Initiating and Intensifying Insulin Therapy in Patients With Type 2 Diabetes

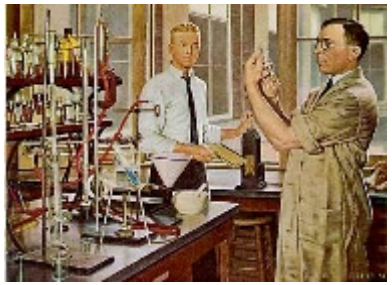
Initiation and Intensification of Insulin Therapy in Patients With Type 2 Diabetes – An Overview

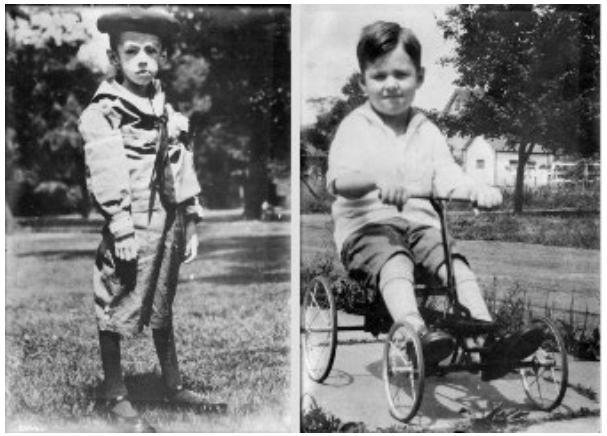
This presentation will discuss:

- Insulin evolution over the last century
- Strategies to select and initiate insulin treatment in patients with T2D
- Current treatment algorithms and the benefits of early insulinization
- The profiles of available basal and prandial insulin formulations
- Insulin delivery routes and formulations, including emerging options
- Therapeutic inertia and treatment intensification
- Using insulin therapy in combination with other antihyperglycemic agents
- Insulin safety, including cardiovascular safety and hypoglycemia risk

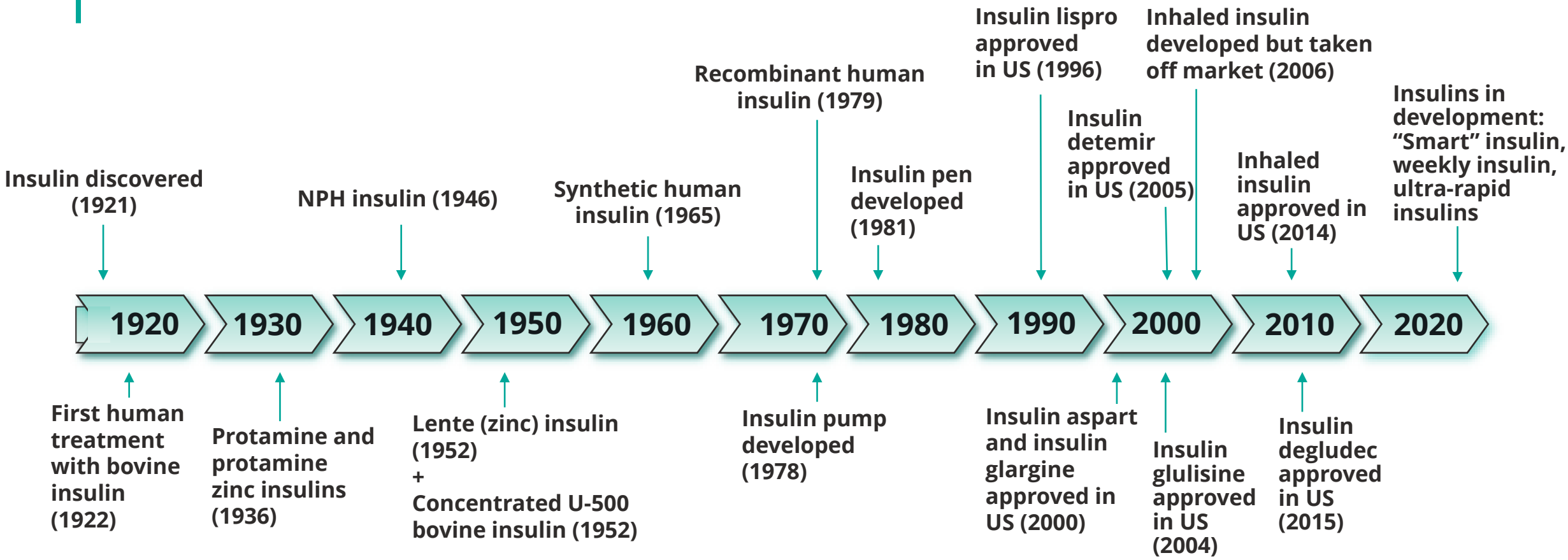
T2D, type 2 diabetes.

Celebrating 100 Years of Insulin Development: 1921-2021





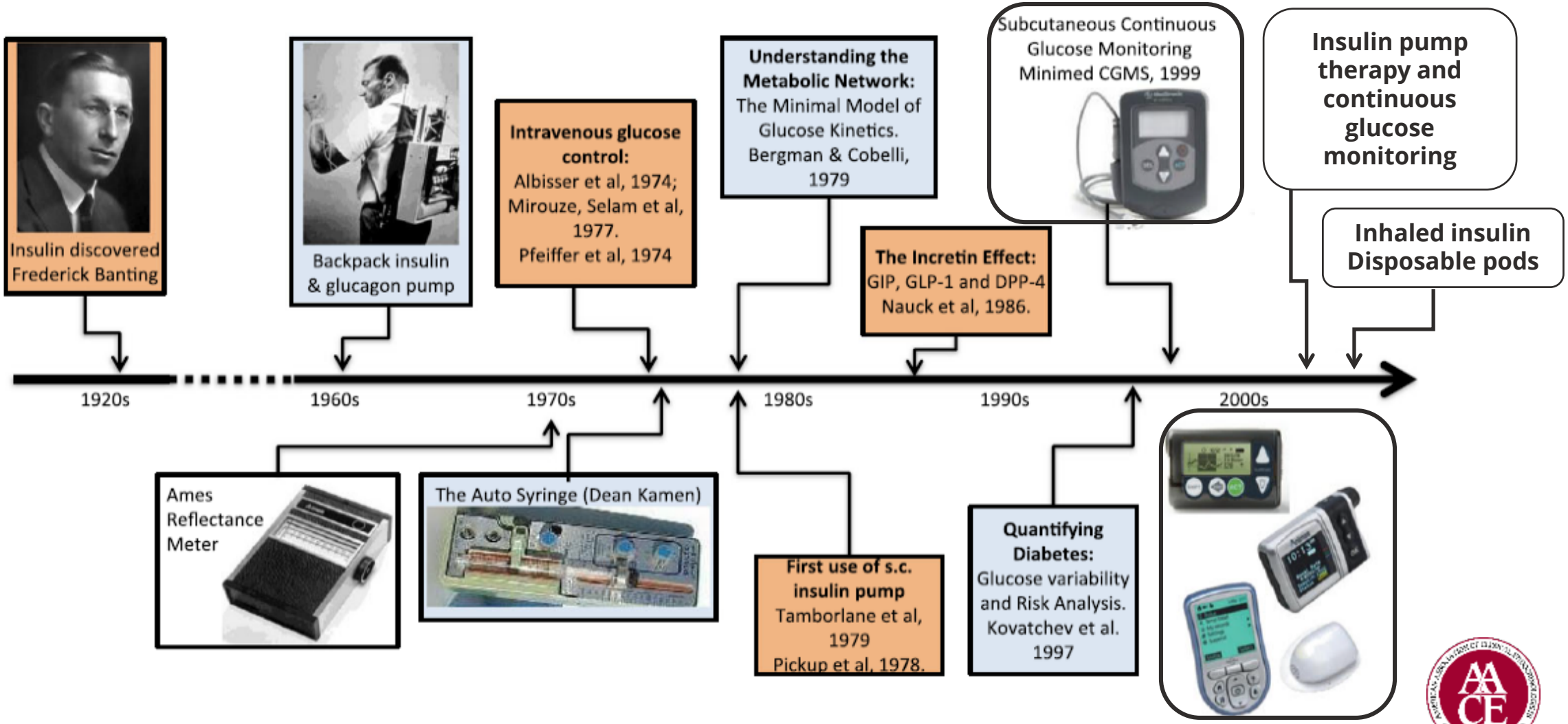
A Century of Insulin Development and Evolution



NPH, neutral protamine Hagedorn; US, United States.

Tattersall RB. In: Pickup JC, Williams G, eds. *Textbook of Diabetes*. 3rd ed. Blackwell Science: Malden, MA; 2003:1.1-1.22; Drugs@FDA; http://diabetes.webmd.com/news/20071018/pfizer-quits-inhaled-insulin-exubera; https://www.healio.com/news/endocrinology/20200518/the-future-of-insulin-pills-patches-weekly-formulation-could-change-diabetes-management.

A Timeline of Diabetes Technology



Adapted from: Kovatchev B. *Bioelectronic Medicine*. 2018;4(14).

Selecting Insulin vs Non-insulin Therapy in Patients With T2D

- Insulin is the most potent antihyperglycemic agent.[1]
- Many factors must be considered when choosing to initiate insulin therapy vs other antihyperglycemic agents.[1]
- Therapeutic selection for patients with T2D should be individualized based on patient and medication attributes.[1,2]
  - **Patient attributes**: Initial A1C level, diabetes duration, obesity status, age, hypoglycemia risk, and other comorbidities.
  - **Medication attributes**: Efficacy, mechanism of action, hypoglycemia risk, risk of weight gain, adverse events, tolerability, ease of use, likely adherence, and cost.
- With the goals of safety and risk reduction, select therapy that reflects the patient's cardiac, cerebrovascular, and renal status.[1,2]

T2D, type 2 diabetes.

1. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139. 2. American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212.

AACE Glycemic Control Algorithm:
When to Consider Insulin Therapy in Patients With T2D

Strong consideration as initial therapy →

A1C >9.0% and/or symptomatic hyperglycemia; with or without other antihyperglycemic agents

Option for consideration as initial therapy →

In combination with 1-2 other antihyperglycemic agents when A1C is ≥7.5%-9.0%

As treatment intensification →

Added to monotherapy or dual therapy when A1C goals are not met after 3 months

- Patients taking 2 oral agents with A1C >8.0% and/or long-standing T2D are less likely to reach target A1C with a 3rd non-insulin agent.
- Adding a 3rd non-insulin agent may successfully reduce glycemia in some patients, but many will eventually require insulin.

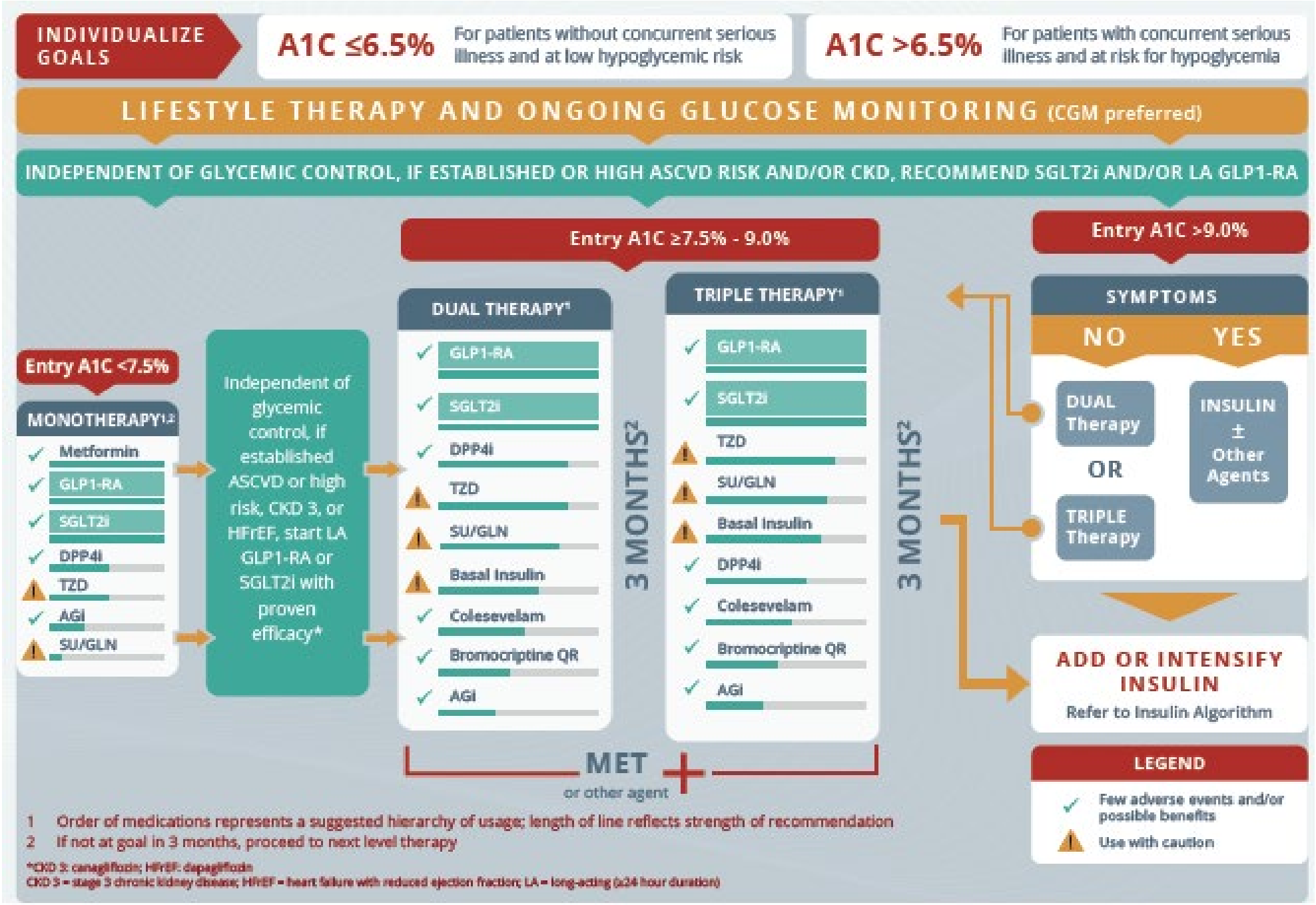
Choice of treatment depends on patient and medication

AACE, American Association of Clinical Endocrinologists; GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes.

Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139.

AACE Glycemic Control Algorithm

AGi, alpha-glucosidase inhibitor; **ASCVD**, atherosclerotic cardiovascular disease; **CGM**, continuous glucose monitoring; **CKD**, chronic kidney disease; **DPP4i**, dipeptidyl peptidase-4 inhibitor; **GLN**, glinides; **GLP-1 RA**, glucagon-like peptide-1 receptor agonist; **HFrEF**, heart failure with reduced ejection fraction; **LA**, long-acting; **MET,** metformin; **QR**, quick-release; **SGLT2i**, sodium-glucose cotransporter 2 inhibitor; **SU**, sulfonylurea; **T2D**, type 2 diabetes; **TZD**, thiazolidinedione.



Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139.

ADA Overall Approach to Glucose-Lowering Medication: When to Consider Insulin Therapy in Patients With T2D

- The early introduction of insulin should be considered in the setting of ongoing catabolism (weight loss, hypertriglyceridemia, ketosis), symptoms of hyperglycemia, A1C levels >10%, and/or blood glucose levels ≥300 mg/dL.
- Insulin can be added to metformin (first-line therapy) if the A1C target is not achieved after 3 months.
- Due to the progressive nature of T2D, many patients eventually require and benefit from insulin therapy.

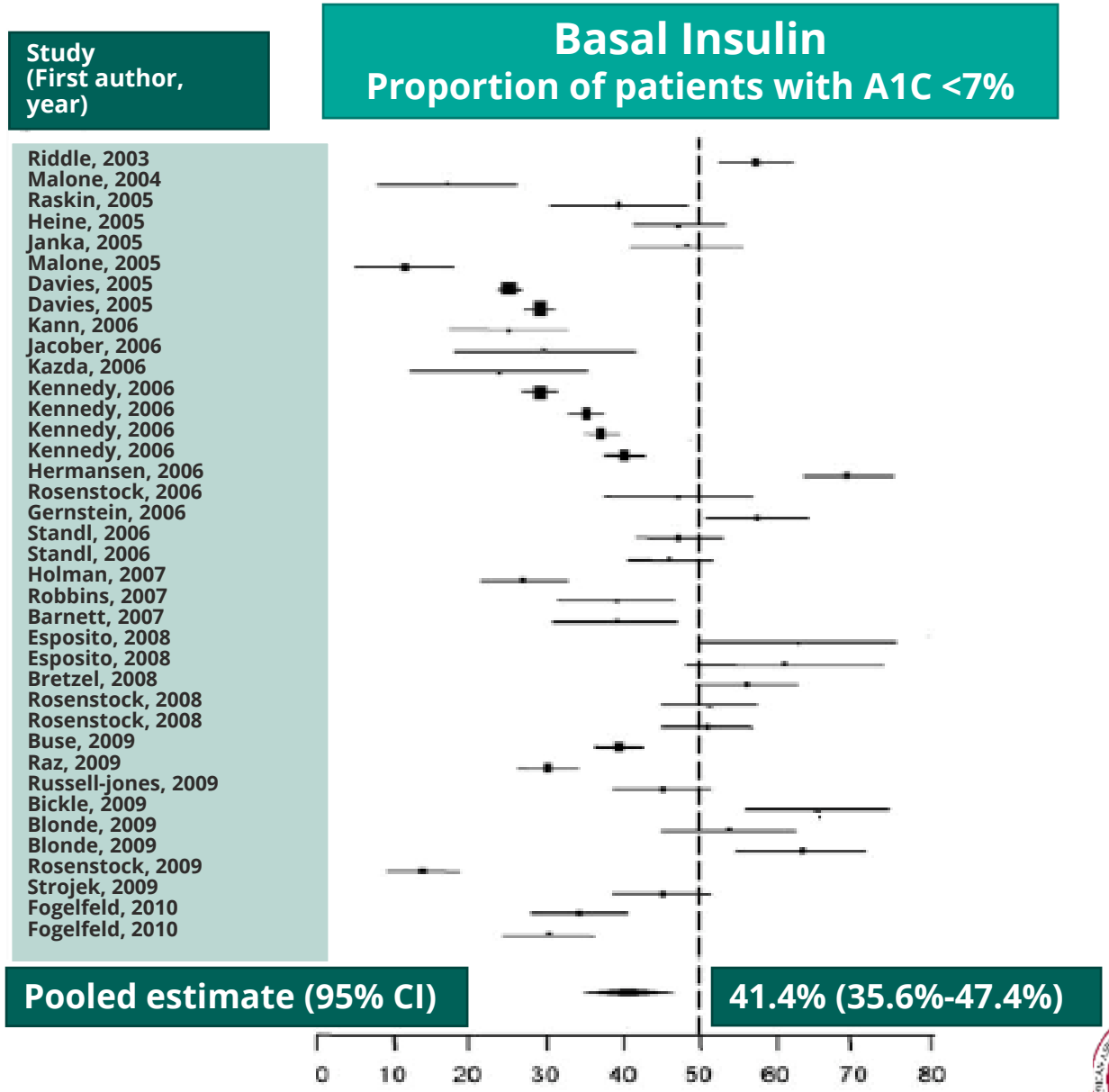
Agents other than insulin may be preferred;
choice of treatment depends on patient and medication attributes.

