLixi

Insulin degludec
+
Liraglutide

IDegLira

FRCs have been investigated in multiple populations of adults with T2D*

Insulin-naïve uncontrolled on OADs

LixiLan-O[1]

30-week, open-label, randomized
- iGlarLixi + met (n=469)
- iGlar + met (n=467)
- Lixi + met (234)

DUAL I[2]

26-week, open-label, randomized
- IDegLira OD + met ± pio (n=834)
- IDeg OD + met ± pio (n=414)
- Lira OD + met ± pio (n=415)

Uncontrolled on basal insulin

LixiLan-L[3]

30-week, open-label, randomized
- iGlarLixi ± met (n=367)
- iGlar ± met (n=369)

DUAL II[4]

26-week, open-label, randomized
- IDegLira OD + met ± SU/glinide (n=199)
- IDeg OD + met ± SU/glinide (n=199)

Uncontrolled on OADs and QD, BID or QW GLP-1 RAs

LixiLan-G[5]

26-week, open-label, randomized
- Continue unchanged GLP-1 RA + met ± pio ± SGLT-2 inhibitor (n=257)
- iGlarLixi (n=257)

DUAL III[6]

26-week, open-label, randomized
- Continue unchanged GLP-1 RA + met ± pio ± SU (n=146)
- IDegLira + met ± pio ± SU (n=292)

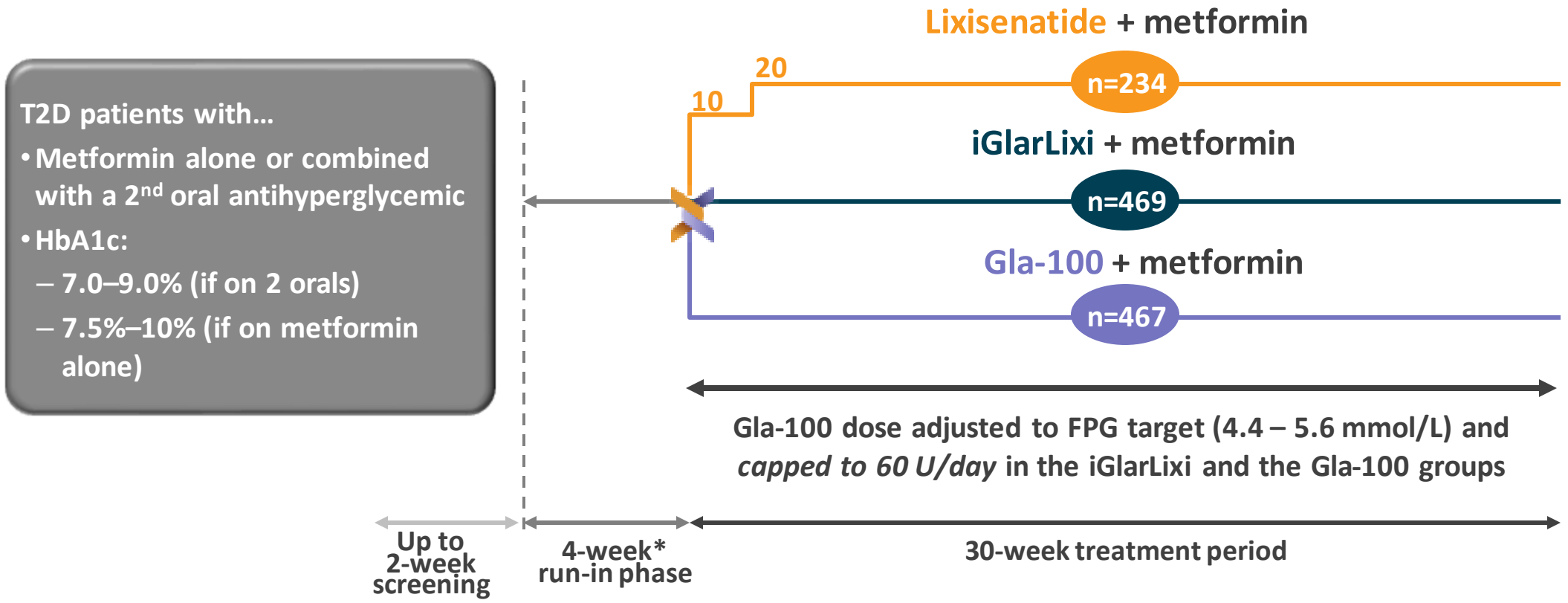
***Note: This is not intended as a direct comparison of studies**

BID, twice daily; IDeg, insulin degludec; IDegLira, insulin degludec + liraglutide; iGlar, insulin glargine 100 U; iGlarLixi; insulin glargine + lixisenatide; Lira, liraglutide; Lixi, lixisenatide; met, metformin; OAD, oral anti-diabetes drug; pio, pioglitazone; QD, once daily; QW, once weekly; SU, sulfonylurea

1. Rosenstock J, et al. Diabetes Care 2016;39:2026–35; 2. Gough SC, et al. Lancet Diabetes Endocrinol 2014;2:885–93; 3. Aroda V, et al. Diabetes Care 2016;39:1972–80; 4. Buse JB, et al. Diabetes Care 2014;37:2926–33; 5. Blonde L, et al. Diabetes Care 2019;42:2108–16; 6. Linjawi S, et al. Diabetes Ther 2017;8:101–14

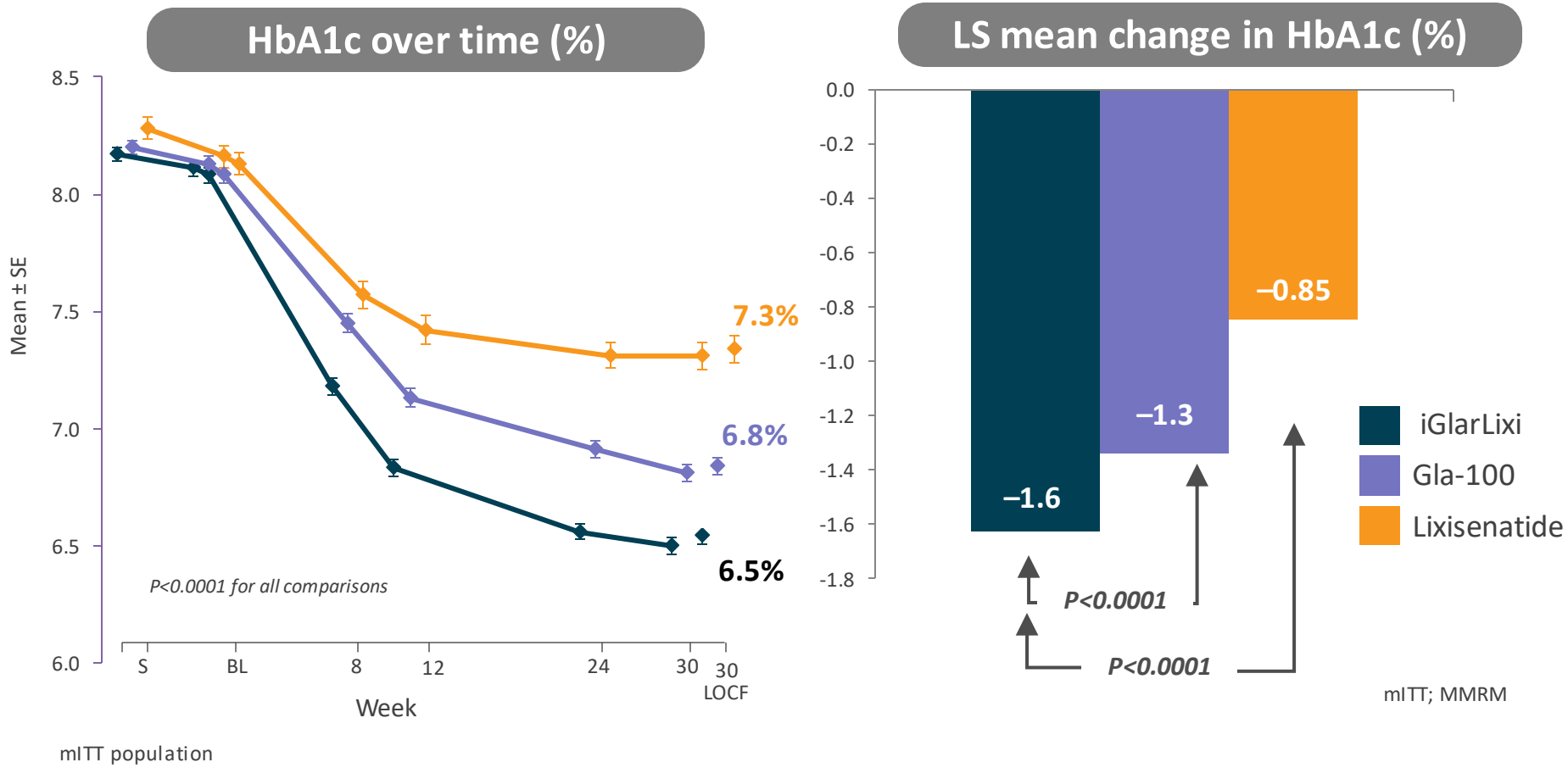
Study Design

- Phase 3, randomized, open-label, active-controlled, parallel-group, 30-week, study
- 1170 patients with T2DM on 1 or 2 oral antihyperglycemic therapies with elevated A1c



Rosenstock J et al. Diabetes Care 2016 Nov;39(11):2026-2035

More A1c reduction with iGlarLixi



LS mean difference vs Gla-100: –0.3 (95% CI –0.38 to –0.19)

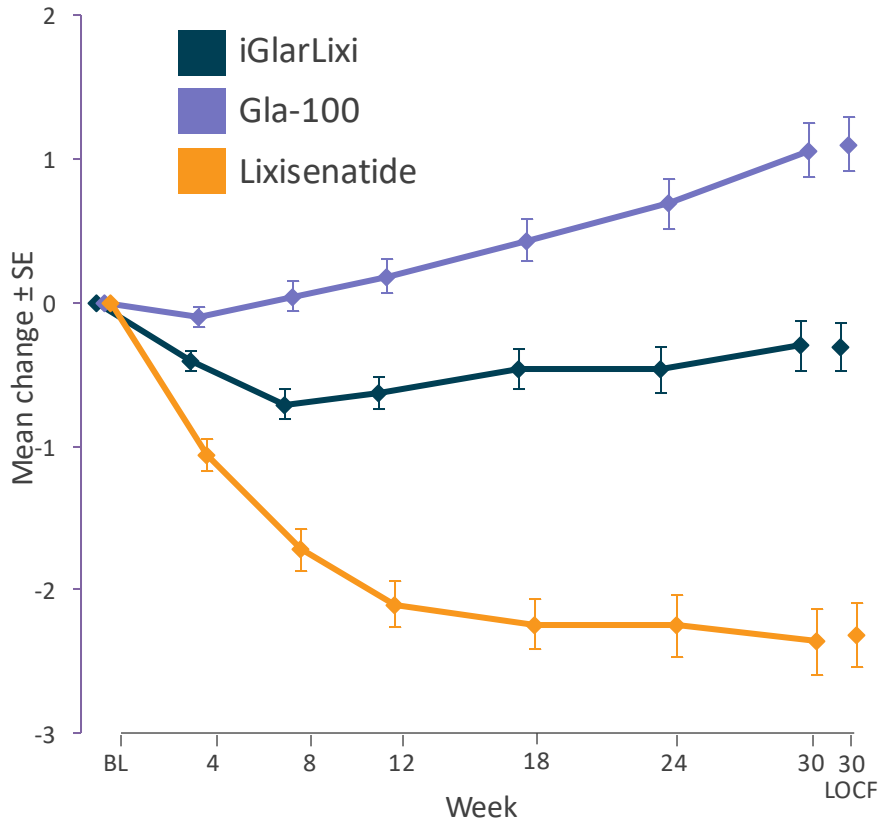
LS mean difference vs Lixisenatide: –0.8 (95% CI –0.9 to –0.66)

BL=Baseline; MMRM=Mixed-effect model with repeated measures; S: Screening.

