New Options for Insulin Therapy

Daniel Einhorn, MD, FACP, FACE

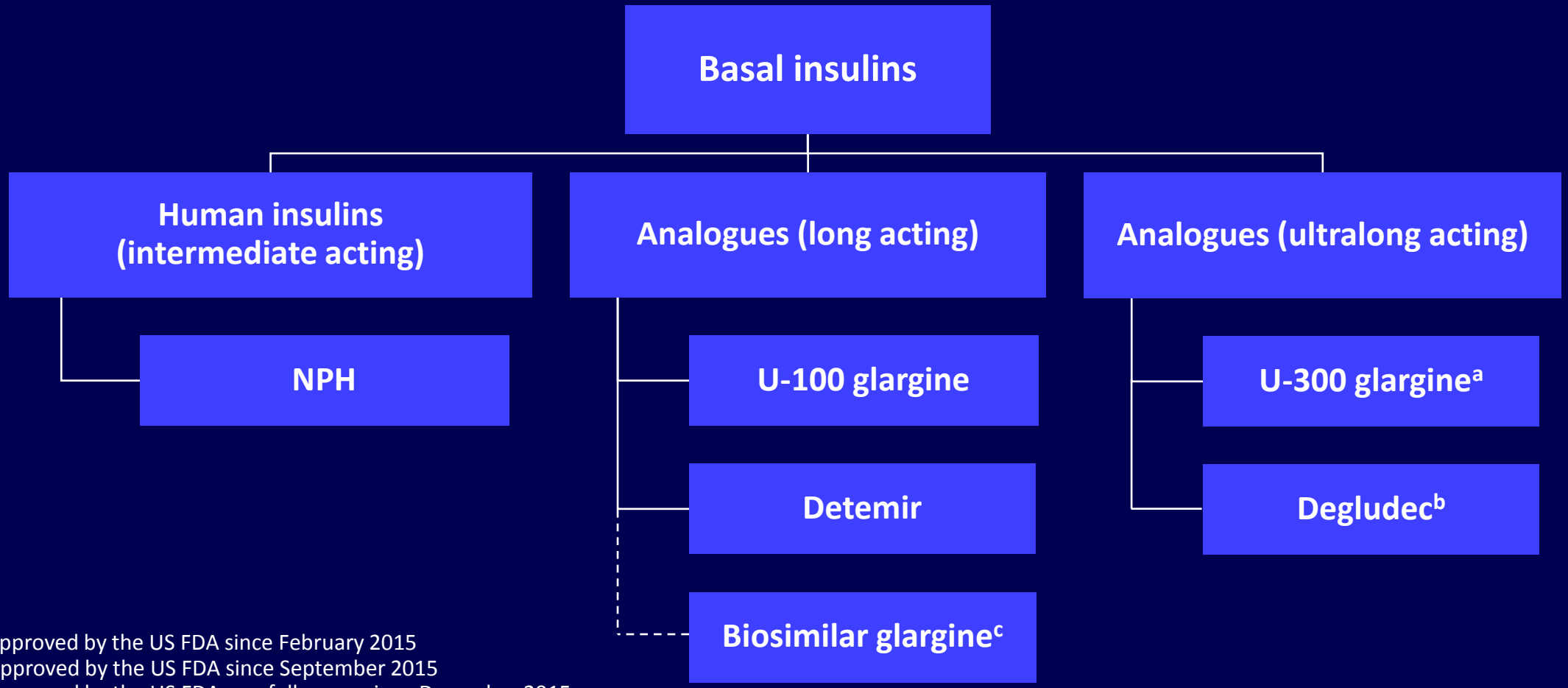
Medical Director, Scripps Whittier Diabetes Institute

Clinical Professor of Medicine, UCSD

La Jolla, CA

New Options for Basal Insulins

Current and Emerging Basal Insulins: United States



[a] Approved by the US FDA since February 2015
[B] Approved by the US FDA since September 2015
[C] Approved by the US FDA as a follow-on since December 2015
US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

Biosimilar Glargine[a] Has Equivalent Efficacy and Hypoglycemia as Glargine[1-3]

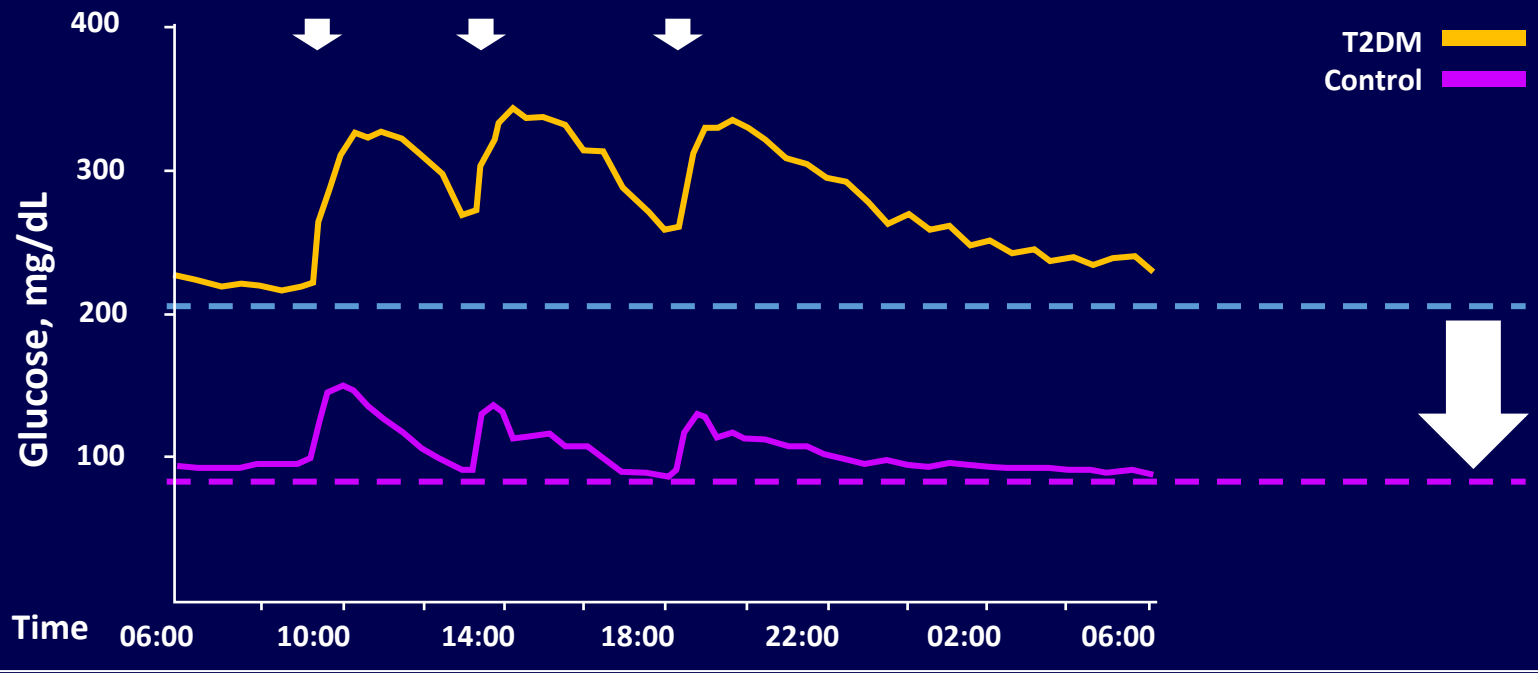
Parameter		Biosimilar U-100 GLAR (n = 376)	U-100 GLAR (n = 380)
A1C	A1C at baseline, %	8.34	8.31
	ΔA1C, %	−1.29 *Noninferior to GLAR*	−1.34
	A1C < 7%, %	49	53
Hypoglycemia, EPY	Overall	21.3[b]	22.3[b]
	Severe	0.04	0.01
Median insulin-antibody binding, %		1.07	0.65
Body weight, kg	Baseline	90	90
	Δ	1.8	2.0

- **No statistically significant differences between biosimilar GLAR and GLAR were observed in any parameter[1,3]**
- **Biosimilarity is not the same as generic equivalency[3,4]**

[a] Approved by the US FDA as a follow-on since December 2015
[b] 2 patients in each group reported severe hypoglycemia

1. Rosenstock et al. *Diabetes Obes Metab*. 2015;17:734-741; 2. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/205692 Orig1s000TAltr.pdf; 3. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/ human/002835/WC500175383.pdf; 4. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf.

Rationale for and Limitations of Basal Insulin Therapy in T2DM



Basal insulin therapy should reduce fasting hyperglycemia[1,2]

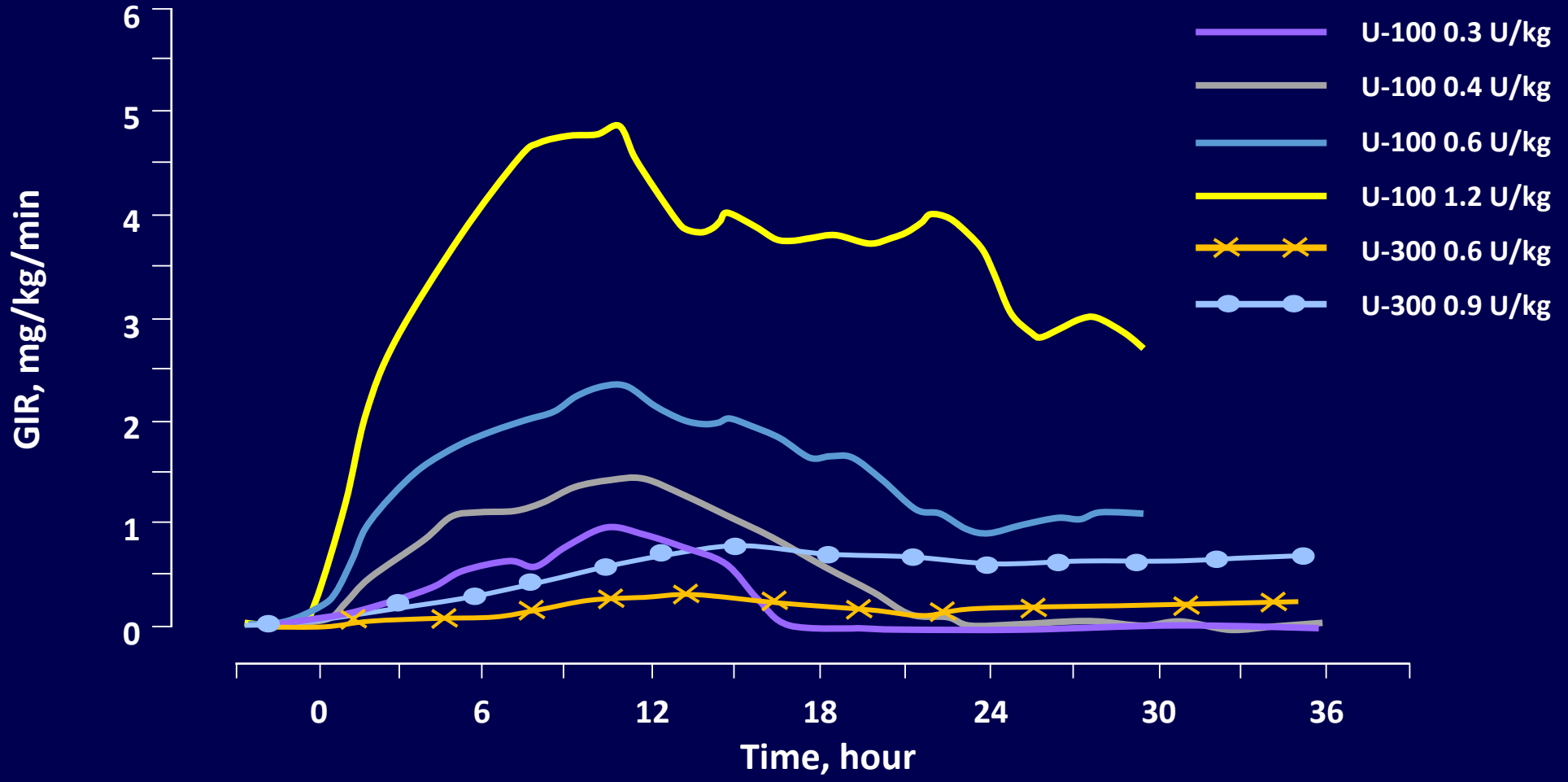
Detemir and glargine more nearly resemble physiological basal insulin than NPH, but they[3]:

- **May not have 24-h duration of action**
- **Have substantial within-patient variability, increasing rates of nocturnal hypoglycemia**

Arrows above graph denote meal times.

1. Polonsky KS, et al. *N Engl J Med.* 1988;318:1231-1239.
2. Zinman B. *N Engl J Med*. 1989;321:363-370.
3. Garber AJ. *Diabetes Obes Metab*. 2014;16:483-491.

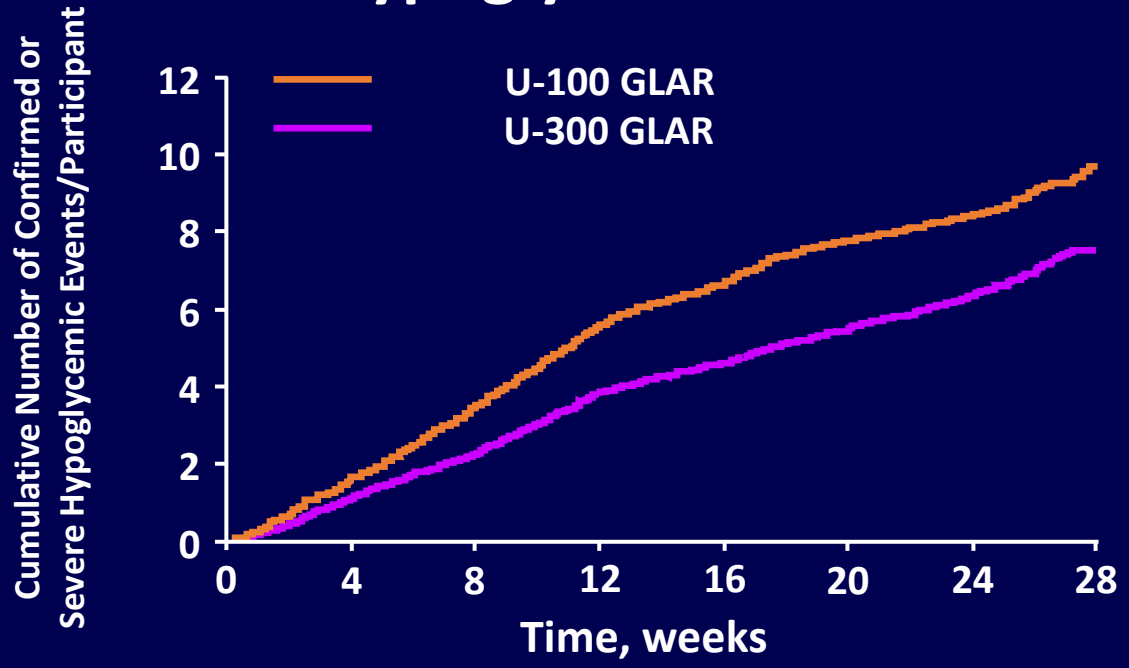
Pharmacodynamics of U-100 vs U-300 Insulin Glargine in Healthy Individuals



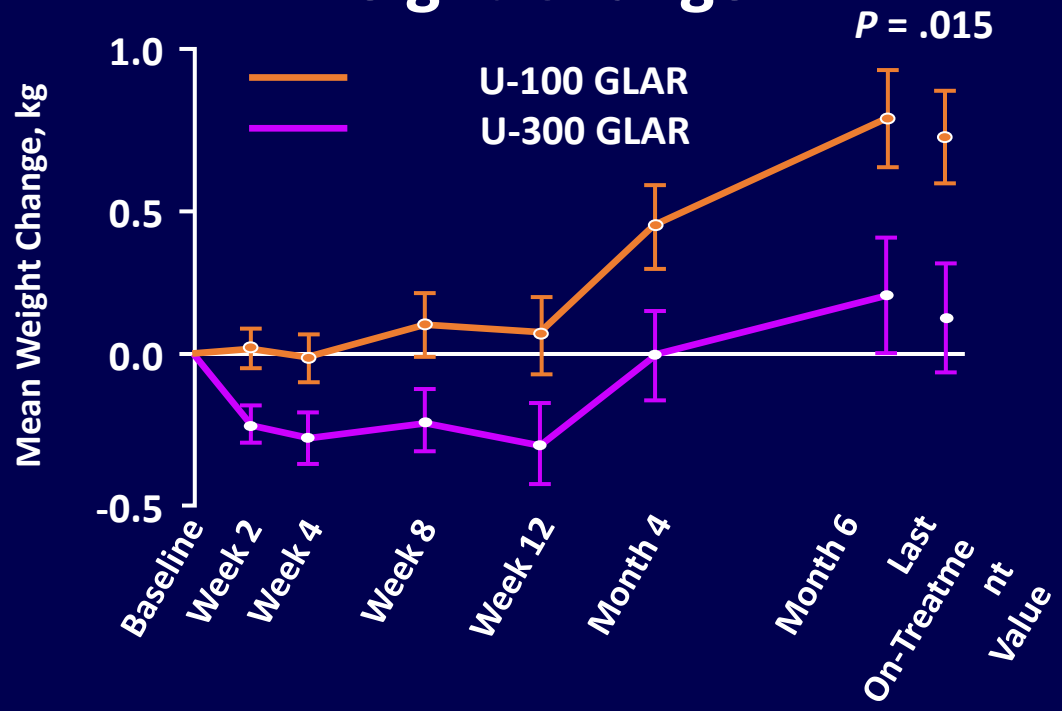
http://www.google.com/patents/US20120122774.

U-300 Insulin Glargine vs U-100 Insulin Glargine in Patients With T2DM

Hypoglycemia



Weight Change



Equivalent A1C reduction with U-300 glargine and U-100 glargine

28-week, open-label, treat-to-target RCT; N = 811; BL weight, 98.0 kg to 98.7 kg; mean BMI, 34.8 kg/m^2; hypoglycemia defined in accordance with ADA criteria (assistance needed or confirmed BG ≤ 70 mg/dL).

Yki-Jarvinen et al. *Diabetes Care*. 2014;37:3235-3243.