ADA, American Diabetes Association; T2D, type 2 diabetes.

American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212.

Achievement of A1C <7% With Basal Insulin Regimen in T2D

- Systematic review (29 RCTs, N=17,588 patients) evaluating the effectiveness of insulin analog regimens
- A1C <7% achieved in 41.4% (95% CI: 35.6%, 47.4%)
- Predictors of response: first insulin treatment; lower insulin dose; use of 2 OADs
- Over 30 days, mean/median hypoglycemia with basal insulin was 0.50/0.39 events/patient
- Weight gain: 1.8 kg (95% CI: 1.2, 2.1)



CI, confidence interval; OAD, oral antidiabetic drug; RCT, randomized controlled trial.

1. Giugliano D, et al. *Res Clin Pract*. 2011;92(1):1-10.

Very Early Insulinization in T2D

- Evidence suggests that early, short-term insulin treatment can improve glycemic control and preserve beta-cell function in patients with newly diagnosed T2D and severe, symptomatic hyperglycemia.[1-3]
- By treating patients with insulin before diabetes has progressed (typically for 2 weeks to 3 months), glucolipotoxicity is rapidly reversed, and beta-cells are given the chance to "rest." [1-3]
- Several controlled and uncontrolled studies have shown that intensive, early, short-term insulin therapy can lead to sustained normoglycemia for up to 12 months in ~31%-51% of patients.[1,4-9]
  - This treatment approach may also preserve residual beta-cell function, enabling the effective, future use of non-insulin antihyperglycemic agents.[1,6,7]

T2D, type 2 diabetes.

1. Raz I, et al. *Diabetes Care.* 2013; 36(suppl 2):S190-S197. 2. Owens DR. *Diabetes Technol Ther*. 2013;15(9):776-785. 3. Hanefield M. *Diabetes Metab*. 2014;40(6):391-399; 4. Ilkova H, et al. *Diabetes Care*. 1997;20(9):1353-1356. 5. Ryan EA, et al. *Diabetes Care*. 2004;27(5):1028-1032. 6. Li Y, et al. *Diabetes Care*. 2004;27(11):2597-2602. 7. Weng J, et al. *Lancet*. 2008;371(9626):1753-1760. 8. Chen HS, et al. *Diabetes Care*. 2008;31(10):1927-1932. 9. Mu PW, et al. *Diabetes Metab Res Rev*. 2012;28(3):236-240.

Patients With Ketosis-Prone T2D Require Early Insulinization

- Ketosis-prone T2D is characterized by the new, acute onset of hyperglycemia with ketoacidosis, requiring hospitalization.[1]
- Patients often have a family history of T2D and are predominantly:[1-4]
  - Black or Latino
  - Middle-aged (but can be younger)
  - Overweight and/or obese
  - Male
- Patients present with impaired insulin secretion and action;[3] the clinical course resembles T2D.[1]
- Treatment requires intensive, initial insulin for several weeks to months.[1,3]
- Following insulin discontinuation, metabolic abnormalities typically improve, and a proportion of patients enter a period of near-normoglycemic remission.[1,3]

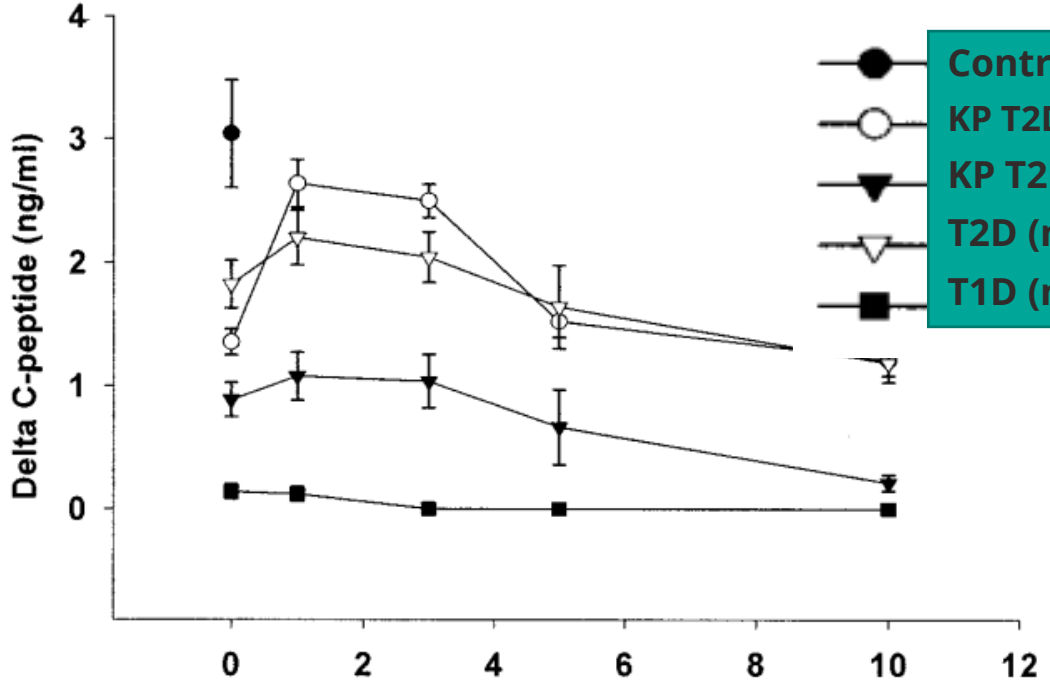
T2D, type 2 diabetes.

1. Lebovitz HE, et al. *Curr Diab Rep*. 2018;18(11):120. 2. Wang X, et al. *Biomed Rep*. 2015; 3(4):439-442. 3. Umpierrez GE. *Diabetes Care*. 2006;29(12):2755-2757. 4. Balasubramanyam A, et al. *Endocr Rev*. 2008:29(3):292-302.

Early Insulinization in Patients With Ketosis-Prone T2D: 40.5% Remained in Remission at 10 Years' Follow-up

- Cohort study of 111 hospitalized patients with KP T2D (both insulin-dependent and nondependent) of Sub-Saharan African descent
- With early treatment, a majority (75.7%) achieved remission from insulin dependence:
  - Mean time to remission, 14.3 weeks
  - Mean duration of remission, 40.5 ± 23.2 months
- At 10 years of follow-up, 40.5% of patients remained in remission
- Study also included patients with T1D T2D, and controls (see Figure)

Ten-year beta-cell secretory reserve following early intensive insulin therapy, with T1D or T2D (with or without KP in T2D) and controls



ID, insulin-dependent; **KP**, ketosis-prone; **NID**, non-insulin dependent; **T1D**, type 1 diabetes; **T2D**, type 2 diabetes.

1. Mauvais-Jarvis F, et al. *Diabetes*. 2004;53(3):645-653.

Characteristics of Basal Insulins

- Typically administered as a single daily dose, they can be added to oral agents.[1,2]
- They restrain hepatic glucose production and limit between-meal and overnight hyperglycemia.[1]
- Basal insulin analogs are preferred over NPH insulin because a single basal analog dose provides a relatively flat serum insulin concentration for ≥24 hours.[2]
- Long-acting basal analogs (glargine U100 or detemir) have been shown to reduce the risk of symptomatic and nocturnal hypoglycemia vs NPH insulin.[1,2]
- The newest ultralong-acting basal insulin formulations (glargine U300, degludec U100, and U200) have more prolonged and stable pharmacokinetic and pharmacodynamic characteristics than glargine U100 and detemir.[2]
  - They may confer lower hypoglycemia risk.[1,2]
  - Degludec U200 and glargine U300 are more concentrated than their U100 formulations, allowing for higher doses of basal insulin administration per volume injected.[1]
- Regular U-500 insulin has delayed onset and a longer duration of action; it functions similarly to an intermediate-acting (NPH) insulin and can be used as 2 or 3 daily injections.[1]

NPH, neutral protamine Hagedorn; T2D, type 2 diabetes.

1. American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212. 2. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139.

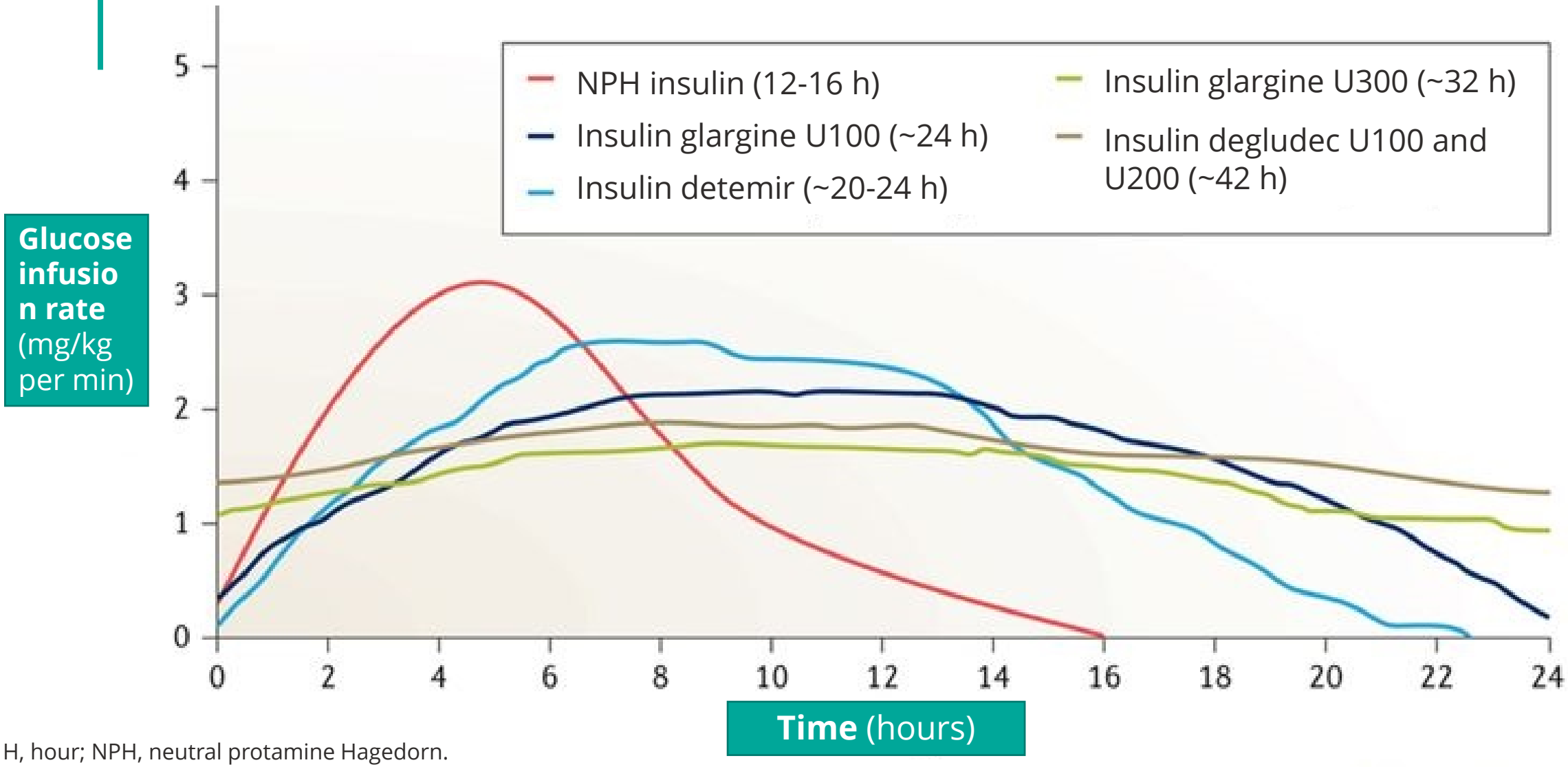
Available Basal Insulins

	NPH Insulin[1-2]	Insulin Glargine*[1,3-4]	Insulin Detemir[5-6]	Glargine U300[7-8]	Insulin Degludec U100 and U200[9]
Insulin type	Human; intermediate-acting	Analog; long-acting	Analog; long-acting	Analog; ultralong-acting	Analog; ultralong-acting
Onset	1-2 hours	1.5 hours	3-4 hours	6 hours	1 hour
Peak	4-10 hours	Flat	Relatively flat	Flat	Flat
Effective duration	14+ hours	≤24 hours	≤24 hours	≤36 hours	≤42 hours
Half-life	Unknown	12.5 hours	5-7 hours	17-19 hours	~25 hours
Steady state	Unknown	2-4 days	2 days	3-4 days	3-4 days

* Pharmacodynamic properties of biosimilar insulin glargine are similar to that of insulin glargine.

1. Donner T, et al. In: *Endotext*. South Dartmouth (MA): MDText.com, Inc. 2. Humulin N (isophane insulin human suspension) [prescribing information]. Lilly USA; 2019. 3. Heise T, et al. *Endocrine Abstracts.* 2012;28:188. 4. Lantus® U-100 Summary of Product Characteristics. Sanofi; updated March 24, 2020. 5. Levemir® (insulin detemir injection) [prescribing information]. Novo Nordisk Inc.; 2020. 6. Bott S, et al. *Diabet Med*. 2006;23(5):522-528. 7. Toujeo® (insulin glargine injection) U-300 [prescribing information]. Sanofi-Aventis US LLC; 2019. 8. Rosselli JL, et al. *J Pharm Technol*. 2015;31(5):234-242. 9. Tresiba® (insulin degludec injection) [prescribing information]. Novo Nordisk Inc.; 2019.

Basal Insulin Action Profiles



H, hour; NPH, neutral protamine Hagedorn.

Mathieu C, et al. *Nat Rev Endocrinol*. 2017;13:385-399.

Median Cost of Insulin Products in the US

Average Wholesale Price per 1,000 Units of Specified Dosage Form/Product[1]

	Compound	Dosage form/product	AWP
Rapid-acting	Lispro follow-on product	U-100 vial U-100 prefilled pen	$157 $202
	Lispro	U-100 vial U-100 3 mL cartridges U-100 prefilled pen U-200 prefilled pen	$330 $408 $424 $424
	Glulisine	U-100 vial U-100 prefilled pen	$341 $439
	Aspart (original and faster-acting)	U-100 vial U-100 3 mL cartridges U-100 prefilled pen	$347 $430 $447
	Inhaled insulin	Inhalation cartridges	$924
Short-acting	Human regular	U-100 vial	$165
Intermediate-acting	Human NPH	U-100 vial U-100 prefilled pen	$165 $377
Concentrated human regular	U-500 human regular insulin	U-500 vial U-500 prefilled pen	$178 $230
Long- and ultralong-acting	Glargine follow-on	U-100 prefilled pen U-100 vial; U-100 prefilled pen	$261 $340
	Glargine	U-300 prefilled pen	$346
	Detemir	U-100 vial; U-100 prefilled pen	$370
	Degludec	U-100 vial; U-100 prefilled pen U-200 prefilled pen	$407 $407

AWP, average wholesale price; COVID-19, coronavirus disease 2019; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NPH, neutral protamine Hagedorn; PAP, patient assistance program.

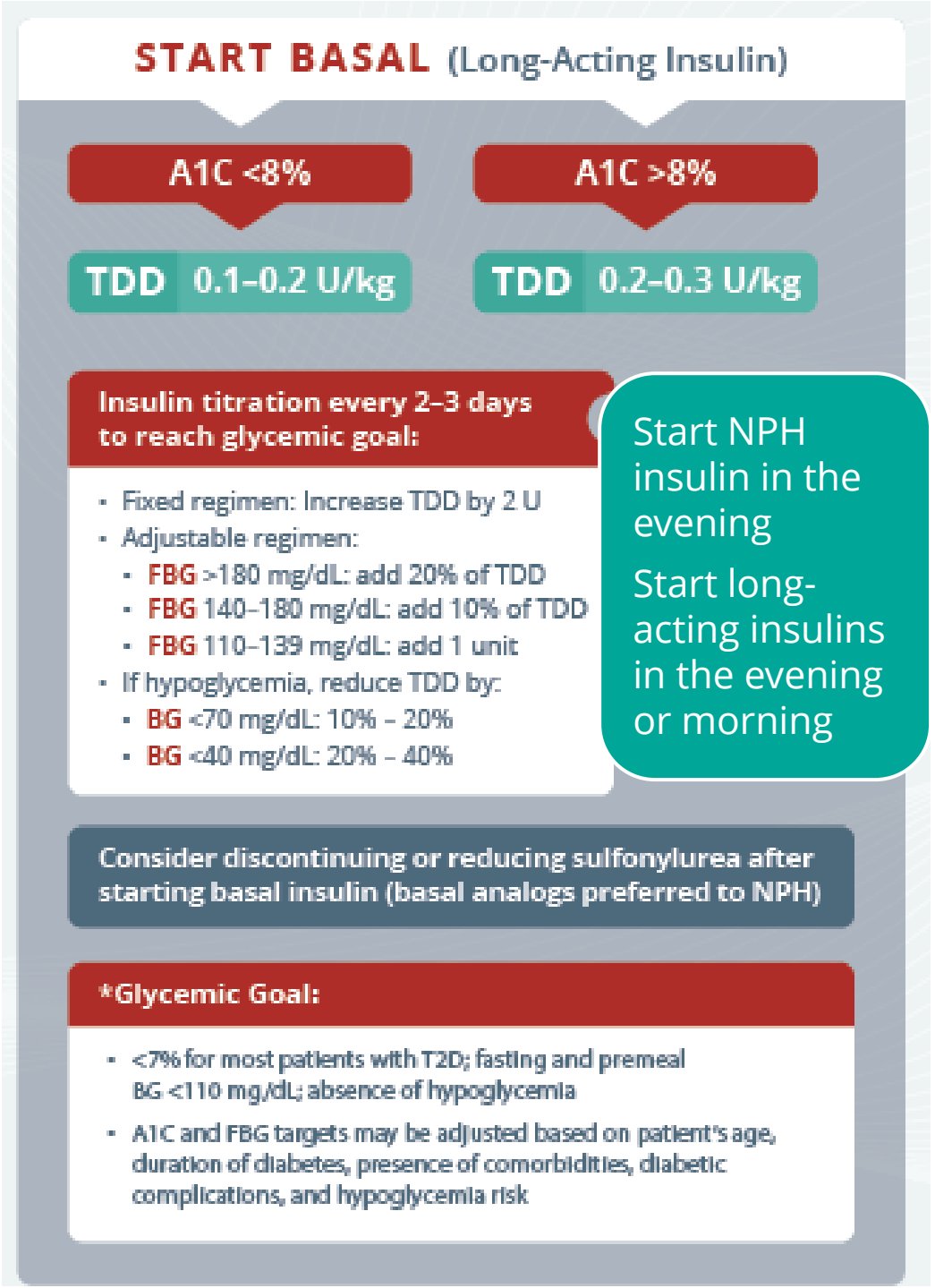
- Insulin cost has steadily risen over past 2 decades, burdening patients and contributing to nonadherence.[1]
- Some PAPs provide low/no-cost insulin products.[2]
- Human insulins are available for ~$25/vial at Walmart and Sam's Club.[3]
- Some prices are temporarily lowered due to COVID-

Drug Category	Compound	Dosage form/product	AWP
Premixed insulin products	NPH/regular 70/30	U-100 vial U-100 prefilled pen	$165 $377
	Lispro 50/50	U-100 vial U-100 prefilled pen	$342 $424
	Lispro 75/25	U-100 vial U-100 prefilled pen	$342 $424
	Aspart 70/30	U-100 vial U-100 prefilled pen	$360 $447
Premixed insulin/GLP-1 RA products	Glargine/lixisenatide	100/33 prefilled pen	$565
	Degludec/liraglutide	100/3.6 prefilled pen	$832

1. American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212. 2. https://www.healthline.com/health/insulin-medication-comparing-patient-assistance-programs#1. 3. https://www.thediabetescouncil.com/relion-insulin-everything-need-know/. 4. https://www.drugtopics.com/diabetes/insulin-affordability-options-expand-during-covid-19.