Rosenstock J et al. Diabetes Care 2016 Nov;39(11):2026-2035

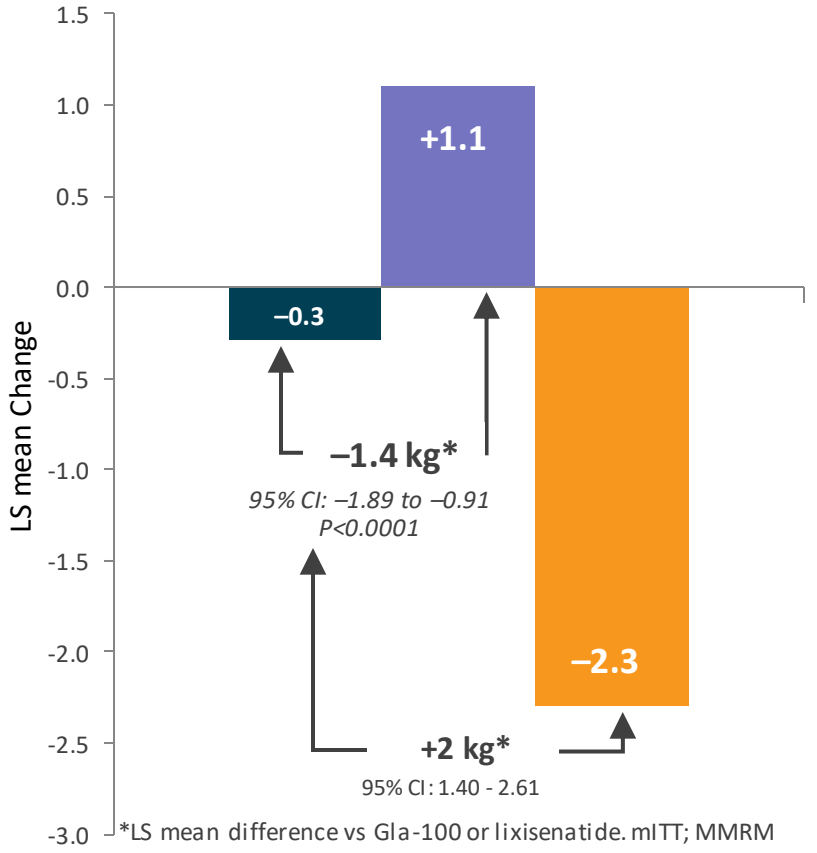
Weight neutral with iGlarLixi

Change in body weight (kg)



mITT population

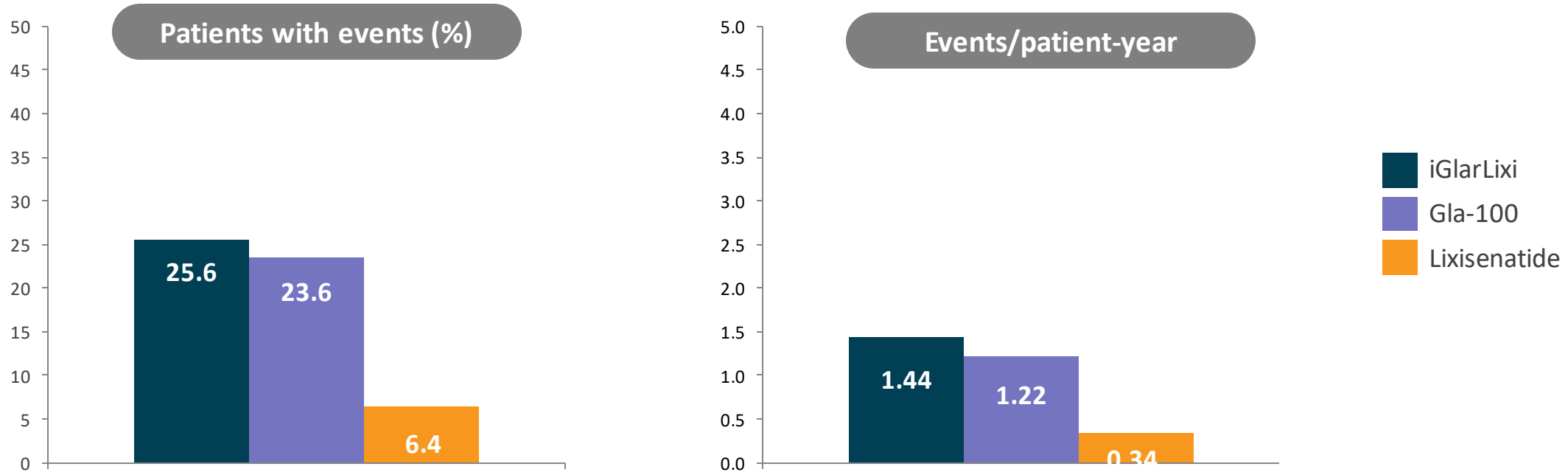
Baseline	89.4 kg	89.8 kg	90.8 kg



*LS mean difference vs Gla-100 or lixisenatide. mITT; MMRM

Rosenstock J et al. Diabetes Care 2016 Nov;39(11):2026-2035

Similar document symptomatic hypoglycemia (≤3.9 mmol/L) with iGlarLixi and iGlar



Only 1 patient in the Gla-100 group experienced a severe hypoglycemic event

Safety Population

Rosenstock J et al. Diabetes Care 2016 Nov;39(11):2026-2035

Fewer GI adverse events with iGlarLixi vs Lixi

Patients, n (%), with at least one…	iGlarLixi (n=469)	Gla-100 (n=467)	Lixisenatide (n=233)
TEAE			
Any	267 (56.9%)	227 (48.6%)	157 (67.4%)
Serious	18 (3.8%)	19 (4.1%)	9 (3.9%)
Leading to Death	2 (0.4%)	3 (0.6%)	1 (0.4%)
Leading to Discontinuation	12 (2.6%)	9 (1.9%)	21 (9%)
GI TEAEs			
Nausea	45 (9.6%)	17 (3.6%)	56 (24%)
Vomiting	15 (3.2%)	7 (1.5%)	15 (6.4%)
Diarrhea	42 (9%)	20 (4.3%)	21 (9%)

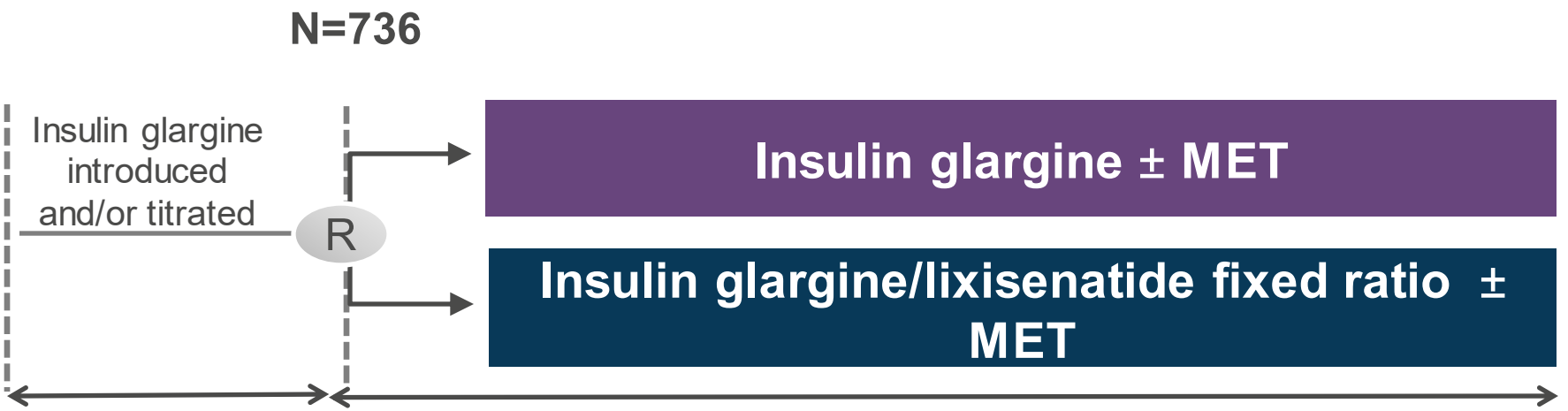
TEAE=treatment emergent adverse event.