Safety and Efficacy of U-300 Glargine vs Other Basal Insulins—Network Meta-analysis

Comparator	U-300 GLAR	U-100 GLAR	DET	NPH	DEG	Premixed Insulin
Δ A1C	Ref	Same	Same	Same	Same	Same
Δ Weight	Ref	Same	Same	Same	Same	Same
Nocturnal hypoglycemia	Ref	More[a]	More	More[a]	More	More[a]
Documented symptomatic hypoglycemia	Ref	More	More	More	More	More

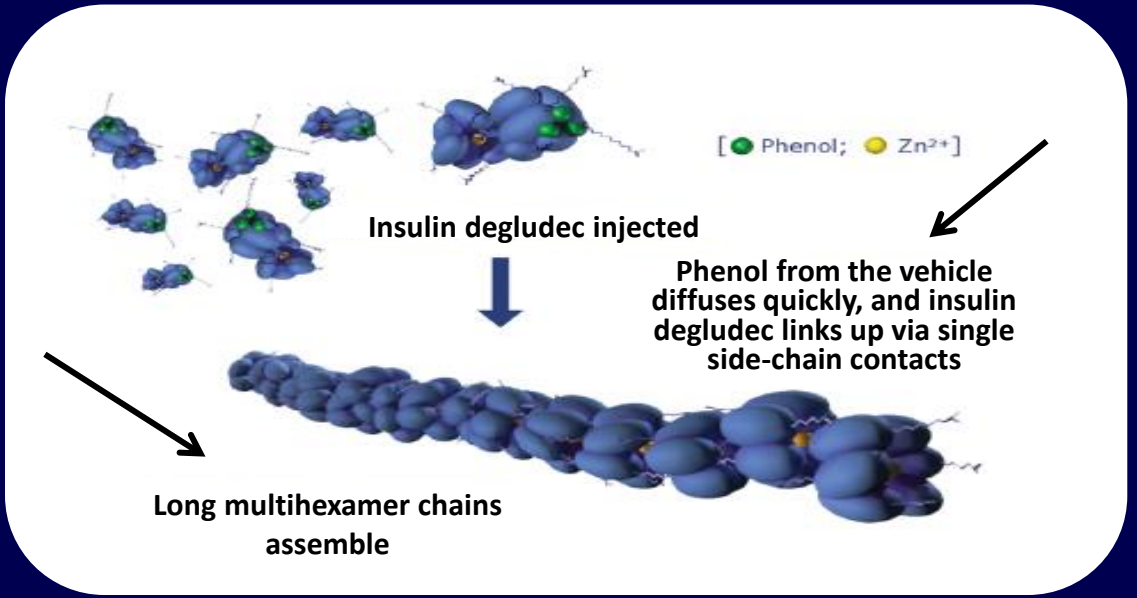
- **U-300 glargine is associated with a 32%-79% lower risk of nocturnal hypoglycemia than other basal insulins**

Systematic literature review of 44 trials.
Same, equivalent.
More, numerical higher.
[a] Statistically significant difference, *P* < .05.
Wang et al. *Diabetes*. 2015;64(suppl 1):A26 [abstract 99-OR].

Newly Approved Basal Insulin Degludec: Novel Mechanism of Action

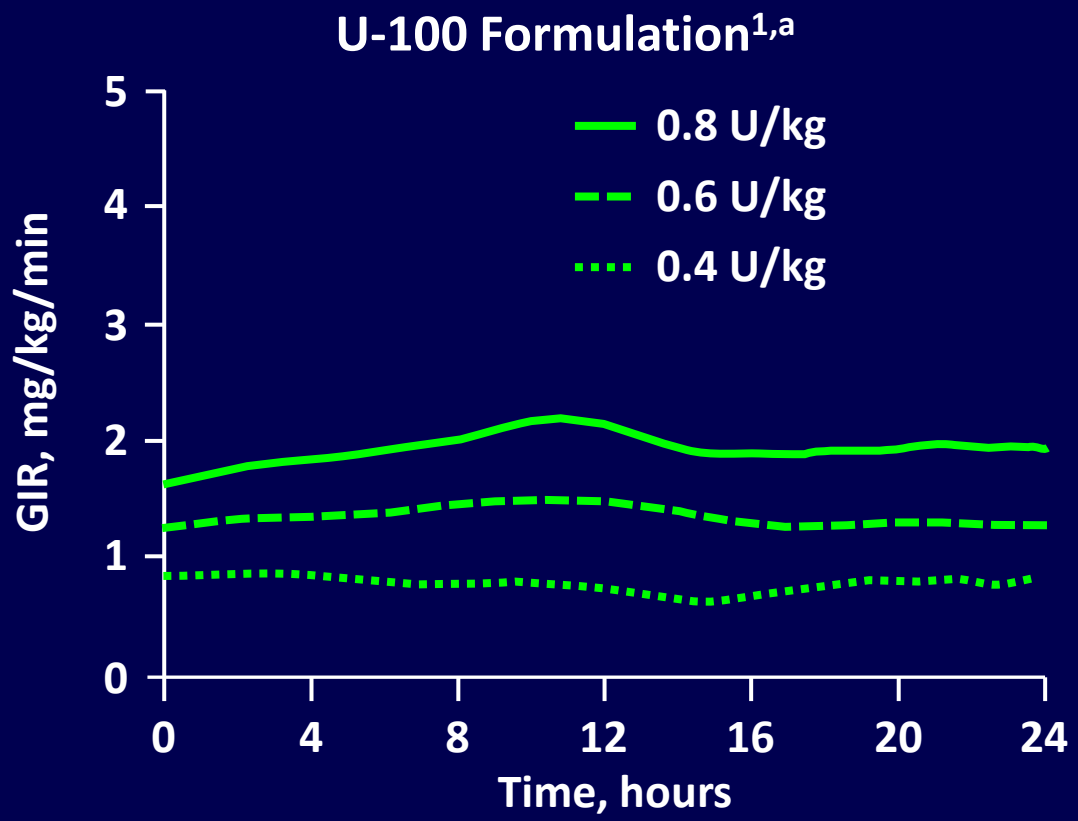
Insulin Degludec[1,2]

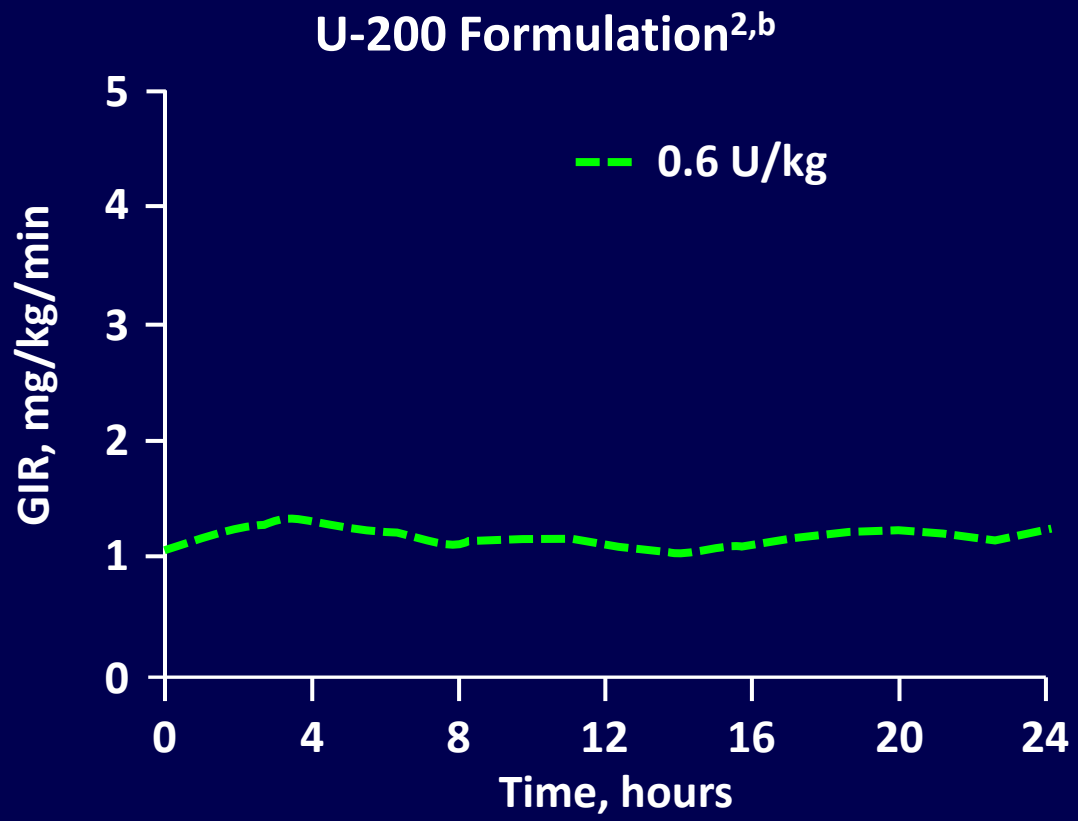
- Dihexamers (69 kDa) form soluble multihexamers after injection
- Multihexamers (> 5000 kDa) disassemble slowly
- Monomers are released rapidly after hexamers disassemble



1. Jonassen et al. *Pharm Res*. 2012;29:2104-2114; 2. Haahr, Heise. *Clin Pharmacokinet*. 2014;53:787-800.

Pharmacodynamics of Insulin Degludec U-100 and U-200 in Patients With T2DM





[a] Glucose clamp study in patients with T2DM (n = 49).
[b] Glucose clamp study in patients with T2DM (n = 16).

1. Heise T, et al. *Diabetes Obes Metab*. 2012;14:944-950.
2. Heise T, et al. *Diabetes*. 2012;61(suppl 1):A91 [abstract 349-OR].

Degludec vs U-100 Glargine: Outcomes at 78-104 Weeks

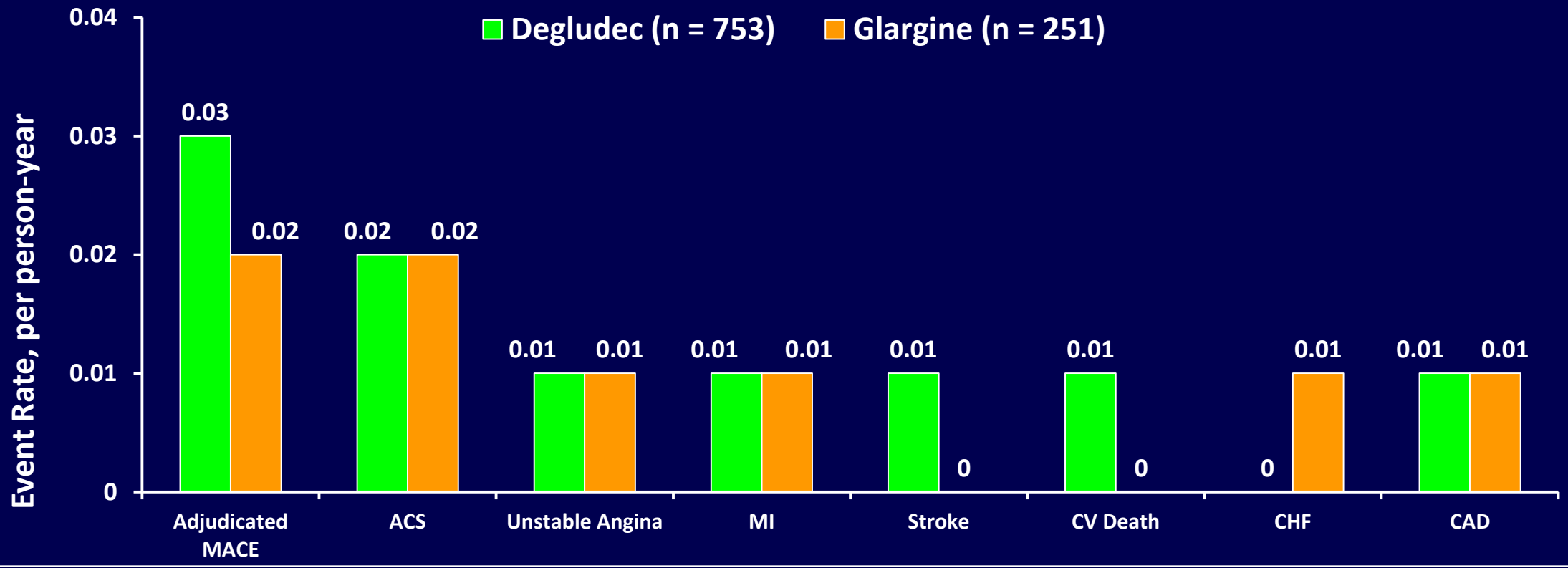
	BEGIN Once Long[1,a,b] 104 weeks, N = 1030 (n = 725 in extension)	BEGIN Basal-Bolus Type 2[2,a,c] 78 weeks, N = 1006 (n = 757 in extension)
Comparator	U-100 GLAR	U-100 GLAR
Δ A1C	Same	Same
Δ Weight	Favors GLAR 2.7 vs 2.4 kg	DEG better[d] 4.0 vs 4.4 kg
Nocturnal hypoglycemia	DEG better[e]	DEG better[e]
Documented symptomatic hypoglycemia	Favors DEG	DEG better[e]

Degludec has equivalent efficacy, with 31%-43% less nocturnal hypoglycemia than U-100 glargine

[a] Data shown for extension trial set from beginning to end of trial.
[b] Insulin naive with OADS (MET ± PIO ± DPP-4i).
[c] Insulin experienced, on basal-bolus insulin ± MET.
[d] Data shown for safety analysis set.
[e] Statistically significant superiority.

1. Rodbard HW, et al. *Diabet Med*. 2013;30:1298-1304.
2. Hollander P, et al. *Diabetes Obes Metab*. 2015;17:202-206.

Degludec vs Glargine Cardiovascular Adverse Events—BEGIN Basal-Bolus Type 2, 78 Weeks



Cardiovascular adverse event rates were low and similar for degludec and glargine[2]

ACS, acute coronary syndrome; CAD, coronary artery disease. Patients with stroke, NYHA III or IV heart failure, MI, unstable angina, CABG, or angioplasty within 6 months of first study visit were excluded from trial enrollment.[1] At baseline, patients were aged 58-59 years, with ≈ 13.5 years' diabetes duration[1,2]

1. Garber AJ, et al. *Lancet*. 2012;379:1498-1507.
2. Hollander P, et al. *Diabetes Obes Metab*. 2015;17:202-206.

Investigational Weekly Insulins

Compound ID	Mechanism of Protraction	Tested in	Duration of Action
PE0139[1]	Inert repeating polymeric elastin-like peptide on C-terminus of recombinant human monomeric insulin	Patients with T2DM	$T_{½\ max}$ = 51-73 h (2-3 days)
HM12470[2]	Conjugated soluble insulin and a non-glycosylated Fc carrier via a nonpeptidyl linker	Animal models	$T_{½\ max}$ = 132 h (5.5 days)
AB101[3]	Microsphere pegylated human recombinant insulin	Animal models	C_{max} > 30 ng/mL at 7-9 days postdose

Once-weekly injectable agents may be preferred by patients to once-daily agents[4,5]

1. Marquez F, et al. *Diabetes*. 2015;64(suppl 1):A26 [abstract 100-OR].
2. Huh Y, et al. *Diabetes*. 2015;64(suppl 1A):LB22 [abstract 86-LB].
3. Roberts BK, et al. *Diabetes.* 2015;64(suppl 1):A25-A26 [abstract 97-OR].
4. Hauber AB, et al. *Diabetes Ther*. 2015;6:75-84.
5. Boegelund M, et al. *Diabetes*. 2015;64(suppl 1):A349 [abstract 1341-P].

Summary

- Subcutaneous insulin injection does not exactly mimic endogenous insulin secretion
- Ultralong-acting basal insulins have a flatter time-action profile and may be even less likely to cause nocturnal hypoglycemia than first-generation insulin analogues

U-300 Glargine	Degludec	Peglispro*

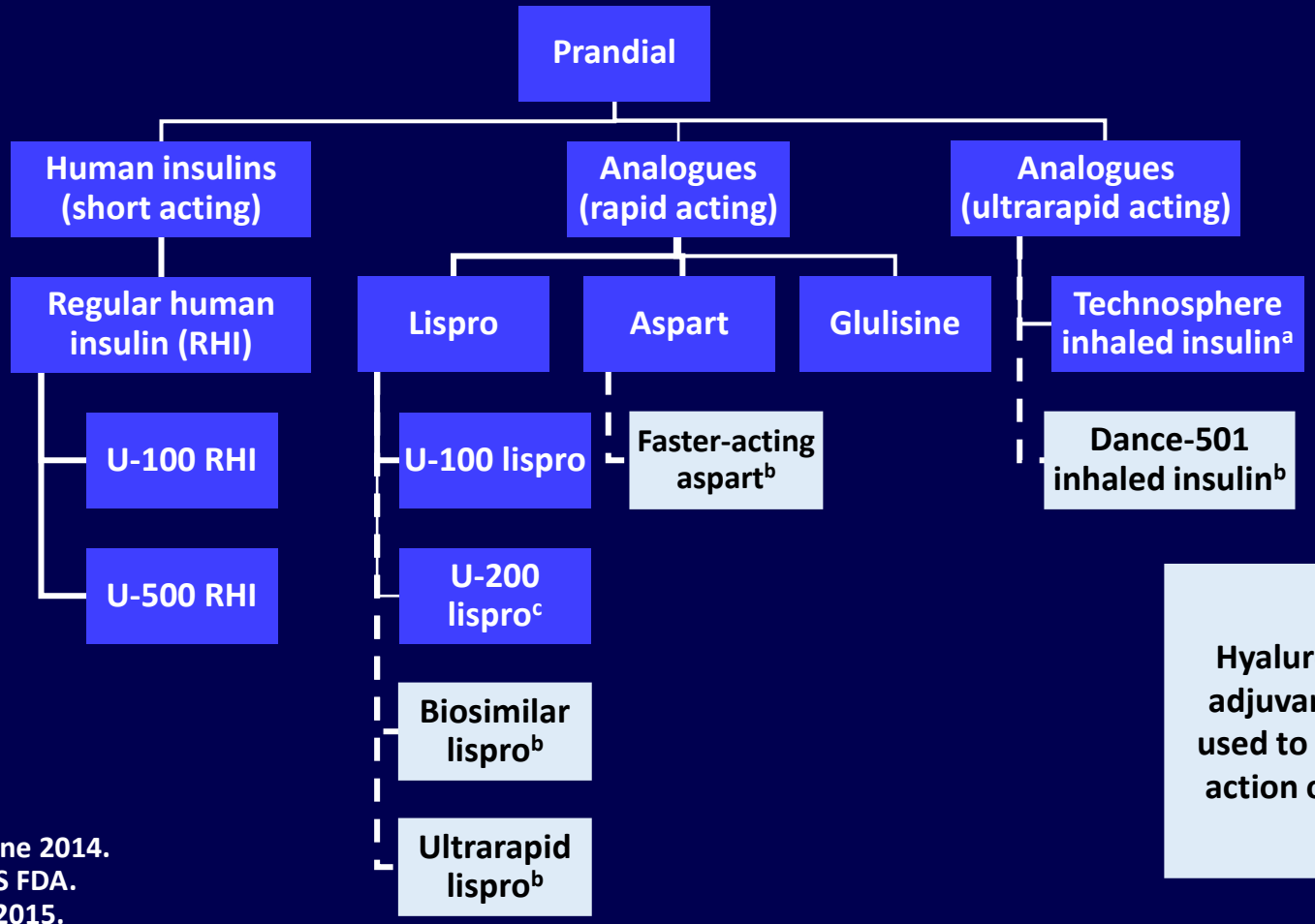
• Approved
• Same molecule as U-100 glargine
• Compared with U-100 glargine:
  • Equally effective
  • Less nocturnal hypoglycemia
  • Equivalent weight gain
	• Approved
	• Forms multihexamers for slow release
	• Compared with U-100 glargine:
	  • Equally effective
	  • Less nocturnal hypoglycemia
	  • Equivalent weight gain
		• *Development ceased*
		• Greater hepatic action, less peripheral action
		• Compared with U-100 glargine:
		  • More effective
		  • Less nocturnal hypoglycemia
		  • Less weight gain

- Several insulins designed for once-weekly administration are in early development

*Not FDA approved; development ceased as of Dec 2015.