Adding/Intensifying Insulin in Patients With T2D

- When insulin becomes necessary, add a single daily dose of basal insulin to the regimen.
- Adjust dosage at regular and initially short intervals, measured in days, to achieve targeted glycemic goal while avoiding hypoglycemia.



BG, blood glucose; FBG, fasting blood glucose; NPH, neutral protamine Hagedorn; TDD, total daily dose.

Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139.

Avoiding Therapeutic Inertia During Treatment Intensification

Clinical or therapeutic inertia occurs when treatment is not initiated or intensified, despite a patient not achieving their A1C goal.[1]

- All patients should be educated on the progressive nature of T2D.[2,3]
- Avoid using insulin as a threat or sign of personal failure or punishment.[2,4]
- Do not delay intensification if treatment is not meeting goals; timely glycemic control has a beneficial effect on patient outcomes.[2,4]
- Reevaluate regimen every 3-6 months and adjust/intensify as needed.[2,5]
- If goals not met with OADs, it is recommended to intensify treatment to injectable agent (GLP-1 RA or insulin).[2,5]

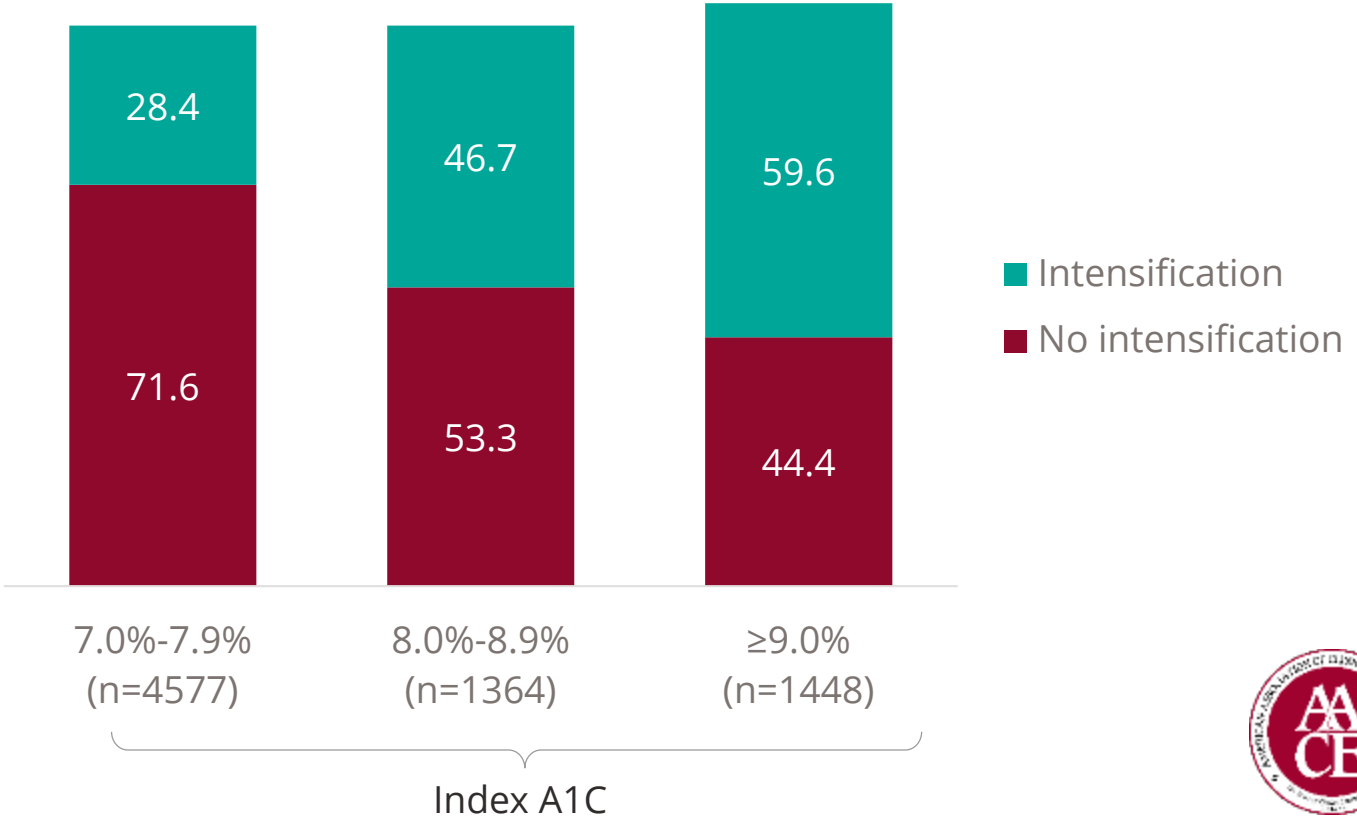
GLP-1 RA, glucagon-like peptide-1 receptor agonist; OADs, oral antidiabetic drugs; T2D, type 2 diabetes.

1. Okemeh J. *Adv Ther*. 2018:1735-1745; 2. American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212. 3. Khunti K, et al. *Diabetes Care*. 2013;36(11):3411-3417. 4. Meece J. *Diabetes Educ*. 2006;32(suppl 1):S9-S18. 5. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139.

Rates of Treatment Intensification and Non-intensification in Patients With T2D

Treatment intensification rates (by A1C) in the 6-month period following A1C ≥7%

- Retrospective electronic health records analysis of Cleveland Clinic patients (N=7389; 2005-2016)
- Overall, 63% did not receive therapeutic intensification in the 6 months following an elevated A1C measurement



T2D, type 2 diabetes.

1. Pantalone KM, et al. *Diabetes Care*. 2018;41(7):e113-e114.

Patient-Related Factors for Delaying Insulin Therapy

- Misconceptions
  - Progression to insulin signifies failure to control disease
  - Insulin is toxic, may lead to amputations, blindness, or other complications[1,2]
- Fear of needles/injections, weight gain, hypoglycemia[1,2]
- Lack of information, experience, and/or support managing insulin regimens[1,2]
- Inconvenient, time-consuming[1]
- Concerns about potential permanence of therapy[2]
- Complexity of regimen[2]
- Cost[1,2]

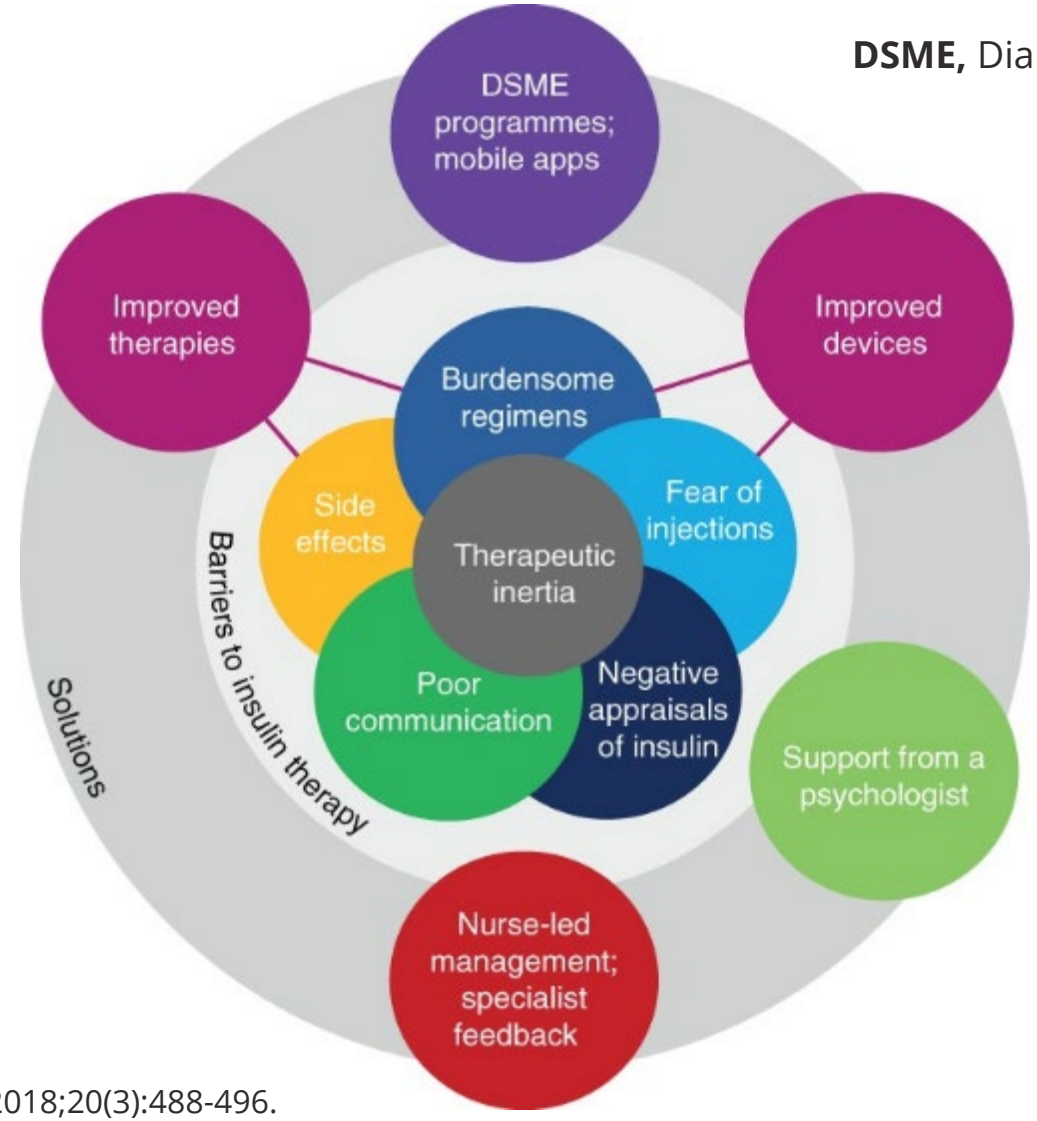
1. Meece J. *Diabetes Educ*. 2006;32(suppl 1):S9-S18. 2. Karam SL, et al. *Diabetes Spectr*. 2020;33(1):8-15.

Real-World Choices Depend on the Patient

- Key variables, factors to consider[1,2]
  - Patient preference for simpler regimen
  - Frequency of self-monitoring of blood glucose
  - Lifestyle variability, including meal timing and carbohydrate intake
  - Presence of postprandial hyperglycemia
  - Patient's ability to follow the prescribed regimen
  - Educational and emotional support available to patient
  - Patient dexterity issues, age, visual impairment
  - Cost barriers, insurance coverage

1. American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212. 2. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139.

Barriers to Insulin Therapy and Strategies to Overcome Them



DSME, Diabetes self-management education.

Russell-Jones D, et al. *Diabetes Obes Metab*. 2018;20(3):488-496.

Available Delivery Routes for Insulin Administration

Subcutaneous

- Syringes
- Pens
- Disposable pods (basal/bolus)
  - V-Go® (1/day)
  - OmniPod DASH™ (2-3/day)
- Insulin pumps (basal/bolus)

Other methods

- Inhaled (Afrezza®)
- Intravenous (hospital use)

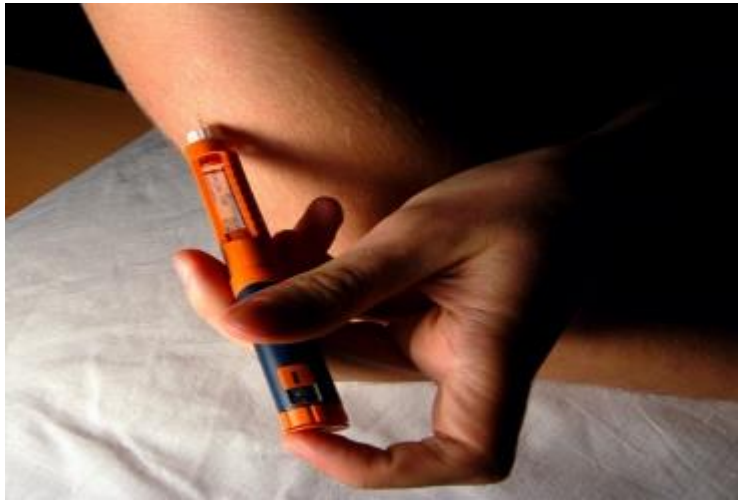
Insulin Pens:
One Strategy to Overcome Therapeutic Inertia

Advantages[1,2]

- Convenience; syringe and vial combined in 1 device
- Improved patient satisfaction and adherence
- Greater dosing accuracy
- Ease of use
- Greater portability
- Mealtime flexibility
- Less reported pain
- Social acceptability and improved quality of life

Barriers[3]

- Potentially higher costs than insulin vials
- Insurance coverage



1. Pearson TL. *J Diabetes Sci Technol*. 2010;4(3): 522-531. 2. American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212.

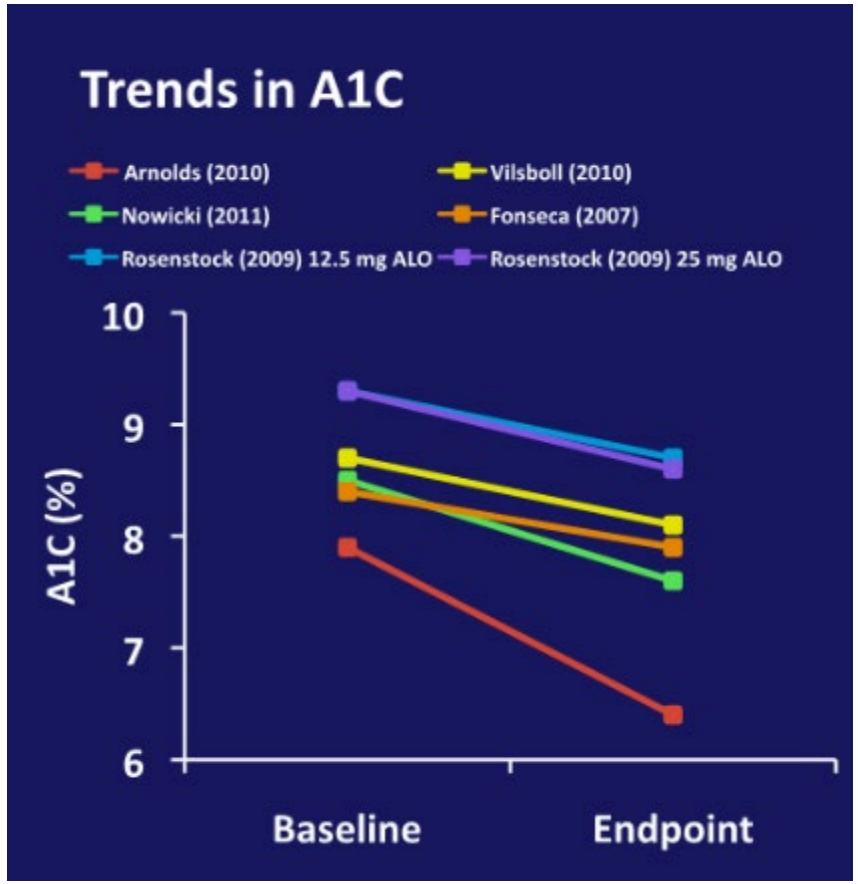
Basal Insulin in Combination With Non-insulins to Cover Postprandial Glucose Excursions

- A GLP-1 RA, SGLT2i, or DPP4i can be added to basal insulin to achieve glucose targets.[1]
- When added to insulin, incretins and SGLT2 inhibitors enhance glucose reductions.[1]
- Incretins and SGLT2 inhibitors may promote weight loss without increasing hypoglycemia risk.[1]
  - Insulin dose reductions may be necessary to reduce hypoglycemia risk; monitor and adjust as approriate.[2-3]
- Incretins also increase endogenous insulin secretion in response to meals, reducing postprandial hyperglycemia.[1]
- Basal insulin + a GLP-1 RA may offer greater efficacy than oral agents; fixed-ratio combinations are available.[1,4]
  - Basal insulin dose may need to be reduced to avoid hypoglycemia.[1]

DPP4i, dipetydl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

1. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139. 2. Victoza® (liraglutide injection) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc.; 2019. 3. Jardiance® (empagliflozin) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2020. 4. American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212.

Basal Insulin Plus Incretin Therapy in T2D: DPP-4 Inhibitors



- Systematic review of 5 RCTs evaluating DPP4i (ALO, SAXA, SITA, VILDA) combined with basal insulin in patients with T2D (N=1502)
- The combination of DPP4i with insulin improved glycemic control without excess hypoglycemia and with less weight gain than non-incretin-based therapies

Author, year	Fonseca, 2007	Rosenstock, 2009	Arnolds, 2010	Visboll, 2010	Nowicki, 2011
Intervention	**VILDA** + **INS** vs **INS** + **PBO**	**ALO** (12.5 mg) + **INS** ± **MET** vs **ALO** (25 mg) + **INS** ± **MET** vs **PBO** + **INS** ± **MET**	**GLA** + **MET** + **EXE** vs **GLA** + **MET** + **SITA** vs **GLA** + **MET**	**SITA** + **INS** ± **MET** vs **INS** ± **MET** + **PBO**	**SAXA** + **INS** ± **OAD** vs **INS** ± **OAD** + **PBO** in patients with **CKD**
All hypoglycemic episodes (major)	113 vs 185 (0 vs 6)	35 vs 35 vs 31* (0 vs 1 vs 6)	47 vs 12 vs 10 (0 vs 0 vs 0)	155 vs 76 (2 vs 1)	17 vs 19 (0 vs 2)

* Number of patients reporting ≥1 event

ALO, alogliptin; CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase 4 inhibitor; EXE, exenatide; GLA, glargine; INS, insulin; MET, metformin; OAD, oral antidiabetic drug; PBO, placebo; RCT, randomized controlled trial; T2D, type 2 diabetes; SAXA, saxagliptin; SITA, sitagliptin; VILDA, vildagliptin.