Rosenstock J et al. Diabetes Care 2016 Nov;39(11):2026-2035

Study Design

- Phase 3, randomized, open-label, active-controlled, parallel-group, 30-week, study
- 736 patients with T2DM inadequately controlled with basal insulin ± NIAHAs

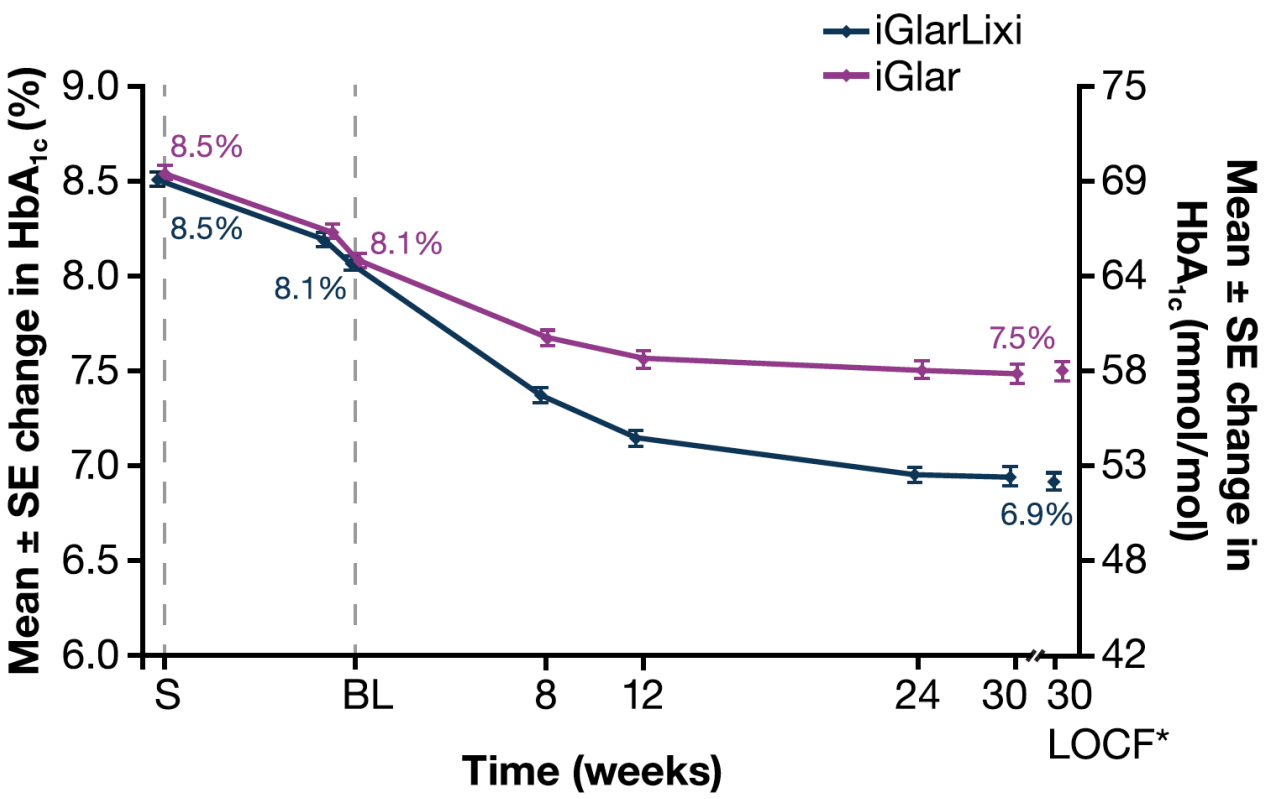
Key inclusion criteria
- T2DM ≥1 year
- A1C ≥7.5–10.0%
- Basal insulin ≥ 6 months
- Stable basal insulin ≥ 3 months
- Stable (±20%) total daily basal insulin dose (15-40 U/d) ≥ 2 mos
- If on NIAHAs then stable ≥ 3 mos
- Fasting FPG ≤ 10.0 mmol/L for patients on NIAHAs other than MET and ≤ 11.1 mmol/L for patients on basal insulin ± MET

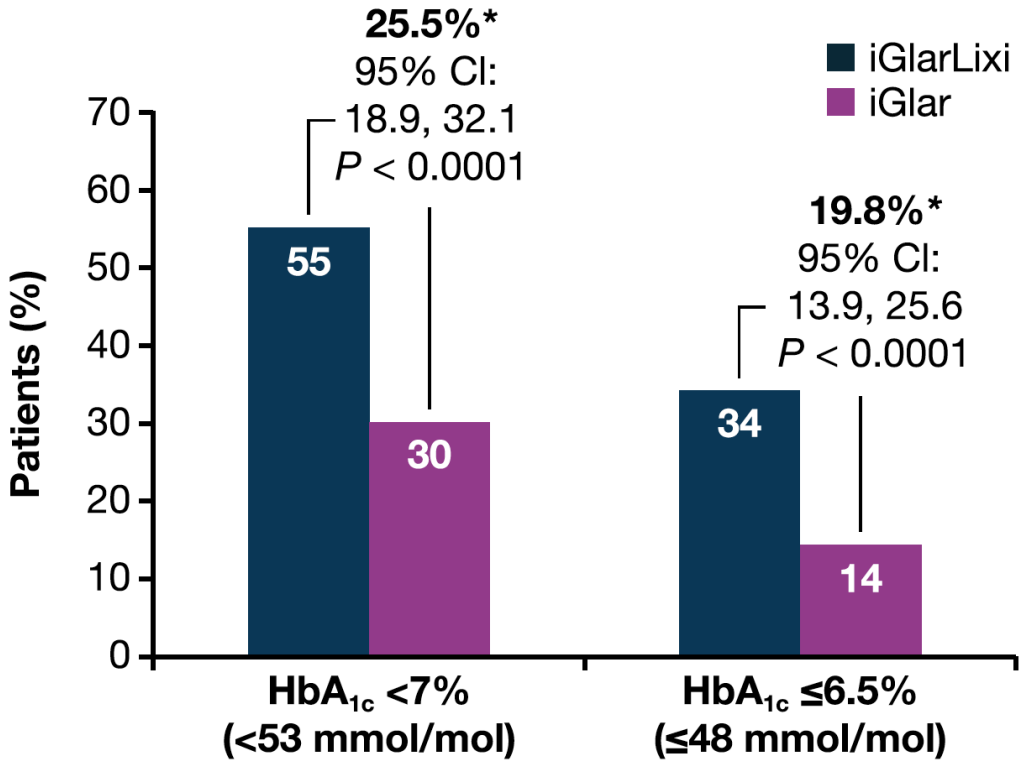


- Mean SMPG ≤7.8 mmol/L for 7 days before randomization
- Average insulin glargine daily dose >20 U or ≤50 U the week before randomization

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

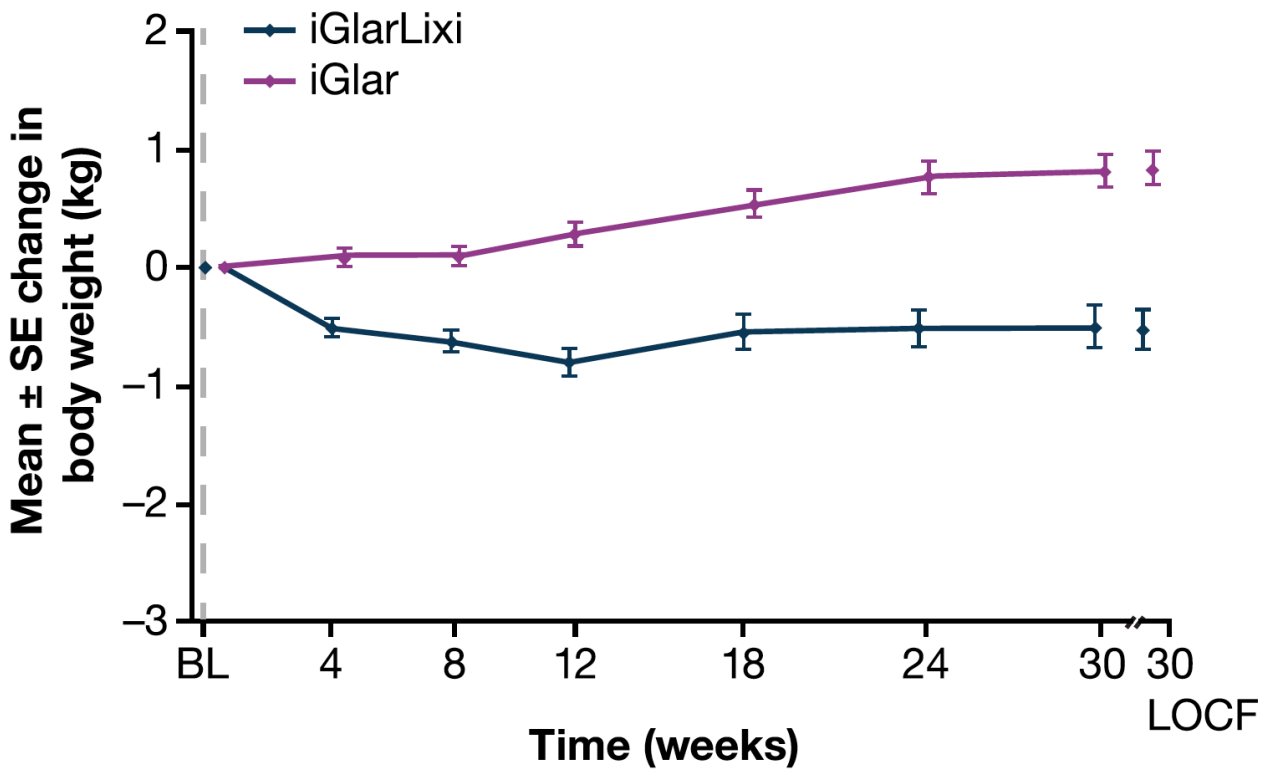
More A1c reduction with iGlarLixi

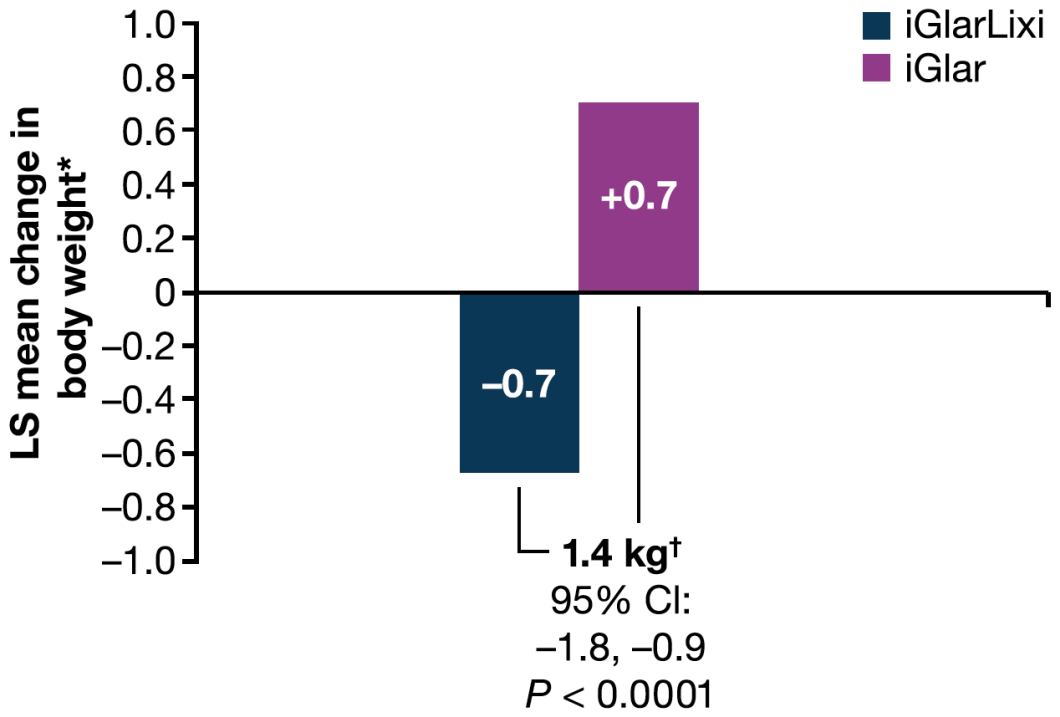




Aroda V, et al. Diabetes Care 2016;39:1972–80

Slight weight loss with iGlarLixi





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

So far …

- iGlarLixi superior to basal alone or lixisenatide
- iGlarLixi superior to optimizing basal insulin

For which patients should we consider fixed ratio combination?