New Options for Prandial Insulins

Current and Emerging Prandial Insulins: United States



Hyaluronidase is an adjuvant that can be used to accelerate the action of any insulin[b]

[a] Approved by the US FDA since June 2014.
[b] Not currently approved by the US FDA.
[c] Approved by the US FDA in May 2015.

US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

A1C < 8%	A1C > 8%
TDD 0.1–0.2 U/kg	TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - **FBG** > 180 mg/dL: add 20% of TDD
  - **FBG** 140–180 mg/dL: add 10% of TDD
  - **FBG** 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - **BG** < 70 mg/dL: 10% – 20%
  - **BG** < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

***Glycemic Goal:**

- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

Glycemic Control Not at Goal*

INTENSIFY (Prandial Control)

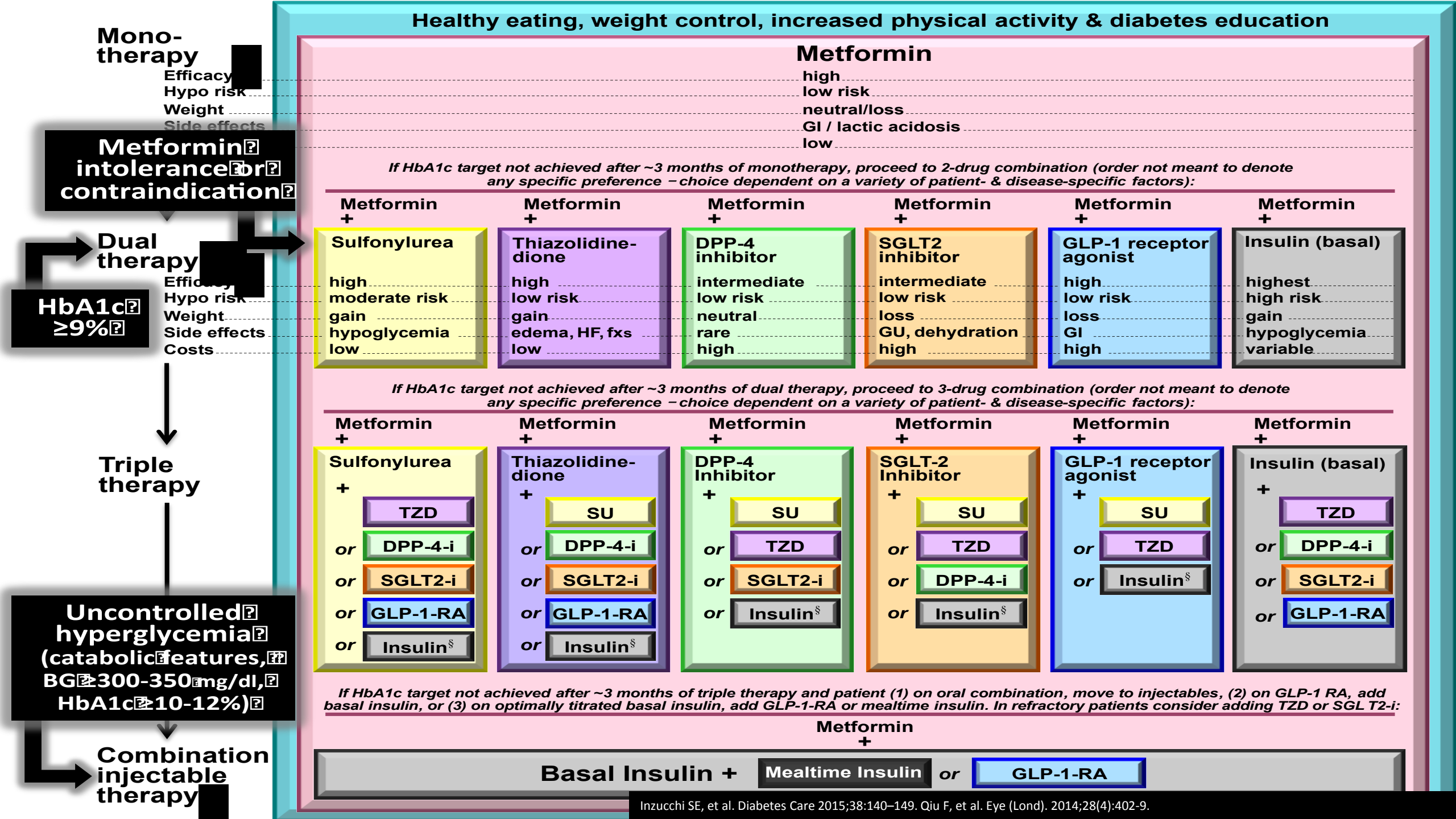
Add GLP-1 RA
Or SGLT-2i
Or DPP-4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3	Basal Bolus
• Begin prandial insulin before largest meal • If not at goal, progress to injections before 2 or 3 meals	• Begin prandial insulin before each meal • 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
• Start: 10% of basal dose or 5 units	• Start: 50% of TDD in three doses before meals

Insulin titration every 2–3 days to reach glycemic goal:

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%



Inzucchi SE, et al. Diabetes Care 2015;38:140–149. Qiu F, et al. Eye (Lond). 2014;28(4):402-9.

Approach to Starting and Adjusting Insulin

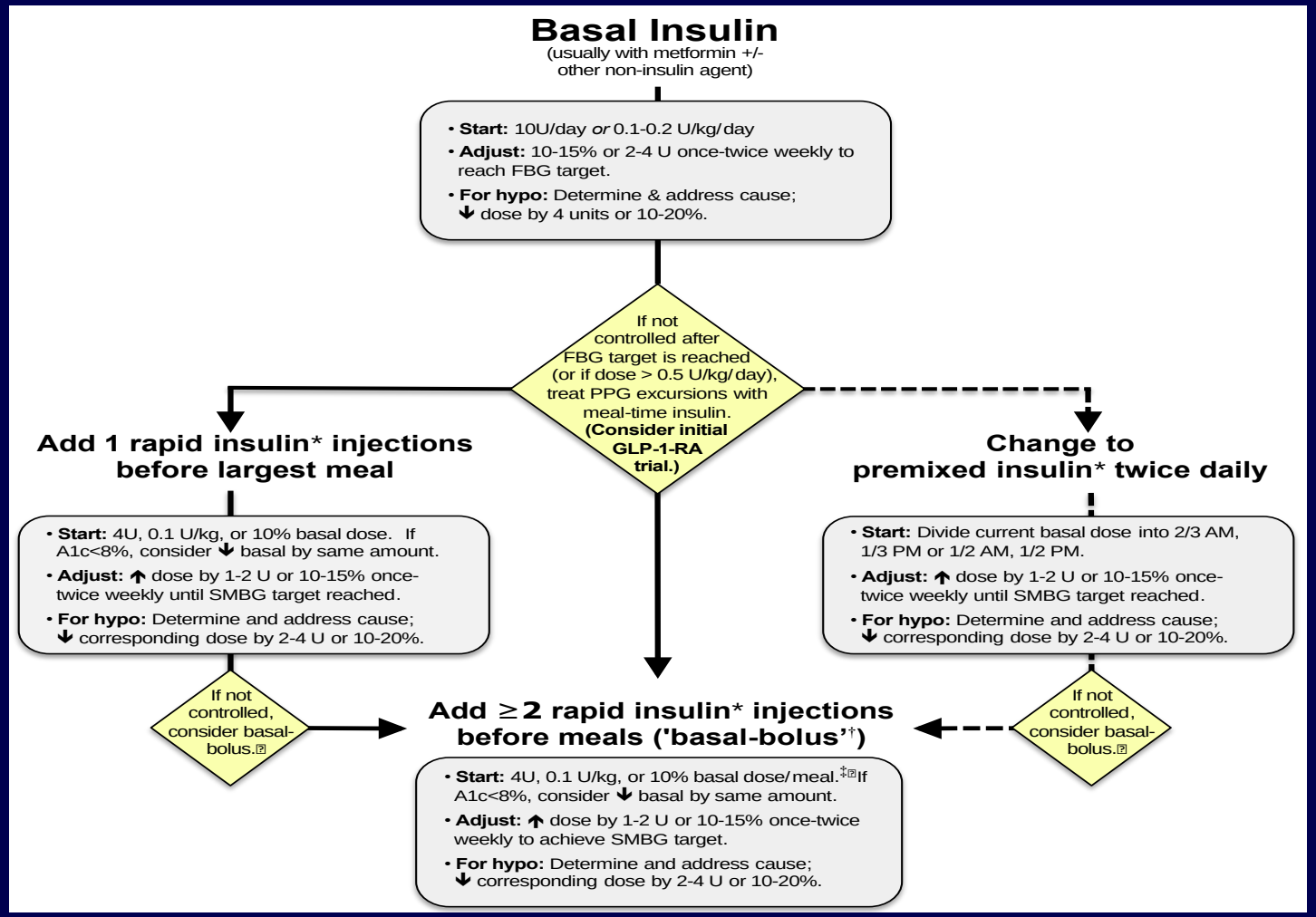
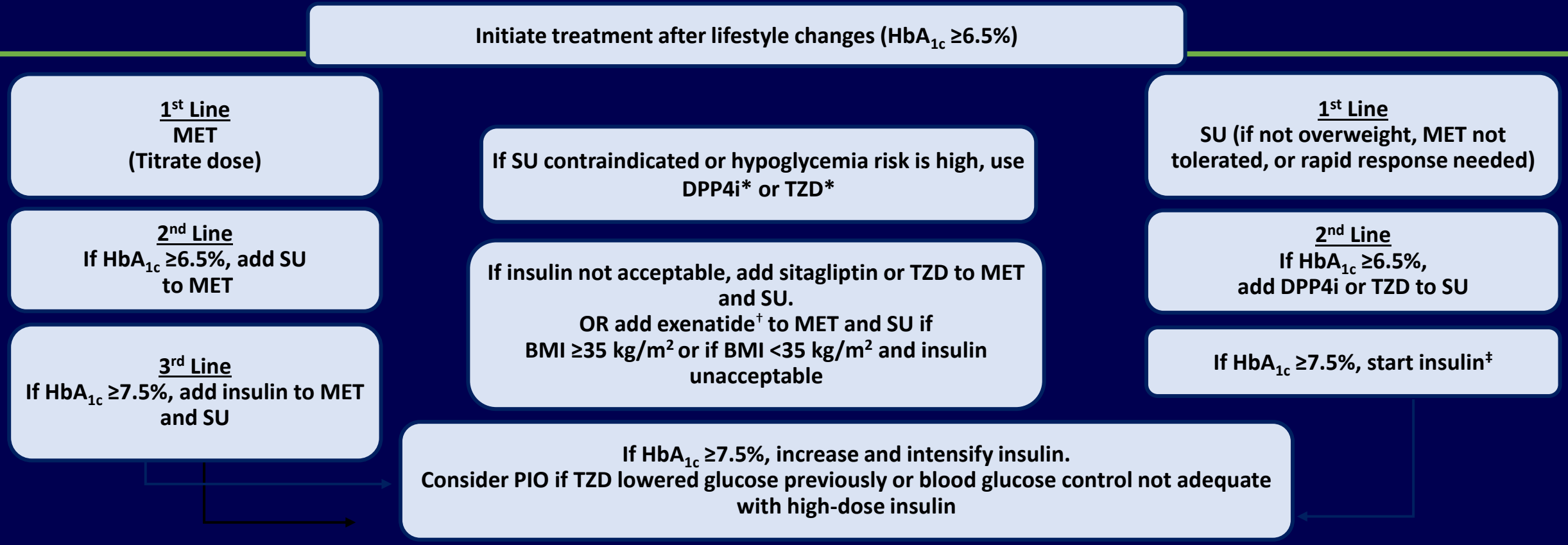


Figure 3: Approach to starting and adjusting insulin in T2DM

Inzucchi SE, et al. Diabetes Care 2015;38:140–149. Qin P, et al. Eye (Lond). 2014;28(4):382-9.

Treatment Algorithm: NICE



*Only continue DPP4i or TZD here if HbA_{1c} reduction is ≥0.5% in 6 months; †Only continue exenatide if HbA_{1c} reduction is ≥1% and weight loss is ≥3% of initial body weight at 6 months; ‡Continue with metformin and SU (and acarbose if used) but only continue other drugs that are licensed for use with insulin. Review the use of SU if hypoglycemia occurs.

GLP=glucagon-like peptide; MET=metformin; NICE=National Institute for Health and Care Excellence; PIO=pioglitazone; SU=sulfonylurea.

NICE. Type 2 Diabetes in Adults: Management. http://www.nice.org.uk/guidance/ng28. Published December 2015. Accessed February 16, 2016.

Treatment Algorithm: JDS

Lifestyle Modification

1st Line
(HbA1c <7.0% or HbA1c [JDS] <6.6%)
Treatment with oral hypoglycemic agent
(MET, TZD, DPP4i, SU, AGI) or GLP1RA or insulin

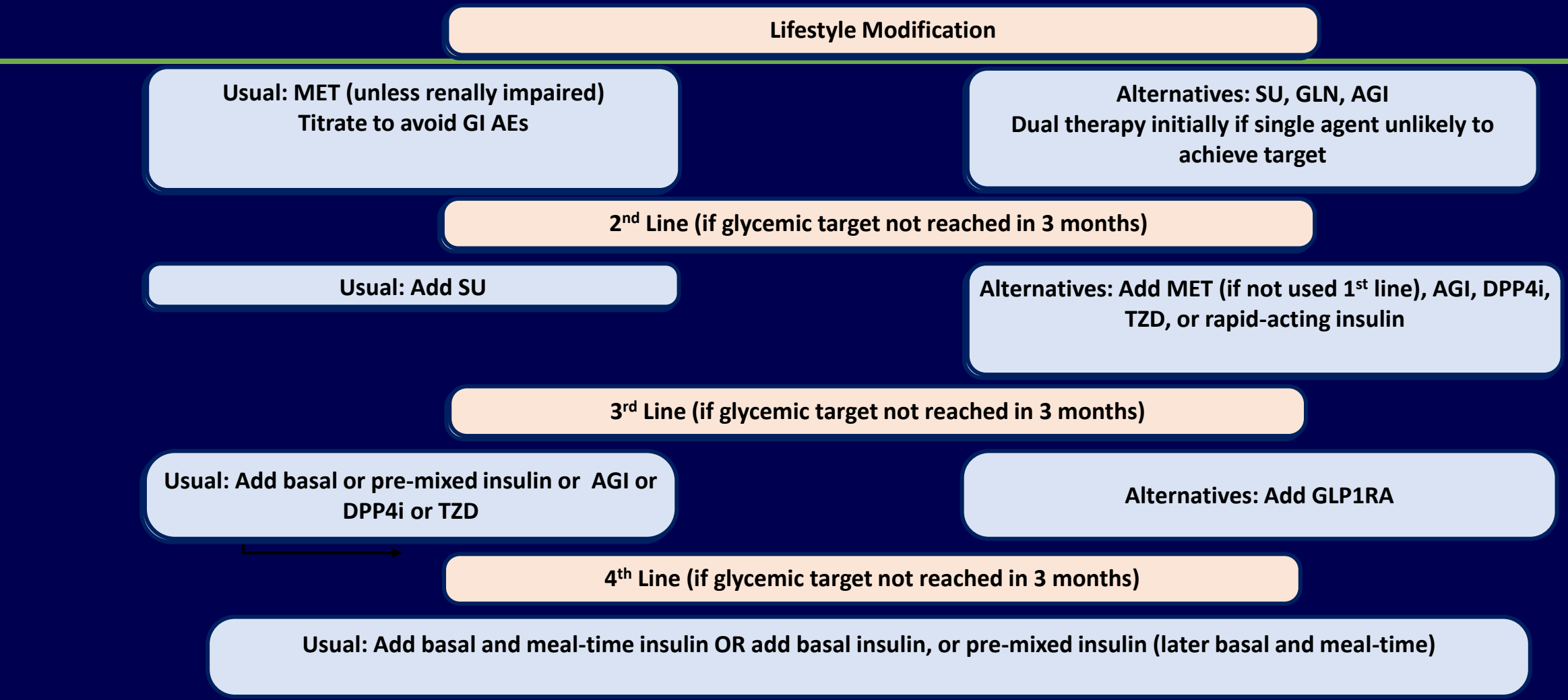
2nd Line

A) Treatment with increased dose of oral hypoglycemic agent or their combination
B) Switch to insulin or oral hypoglycemic agent in combination treatment with insulin
C) Switch to GLP1RA or oral hypoglycemic agent in combination with GLP1RA

3rd Line
Intensive insulin therapy

JDS. *Goals and Strategies for Diabetes Management.* http://www.jds.or.jp/common/fckeditor/editor/filemanager/connectors/php/transfer.php?file=/uid000025_474C323031335F656E2D30322E706466. Accessed April 1, 2014.