1. Rizos EC, et al. *Curr Vasc Pharmacol*. 2013;11(6):992-1000.

Basal Insulin Plus SGLT2 Inhibitors in T2D

CANA RCT (N=2072, 18 weeks); patients inadequately controlled on insulin ± OADs

- A1C change with CANA 100 and 300 mg vs PBO: -0.6% and -0.7%; (*P*<0.001 for both)[1]

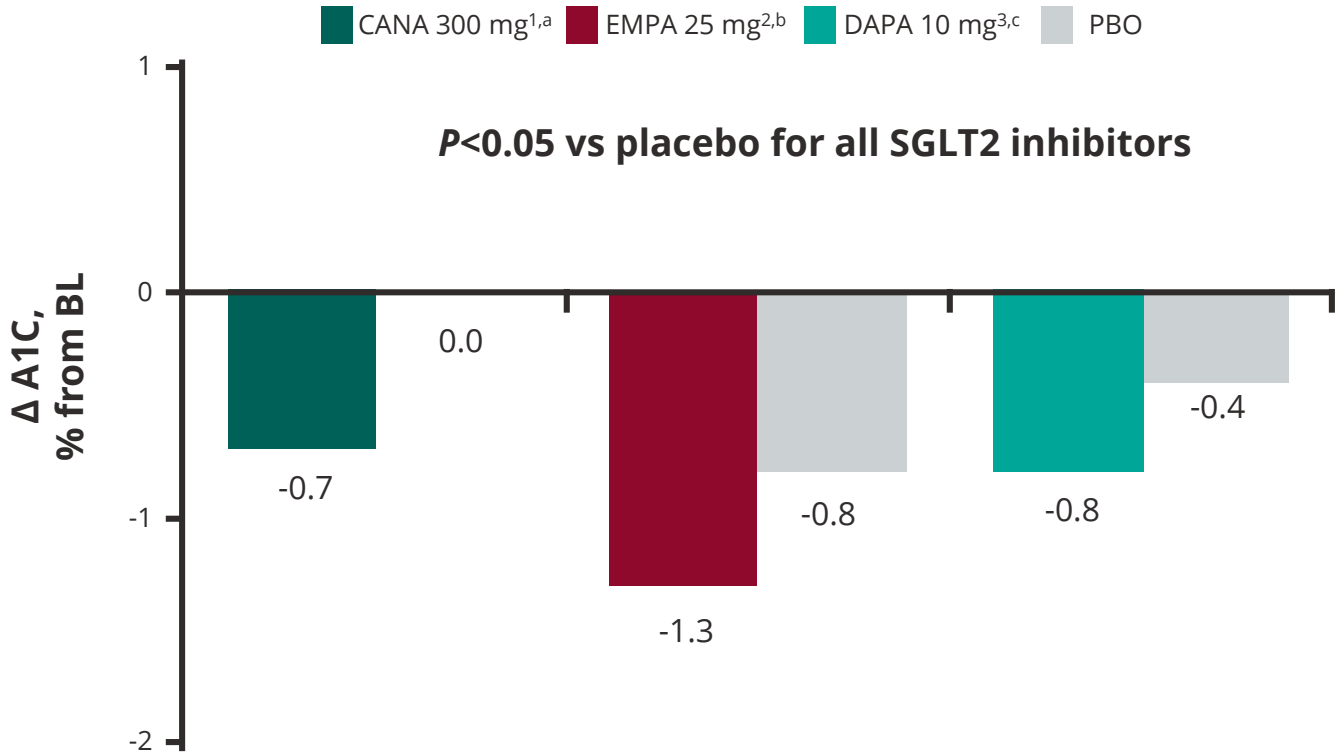
EMPA RCT (N=563, 52 weeks); patients inadequately controlled on insulin ± MET

- A1C change with EMPA 10 and 25 mg vs PBO: -0.4% and -0.5%; (*P*<0.001 for both)[2]

DAPA RCT (N=808, 104 weeks); patients inadequately controlled on insulin ± OADs

- A1C change with DAPA 5mg/10mg and 10 mg vs PBO: -0.4% and -0.5%; (*P*<0.001 for both)[3]

In the CANA and EMPA studies, patients treated with SGLT2i had statistically significant weight loss vs PBO[1,2]



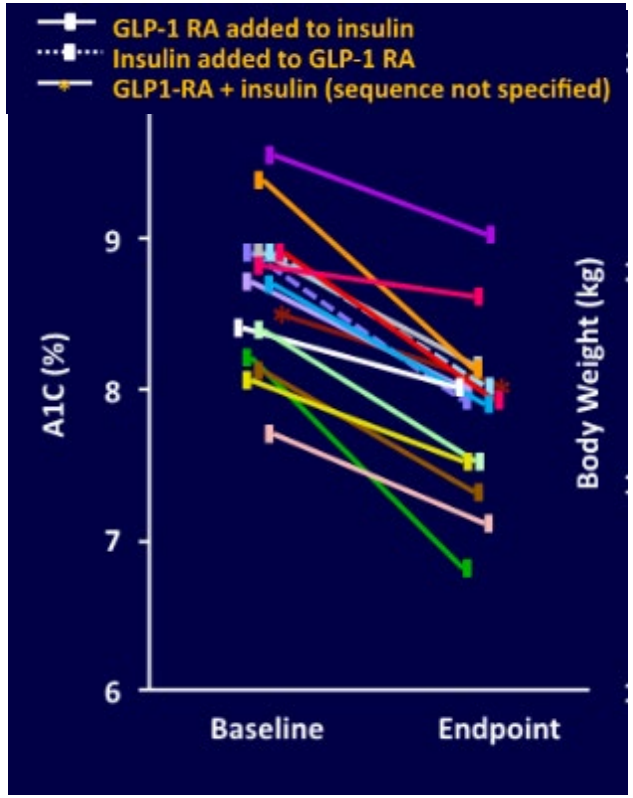
[a] 18 weeks; BL A1C 8.3% (mean); basal, bolus, or basal-bolus; ≈60% to 65% on basal-bolus; [b] 52 weeks; BL A1C 8.29%-8.39%; multiple daily insulin (basal-bolus) injections, insulin titrated weeks 19 to 40; [c] 104 weeks; BL A1C 8.46%-8.62%; 17% on basal only, 83% on bolus or basal-bolus (≈48% basal-bolus, ≈35% bolus only).

BL, baseline; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; MET, metformin; OAD, oral antidiabetic drug; PBO, placebo; RCT, randomized controlled trial; SLGT2i, sodium-glucose cotransporter-2 inhibitor.

1. Neal B, et al. *Diabetes Care*. 2015;38:403-411.
2. Rosenstock J, et al. *Diabetes Care*. 2014;37:1815-1823.
3. Wilding J, et al. *Diabetes Obes Metab*. 2014;16:124-136.

Basal Insulin Plus Incretin Therapy in T2D: GLP-1 RAs

Systematic review (RCTs and real-world studies), representing ~5000 patients with T2D



- Review analyzed the safety and efficacy of insulin + GLP-1 RA combination therapy.
- Combination therapy improved glycemic control without increased weight gain or hypoglycemia.
- Relative treatment benefit was influenced by insulin titration patterns.
  - Aggressive insulin titration to optimize glycemic control yielded less weight loss benefit.
  - Insulin sparing was associated with greater weight loss but more modest glycemic control.

GLP-1 RA, glucagon-like peptide-1 receptor agonist; RCT, randomized controlled trial; T2D, type 2 diabetes.

Balena R, et al. *Diabetes Obes Metab*. 2013;15(6):485-502.

Fixed-Ratio Combinations of Basal Insulin and GLP-1 RA

- iGlarLixi 100/33
- Insulin glargine and lixisenatide injection
- Approved by FDA November 2016
- Indication: Adults with T2D inadequately controlled on basal insulin (<60 units daily) or lixisenatide
- 1 unit contains:
  - 1 U insulin glargine and
  - 0.33 mcg lixisenatide
- Administered SC once daily
- Starting dose: 15 or 30 units (15 or 30 U insulin glargine and 5 or 10 mcg lixisenatide)
- SoloStar® pen

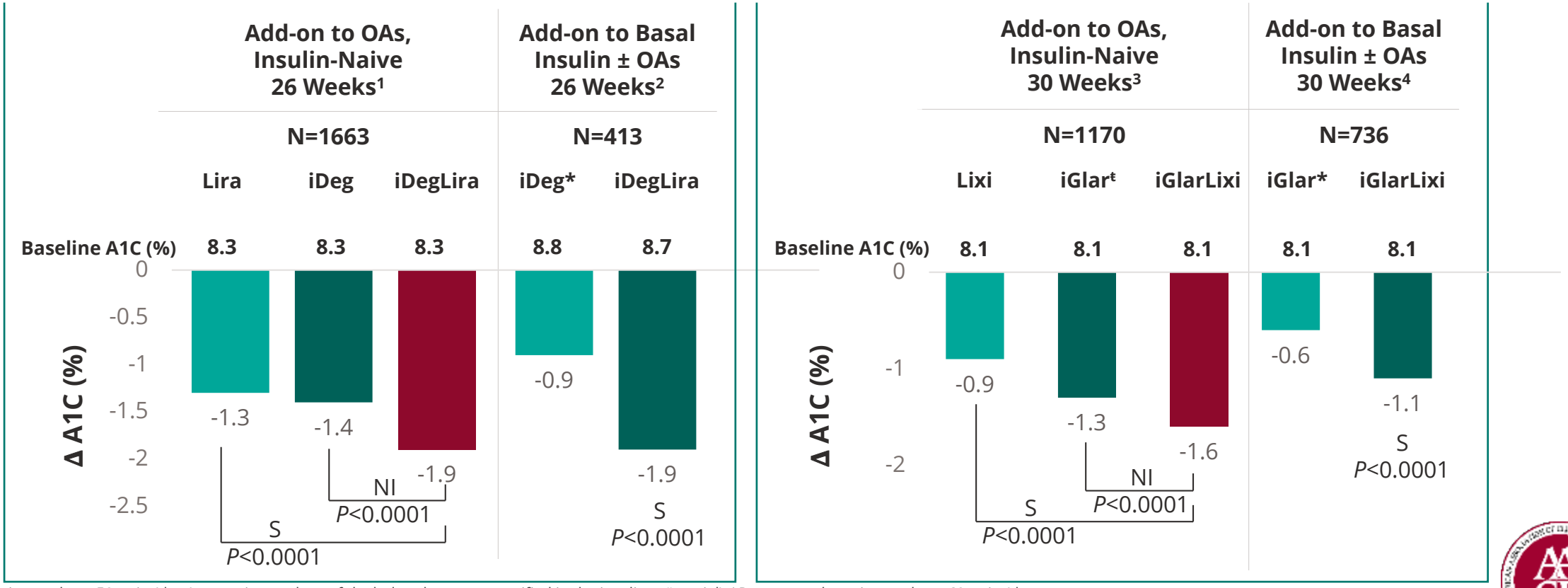
- iDegLira 100/3.6
- Insulin degludec and liraglutide injection
- Approved by FDA November 2016
- Indication: Adults with T2D inadequately controlled on basal insulin (<50 units daily) or liraglutide
- 1 unit contains:
  - 1 U insulin degludec and
  - 0.036 mg liraglutide
- Administered SC once daily
- Starting dose: 16 units (16 U insulin degludec and 0.58 mg liraglutide)
- FlexTouch® pen

FDA, US Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonist; iDegLira, insulin degludec and liraglutide; iGlarLixi, insulin glargine and lixisenatide; SC, subcutaneous; T2D, type 2 diabetes.

Soliqua™ 100/33 (insulin glargine and lixisenatide injection) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis US. November 2016.
Xultophy® 100/3.6 (insulin degludec and liraglutide injection) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc.; 2016.

Glucose Control With Fixed-Ratio Combinations of Basal Insulin and GLP-1 RA

Phase 3 RCTs in patients with T2D showed improved glycemic control with fixed-ratio basal insulin and GLP-1 RA combination compared with individual components administered alone



* Per protocol maximum dose: 50 units/day (no maximum dose of degludec alone was specified in the insulin naïve trial). ‡ Per protocol maximum dose: 60 units/day.

GLP-1 RA, glucagon-like peptide-1 receptor agonist; iDeg, insulin degludec; iDegLira, insulin degludec and liraglutide; iGlar, insulin glargine; iGlarLixi, insulin glargine and lixisenatide; Lira, liraglutide; Lixi, lixisenatide; NI, noninferior; OA, oral agent; S, superior; T2D, type 2 diabetes.

1. Gough SC, et al. *Lancet Diabetes Endocrinol*. 2014;2:885-893. 2. Buse JB, et al. *Diabetes Care*. 2014;37:2926-2933. 3. Rosenstock J, et al. *Diabetes Care*. 2016;39:2026-2035. 4. Aroda VR, et al. *Diabetes Care*. 2016;39:1972-1980.

When Basal Insulin Is Not Enough to Control Glycemia

- Patients whose glycemia remains uncontrolled while receiving basal insulin in combination with oral agents or GLP-1 RAs may require mealtime insulin to cover postprandial hyperglycemia.[1,2]

Basal Plus Prandial
Prandial insulin added to 1, 2, or 3 meals[1]

Basal-Bolus
Prandial insulin added to every meal[1]

Premixed
Combination short- and intermediate-acting insulin[2]

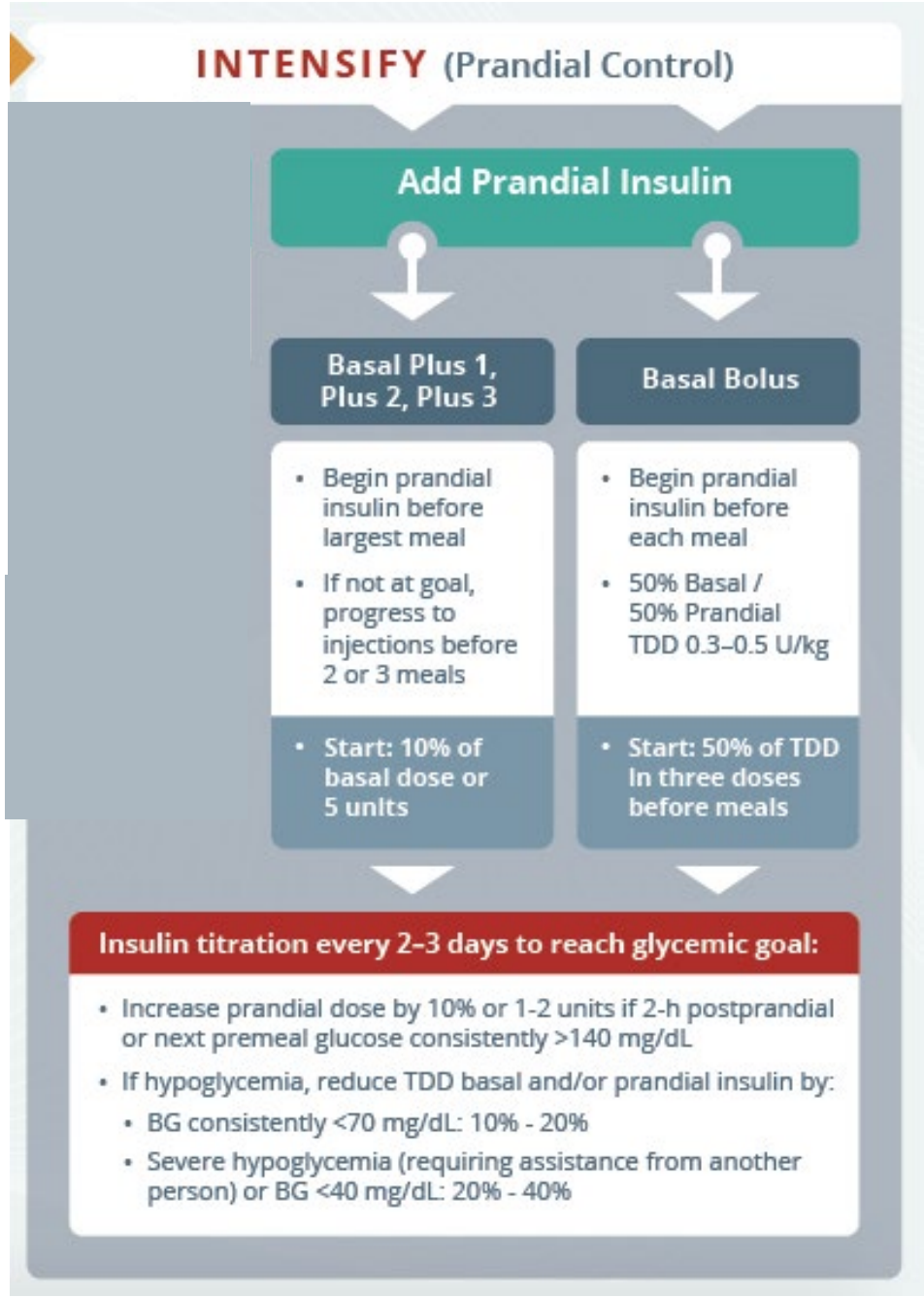
DPP4i, dipetydl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

1. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139. 2. American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212.

Prandial Insulin Intensification

- Consider prandial insulin when basal insulin TDD is >0.5 U/kg[1]
  - Beyond this dose, hypoglycemia risk increases without A1C benefit[1]
- **Basal plus**: Cover largest meal with prandial insulin; add additional meal coverage in stepwise fashion, as needed[1,2]
  - Rapid-acting injectable insulin analogs and inhaled insulin associated with less hypoglycemia than regular human insulin[1]

- **Basal-bolus:** Most effective insulin regimen[1]
  - Greater flexibility for patients who have variable mealtimes and/or meal carbohydrate content[1]
  - Associated with weight gain; MDI and cost may impede adherence[1,3]
- **Titrate dose** based on blood glucose and formulation PD profile[2]
- Some oral agents may need to be discontinued[2]



BG, blood glucose; h, hour; MDI, multiple daily injections; PD, pharmacodynamic; TDD, total daily dose.

1. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139. 2. American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212. 3. Wallia A, et al. *JAMA*. 2014;311(22):2315-25.