- First injectable after OADs
- Advance from basal insulin

- Advance from GLP-1 RA
- Simplify insulin regimen

iGlarLixi fixed-ratio combination is administered once daily in an easy-to-use pen[1,2]

Click here to return to message

- Similar physicochemical features of insulin glargine and lixisenatide allow co-formulation in a defined fixed ratio for delivery as a single daily injection[1]
- iGlarLixi is available in two pre-filled pens, providing different dosing options[2]

SoloStar® pen

Familiar to patients, nurses and PCPs due to usage with Lantus® (insulin glargine 100 U/mL)[3]

iGlarLixi 10–40 U pen[1,2]

Insulin glargine 100 U/mL: 10–40 U/day
Lixisenatide 50 µg/mL: 5–20 µg/day
(2:1 dose ratio iGlar:Lixi)

iGlarLixi 30–60 U pen[1,2]

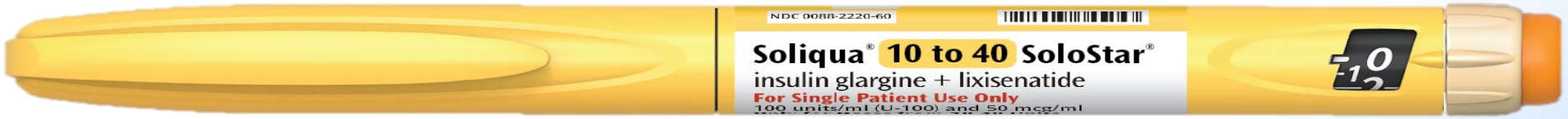
Insulin glargine 100 U/mL: 30–60 U/day
Lixisenatide 33 µg/mL: 10–20 µg/day
3:1 dose ratio iGlar:Lixi

PCP, primary care provider.

1. Rosenstock J, et al. Diabetes Care 2016;39:2026–35.
2. Suliqua® (insulin glargine 100 U/mL and lixisenatide 50 µg/mL) Summary of Product Characteristics, 2017.
3. Toscano D, et al. J Diabetes Sci Technol 2012;6:686–94.

When a patient is **Insulin Naive**….

Start with 10 units



Highlights from the EU SmPC are provided here; please refer to the SmPC for more detailed information.
Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002445/WC500140401.pdf (Last accessed: Nov 2018)

When a patient is **on Basal Insulin**…

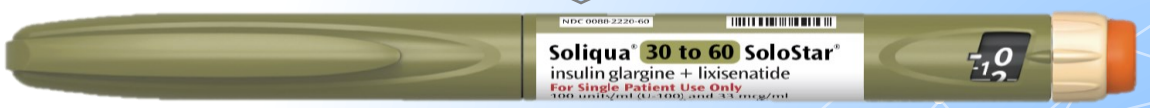
What is the previous Basal Insulin* Dose?

If < 30 units

Start with 20 units

If > 30 units

Start with 30 units



* For twice-daily basal insulin or Toujeo:Reduce by 20% the total daily dose previously used

Highlights from the EU SmPC are provided here; please refer to the SmPC for more detailed information.
Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002445/WC500140401.pdf (Last accessed: Nov 2018)

Dose titration with iGlarLixi

Dosing should be **titrated based on FPG** in accordance with individual patient needs

If the patient starts with the iGlarLixi (10–40) pen, the dose may be **titrated up to 40** dose steps with this pen

For doses >40 dose steps/day, titration must be continued with the iGlarLixi (30–60) pen

If the patient starts with the iGlarLixi (30–60) pen, the dose may be **titrated up to 60** dose steps with this pen

For total daily doses >60 dose steps/day, iGlarLixi must not be used

Highlights from the EU SmPC are provided here; please refer to the SmPC for more detailed information.
Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002445/WC500140401.pdf (Last accessed: Nov 2018)

Introduction

Diabetes Care Volume 44, July 2021

Weekly Insulin Becoming a Reality

Jay S. Skyler

Diabetes Care 2021;44:1459–1461 | https://doi.org/10.2337/dci21-0011

Weekly Insulin Becoming a Reality

Jacques Mirouze wrote, insulin is “a non-stop revolution”

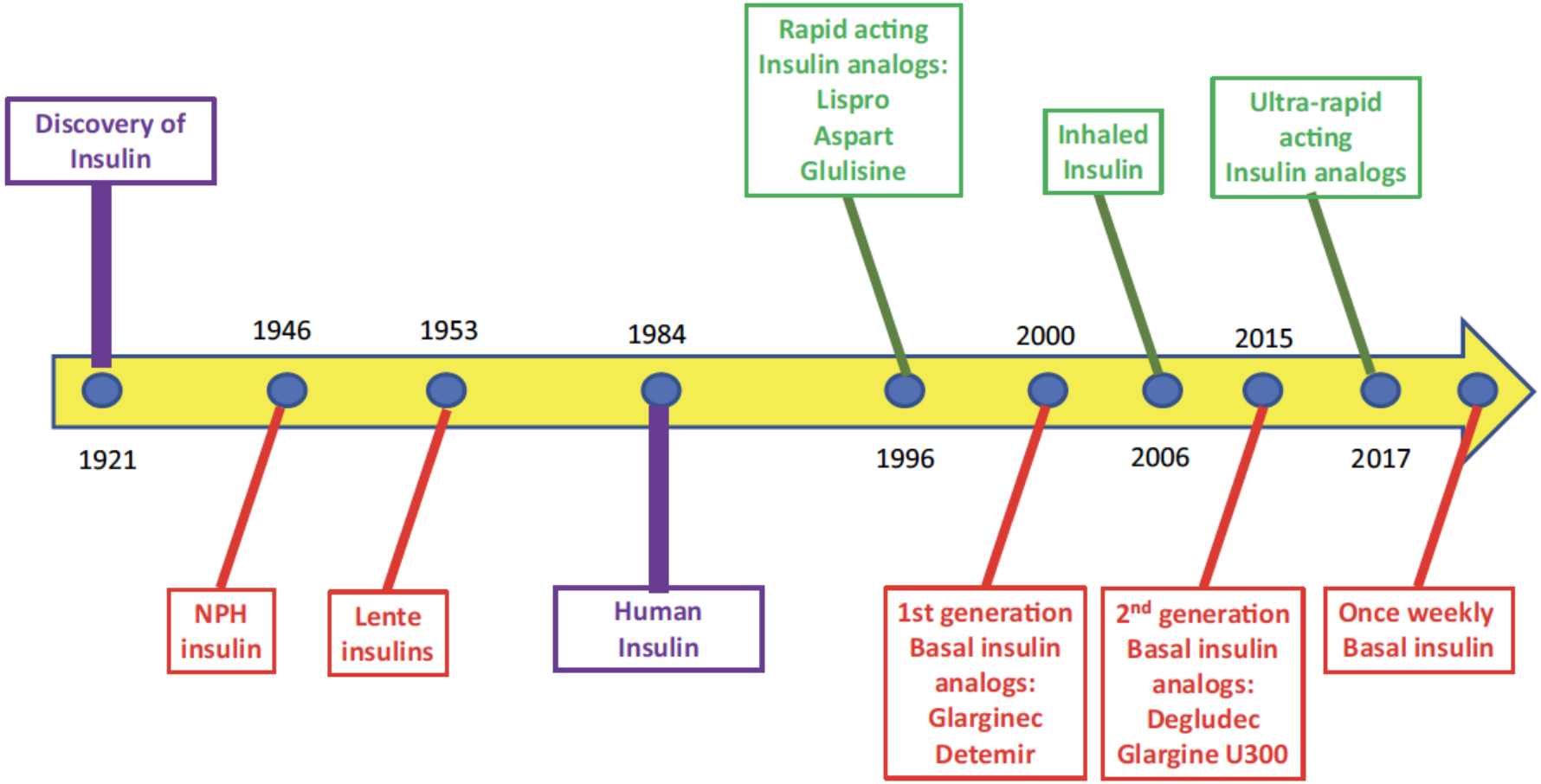


Figure 1—Timeline of major clinical developments in insulin’s evolution. Green highlights meal-related insulin developments; red highlights basal insulin developments; and purple highlights discovery of insulin and development of human insulins.

Introduction

- Weekly insulin has the potential to be transformational in our management of diabetes.

This is most likely to be the case in T2DM

- It would dramatically reduce the burden of daily insulin injections
- Likely increase adherence and persistence with therapy

- Just as weekly GLP-1 RA therapy has done.

Diabetes Metab Syndr Obes 2016;9:201–205

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Articles from the An insulin centennial: Past, present, and future Special Issue,
Edited by Alexander Kokkinos and Eleuterio Ferrannini

Basal weekly insulins: the way of the future!

Julio Rosenstock [a,*], Stefano Del Prato [b]

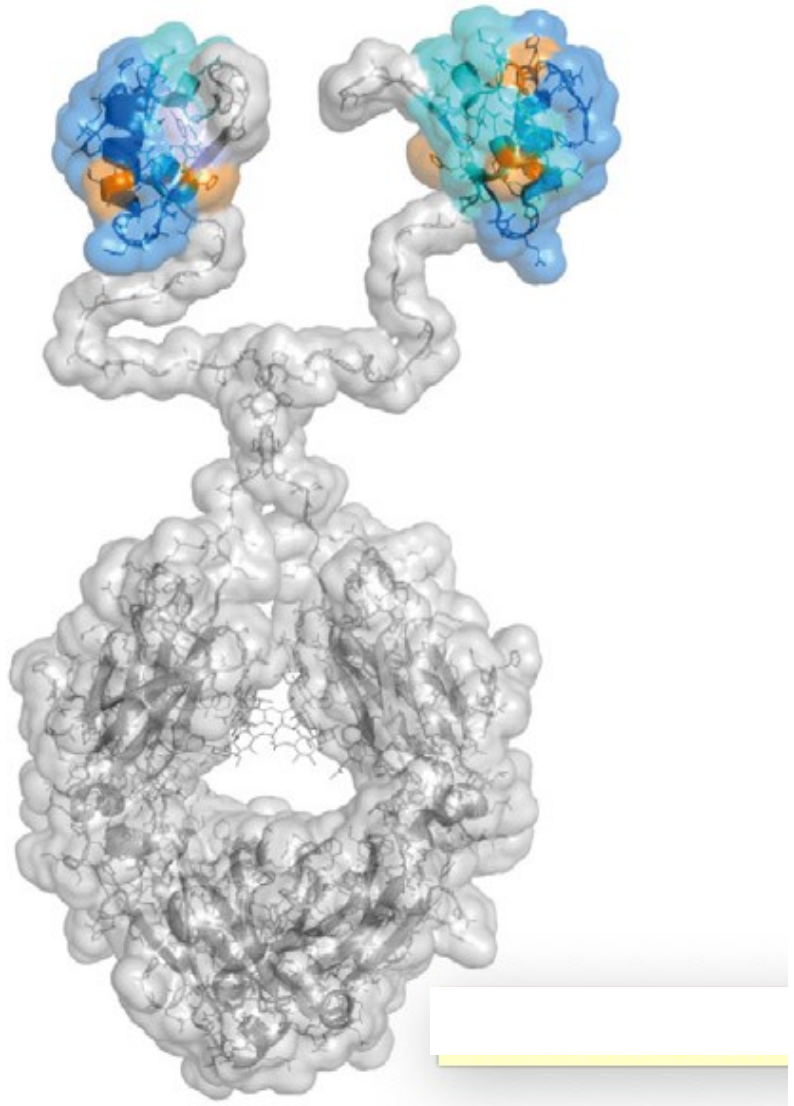
Two novel once-weekly insulins

1- Basal insulin Fc (BIF)

2- Insulin icodec

Basal weekly insulin BIF

- Linking insulin to the fragment crystallizable (Fc) region of IgG extends the insulin's half-life because the fusion protein benefits from the same recycling pathway that confers a relatively long half-life to endogenous IgG .