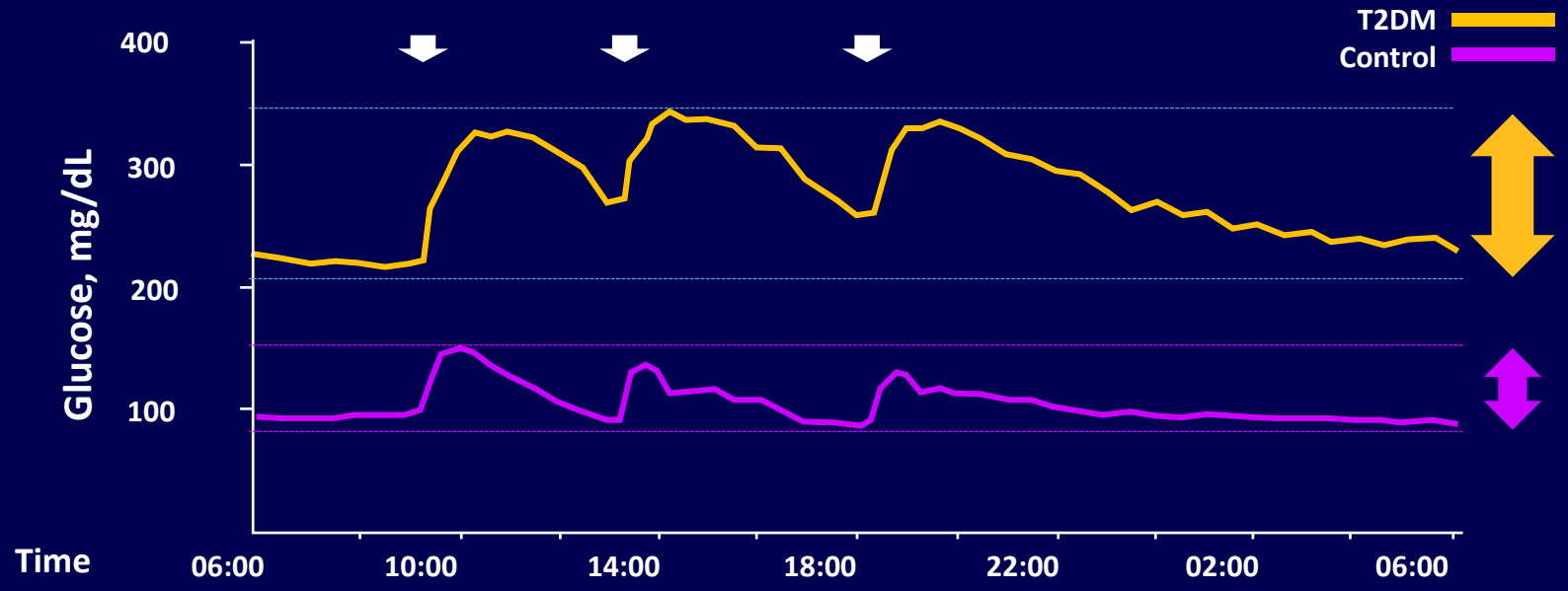
Treatment Algorithm: IDF



GI = gastrointestinal; GLN = meglitinide.

IDF. *Treatment Algorithm for People with Type 2 Diabetes*. http://www.idf.org/treatment-algorithm-people-type-2-diabetes Accessed February 10, 2016.

Rationale for and Limitations of Prandial Insulin Therapy in T2DM



Bolus (prandial) insulin therapy should reduce postprandial glucose excursions[1,2]

- **Aspart, glulisine, and lispro more nearly resemble physiological prandial insulin than regular human insulin, but they[3]:**
  - **May not be absorbed rapidly enough, resulting in postprandial hyperglycemia**
  - **May peak late (up to 120 min postinjection), resulting in hypoglycemia hours after a meal**
- **Faster-acting, shorter-duration insulin is needed for closed-loop insulin therapy**

Arrows above graph denote meal times.

1. Polonsky KS, et al. *N Engl J Med.* 1988;318:1231-1239.
2. Zinman B. *N Engl J Med*. 1989;321:363-370.
3. Cobelli C, et al. *Diabetes*. 2011;60:2672-2682.

Why Is Basal Insulin So Successful?

- Patients see it working – obvious
- Once dose established, not much glucose monitoring
- Timing of dosing flexible
- Relatively low rate of hypoglycemia
- Relatively little weight gain
- Perceived as safe

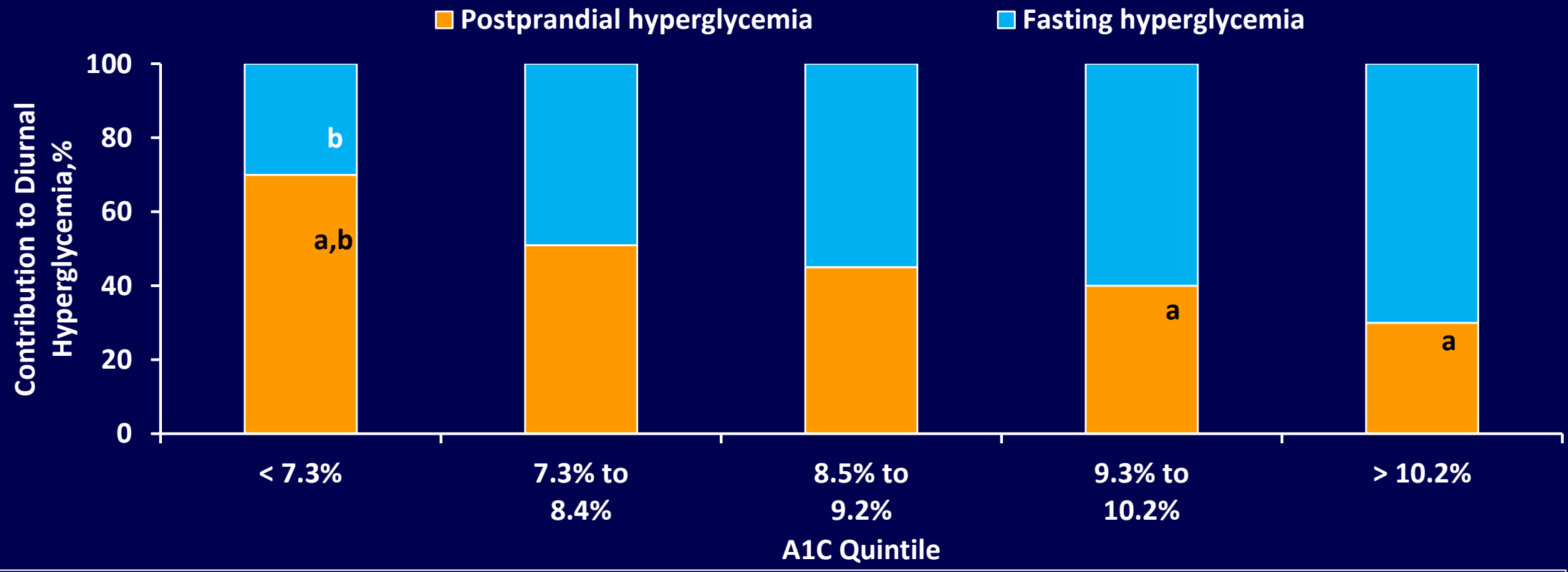
Why Is Prandial Insulin Always Last?

- Timing of dose needs to be relatively strict
- Dose has to be adjusted for multiple variables
- More glucose monitoring is required
- Glucose monitoring can never stop
- Hypoglycemia risk
- Interrupts the flow of the day – constant reminder of DM

What Would Move Prandial Insulin to Earlier?

- Make it more faster – more physiologic
- Make it less expensive
- Make it more convenient – *simplify* dosing protocols
- Combo with basal
- VGO and more type 2s on pumps (Bionic Pancreas)

Relative Contribution of Postprandial Hyperglycemia to Overall Glycemic Control

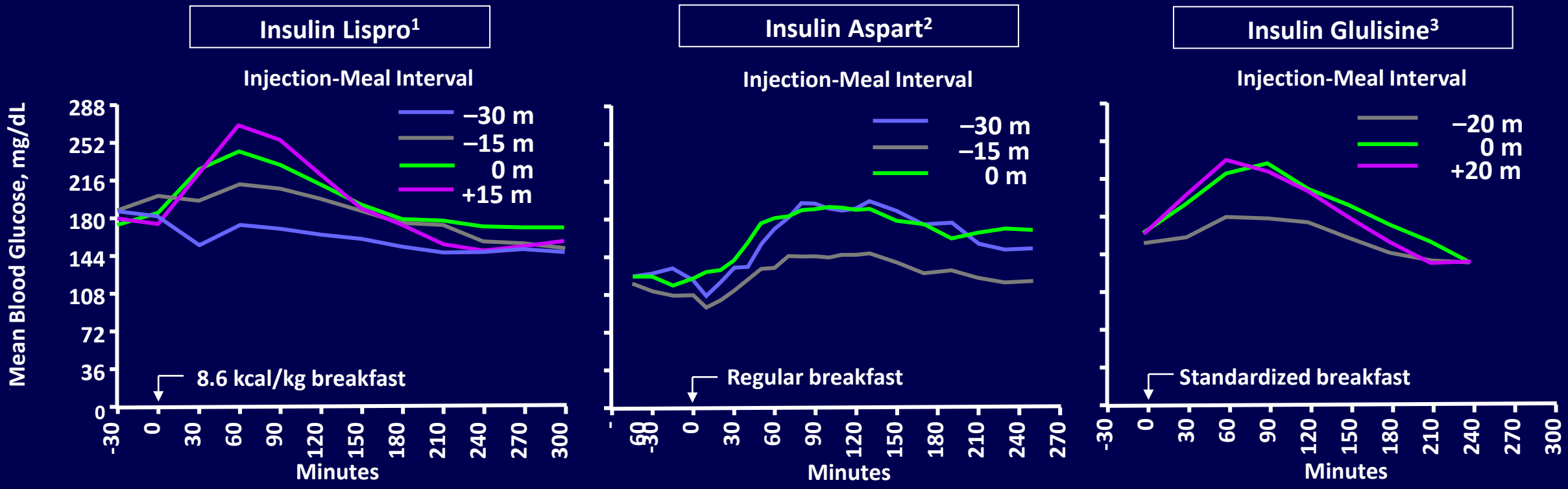


The relative contribution of postprandial hyperglycemia to overall hyperglycemia is greater as A1C nears 7%

[a] **Significantly different between fasting and postprandial.**
[b] **Significantly different from all other quintiles.**

Monnier L, et al. *Diabetes Care*. 2003;26:881-885.

Timing of Prandial Insulin Injections



- Injecting 15 to 20 minutes before meal may reduce PPG more than injecting at mealtime[1-3]
- Regular human insulin needs to be injected 30 to 45 minutes before meals[4,5]

1. Rassam AG, et al. *Diabetes Care*. 1999;22:133-136; 2. Luijf YM, et al. *Diabetes Care*. 2010;33:2152-2155; 3. Cobry E, et al. *Diabetes Technol Ther*. 2010;12:173-177; 4. American Diabetes Association. *Practical Insulin: A Handbook for Prescribing Providers*. 3rd ed. 2011:1-68; 5. Skyler JS. In: Lebovitz HE, ed. *Therapy for Diabetes Mellitus and Related Disorders*.

Efficacy and Safety of Analogue vs RHI Prandial Insulin Injections—Meta-Analysis

Key Findings

- Greater A1C reduction (0.1%; $P = .037$)
- Greater 2-h PPG reduction at breakfast and dinner (≈ 10-12 mg/dL; $P < .001$)
- Possibly less frequent severe hypoglycemia ($OR_{MH} = 0.61$; P = NS)
- Unable to meta-analyze nonsevere hypoglycemia

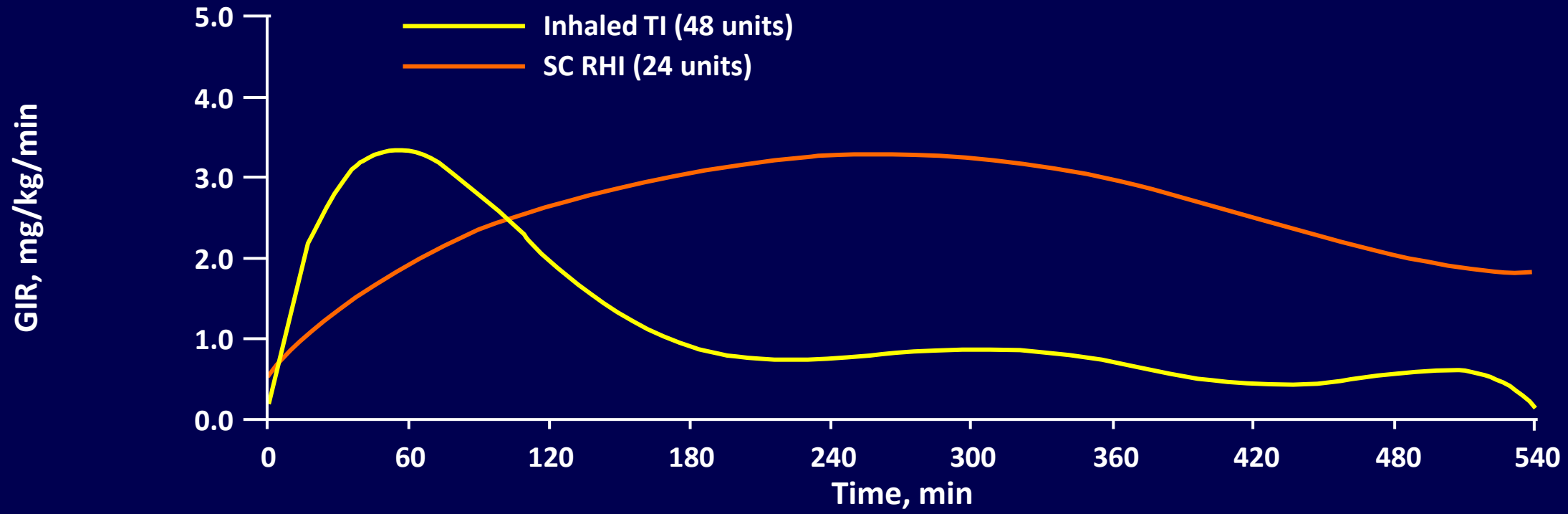
Conclusions

- Prandial analogues have slightly greater efficacy and possibly less risk of severe hypoglycemia than RHI
- Comparative efficacy analyses among prandial insulin analogues is not possible with available data

Meta-analysis of 13 trials of 4361 individuals with T2DM.

Mannucci E, et al. *Diabetes Obes Metab*. 2009;11:53-59.

Inhaled Insulin (Technosphere) in T2DM



- **Duration of action for inhaled insulin is much shorter than for RHI[1]**
- **Almost complete PPG suppression has been observed in a double-blind, placebo-controlled trial in insulin-naive patients with T2DM using OADs[2]**

1. Rave K, et al. *J Diabetes Sci Technol*. 2008;2:205-212.
2. Rosenstock J, et al. *Diabetes Care*. 2015;38:2274-81..

Efficacy and Safety of Inhaled Prandial Insulin—Meta-Analysis

Meta-analysis of 12 trials with 5273 individuals with T1DM or T2DM

Findings (risk differences vs SC insulin)

- A1C reduction favors SC insulin (0.16%; $P < .05$)[a]
- Hypoglycemia risk favors inhaled insulin (OR 0.61; $P < .05$)
- Weight gain favors inhaled insulin (–1.6 kg; $P < .05$)

Adverse effects more common with inhaled insulin

- Mild, transient, dry cough (OR 7.82; $P < .05$)
- Slight decline in FEV_1 (–0.04 L; $P < .05$)

Recommendations

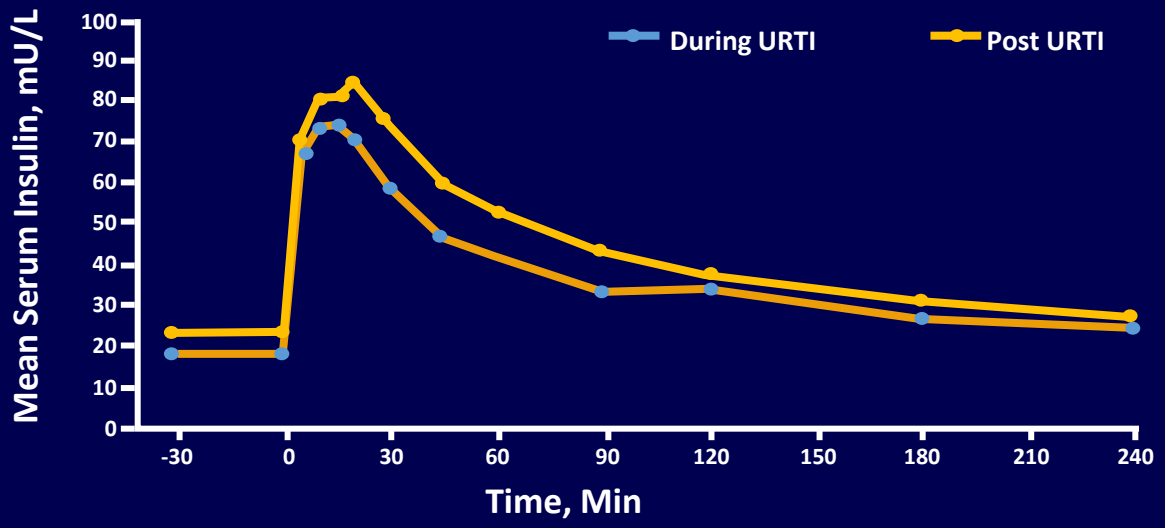
- For nonpregnant, nonsmoking adults free of pulmonary disease who are needlephobic and would otherwise delay initiating or intensifying insulin therapy

[a] **Noninferiority study designs may have biased this comparison.**

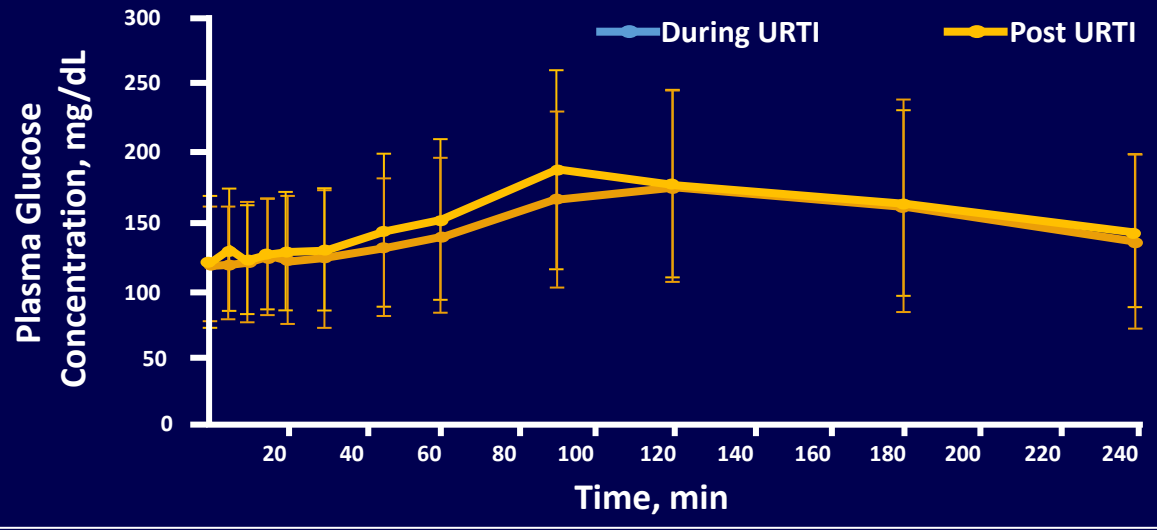
Westcott GP, et al. *Diabetes*. 2015;64(suppl 1A);LB25 [abstract 96-LB].