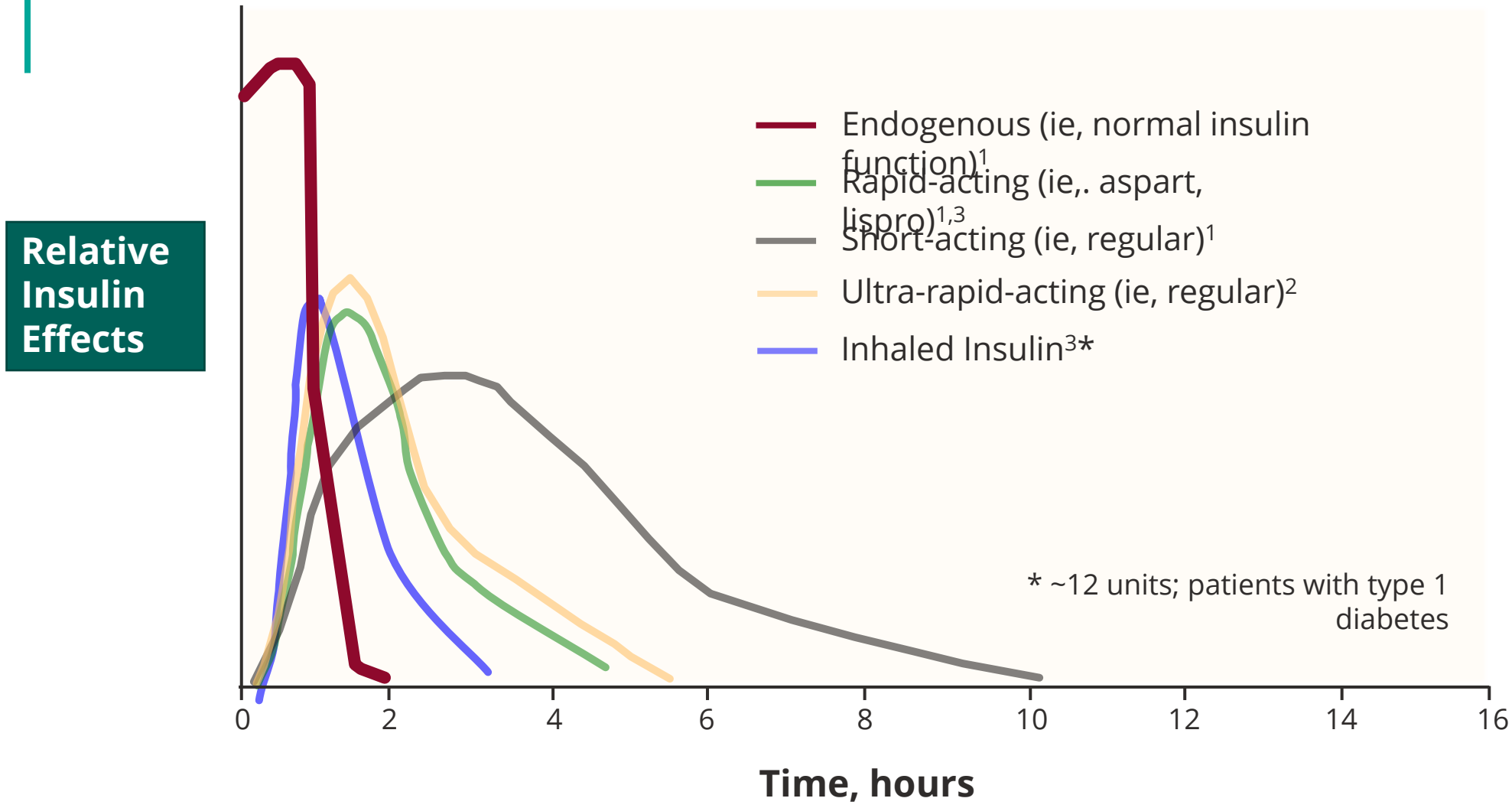
Available Prandial Insulins

	Insulin Lispro[1,2,3]		Insulin Aspart[1,4,5]		Insulin Glulisine[1,6]	Regular Human Insulin[1,2]	Inhaled Insulin[7]
Insulin type	Analog; rapid-acting	Analog; faster-acting	Analog; rapid-acting	Analog; faster-acting	Analog; rapid-acting	Human; short-acting	Analog; rapid-acting
Onset	≤15 minutes	~17 minutes	≤15 minutes	≤5 minutes	0.25-0.5 hours	1 hour	~12 minutes
Peak	1 hour	~2 hours	1-3 hours	1 hour	0.5-1 hour	2-4 hours	35-55 minutes
Effective duration	3-5 hours	5-6 hours	3-5 hours	3-4 hours	4 hours	5-8 hours	1.5-3.0 hours
Half-life	1 hour	44 minutes	1.4 hours	1.1 hours	42 minutes	1.5 hours	2.0-3.5 hours

Responses to inhaled insulin are dose-dependent
Only consider inhaled insulin on an individual basis
Dose conversion is required, as is initial and ongoing evaluation of lung function
Contraindicated in patients with chronic lung disease[7]

1. Donner T, et al. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. 2. Humalog (insulin lispro injection, USP [rDNA origin]) [prescribing information]. Indianapolis, IN: Lilly USA, LLC; 2007. 3. Lyumjev™ (insulin lispro-aabc) injection [prescribing information]. Indianapolis, IN: Eli Lilly and Company; 2020. 4. NovoLog® (insulin aspart injection) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc.; 2019. 5. Fiasp® (insulin aspart injection) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc.; 2020. 6. Apidra® (insulin glulisine [rDNA origin] injection) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis US LLC.; 2008. 7. Afrezza® (insulin human) Inhalation Powder [prescribing information]. Danbury, CT: MannKind Corporation; 2019.

Prandial Insulin Action Profiles

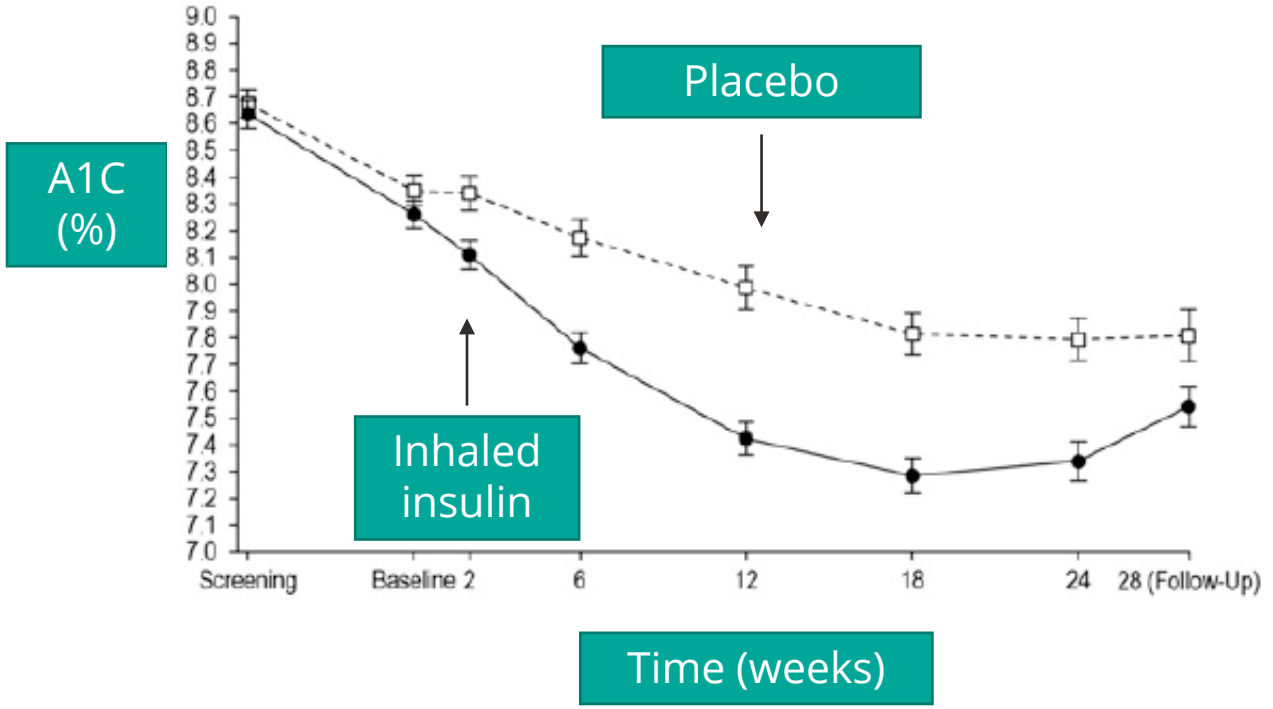


Adapted from: 1. Freeman JS. *JAOA*. 2009;109(1):26-36; 2. Heise T, et al. D*iab Obes Metab*. 2020; EPUB. 2. Afrezza® (insulin human) Inhalation Powder [prescribing information]. Danbury, CT: MannKind Corporation; 2019.

A1C Reductions and Hypoglycemia With Inhaled Insulin (Afrezza®)

- A1C reductions with inhaled insulin were significantly greater than placebo.[1]
- Patients taking inhaled insulin had a higher incidence of hypoglycemia vs placebo.[1]
  - All events, 67.8% vs 30.7%; *P*<0.0001
  - Severe events, 5.7% vs 1.7%; *P*=0.09.
- Patients receiving inhaled insulin weight gain (~1 lb) vs weight loss (~2.4 lb) with placebo (*P*<0.0001).[1]
- Coughing was most common adverse event with inhaled insulin.[1,2]

Double-blind, 24-week RCT (N=176) comparing prandial inhaled insulin vs prandial inhaled placebo (patients with T2D)[1]

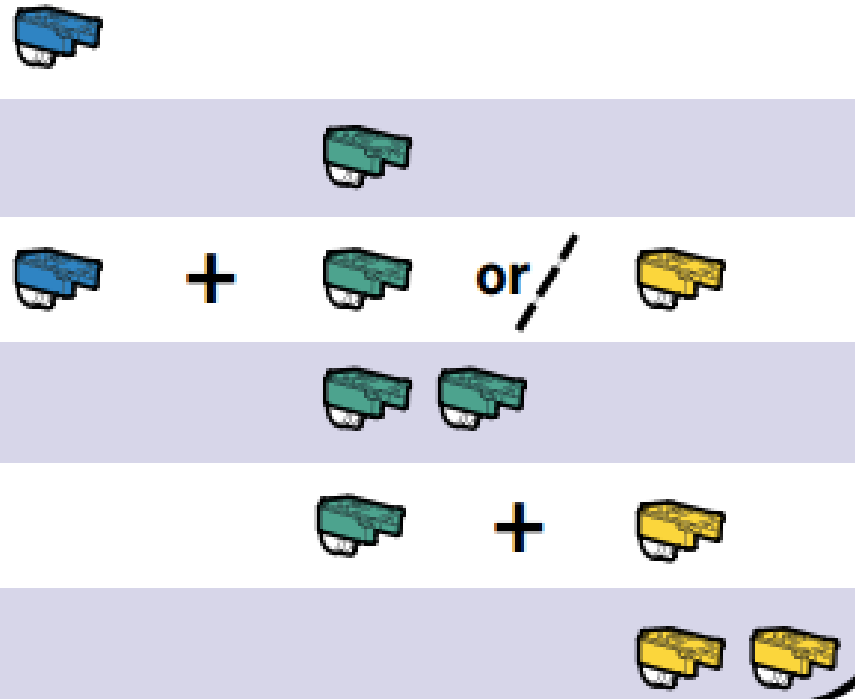


RCT, randomized controlled trial; T2D, type 2 diabetes.

1. Rosenstock J, et al. *Diabetes Care.* 2015;38:2274-2281. 2. Afrezza® (insulin human) Inhalation Powder [prescribing information]. Danbury, CT: MannKind Corporation; 2019.

Inhaled Insulin, Dose Conversion Table

Injected Mealtime Insulin Dose	Inhaled Insulin Dose	# of Cartridges Needed		
		4 unit (blue)	8 unit (green)	12 unit (yellow)
up to **4** units	**4** units			
5-8 units	**8** units			
9-12 units	**12** units			
13-16 units	**16** units			
17-20 units	**20** units			
21-24 units	**24** units			



Afrezza® (insulin human) Inhalation Powder [prescribing information]. Danbury, CT: MannKind Corporation; 2019.

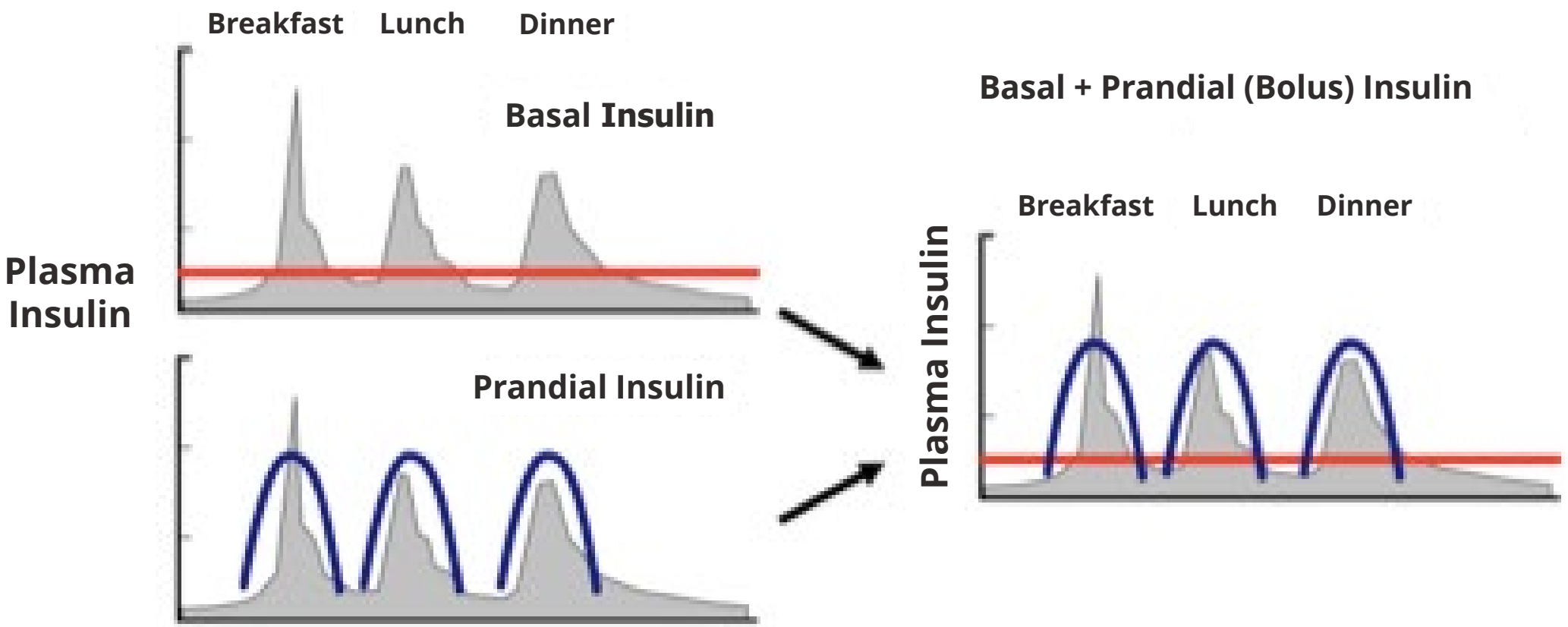
Basal-Bolus Insulin Regimens in T2D

- **Advantages**[1]
  - Effective in approximately two-thirds of patients in achieving A1C goals

- **Disadvantages**[2,3]
  - Multiple injections
  - Low adherence
  - Potential for weight gain
  - Hypoglycemia risk

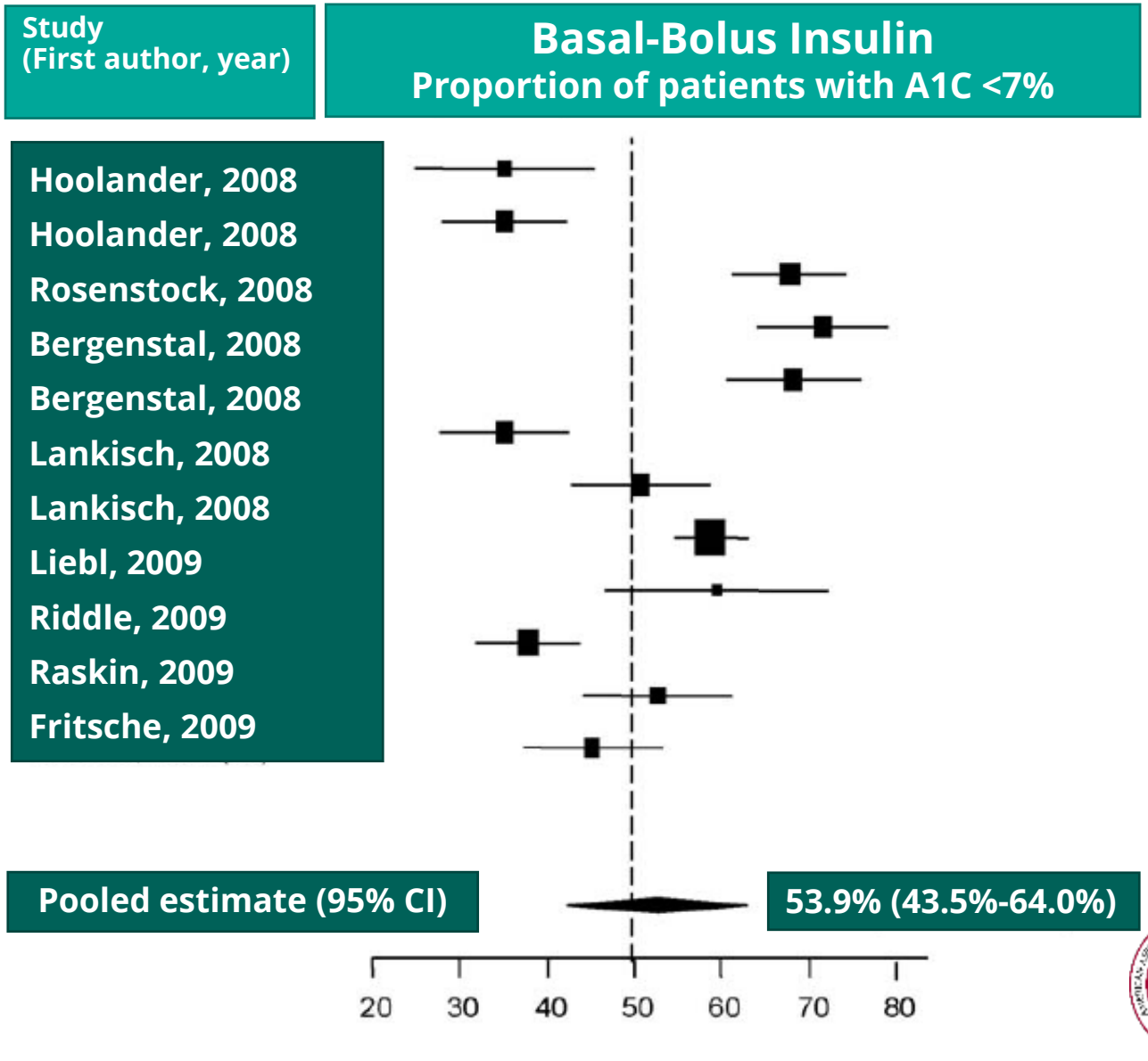
1. Bergenstal RM, et al. *Diabetes Technol Ther*. 2019:21(5)273-285. 2. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139.
3. American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212.