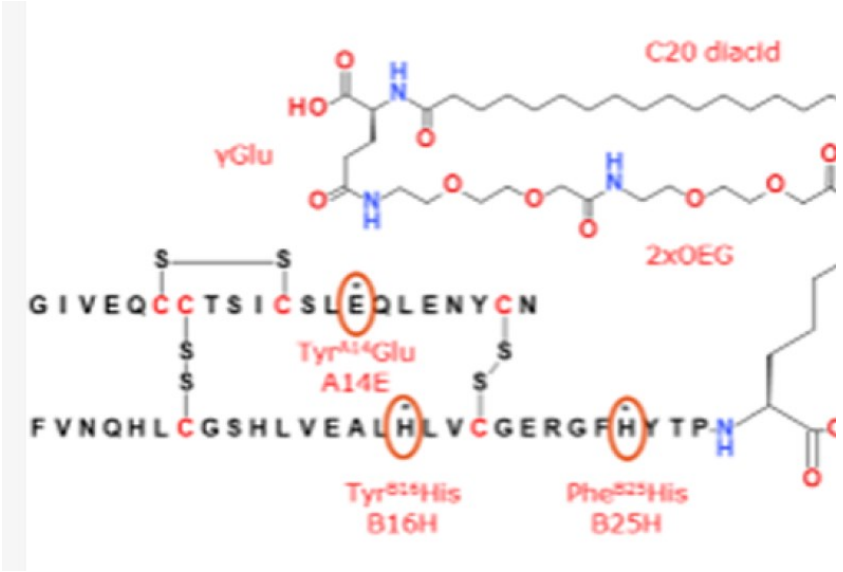
FcRn across the therapeutic spectrum. Int J Mol Sci. 2021; 22.[56] Rath

Insulin icodec

The attachment of a 20-carbon fatty diacid (icosanedioic acid) to the B chain of the insulin molecule allows **strong reversible binding to albumin.**

Additionally, three amino acid substitutions, at A14, B16, and B25, enhance stability **and minimize enzymatic degradation.**

These modifications also **reduce the insulin receptor binding affinity** of icodec and subsequent insulin receptor-mediated clearance, to confer a longer half-life



Points to be briefly reviewed

1-Will the risk of hypoglycemia be manageable?

2- Which patients are likely to be candidates for a potential once-weekly insulin option?

3-How will once-weekly basal insulin be used with other agents for diabetes?

4-In practice, what impact is once-weekly basal insulin likely to have on clinical inertia and patient adherence?

1-Will the risk of hypoglycemia be manageable?

- Evidence to date has been reassuring, indicating that the risk of level 2 or 3 hypoglycemic events with once-weekly insulin is relatively low and not greater than that associated with once-daily basal insulin

- There have been no episodes of hypoglycemia in patients treated with insulin icodec that have not responded to standard corrective measures and only one episode of severe (level 3) hypoglycemia, which was treated successfully with oral carbohydrate alone .

Rosenstock J, Bajaj HS, Janež A, Silver R, Begtrup K, Hansen MV, et al. Once-weekly insulin for type 2 diabetes without previous insulin treatment. N Engl J Med. 2020;383:2107–16.

2-Will the risk of hypoglycemia be manageable?

recovery time

- Concerns that patients may have a slow recovery from hypoglycemia with once-weekly insulin, which maintains constant insulin levels, did not bear out.
- Indeed, recovery with once-weekly insulin proved to be no different than that with once-daily basal insulin when given 3–4 h before; people still recovered rapidly from hypoglycemia, even when there was ‘plenty of insulin on board’.

2-Which patients are likely to be candidates for a potential once-weekly insulin option?

- **People with T2D** with inadequate glycemic control while receiving multiple glucose-lowering agents are the likely candidates for once weekly insulin

- It is likely that treatment adherence and quality of life may be considered as well when selecting the best candidates.

2-Which patients are likely to be candidates for a potential once-weekly insulin option?

- Requiring one rather than seven injections per week will reduce the workload of visiting nurses or family members.

- Education of both clinicians and patients will also be required to address any psychological impact of administering large, once-weekly insulin doses (daily dose times seven).

2-Which patients are likely to be candidates for a potential once-weekly insulin option?

- Although using **once-weekly insulin in T1D is more challenging** than in T2D, the potential benefits make it worth pursuing.

- Fewer injections for people receiving multiple-dose injection therapy are inherently desirable and may improve adherence and glucose control in patients **liable to miss doses, especially teenagers.**

- An interesting possibility is that having a **relatively constant level of insulin might reduce the frequency of diabetic ketoacidosis**, which is still an issue in T1D.

3- How will once-weekly basal insulin be used with other agents for diabetes?

- However, a fixed ratio of once-weekly insulin icodec and once-weekly semaglutide has huge potential and is currently in phase 1 clinical development.

- Currently available **fixedratio combinations** of a basal insulin and a GLP-1 RA – IDegLira and iGlarLixi – have strong efficacies, reassuring safety profiles, and reduced injection burdens.

Switching to Once-Weekly Insulin Icodec Versus Once-Daily Insulin Glargine U100 in Type 2 Diabetes Inadequately Controlled on Daily Basal Insulin: A Phase 2 Randomized Controlled Trial

Harpreet S. Bajaj,[1,2] Richard M. Bergenstal,[3] Andreas Christoffersen,[4] Melanie J. Davies,[5,6] Amoolya Gowda,[4] Joakim Isendahl,[4] Ildiko Lingvay,[7] Peter A. Senior,[8] Robert J. Silver,[9] Roberto Trevisan,[10] and Julio Rosenstock[11]

Diabetes Care 2021;44:1586–1594 | https://doi.org/10.2337/dc20-2877

Objective

- This trial investigated two approaches for switching to icodec versus once-daily insulin glargine 100 units/mL in people with T2DM receiving daily basal insulin and one or more oral glucose-lowering medications.

RESEARCH DESIGN AND METHODS

- Multicenter, open-label, treat-to-target phase 2 trial randomized (1:1:1) eligible basal insulin–treated (total daily dose 10–50 units) people with T2DM (HbA1c 7.0–10.0%) to:

- Icodec with an initial 100% loading dose (in which only the first dose was doubled [icodec LD])

- Icodec with no loading dose (icodec NLD)

- IGlar U100 for 16 weeks.

RESEARCH DESIGN AND METHODS

- Primary end point was percent time in range (TIR; 70–180 mg/dL) during weeks 15 and 16, measured using CGM.

Key secondary end points included:

- HbA1c
- Adverse events (AEs)
- Hypoglycemia.

Estimated mean TIR during weeks 15 and 16 was
72.9% (icodec LD; n = 54)
66.0% (icodec NLD; n = 50)
65.0% (IGlar U100; n = 50),

with a statistically significant difference favoring icodec LD versus IGlar U100 (7.9%-points [95% CI 1.8–13.9]).

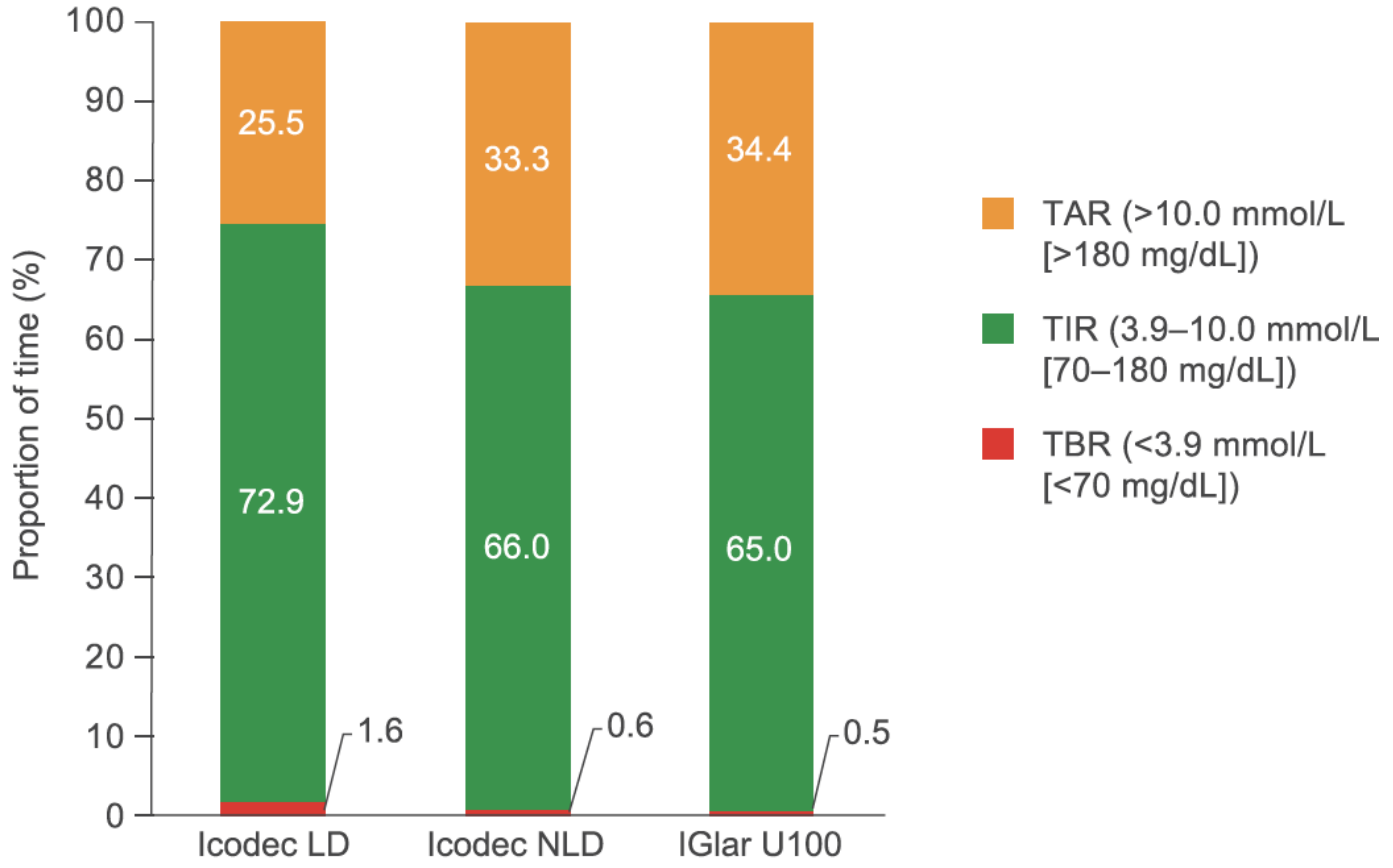


Figure 1—TIR during the last 2 weeks of the treatment period (full analysis set). TIR was the primary end point. TAR, time above range; TBR, time below range.