Effect of Upper Respiratory Infection on Inhaled Insulin PK/PD

Serum Insulin Concentrations



Plasma Glucose Concentrations During Each 4-Hour Meal Challenge[a]

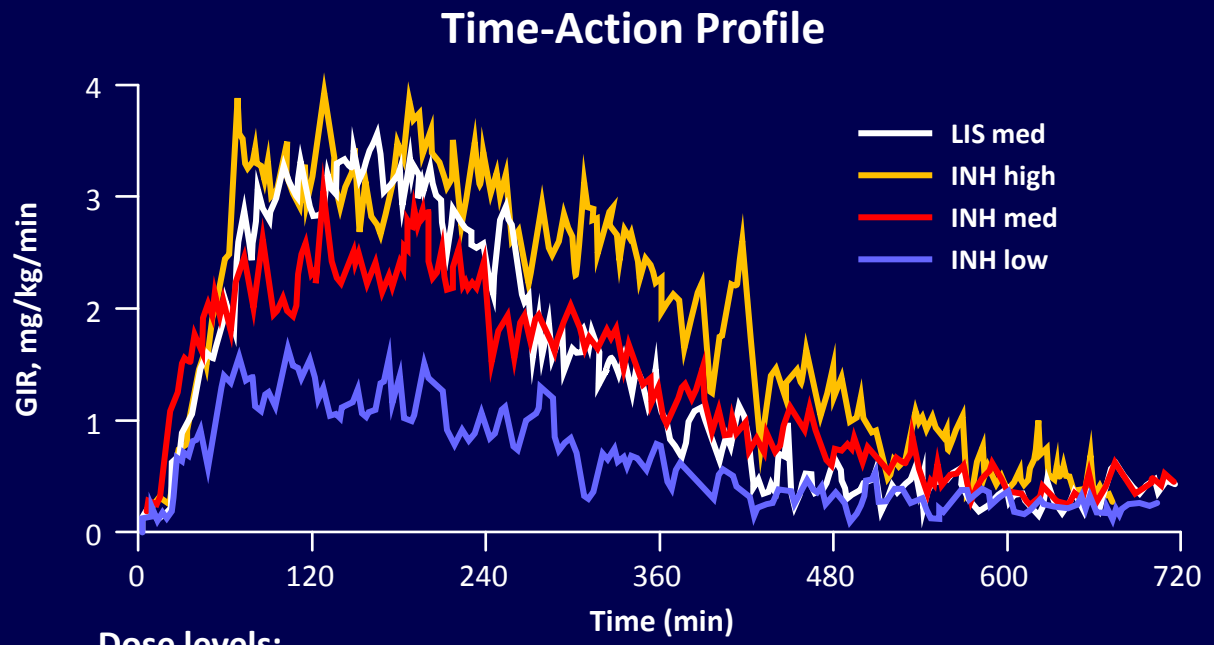


- **URTI did not significantly affect the PK/PD properties of inhaled insulin[1]**
- **If patients are unable to perform proper inhalation, they should administer insulin subcutaneously[1]**
- **Another RCT showed that mild to moderate COPD did not significantly alter the PK properties of inhaled insulin[2]**

2-period study of 20 patients with T1DM or T2DM who developed a symptomatic URTI while being treated with inhaled insulin in a phase 3 RCT[1]. LRTI was not evaluated. [a] Data are mean ± SD.

1. Levin PA, et al. *Diabetes*. 2015;64(suppl 1A):LB24 [abstract 94-LB].
2. Potocka E, et al. *Curr Med Res Opin.* 2010;26:2347-2353.

Dance-501 Inhaled Human Insulin[a] (in T2DM)



Dose levels:

- **LIS med:** 18 U
- **INH high:** 207.7 IU, equivalent to SC: 27 IU
- **INH med:** 138.5 IU 18 IU
- **INH low:** 69.2 IU 9 IU

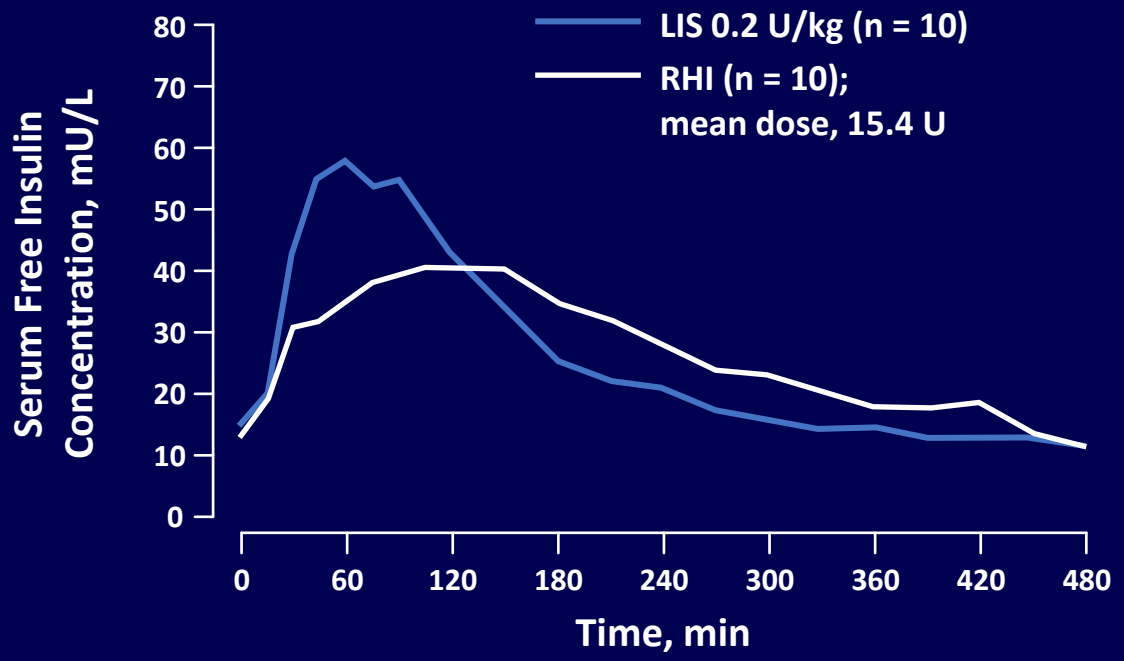
- **Inhaler device produces a fine mist of aerosolized liquid human insulin for inhalation**
- **Coughing observed in 0.6% of inhalations**
- **No clinically relevant changes in measures of lung function at postinhalation or during follow-up**

Randomized crossover trial of 24 patients with T2DM with normal lung function.
[a] Dance-501 is not currently approved by the US FDA.

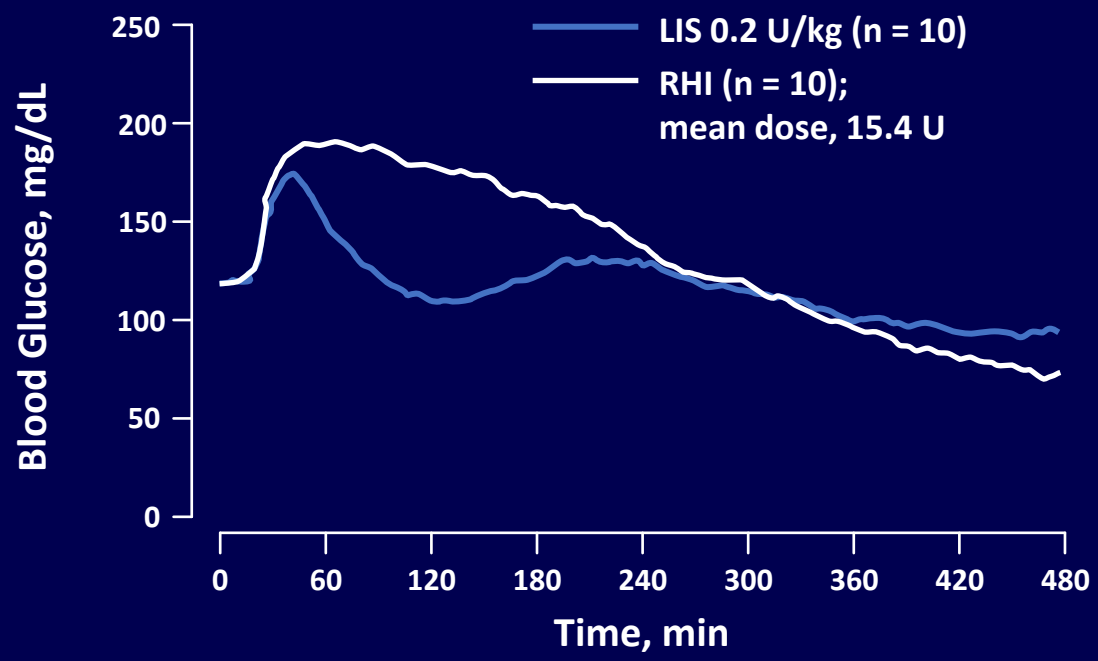
Zijlstra E, et al. *Diabetes*. 2015;64(suppl 1):A248 [abstract 978-P].

U-200 Lispro

Pharmacokinetics



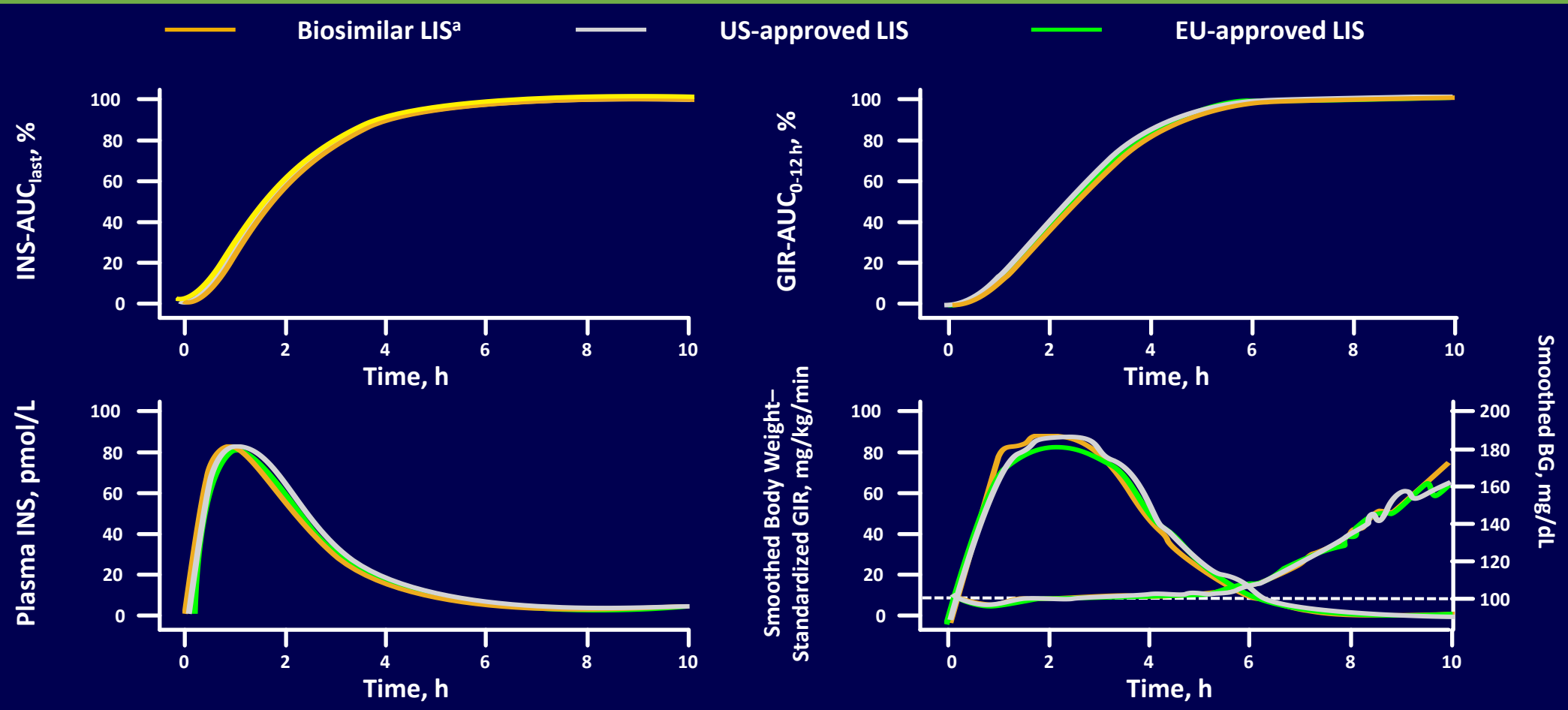
Pharmacodynamics



Potentially offers the advantage of a smaller injection volume for patients with high prandial insulin requirements

PK/PD data generated from a study of 10 patients with T1DM.
http://uspl.lilly.com/humalog/humalog.html#pi.

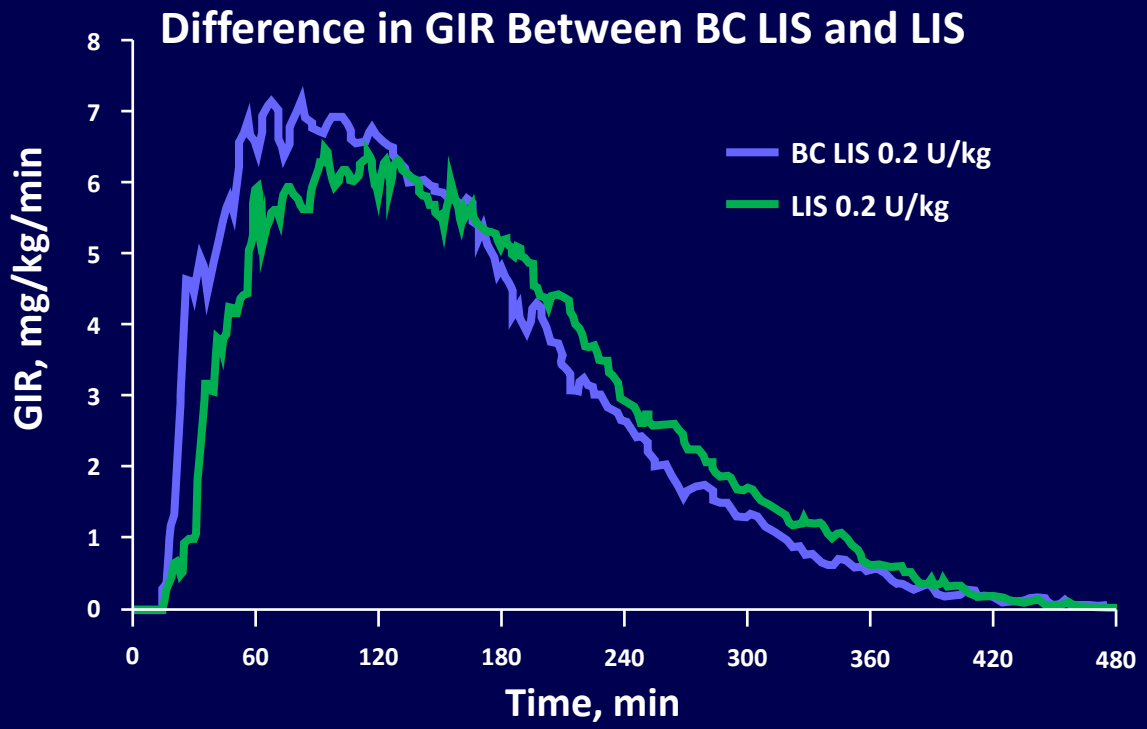
Biosimilar Lispro vs 2 Approved Lispro Formulations (in T1DM)

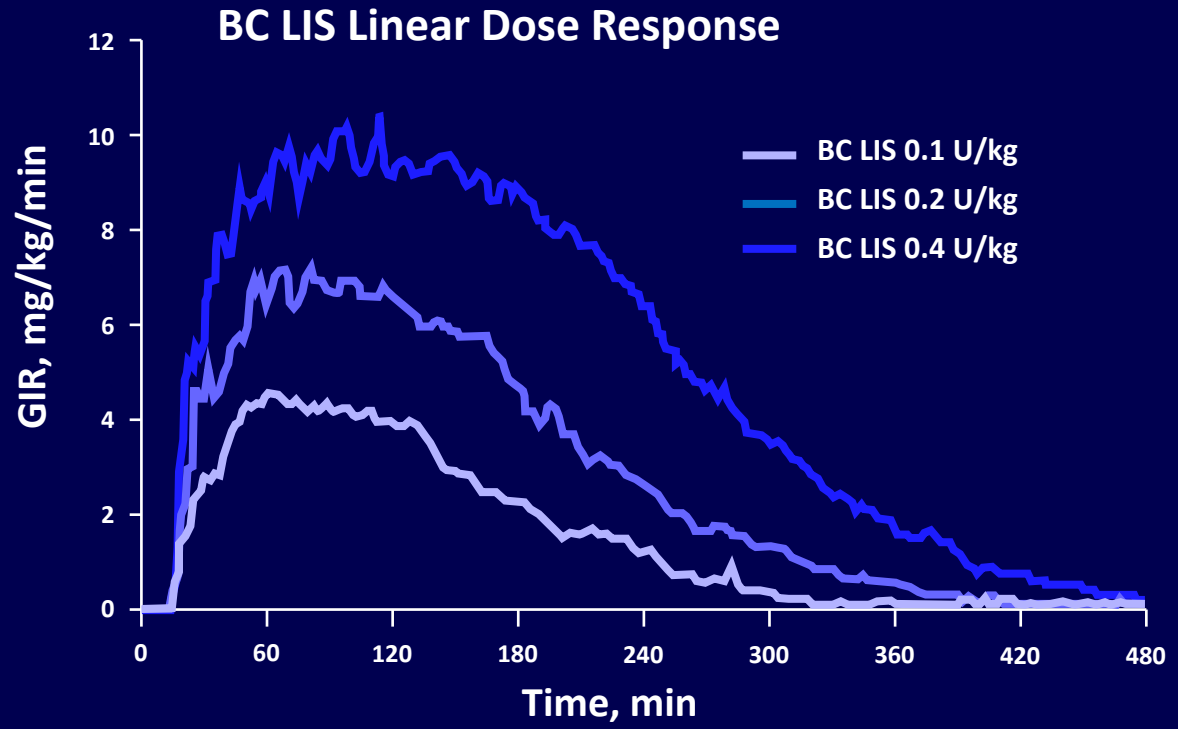


[a] **Biosimilar lispro (SAR342434) is not currently approved by the US FDA.**

Nowotny et al. *Diabetes.* 2015;64(suppl 1):A261-A262 [abstract 1022-P].