The Basal-Bolus Approach to Insulin Delivery



Achievement of A1C <7% with Basal-Bolus Insulin Regimens in T2D

- Systematic review of 8 RCTs (N=2114) evaluated effectiveness of basal-bolus insulin regimens
- A1C <7% achieved in 53.9% (95% CI: 43.5%, 64.0%)
- Hypoglycemic events (mean/patient/30 days): 0.88 (95% CI: 0.35, 1.3)
- Weight gain: 2.8 kg (95% CI: 1.8, 3.7)
- Escalation from basal to basal-bolus increases success rate in an additional ~12%-14% of patients



CI, confidence interval; RCT, randomized controlled trial.

Giugliano D, et al. *Res Clin Pract*. 2011;92(1):1-10.

Premixed Insulin Analogues in Patients With T2D

Premixed insulin combines long- and short-acting insulin in a single formulation

Benefits[2,4]

- Simple and convenient (twice-daily administration)
- Basal-bolus in 1 medication

Disadvantages[2]

- Higher risk of hypoglycemia
- Less flexibility

Initiation and Titration

- Insulin naïve patients →10-12 units or 0.3 u/kg[4]
- Split dose (50/50 morning and evening)[4]
- Existing basal → unit-to-unit conversion
- Existing basal-bolus → reduce TDD by 20%-30%[4]
- Titrate 1-2 units, or 10%-15%, 1-2x weekly, until goal[4]
- Increase TDD by 10% if FPG or premeal blood glucose >180 mg/dL[1,4]

Dose Adjustment[4]

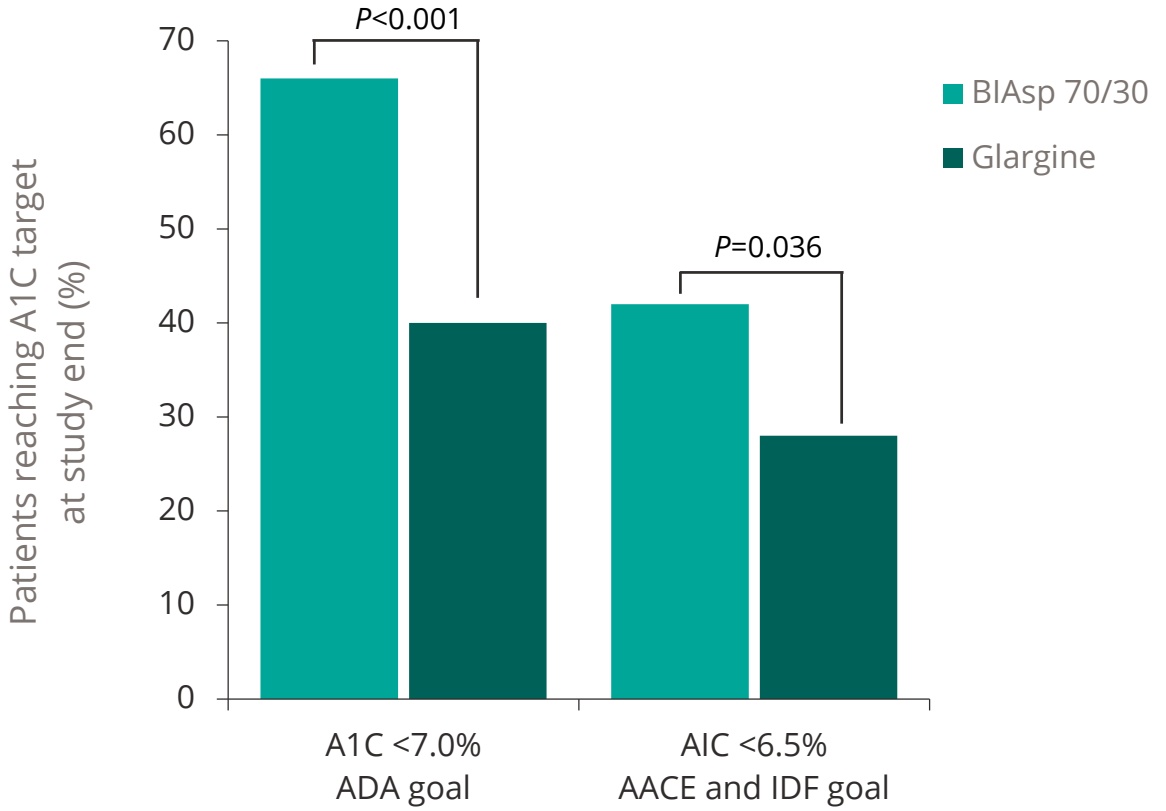
Lowest pre-meal blood glucose level	Adjustment for next dose
≥126 mg/dL	+2 units
73-124 mg/dL	0
≤72 mg/dL	-2 units

FPG, fasting plasma glucose; T2D, type 2 diabetes; TDD, total daily dose.

1. Handelsman Y, et al. *Endocr Pract*. 2015;21(S1). 2. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139. 3. American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212. 4. Wu T, et al. *Diabetes Ther*. 2015;6(3):273-287.

INITIATE Study: More Patients With T2D Reached A1C Target With BIAsp 70/30 Than Glargine

- 28-week randomized, open-label, treat-to-target study
- The efficacy and safety of BIAsp 70/30 were compared with once-daily insulin glargine in patients with T2D (N=209) inadequately controlled on OADs
- Significantly more BIAsp 70/30 patients reached target A1C vs glargine patients
  - A1C <7.0%: 66% vs 40%
  - A1C ≤6.5%: 42% vs. 28%



AACE, American Association of Clinical Endocrinology; ADA, American Diabetes Association; BIAsp, biphasic insulin aspart; IDF, International Diabetes Federation; OAD, oral antidiabetic drug; T2D, type 2 diabetes.

Raskin P, et al. *Diabetes Care.* 2005;28:260-265.

Insulin Pump Therapy in Patients With T2D

According to AACE Guidelines, insulin pump therapy may improve QoL and can be considered in patients with T2D who are insulin-dependent and not meeting glycemic goals with MDIs

Ideal Candidates

- Motivated to achieve optimal glycemic control
- Currently performing ≥4 daily insulin injections and ≥4 SMBG measurements
- Able and willing to safely and effectively use this complex and time-consuming therapy
- C-peptide positive, but with suboptimal control using maximized basal-bolus injections
- Trained in carbohydrate counting and to calculate insulin correction doses
- Willing to maintain frequent contact with health care team

Poor Candidates

- Not motivated to achieve glucose control
- Unwilling to perform frequent MDI or SMBG
- Previous nonadherence to insulin injections
- Unrealistic expectations of pump therapy
- Belief that pump use will remove patient responsibility for diabetes management
- Concerned that pump will interfere with lifestyle (eg, sports or sexual activity)
- History of serious psychiatric conditions (eg, psychosis, severe depression)

AACE, American Association of Clinical Endocrinologists; MDI, multiple daily injection; QoL, quality of life; SMBG, self-monitoring of blood glucose; T2D, type 2 diabetes.

Grunberger G, et al. *Endocr Pract*. 2014;20(5):463-489.

U-500R Insulin Therapy

- U-500 is a highly concentrated human insulin, introduced in 2016;[1] it is potentially appropriate for the following patients:
  - Require >200 units of insulin per day[2-6]
  - With T2D and obesity and/or severe insulin resistance[3-5]
  - With gestational diabetes and severe insulin resistance[3,4]
  - Postoperative or post-transplant[4] or on high-dose glucocorticoid therapy[3-5]
  - With severe systemic infection[3-5]
  - With genetic defects of insulin action and rare forms of immune-mediated diabetes, such as anti-insulin receptor antibodies (type B insulin resistance syndrome)[3-6]

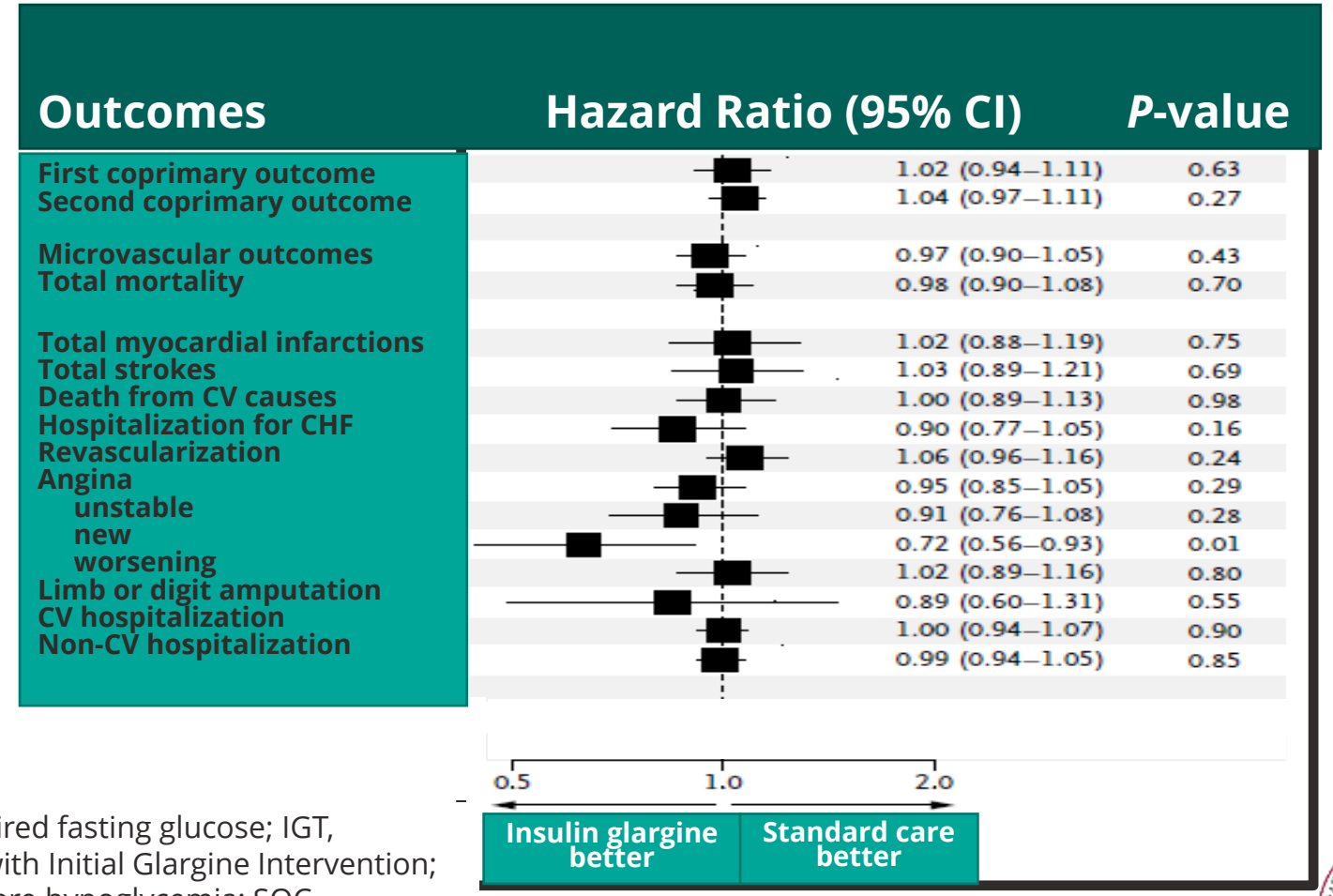
T2D, type 2 diabetes; U-500R, human regular U-500 insulin.

1. Sze D, et al. *Clin Diabetes*. 2018;36(4):319-324. 2. Humulin® R U-500 [US package insert]. Indianapolis, IN: Eli Lilly and Company, 2016. 3. Cochran E, et al. *Diabetes Care.* 2005;28:1240-1244 (updated 30:1035). 4. Lane WS, et al. *Endocr Pract.* 2009;15:71-79. 5. Segal AR, et al. *Am J Health Syst Pharm.* 2010;67:1526-1535. 6. Ovalle F. *Diabetes Res Clin Pract.* 2010;90:231-242.

Cardiovascular Safety of Insulin

ORIGIN Trial: Early Use of Insulin Glargine in Patients With T2D or Pre-diabetes

- RCT of patients (N=12,537) with T2D, IGT, or IFG, at high CV risk, and treated with insulin glargine vs SOC.
- CV outcomes were similar for both groups over a median 6.2 years of follow-up.
- SH rates were higher with insulin glargine vs SOC (1.0 vs 0.3 per 100 PY).



CHF, congestive heart failure; CV, cardiovascular; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ORIGIN, Outcome Reduction with Initial Glargine Intervention; PY, person-years; RCT, randomized controlled trial; SH, severe hypoglycemia; SOC, standard of care; T2D, type 2 diabetes.

ORIGIN Trial Investigators. *N Engl J Med*. 2012;367:319-328.

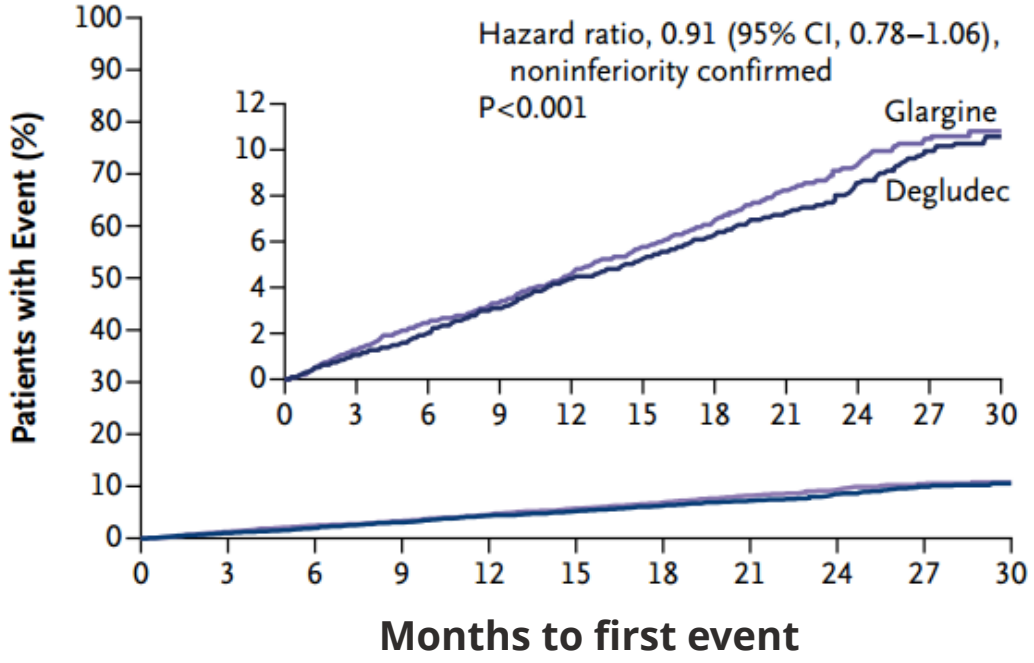
Cardiovascular Safety of Insulin

DEVOTE Trial: Efficacy and Safety of Insulins Degludec vs Glargine in Patients With T2D

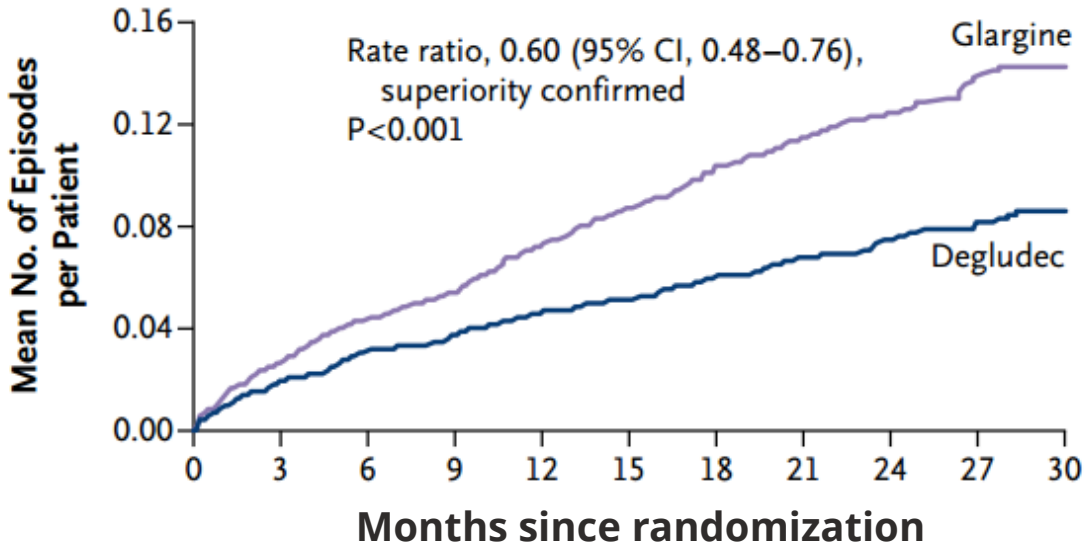
RCT of patients (N=7367) with T2D; 85% with established CVD or CKD

- Degludec was noninferior vs glargine for major CV outcomes
- Degludec significantly reduced hypoglycemia rates vs glargine

Primary Composite Outcome (MACE)



Severe Hypoglycemia



CI, confidence interval; **CKD**, chronic kidney disease; **CV**, cardiovascular; **CVD**, cardiovascular disease; **MACE**, major adverse cardiovascular event; **RCT**, randomized controlled trial; **T2D**, type 2 diabetes.

Marso SP, et al. *N Engl J Med*. 2017;377(8):723-732.