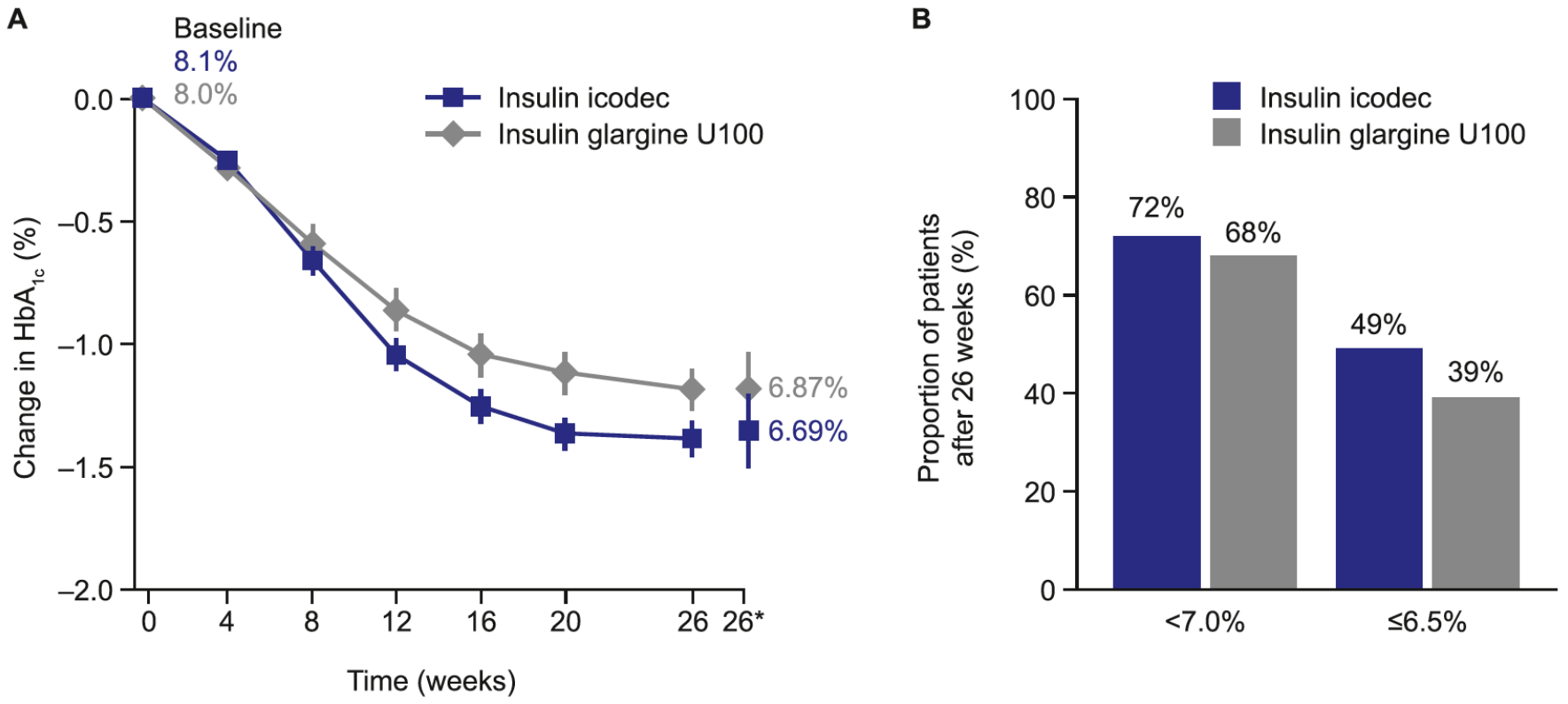
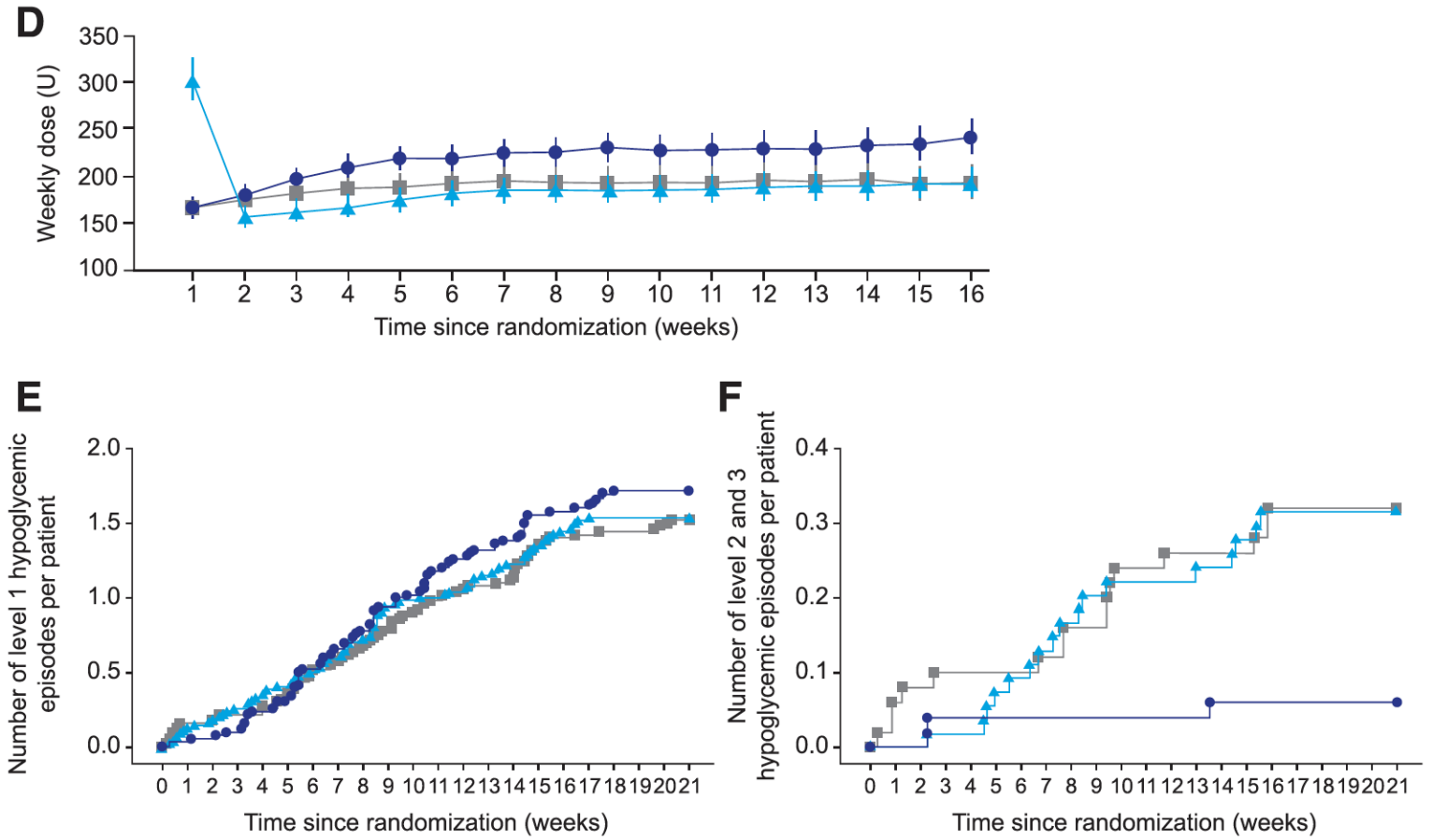


Fig. 3. Glucose-lowering efficacy of once-weekly insulin icodec vs. once-daily insulin glargine U100 in patients with T2D. A, mean change from baseline in HbA_{1c} over time. B, estimated proportions of patients who had reached $HbA_{1c} < 7\%$ or ≤ 6.5% after 26 weeks. In panel A, error bars indicate the standard error and the data shown at week 26* are the estimated mean values and corresponding 95% confidence intervals at week 26, derived on the basis of a mixed model for repeated measures with an unstructured covariance matrix. HbA_{1c}: glycated hemoglobin. T2D: type 2 diabetes.

Comparing Hypoglycemia



incidences and rates of AEs and hypoglycemic episodes were comparable.