Ultrarapid-Acting Insulin Lispro[a] (in T1DM)





- 67% higher GIR for BC lispro in the first hour postinjection ($P < .0001$)[b]
- 18% lower GIR for BC lispro at 3-8 hours postinjection ($P < .02$)[b]

Randomized, 4-period crossover study in 38 male patients with T1DM.

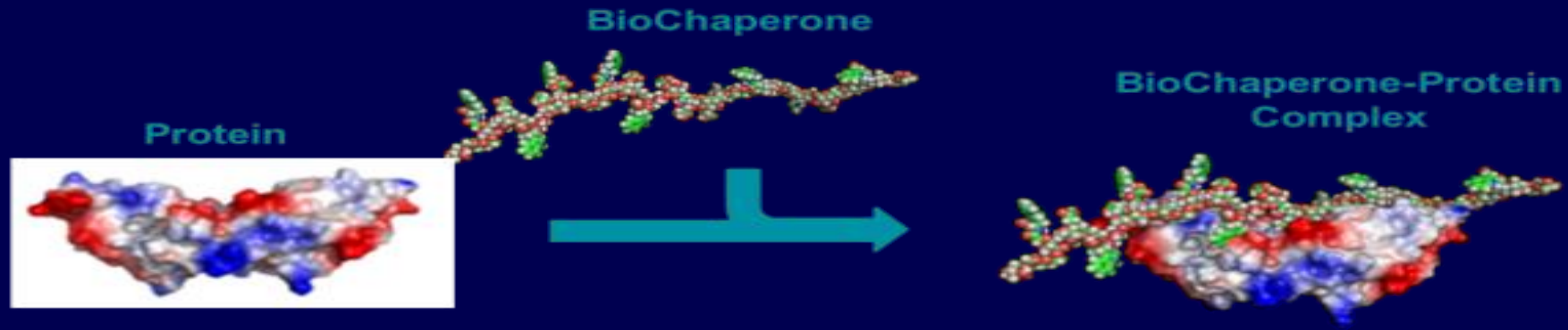
[a] **BC lispro is not currently approved by the US FDA.**

[b] **0.2 units/kg dose.**

Andersen G, et al. *Diabetes*. 2015;64(suppl 1):A248 [abstract 979-P].

ADOCIA and the BioChaperone® Platform

- ADOCIA, founded in 2005, is a biotechnology company specialized in the development of best-in-class medicines from already approved therapeutic proteins.
- ADOCIA designed the BioChaperone® platform technology from innovative polymers, oligomers and small organic compounds. By forming a physical complex with proteins, BioChaperone® protects them from enzymatic degradation and enhances their performance.
- ADOCIA's BioChaperone® platform is bio-inspired from the interactive properties of heparin and growth factors – without the anticoagulation properties of heparin.

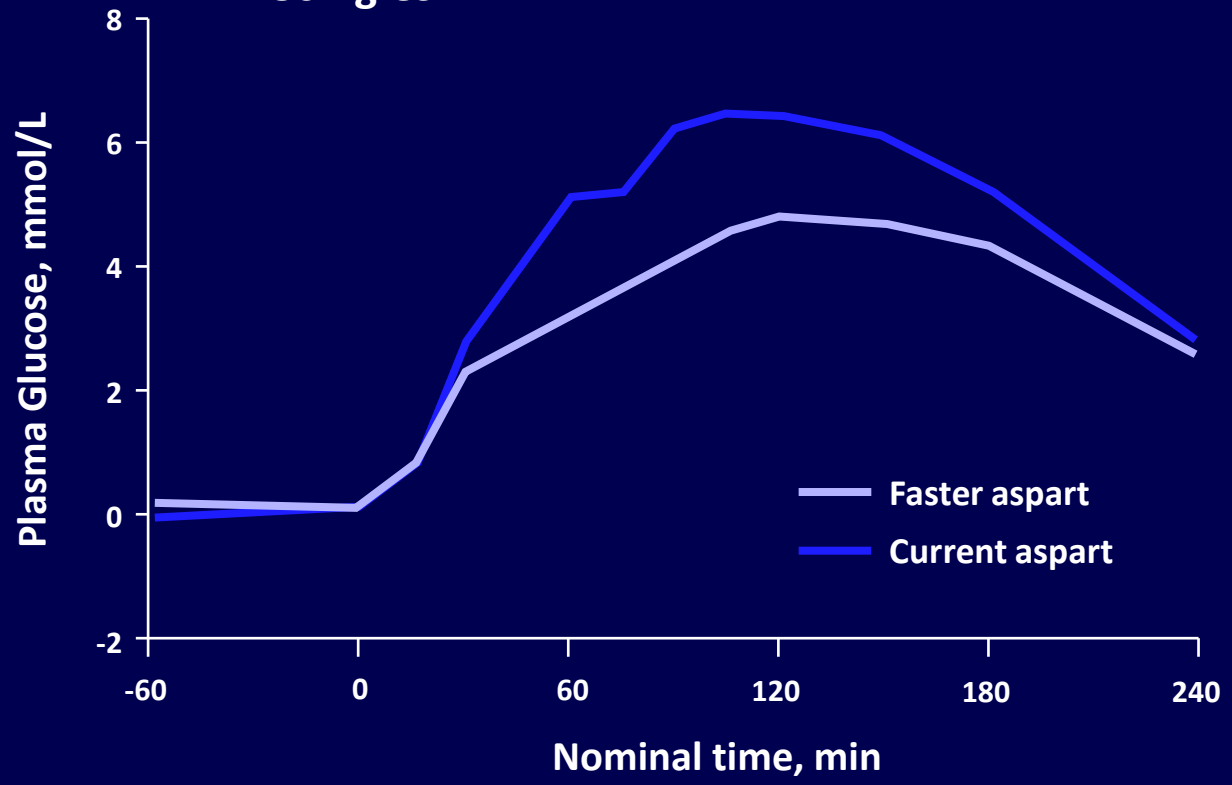


- The library includes ~300 patented polymers, oligomers and small organic compounds to which target proteins are matched to achieve desired performance modification(s).
- The selected BioChaperone® compound forms a physical and reversible complex with the target protein without modifying it – essentially "physically glycosylating" the protein to improve its performance.

Faster-Acting Insulin Aspart[a] (in T1DM)

- 57% earlier onset[1,b]
- 35% earlier $t_{1/2}$[1,b]
- Greater glucose-lowering effect within 90 minutes after dosing[1,b]
- Another study found significantly lower PPG for faster-acting aspart vs currently available aspart in 43 adults with T1DM treated with CSII[2]

PPG Levels in Patients With T1DM Using CSII[2,c]

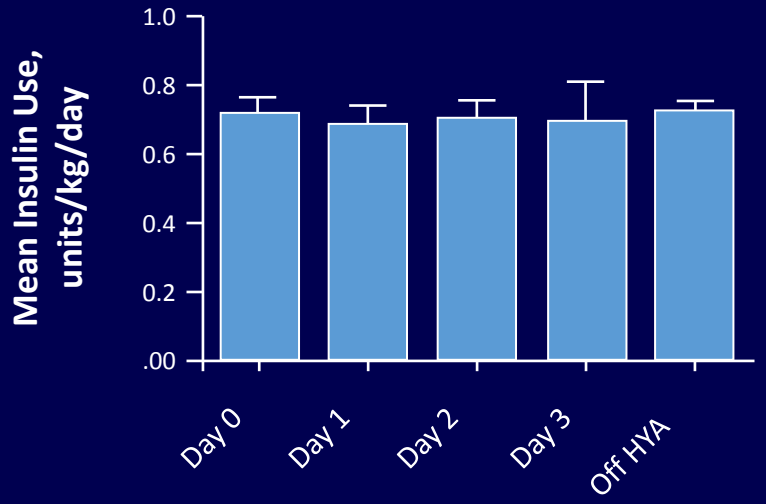


[a] Faster-acting insulin aspart is not currently approved by the US FDA.
[b] Randomized, 3-way crossover study in 52 adults with T1DM.
[c] Baseline adjusted.

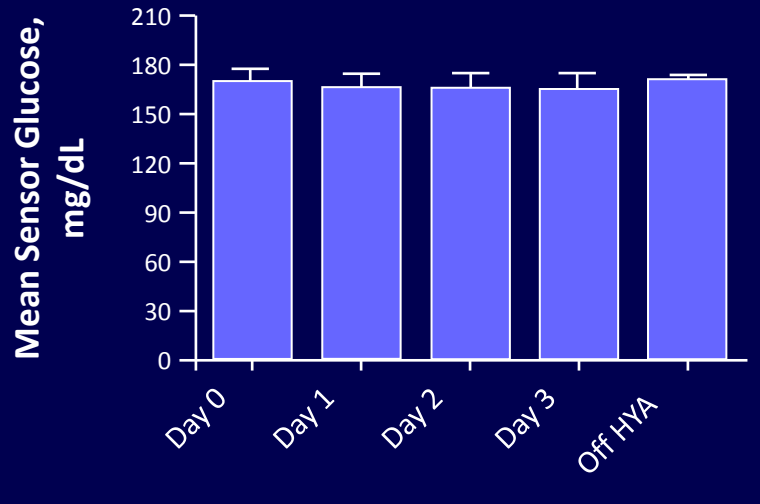
1. Heise T, et al. *Diabetes Obes Metab*. 2015;17:682-688.
2. Bode B, et al. *Diabetes*. 2015;64(suppl 1):A253 [abstract 994-P].

Hyaluronidase-Adjuvanted Insulin[a] Administered by CSII at Home (in T1DM)

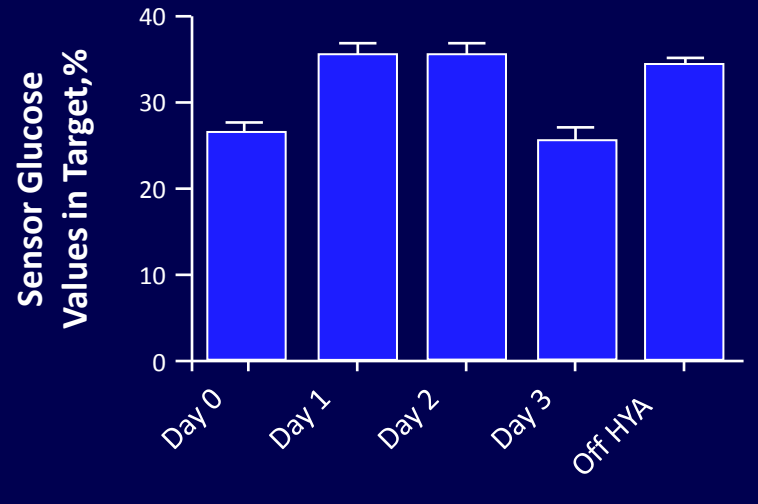
Insulin Use



Sensor Glucose



Sensor Glucose in Target



- **Recombinant hyaluronidase accelerates SC insulin absorption**
- **Previous studies in a controlled setting demonstrated reduced PPG**
- **In this home-based study, improved control was not observed**

HYA, hyaluronidase. 4-week study of 28 patients with T1DM treated with CSII using CGM. Infusion sites remained in place up to 7 days.
[a] Hyaluronidase-adjuvanted insulin is not currently approved by the US FDA.
Wadwa RP, et al. *Diabetes*. 2015;64(suppl 1):A293 [abstract 1139-P].

Overview of Clinical Trials Comparing Premixed Insulin With Basal-Plus or Basal-Bolus Insulin Regimens

	Malek et al[1]	Riddle et al[2]		Giugliano et al[3]	Miser et al[4]
Premixed insulin type (doses/d)	ASP 70/30 (1-3)	ASP 70/30 (2)		LIS 75/25 (1-3) LIS 50/50 (1-3)	LIS 75/25 (2) LIS 50/50 (1-3)
Comparator	DET + 3 ASP	GLAR + 1	GLAR + 3	GLAR + 1-3 LIS	GLAR + 3 LIS
Δ A1C	Same	Same	BBT better[a]	Same	Same
Δ Weight	BBT better[a]	Same	Same	Same	Same
Nocturnal hypoglycemia	Favors BBT	NR	NR	BBT better[b]	Same
Documented symptomatic hypoglycemia	Same	BBT better[a]	BBT better[a]	Same	Same

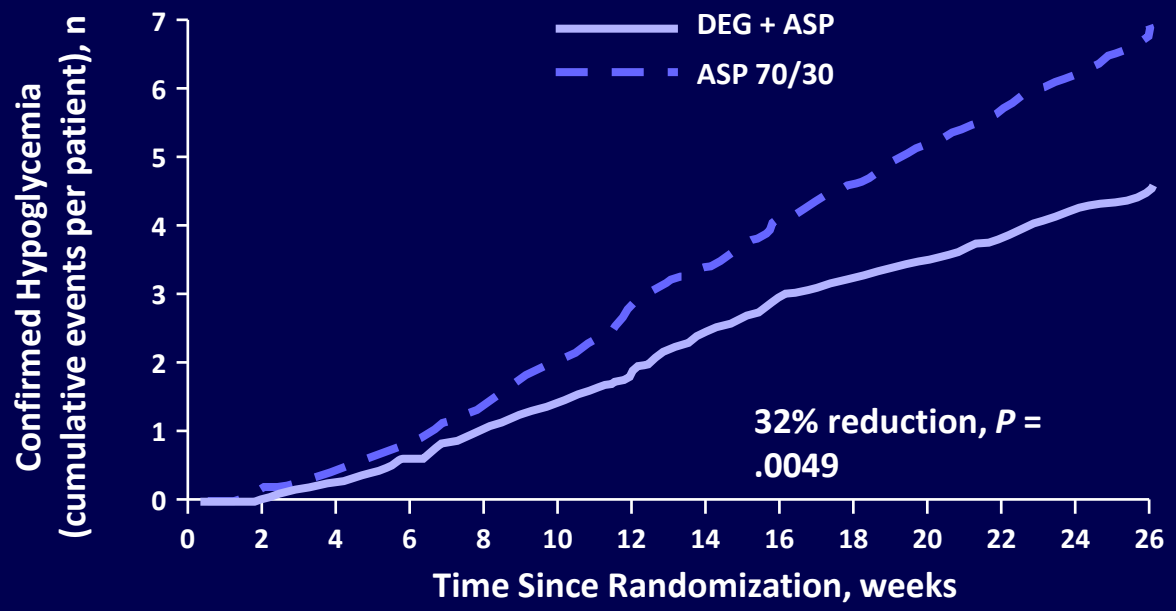
Premixed insulin is as effective as basal-plus or BBT regimens, but hypoglycemia and weight outcomes tend to favor BBT

[a] Statistically significant superiority; $P < .05$
[b] Statistically significant superiority; $P < .02$

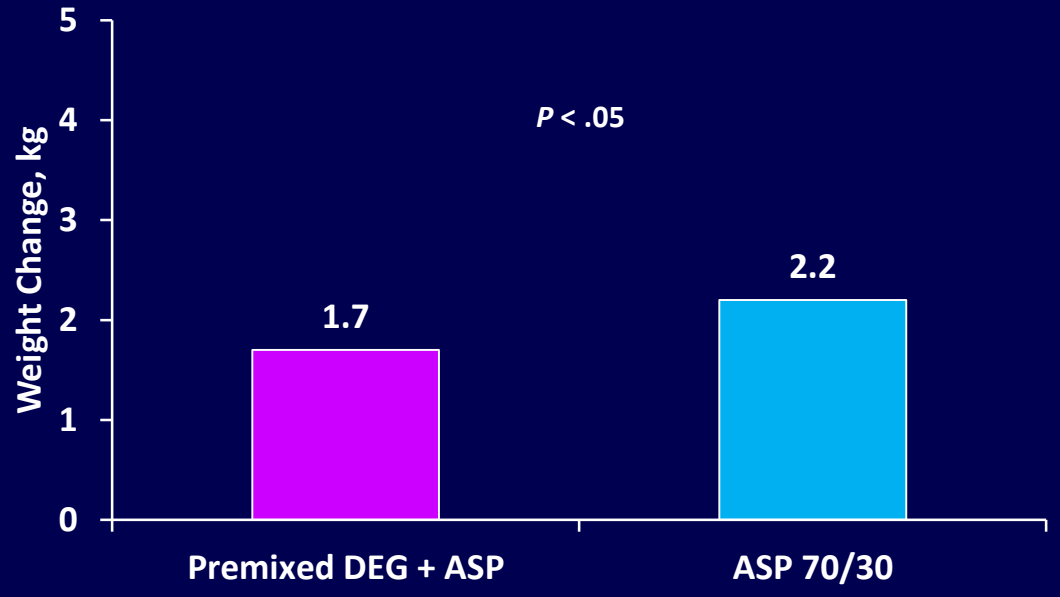
1. Malek R, et al. *Diabetes Metab*. 2015;41:223-230. 2. Riddle MC, et al. *Diabetes Obes Metab*. 2014;16:396-402.
3. Giugliano D, et al. *Diabetes Care*. 2014;37:372-380. 4. Miser WF, et al. *Clin Ther*. 2010;32:896-908.