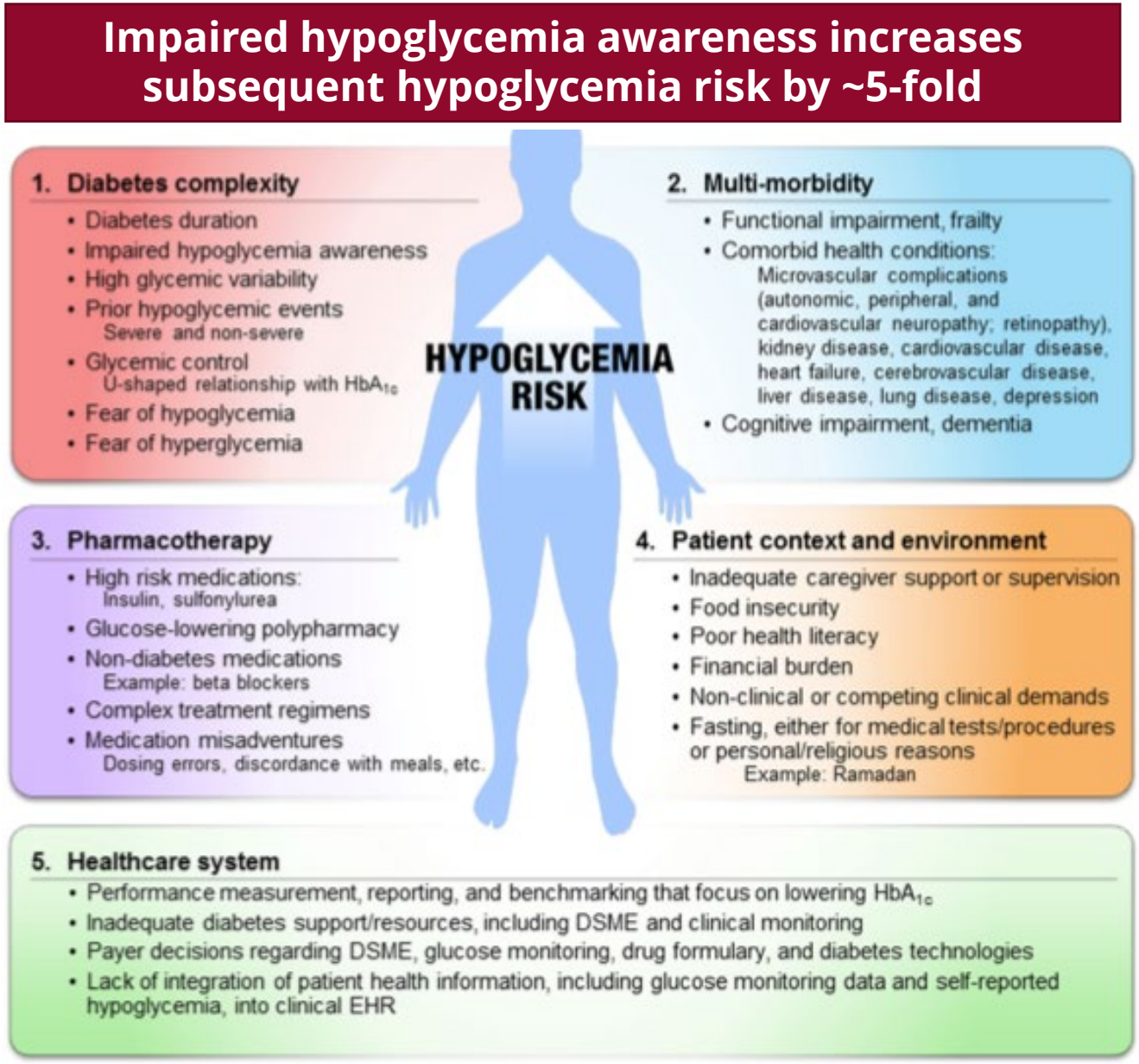
Hypoglycemia With Insulin Therapy: Risks Associated With Hypoglycemia

- Hypoglycemia is a common side-effect of insulin therapy.
- Hypoglycemia and the fear of hypoglycemia limit patients' ability to achieve and maintain optimal glycemic control.
- Severe and prolonged hypoglycemia increases morbidity and mortality.

Organ/System	Consequence
Heart 	Abnormal prolonged cardiac repolarization Cardiac arrythmia Myocardial ischemia Sudden death
Eyes 	Vitreous hemorrhage Worsening of retinopathy
Central nervous system 	Cognitive dysfunction Brain damage, intellectual decline Unusual behavior Seizure, coma Transient ischemic attack, stroke Focal neurological lesions (rare)
Other 	Falls Accidents with injury

American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S1-S212.
Amiel SA, et al. *Diabet Med*. 2008;25:245-254.
Landstedt-Hallin L, et al. *J Intern Med.* 1999;246:299-307. 4. Cryer PE. *J Clin Invest*. 2007;117:866-870.

Hypoglycemia Risk Factors in Patients With T2D



DSME, diabetes self-management education;
EHR, electronic health records; **T2D**, type 2 diabetes.

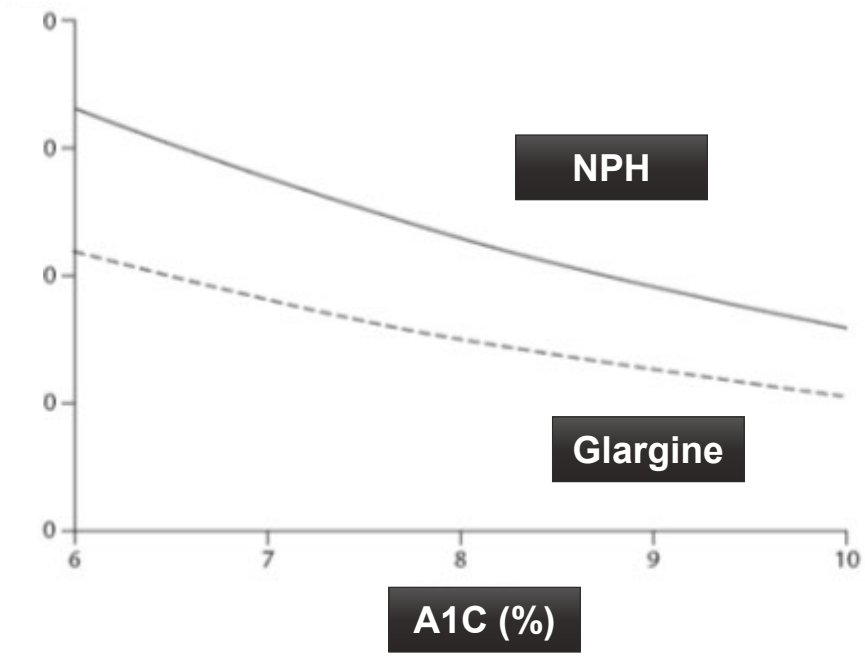
Schopman JE, et al. *Diabetes Res Clin Pract.* 2010;87(1):64-68.

Less Hypoglycemia With Insulin Glargine and Detemir vs NPH Insulin

Data from 6 RCTs used to model hypoglycemia rates with insulin glargine vs NPH in 3656 patients with T2D[1]

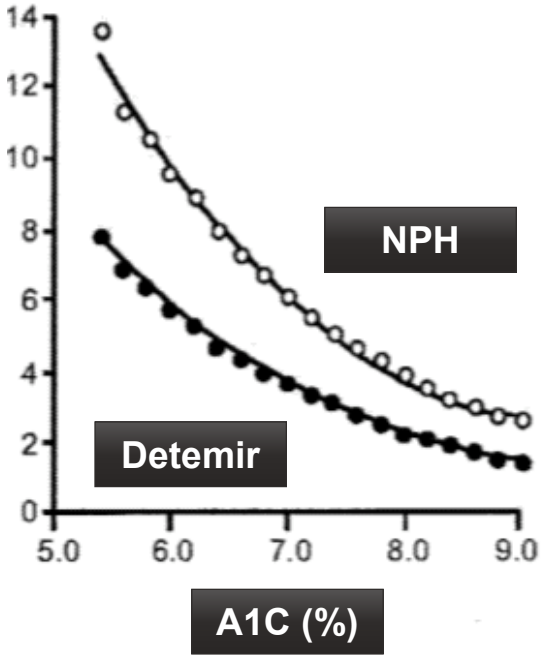
Association between confirmed hypoglycemia (<65 mg/dL)* and end-of-study A1C (*P*=0.021)

*Per 100 person-years



26-week RCT comparing insulin detemir vs NPH as add-on to OADs in 475 insulin-naïve patients with T2D[2]

Relationship between confirmed hypoglycemia incidence and A1C (previous 12 weeks and at study end) (*P*<0.001)

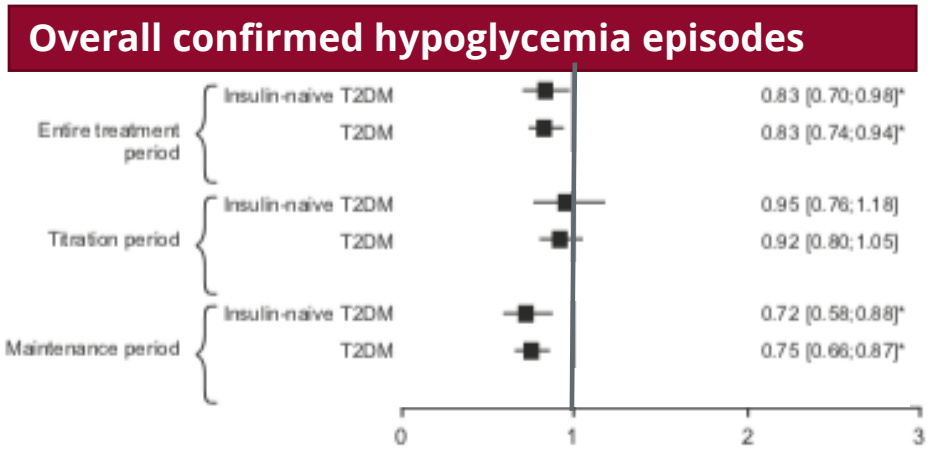


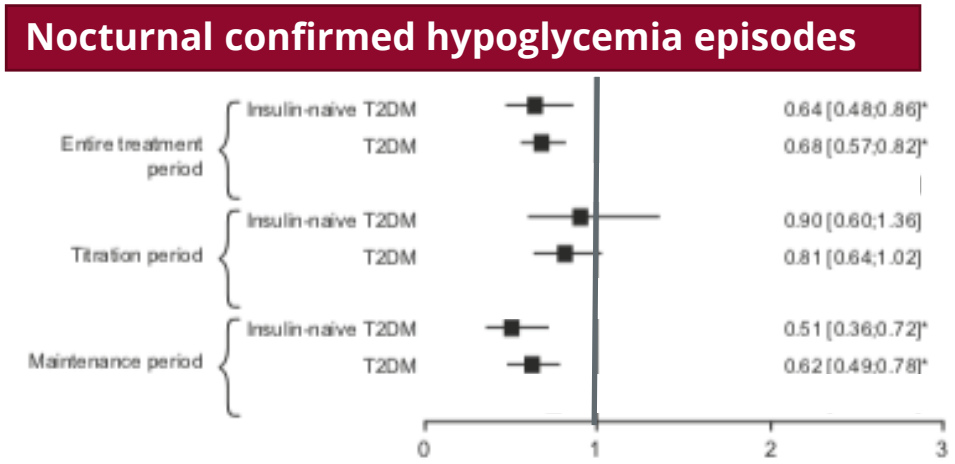
NPH, neutral protamine Hagedorn; OAD, oral antidiabetic drug; RCT, randomized controlled trial; T2D, type 2 diabetes.

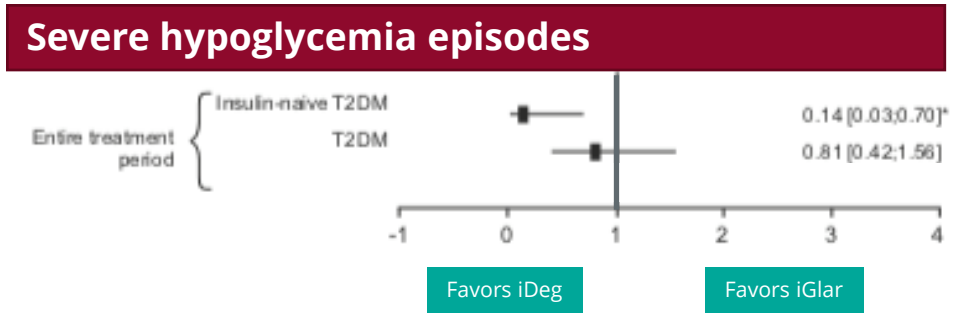
1. Mullins P, et al. *Clin Ther.* 2007;29:1607-1619. 2. Hermansen K, et al. *Diabetes Care*. 2006;29:1269-1274.

Rates of Hypoglycemia Lower With Insulin Degludec vs Insulin Glargine

Meta-analysis of 5 trials in patients with T2D (N=3372) in the iDeg development program, comparing iDeg once daily to iGlar once daily[1,2]







iDeg, insulin degludec; iGlar, insulin glargine; T2D, type 2 diabetes.

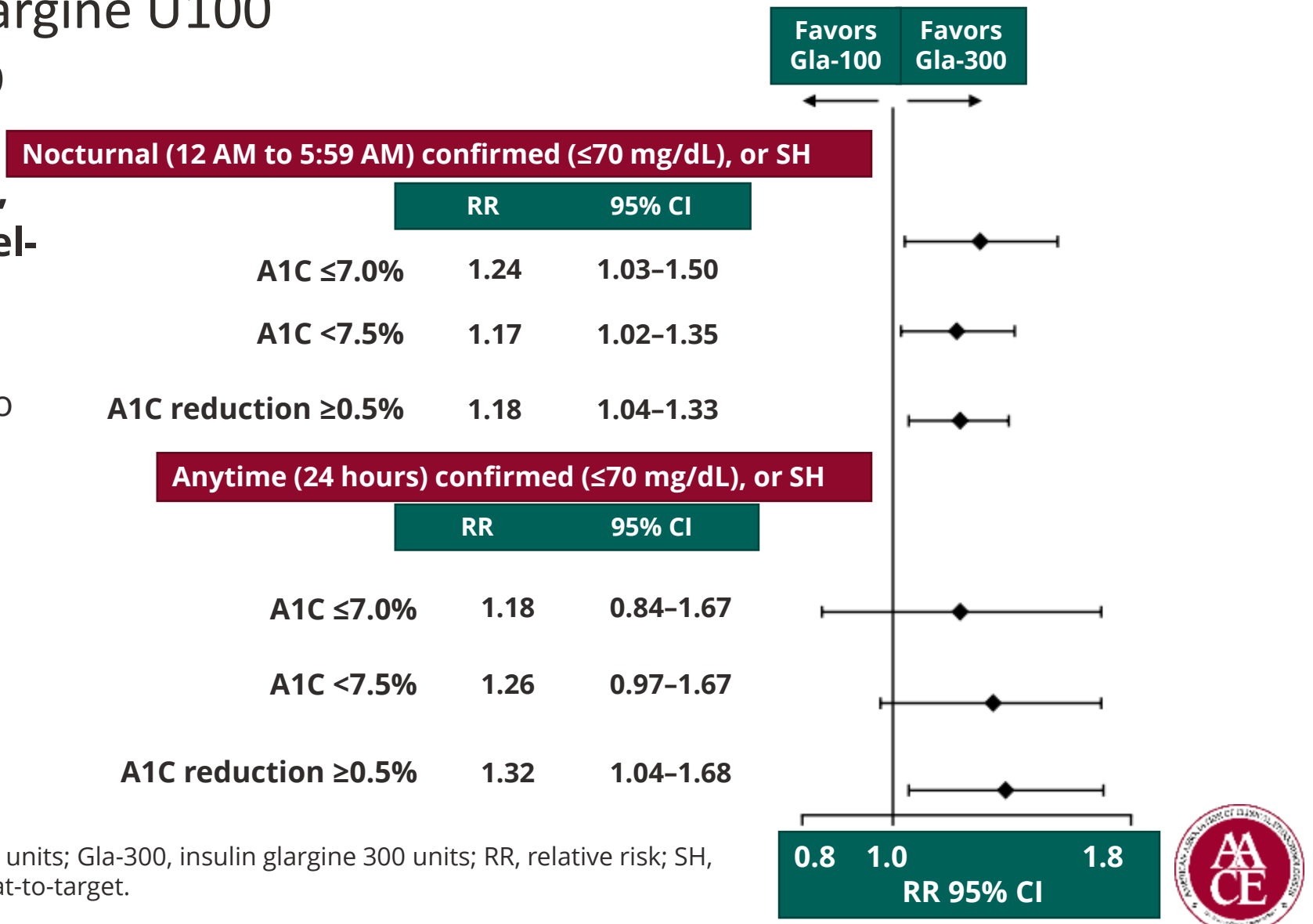
1. Ratner RE, et al. *Diabetes Obes Metab.* 2013;15:175-184.
2. Vora J, et al. *Diabetes Res Clin Pract.* 2015;109:19-31.

Nocturnal Hypoglycemia Lower With Insulin Glargine U300 vs Glargine U100 in Patients With T2D

Multicenter, randomized, open-label, 2-arm, parallel-group, TTT trials

Meta-analysis (12 months) of adults with T2D randomized to Gla-300 or Gla-100

- **EDITION 1**: Insulin with or without metformin
- **EDITION 2**: Insulin in combination with other antihyperglycemic drugs
- **EDITION 3**: Insulin-naive

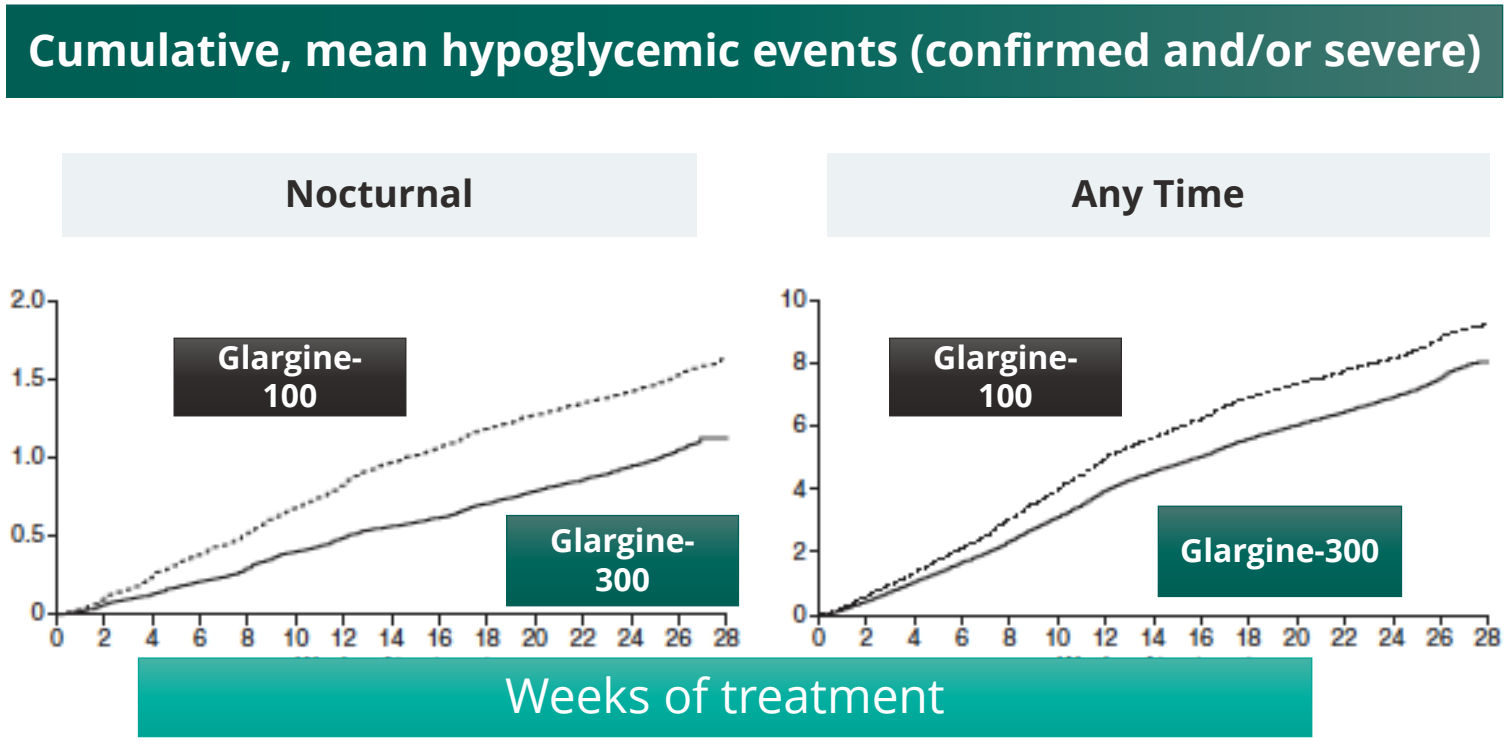


CI, confidence interval; Gla-100; insulin glargine 100 units; Gla-300, insulin glargine 300 units; RR, relative risk; SH, severe hypoglycemia; T2D, type 2 diabetes; TTT, treat-to-target.