Conclusions

01

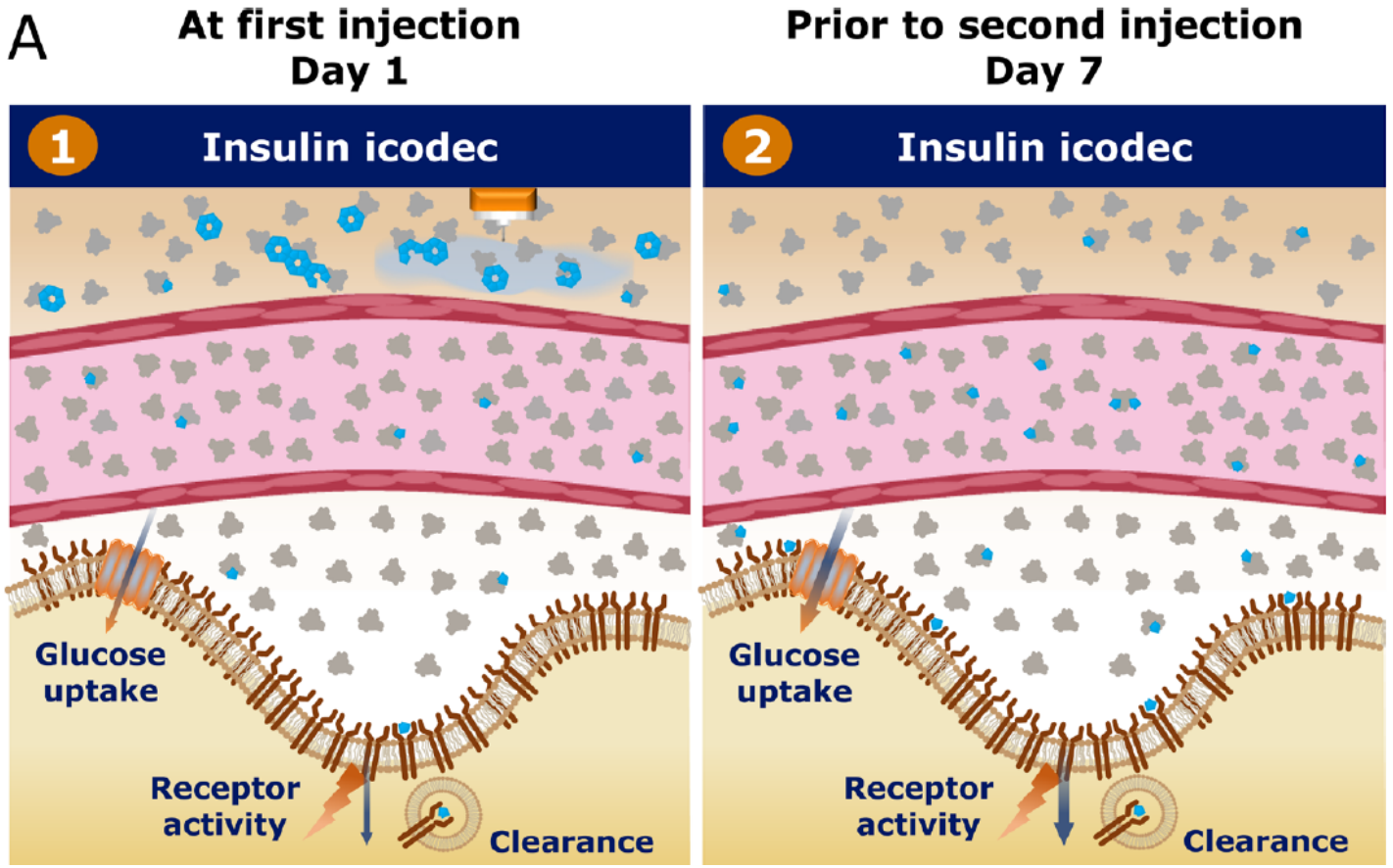
Switching from daily basal insulin to once-weekly icodec was well tolerated and provided effective glycemic control.

02

Loading dose use when switching to once weekly icodec significantly increased percent TIR during weeks 15 and 16 versus once-daily IGlar U100, without increasing hypoglycemia risk.

Distribution of insulin icodec (light blue) bound to albumin (grey) in the different compartments over time from initiation of once-weekly dosing.

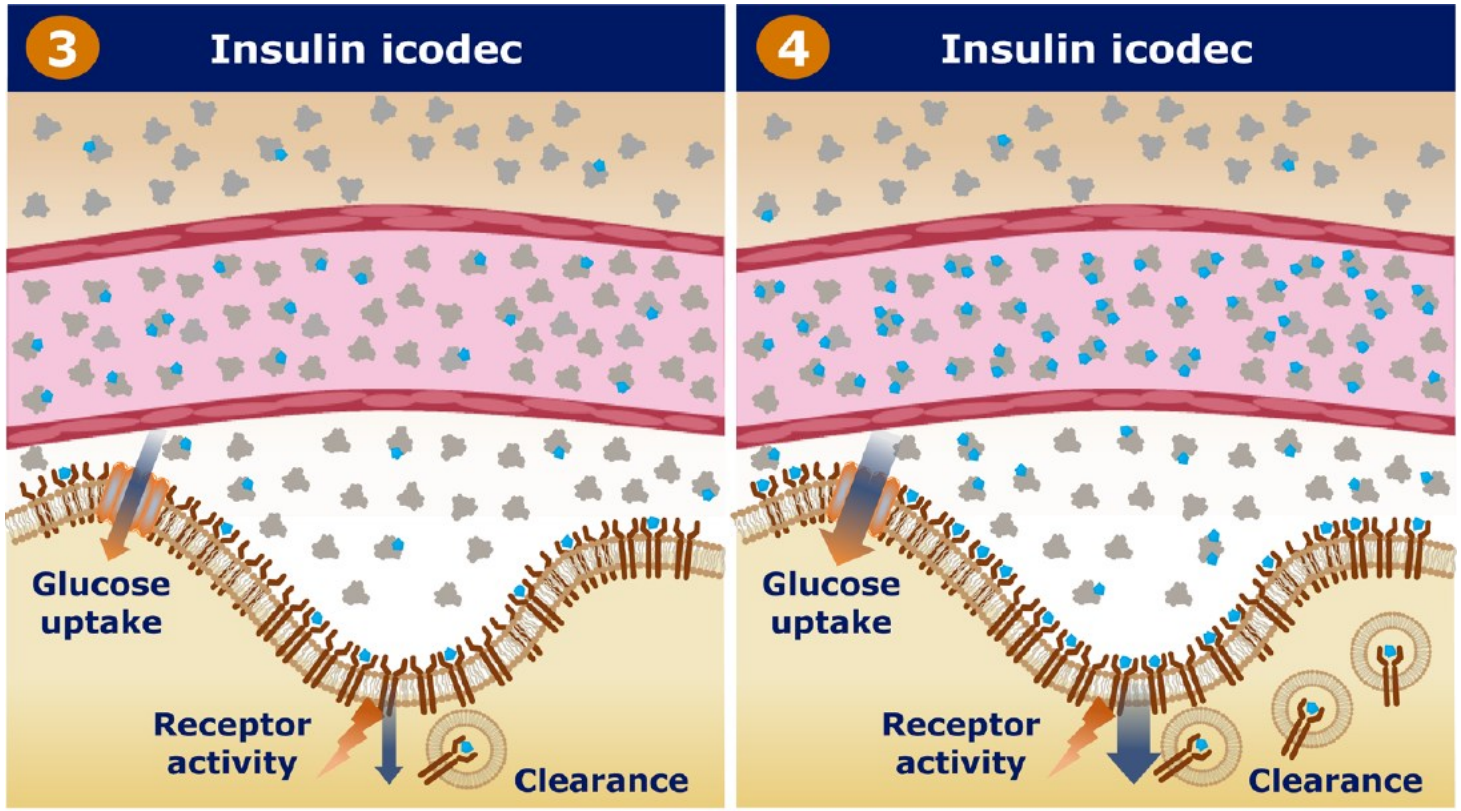
distribution of insulin icodec after the first injection, with the **majority of insulin icodec in the subcutis** and a small proportion absorbed into the blood.



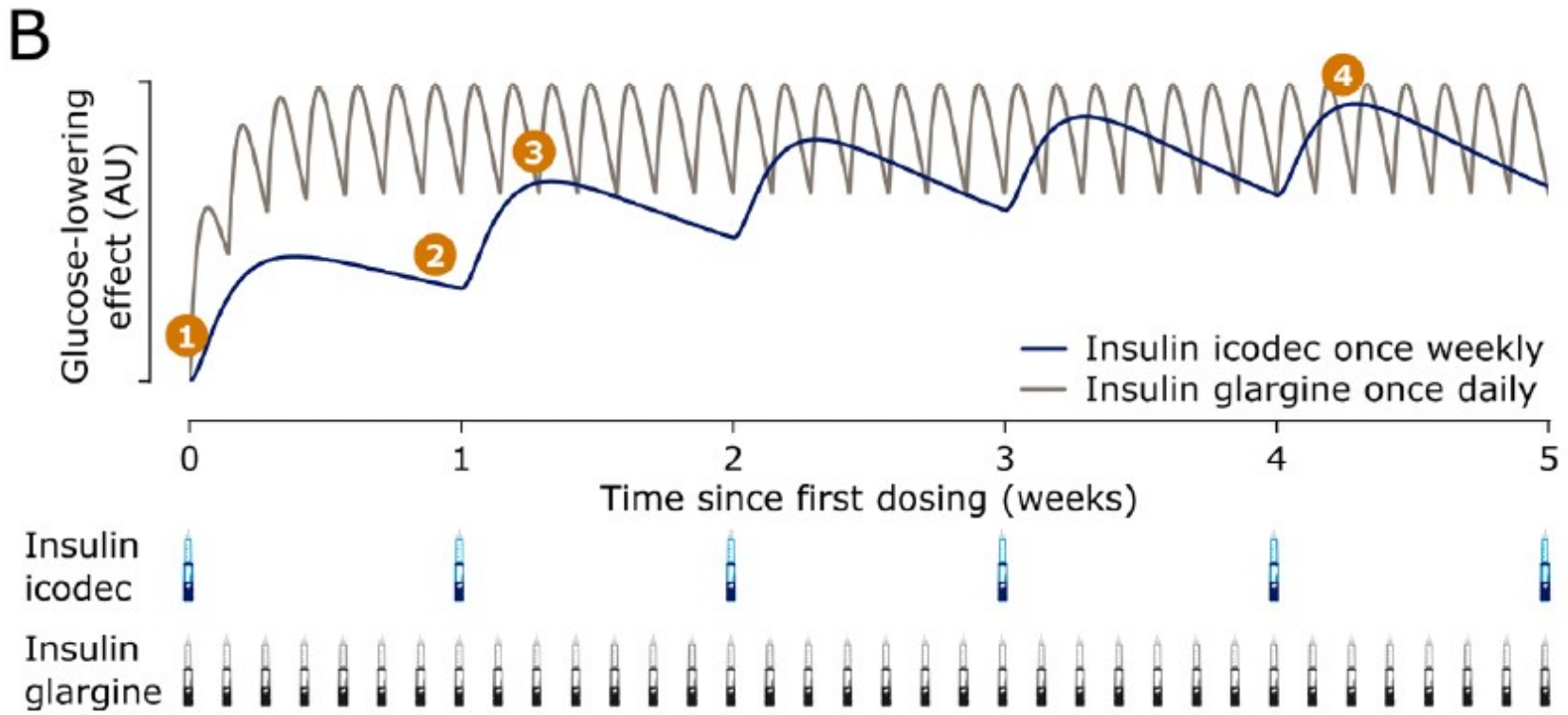
day 7, prior to the second injection, showing that there is still insulin icodec distributed prior to the next injection.

Schematic depiction of build-up to steady state and mechanism of action of insulin icodec.

Charts 3–4: showing the gradual build-up of insulin icodec exposure towards steady state.



Conceptual model showing glucose-lowering effect over time from initiation of once-weekly dosing of insulin icodec and once-daily Dosing of insulin glargine U100 (at comparable dose levels).



Blue curve: insulin icodec; grey curve: insulin glargine U100. Orange labels refer to charts 1–4 in panel A. AU, arbitrary units.