Degludec/Aspart Premixed Insulin

Confirmed Hypoglycemia



Mean Weight Change



Similar A1C change, but more patients attained A1C < 7% without confirmed hypoglycemia using premixed DEG + ASP than with ASP 70/30 (21.8% vs 14.9%; *P* = .041)

446 patients with T2DM previously using premixed or self-mixed insulin with or without oral agents. Both insulins were dosed twice daily. Confirmed hypoglycemia, plasma glucose < 56 mg/dL or assistance required.

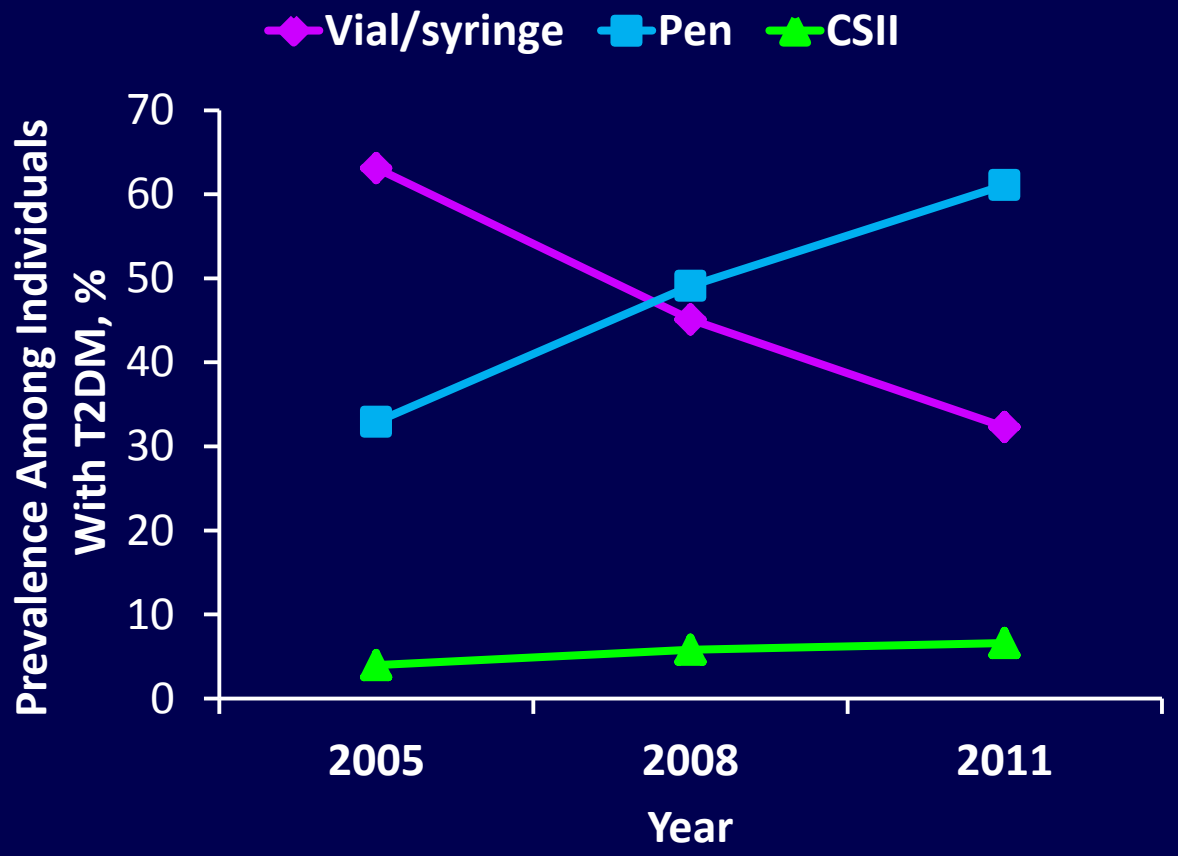
Fulcher GR, et al. *Diabetes Care*. 2014;37:2084-2090.

Summary

- The glucose-suppressing effect of prandial insulins is critically dependent on when the doses are administered relative to meals
- Inhaled insulins have very rapid onset and offset compared with subcutaneous fast-acting insulin
- Faster-acting subcutaneous insulins may reduce PPG concentrations more rapidly than other subcutaneous prandial insulins
- Faster-acting insulins are less likely to cause hypoglycemia than other insulins; patients tend to prefer agents with lower risks of hypoglycemia
- Premixed insulin may be an appropriate alternative to basal-plus or basal-bolus insulin for some patients

Insulin Delivery Technology

Insulin Delivery Technology: Vials/Syringes vs Pens—US, 2005-2011



Analogue insulins are generally administered with a pen[1]

Human insulins are generally administered with vial and syringe[1]

Outcomes with vials and syringes are *never better* than those for pens[2]

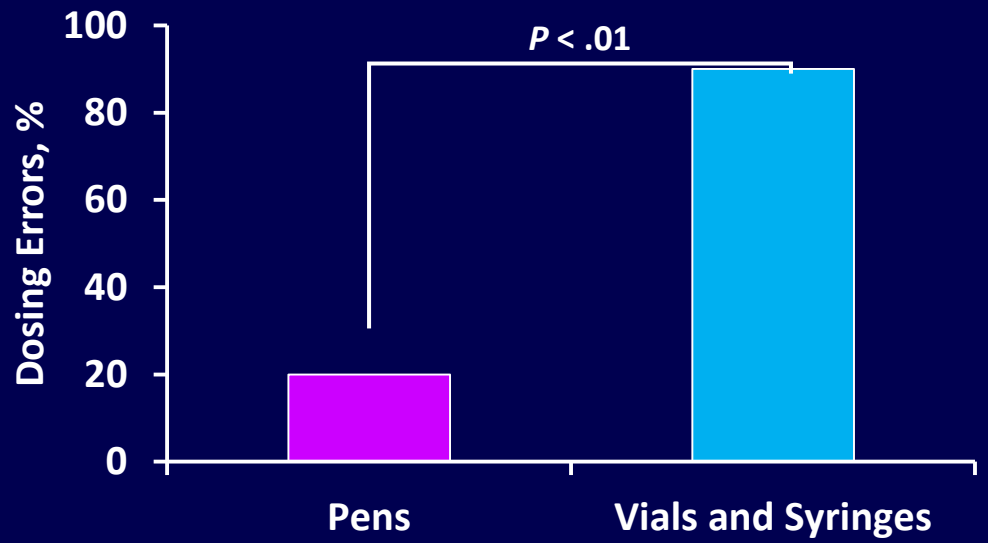
Patient copayments for pens may be *the same* as for vials[3]

Database study of > 20 million privately insured patients with pharmacy benefits.

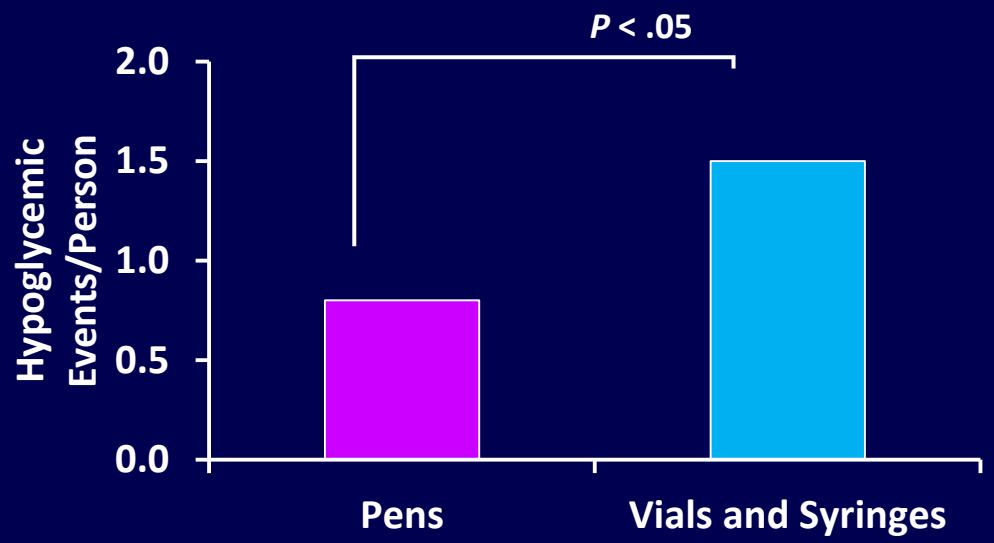
1. Perez-Nieves M, et al. *Curr Med Res Opin.* 2015;31:891-899.
2. Molife C, et al. *Diabetes Technol Ther*. 2009;11:529-538.
3. 2015 Aetna Pharmacy Plan Drug List. https://pbm.aetna.com/portal/asset/2015_IVL_3TierOpen.pdf.

Insulin Pens Are Associated With Lower Risks of Dosing Errors and Hypoglycemia Than Vial-and-Syringe Insulin Delivery

Dosing Errors vs Delivery Device[1]



Hypoglycemia vs Delivery Device[1]



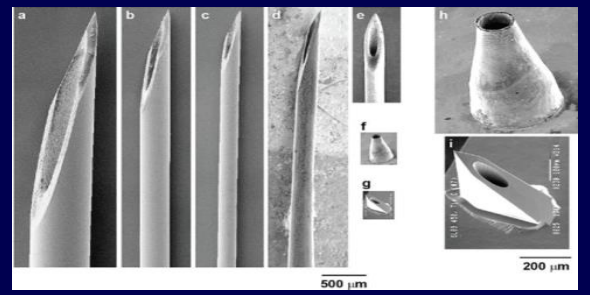
- **Insulin is implicated in 67% of all adverse drug event–related hospitalizations in older adults[2]**
- **With vials and syringes, dosing errors are more common and lead to more hypoglycemic events (1.5 vs 0.4 events, *P* = .01)[1,a]**
- **With pens, dosing errors did not significantly increase hypoglycemic events[1,a]**

Hypoglycemia, BG < 70 mg/dL; [a] Events measured per person.

1. Newton C, et al. AACE Annual Meeting. 2013 [abstract 271].
2. Budnitz DS, et al. *N Engl J Med*. 2011;365:2002-2012.

Needles

- **Hollow microneedles-** *Becton Dickinson*
- Perpendicular 1 mm injection into the intradermal space (as opposed to subcutaneous)
- More rapid uptake
- Reduce pain, anxiety, and fear of injections
- **Ultrafine and ultra-beveled needles-**
- 33 gauge
- Steeper angle in bevel to minimize pain at injection site.



1. Norman J et al. *Pediatr Diabetes* 2013;14(6):459-465.
2. McVey E. *J Diabetes Sci Technol 2012;*6(4);743-754.

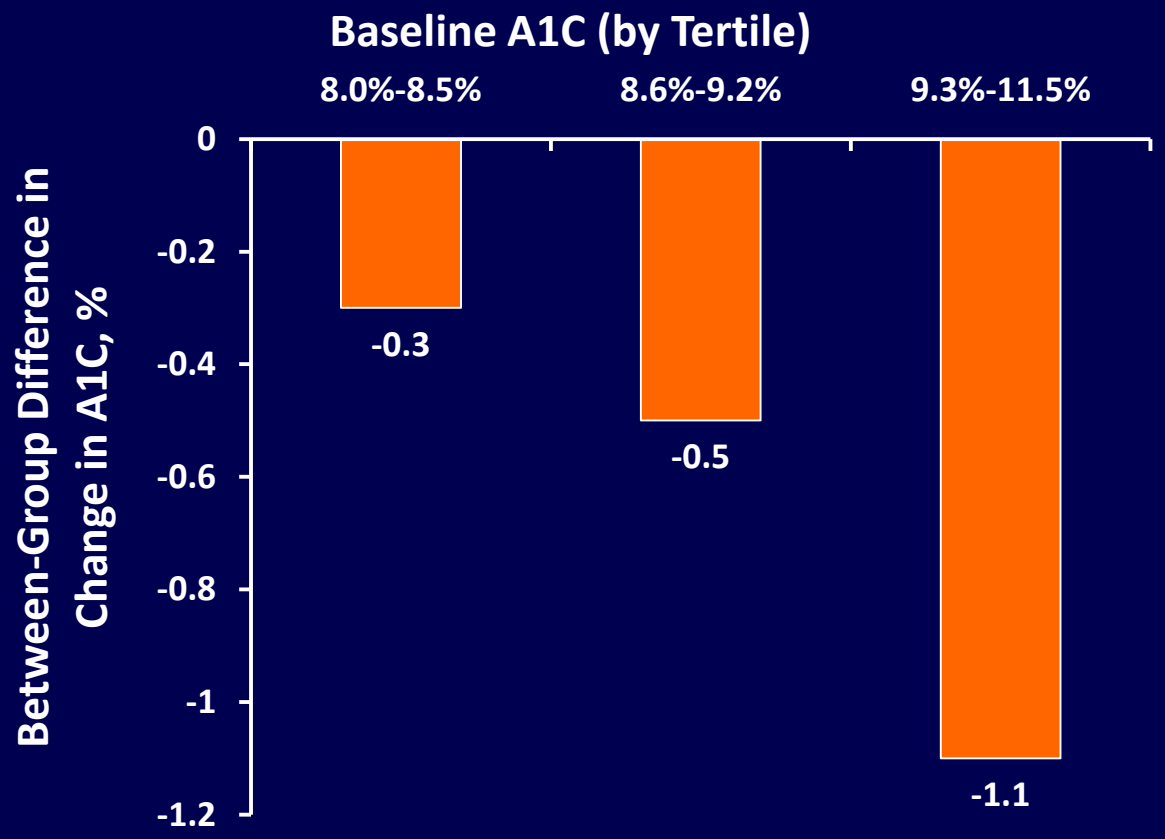
Insulin Pumps Offer Additional Advantages Over Multiple Daily Injections in T2DM—Largest Studies by Pump Type

Study Name	OpT2mise[1]	Lajara et al[2]	Kumareswaran et al[3]
Pump type	Durable CSII pump	Disposable patch pump	Closed-loop insulin delivery
N	331	151	12
Treatment groups	CSII vs MDI	Retrospective database study (3 cohorts: MDI, basal insulin, and insulin naive)	Crossover study comparing CSII with closed-loop insulin delivery
Efficacy	CSII better	CSII reduced A1C in all cohorts	Closed loop better than CSII
Hypo-glycemia	Severe: 1 episode in MDI Nonsevere: no difference	NR	No difference
Weight gain	No difference (1.5 vs 1.1 kg)	NR	N/A

- Newer pumps have high levels of user satisfaction and lower cardiovascular mortality among patients with T1DM[4,5]
- The AACE recommends durable insulin pumps for patients with T2DM with recurrent DKA, frequent severe hypoglycemia, or hypoglycemia unawareness, and for competitive athletes[6]

1. Reznik Y, et al. *Lancet*. 2014;384:1265-1272; 2. Lajara R, et al. *Diabetes.* 2015;64(suppl 1):A278 [abstract 1083-P];
3. Kumareswaran K, et al. *Diabetes Care.* 2014;37:1198-1203; 4. Barnard KD, et al. *J Diabetes Sci Technol.* 2015;9:231-236;
5. Steineck I, et al. *BMJ*. 2015;350:h3234; 6. Grunberger G, et al. *Endocr Pract*. 2010;16:746-762.

Insulin Delivery Technology—Durable Pump

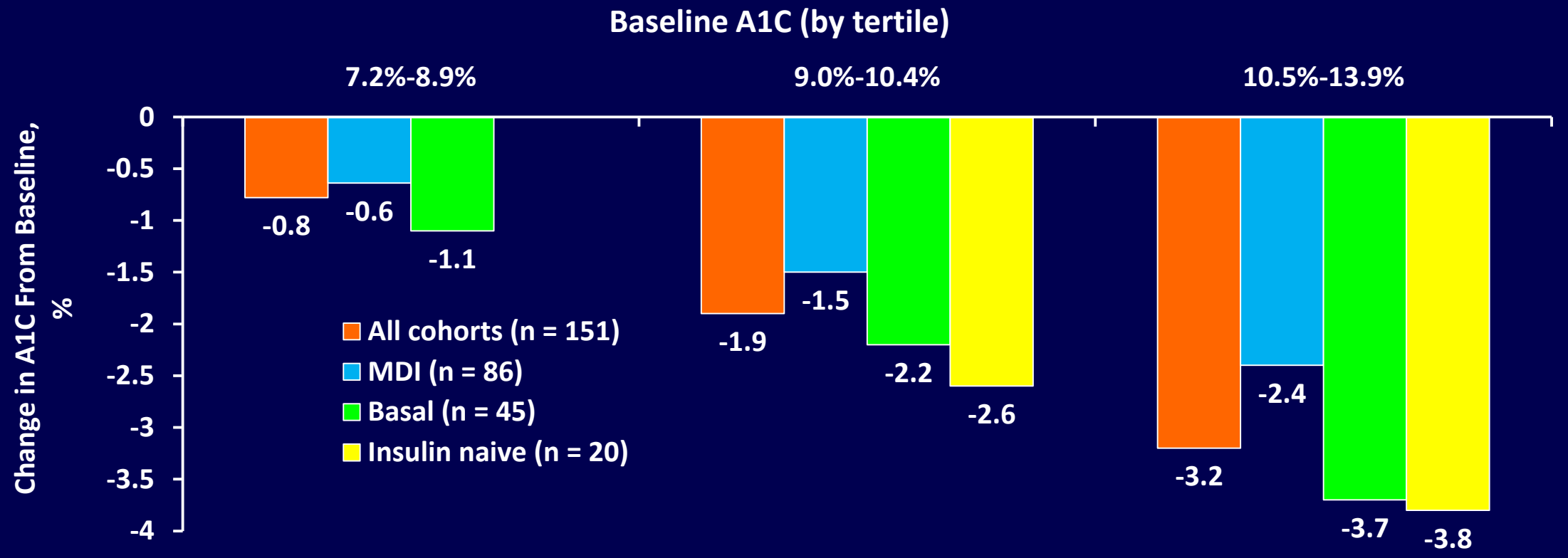


Muliinational RCT of 331 patients with T2DM comparing MDI to CSII, BL A1C = 9%, following a 2-month run-in phase to optimize multiple daily injection. Metformin was the only permitted background medication.