Ritzel R, et al. *Diabetes Obes Metab.* 2018;20:541-548.

Hypoglycemia Lower With Insulin Glargine U300 vs Glargine U100 in Patients With T2D

- EDITION 1, 2, and 3 meta-analysis compared the efficacy and safety of insulin Gla-300 (n=1247) vs Gla-100 (n=1249) over 6 months in patients with T2D.
- They found comparable mean A1C reductions, tolerability, and safety between treatment groups.
- There was less hypoglycemia with Gla-300:
  - Hypoglycemia at any time: Rate ratio (95% CI), 0.86 (0.77, 0.97); *P*=0.0116
  - Nocturnal hypoglycemia: Rate ratio (95% CI), 0.69 (0.57, 0.84); *P*=0.0002

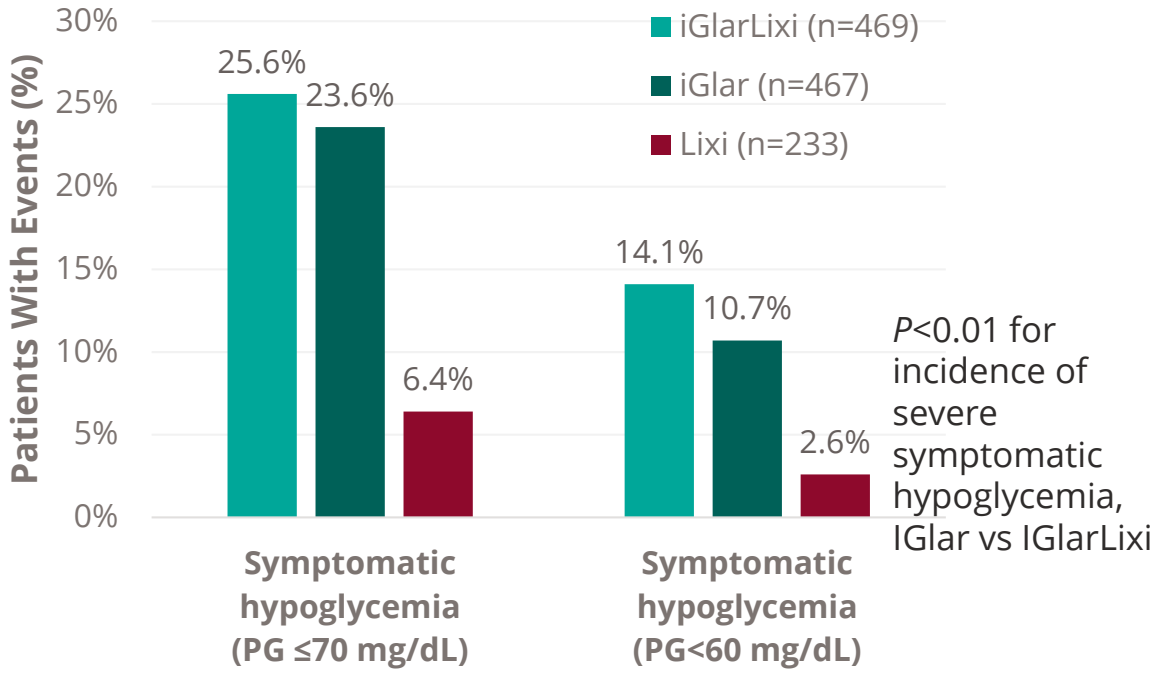


CI, confidence interval; Gla-100; insulin glargine 100 units; Gla-300, insulin glargine 300 units; T2D, type 2 diabetes.

Ritzel R, et al. *Diabetes Obes Metab.* 2015;17(9):859-867.

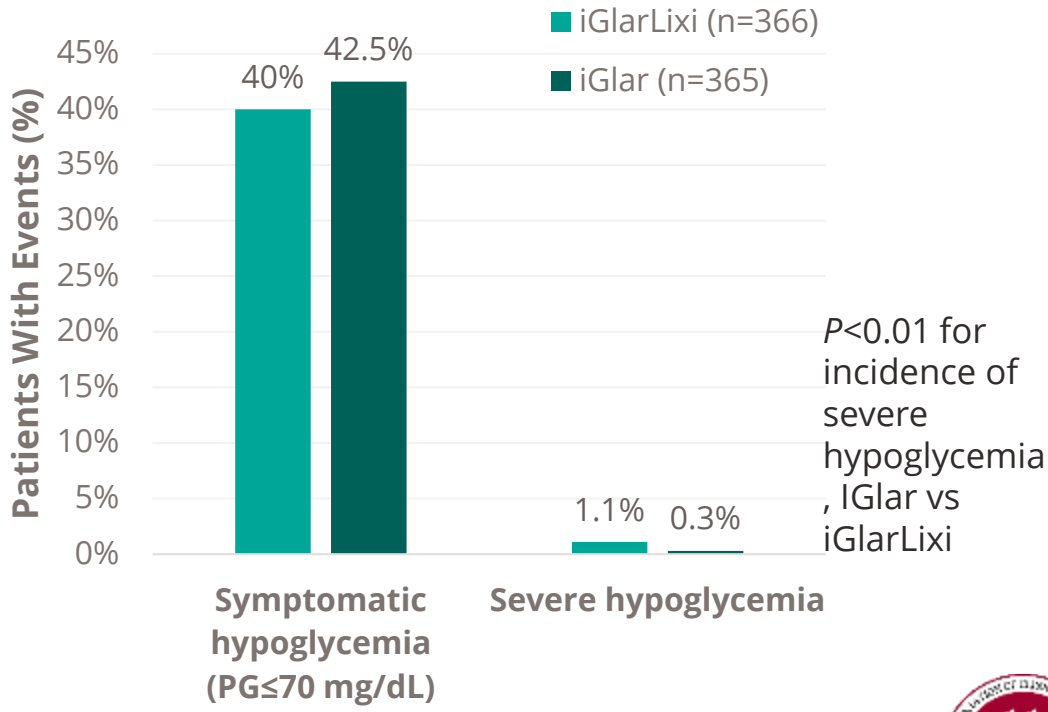
Open-Label, Randomized Trials Evaluating Hypoglycemia in Patients With T2D Using LixiLan (FRC of iGlar + Lixisenatide)

LixiLan-O Trial: Patients with T2D inadequately controlled on oral agents (insulin-naïve) randomized to iGlarLixi, iGlar, or Lixi[1]



P<0.01 for incidence of severe symptomatic hypoglycemia, IGlar vs IGlarLixi

LixiLan-L Trial: Patients with T2D inadequately controlled on basal insulin and metformin randomized to iGlarLixi or iGlar[2]



P<0.01 for incidence of severe hypoglycemia, IGlar vs iGlarLixi

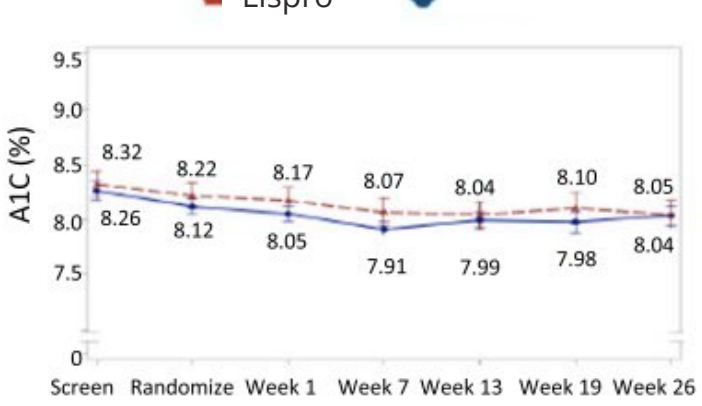
1. Rosenstock J, et al. *Diabetes Care.* 2016;39:2026-2035.
2. Aroda VR, et al. *Diabetes Care.* 2016;39:1972-1980.

FRC, fixed-ratio combination; iGlar, insulin glargine; iGlarLixi, insulin glargine and lixisenatide; Lixi, lixisenatide; PG, plasma glucose; T2D, type 2 diabetes.

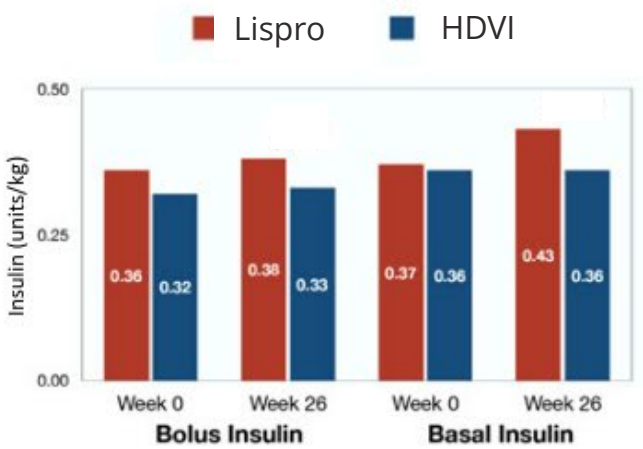
Novel and in Development: Hepatic-Directed Vesicle Insulin for Prandial Use

- HDVI uses a hepatocyte-targeting moiety to improve the hepatic distribution of subcutaneous insulin.
- This multicenter, randomized, 6-month study compared HDVI vs insulin lispro (N=176 patients with T1D).
- Overall, A1C reductions met a preset noninferiority margin—no significant differences between treatments for insulin dosage or hypoglycemia.
- Specific to patients with baseline A1C ≥8.5%:
  - Severe hypoglycemia incidence in the HDVI and lispro arms were 69 and 97 events per 100 person-years (*P*=0.03).
  - Insulin dosages were reduced by 25% in patients who received HDVI vs lispro (*P*=0.02), despite similar A1C outcomes.

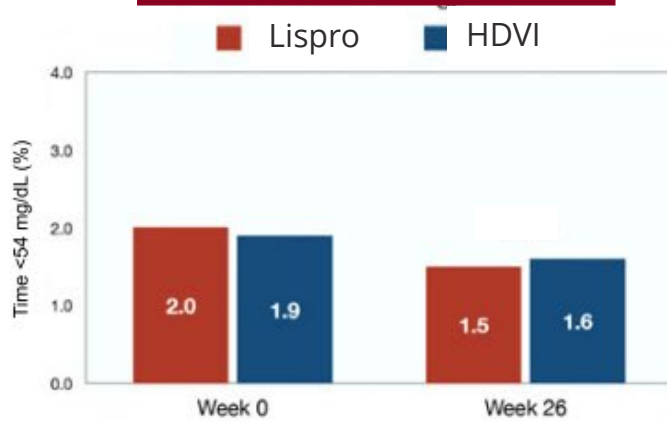
A1C



Insulin dosage



% time with BG <54 mg/dL



Klonoff D, et al. *Diabetes Care*. 2019:42:2154-2157.

HDVI, hepatic-directed vesicle insulin; T1D, type 1 diabetes.

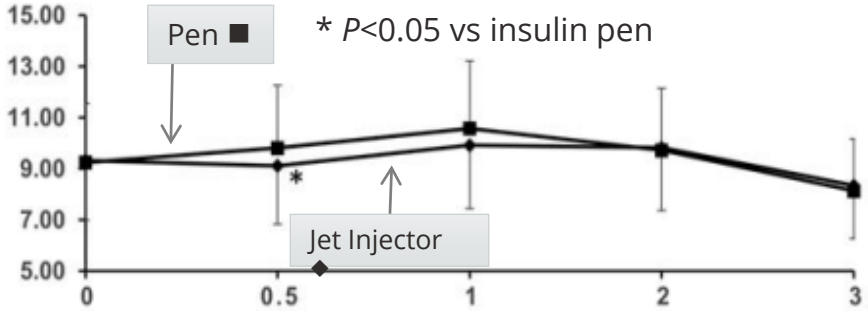
Novel and In Development:
A Jet Injector, Needle-Free Delivery System

Postprandial glucose and insulin concentrations following insulin aspart administration via jet injector or pen; Chinese patients with T2D (N=60)

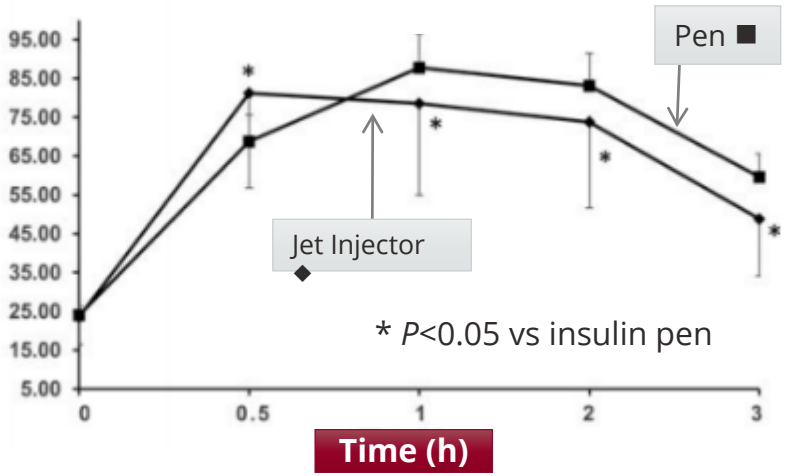
InsuJet™ uses a high-pressure narrow jet to penetrate the skin.

Insulin disperses into subcutaneous adipose tissue with ≥90% efficiency and minimal skin injury and pain.

Postprandial glucose concentration (mmol/L)



Postprandial insulin concentration (μIU/mL)



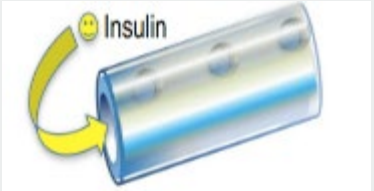
T2D, type 2 diabetes.

Guo L, et al. *Medicine (Baltimore).* 2017;96(1):e5482.

Novel and In Development:
Long-Lasting, Glucose-Responsive ("Smart") Insulin

Smart Insulin is longer-acting than injected insulin. It remains inactive until low blood glucose is detected; insulin action ceases once blood glucose normalizes.

Multiple products are under investigation. Barriers to successful development have included device materials, immune response, and other efficacy and safety concerns.[1]

Patch 	• Adhesive patch placed on skin; delivers insulin via glucose-sensitive microneedles[1] • Potential duration of action: ~1 day[2] • Development status: Animal testing[2]
Nano-implant 	• Battery-operated device, inserted under skin; contains insulin-loaded nanoparticles[1,3] • Potential duration of action: Several months[3] • Development status: Animal testing[3]
Oral 	• Prevents gastrointestinal protein-drug breakdown; permits small intestine permeation[4] • Duration of action: 1 day[5,6] • Development status: Phase 2[5,6]
Gel 	• Closed-loop, insulin/boronate gel-based system[7,8] • Gel dehydrates in response to osmotic pressure, signaling low blood glucose and triggering insulin diffusion[8] • Potential duration of action: ~1 week • Development status: Early animal research[7,8]

1. http://thejdca.org/2018-smart-insulin-an-overview-of-all-projects. 2. Yu J, et al. *Nat Biomed Eng*. 2020;4(5):499-506.
3. https://aibn.uq.edu.au/article/2017/02/nano-implants-remove-pain-diabetes-injections. 4. https://www.oramed.com/technology/. 5. https://plan.core-apps.com/tristar_ada20/abstract/85ae6435-8bc5-4429-8ad8-de44bdeaf718. 6. Rosenstock J, et al. Oral insulin (ORMD-0801) effects on glucose parameters in uncontrolled T2DM on OADs. ADA 80th Scientific Sessions. 7. Matsumoto A, et al. *Sci Adv*. 2017;3(11):eaaq0723. 8. Matsumoto A, et al. *Commun Biol*. 2020;3(1):313.

Summary

- As T2D is progressive in nature, many patients eventually require insulin therapy.
- The choice of initial insulin should be individualized and guided by patient characteristics; however, initiating insulin therapy with a single daily dose of basal insulin is the preferred approach.
- Some evidence suggests that short-term, early intensive insulin treatment may improve glycemic control and preserve beta-cell function in newly diagnosed T2D patients with severe and symptomatic hyperglycemia.
- Patients whose glycemia remains uncontrolled with basal insulin and other oral agents may require the progressive addition of mealtime (prandial) insulin or a GLP1-RA.
- Intensification of insulin therapy should not be delayed if the patient is not meeting goals.
- Newer insulin analogs have similar cardiovascular risk profiles and reduced hypoglycemia rates compared to older insulin formulations.
- Future technology advances and routes for insulin delivery are likely to make insulin more user-friendly, patient-specific, and convenient.

GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes.

Contributors

- AACE would like to thank the following endocrinologists for their contributions.

    - Dr. Georgia Davis, MD
    - Dr. Amit Gupta, DNB, FACP, FRCP (Glasg), FRCP (Edin)
    - Dr. Victor Roberts, MD, FACE, MBA, FACP
    - Dr. Vijay Shivaswamy, MBBBS