ONWARDS 2 trial

- “It could offer people with type 2 diabetes reduced treatment complexity and burden by reducing the number of basal insulin injections from 365 to 52 per year, without compromising management of blood sugar.”

Insulin icodec has achieved significant results in all of its clinical trials.

- Recently ONWARDS 5 reached its primary endpoint with **Icodec demonstrating non-inferiority in reducing HbA1c in patients T2D at week 52 in comparison to once-daily basal insulin analogs.**

- This successful outcome for insulin icodec increases the likelihood of achieving FDA approval next year

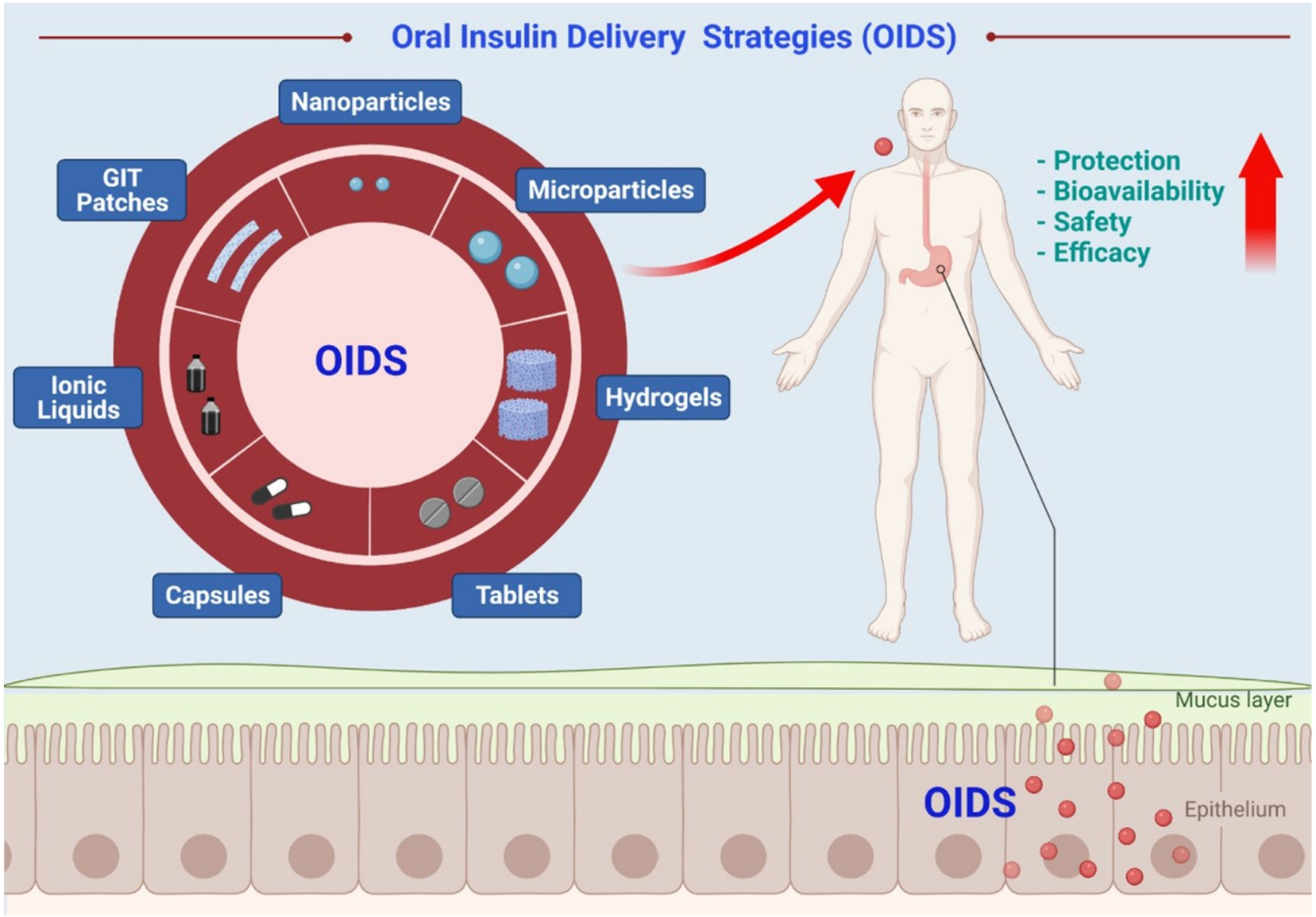
ONWARDS 5 trials

Patients had an overall baseline HbA1c of 8.9% and were observed to have a superior HbA1c reduction of 1.68%, compared with a reduction of 1.31% in 1,085 insulin-naive patients who received once-daily basal insulin (insulin degludec or glargine U100/U300).

Icosema

- It is likely to improve adherence, quality of life and glycemic control for many of their patients.
- KOLs also keenly anticipate the arrival of **icosema**, the icodec and semaglutide combination therapy that is currently in Phase III.

Oral insulins


Oral Insulin Delivery Strategies (OIDS)
Nanoparticles
GIT Patches
Microparticles
OIDS
Ionic Liquids
Hydrogels
Capsules
Tablets
- Protection
- Bioavailability
- Safety
- Efficacy
Mucus layer
OIDS
Epithelium

Received: 25 April 2022 | Revised: 6 November 2022 | Accepted: 7 November 2022

DOI: 10.1111/dom.14922

ORIGINAL ARTICLE

WILEY

Safety and efficacy of an oral insulin (Capsulin) in patients with early-stage type 2 diabetes: A dose-ranging phase 2b study

Roger R. C. New PhD[1,2] | Sukumar Ramanujam B. Tech(chem)[3] | Varsha Chaudhari M. Pharm[3] | Michal Bogus M. Sc(Biotech)[1] | Glen N. Travers B. Com[1] | Gajanan Namjoshi MD[3]

- Diabetes Obes Metab. 2023;25:953–960.

Methods

- A total of 100 individuals (48 males, 52 females) with type 2 diabetes on metformin completed the study according to the protocol.

- The mean (SD) age was 48.5 (6.7) years, BMI 25.7 (2.8) kg/m2 and HbA1c 8.10% (0.65%).

Subjects randomized upon admission were assigned to one of three groups receiving

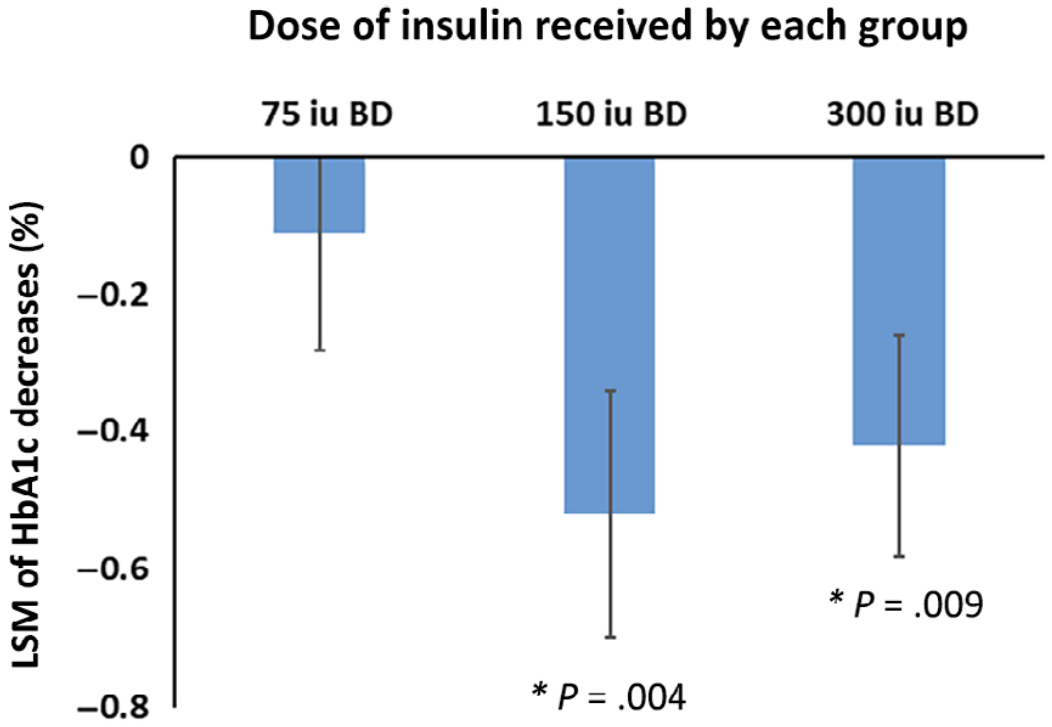
- formulated regular insulin at dose levels of
- *Group A: Capsulin 75 iu (2.5 mg), BD for 12 weeks.*
- *Group B: Capsulin 150 iu (5 mg), BD for 12 weeks.*
- *Group C: Capsulin 300 iu (10 mg), BD for 12 weeks.*

- The primary and secondary endpoints were change from baseline in HbA1c and fasting plasma glucose (FPG), respectively.

Results

- The study met its primary clinical endpoint of a decrease in HbA1c of 0.5% or higher (least square mean decrease 0.52%; P = .004, median decrease 0.6%) in the dose group receiving 150 iu BD

- In a subset of this population, with starting HbA1c values of 9% to 9.5%, an average decrease of 1.575% was observed



* Statistically significant decrease from baseline

Bars are standard errors of the mean

Conclusions

- Capsulin oral insulin administered twice per day at a dose of 150 iu per capsule is safe
- No confirmed treatment-linked hypoglycemic events, and results in significant decreases from baseline in HbA1c, FPG and triglycerides.

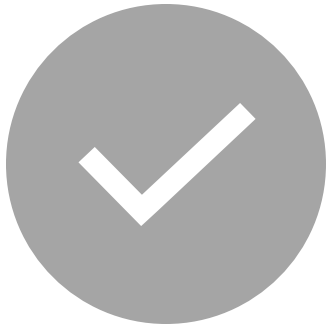
Concluding remarks

- insulin icodec offers similar or better glycemic efficacy compared with daily basal insulin in type 2 diabetes, with good tolerability and encouraging safety results related to hypoglycemia.

- Although important clinical questions remain, reducing the number of basal insulin injections from 365 to 52 administrations per year may be a significant innovation in insulin management since its discovery more than a 100 Years ago

Concluding remarks

Although many unknowns remain, the future looks bright for once-weekly insulins, and data addressing some of the clinical concerns are reassuring.



Phase 3 clinical trials results also validated our predictions!

Insulin innovation: Roadmap to the future

Fig. 4 The flame of hope. Photograph by Ken Lund from Reno, Nevada, USA, CC BY-SA 2.0, via Wikimedia Commons. The Flame of Hope in London, Ontario, Canada, serves as a reminder that insulin manages but does not cure diabetes, and the flame will only be extinguished when a cure is developed