Reznik Y, et al. *Lancet.* 2014;384:1265-1272.

- A1C at 6 months:
  - 7.9% in CSII group vs 8.6% in MDI group
- Decrease in A1C was independent of:
  - Diabetes duration
  - BMI
  - Education level
  - Mild cognitive impairment
  - Daily SMBG tests
- No difference in weight gain
  - 1.5 vs 1.1 kg, CSII vs MDI (*P* = .25)
- Low rates of adverse events
  - More hyperglycemia events in CSII group, 5 events vs 1 event in MDI
  - No difference in nonsevere hypoglycemia

Insulin Delivery Technology—Disposable Patch Pump



- All A1C reductions from baseline were statistically significant ($P < .05$)
- A1C reductions were greater in patients with less intensive insulin therapy at baseline

Retrospective study of 151 patients with T2DM, 6 months after switching to a V-Go patch pump.

Lajara R, et al. *Diabetes.* 2015;64(suppl 1):A278 [abstract 1083-P].

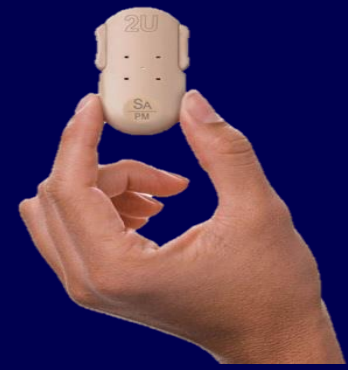
Current and Emerging Disposable Patch Pumps

OmniPod (Insulet)[1,2]

- Basal-bolus device
- Automated cannula insertion
- PDA-like controller
- Up to 200 units/d (U-100)

V-Go (Valeritas)[1,3]

- Basal-bolus device
- Automated basal dose delivery: 20, 30, or 40 units/d
- Manual 2-unit bolus dose delivery (up to 36 units/d)
- 100% mechanical
- No batteries



Finesse (J&J)[1,4]

- Anticipated 2016 launch
- Bolus-only device

1. Schaepelynck P, et al. *Diabetes Metab*. 2011;37(suppl 4):S85-S93; 2. https://www.myomnipod.com/about-omnipod/system-specs.
3. https://www.valeritas.com/indication. 4. http://www.in-pharmatechnologist.com/Drug-Delivery/J-J-to-increase-wearable-insulin-patch-pump-production.

Diabetes Forecast Consumer Guide—Durable Insulin Pumps and CGM, 2015

Pump[1]	Capacity, units (U-100)	Infusion Sets	CGM Integration
Tandem T:flex	480	Luer-lock	No
Roche Accu-Chek Combo	315	Luer-lock	No
Medtronic MiniMed 530G with Enlite	180 or 300	Proprietary	Yes
Medtronic MiniMed Paradigm Real-Time Revel	180 or 300	Proprietary	Yes
Sooil Dana Diabecare IIS	300	Proprietary	No
Animas OneTouch Ping	200	Luer-lock	No
Animas Vibe	200	Luer-lock	Yes

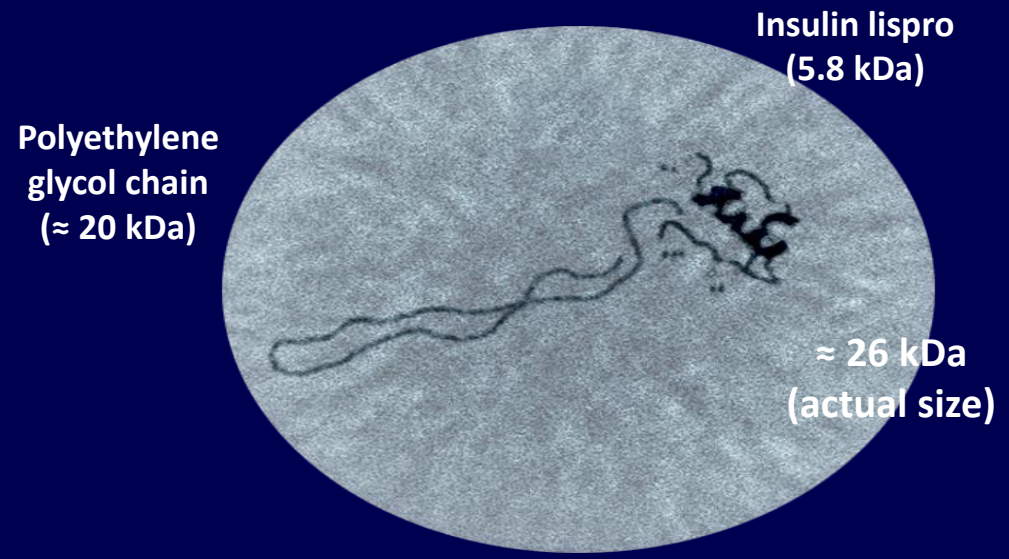
CGM[2]	Sensor duration, days	Software
Dexcom G4 Platinum	7	Proprietary
Medtronic Guardian Real-time	3	Proprietary

1. http://main.diabetes.org/dforg/pdfs/2015/2015-cg-insulin-pumps.pdf.
2. http://main.diabetes.org/dforg/pdfs/2015/2015-cg-continuous-glucose-monitors.pdf.

Peglispro - ? Pointing the Way to More Physiologic Basal Insulin

Insulin Peglispro[1-3]

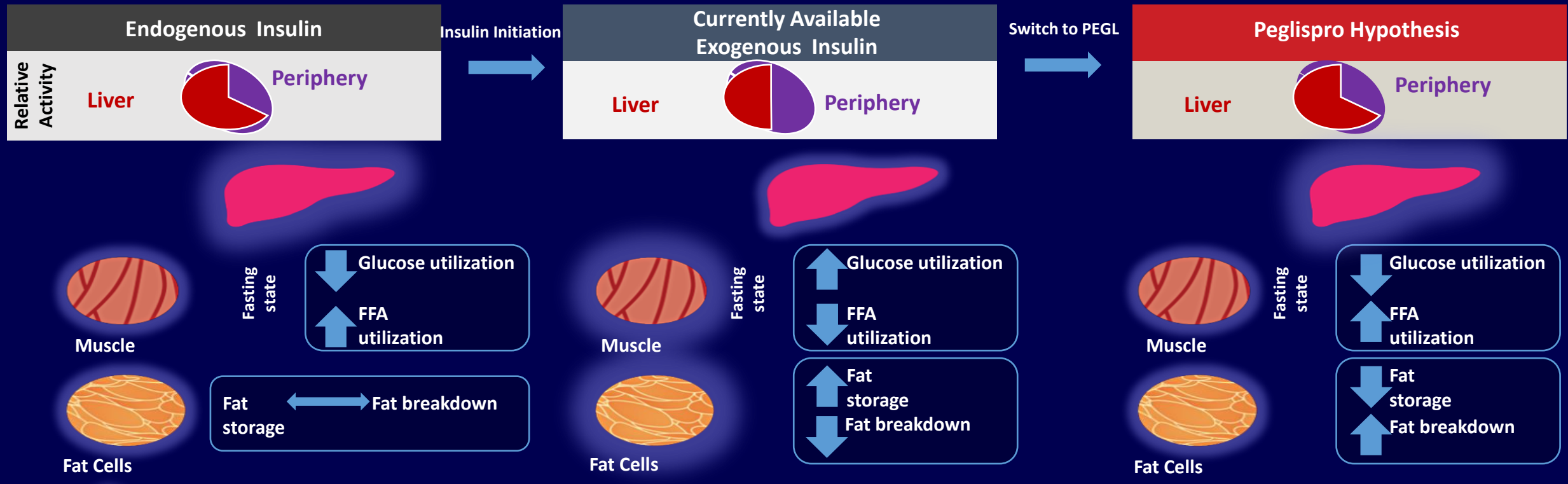
- **Delayed insulin absorption**
- **Reduced renal clearance**
- **Functional size exceeds that of albumin (71-98 kDa vs ≈ 65 kDa)**
- **Large size preserves hepatic distribution and activity**
- **Large size decreases peripheral action**



*Peglispro not FDA approved; development ceased as of Dec 2015.

1. Rosenstock J, et al. *Diabetes*. 2012;61(suppl 1):A263 [abstract 1026-P];
2. Henry RR, et al. *Diabetes Care*. 2014;37:2609-2615; 3. Moore MC, et al. *Diabetes*. 2014;63:494-504.

Endogenous and Exogenous Insulin Effects and Peglispro* Physiology



*Peglispro not FDA approved; development ceased as of Dec 2015.

In patients with T1DM, Peglispro has hepatic activity similar to that of glargine but attenuated peripheral activity, consistent with the characteristics of a hepatopreferential insulin

Mudaliar S, et al. *Diabetes*. 2015;64(suppl 1A):LB22 [abstract 89-LB].

Basal Insulin Peglispro* vs Glargine or NPH

	IMAGINE 2[1] 52 weeks, N = 1538	IMAGINE 4[2] 26 weeks, N = 1369	IMAGINE 5[3] 26 weeks, N = 466	IMAGINE 6[4] 26 weeks, N = 641
Comparator	GLAR	GLAR	GLAR	NPH
Δ A1C	PEGL better[a]	PEGL better[a]	PEGL better[a]	PEGL better[a]
Δ Weight	PEGL better[a]	PEGL better[a]	Equivalent	Equivalent
Nocturnal hypoglycemia	PEGL better[a]	PEGL better[a]	PEGL better[a]	PEGL better[a]
Documented symptomatic hypoglycemia	Favors PEGL	Favors PEGL	Favors PEGL	Favors PEGL

- **Peglispro has higher efficacy (0.2%-0.5% greater A1C reduction), with less nocturnal hypoglycemia (25%-60% less), than glargine or NPH**
- **Peglispro is associated with less weight gain than glargine (mean difference ≈ 0.5-1.0 kg)**

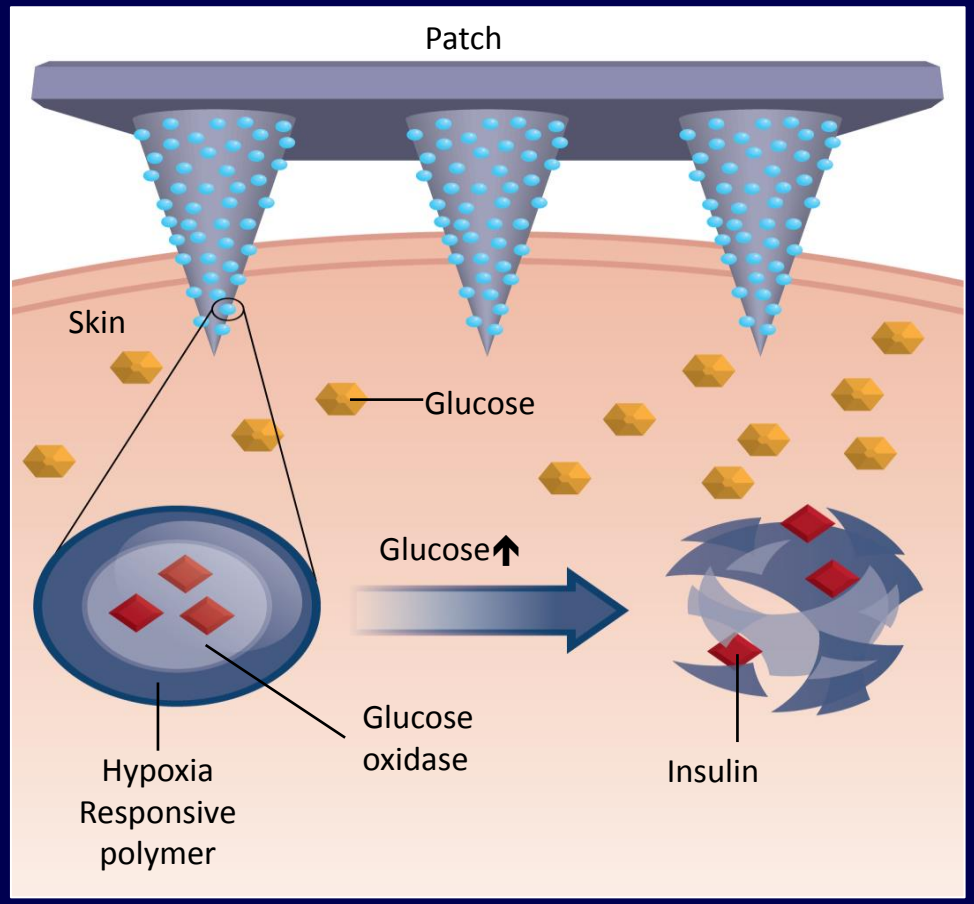
*Not FDA approved; development ceased as of Dec 2015.

[a] Statistically significant superiority, $P < .05$.

1. Davies, et al. *Diabetes*. 2015;64(suppl 1):A24 [abstract 93-OR].
2. Blevins et al. *Diabetes*. 2015;64(suppl 1):A250 [abstract 985-P].
3. Buse, et al. *Diabetes*. 2015;64(suppl 1):A249-A250 [abstract 984-P].
4. Grunberger et al. *Diabetes*. 2015;64(suppl 1):A256 [abstract 1004-P].

Microneedle Patches—Glucose Monitoring and Insulin Delivery in a Single Disposable Device

Not to be confused with patch pumps



6-mm² patch with 121 microneedles (600 µm long)[1]

Glucose oxidase converts glucose to gluconic acid, consuming oxygen[1]

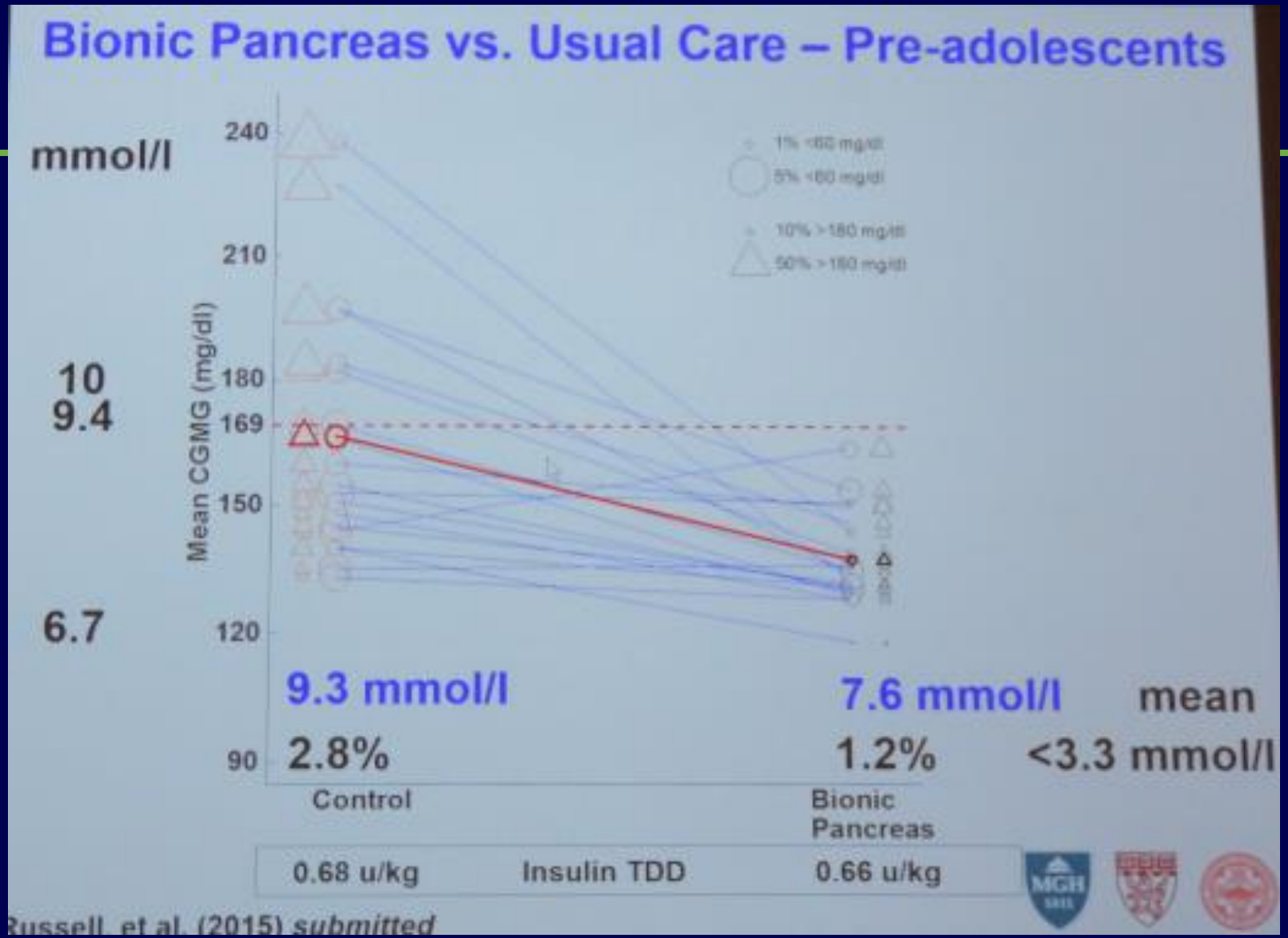
Hypoxia disassembles polymer coating, releasing insulin from nanoparticles[1]

Patch permits glucose-responsive insulin release[1]

Successfully demonstrated in a mouse model of T1DM[2]

1. Veiseh O, Langer R. *Nature*. 2015;524:39-40.
2. Yu J, et al. *Proc Natl Acad Sci U S A.* 2015;112:8260-8265.

2014 Summer Camp Study


Bionic Pancreas vs. Usual Care – Pre-adolescents
mmol/l
240
210
180
169
150
120
90
Mean CGMG (mg/dl)
10
9.4
6.7
9.3 mmol/l
2.8%
7.6 mmol/l
1.2%
mean
<3.3 mmol/l
Control
Bionic Pancreas
0.68 u/kg
Insulin TDD
0.66 u/kg
Russell, et al. (2015) submitted

Summary of New Options in Insulin Therapy

- New longer-acting basal insulins offer flatter, more predictable action that may produce less hypoglycemia and weight gain
- New faster-acting prandial insulins may better control post-prandial glucose with lower risk of hypoglycemia
- Patient acceptance of injectable therapies is excellent as the devices become ever easier to live with
- New technologies will expand pump and sensor use
- The loop is closing
- The cost of insulin therapies needs to be part of the discussion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