Initiation and Adjusting Insulin Therapy, am I doing it right? DMT2

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November 14, 2021

100 Years of Insulin Therapy: A long Successful Path

Disclosures

- No conflict of interest

Learning Objectives

- Identify patient and disease characteristics that help providers to establish appropriate individual glycemic targets.
- Discuss when to initiate insulin therapy based on current ADA Standards of Medical Care and AACE.
- Develop skills for calculating patients' initial insulin dosage and titrating insulin dosages based on individualized glycemic targets.
- Understand the concept of overbasalization and how to avoid it.
- Better understand how to advise patients on their options with regard to insulin therapy regimens.

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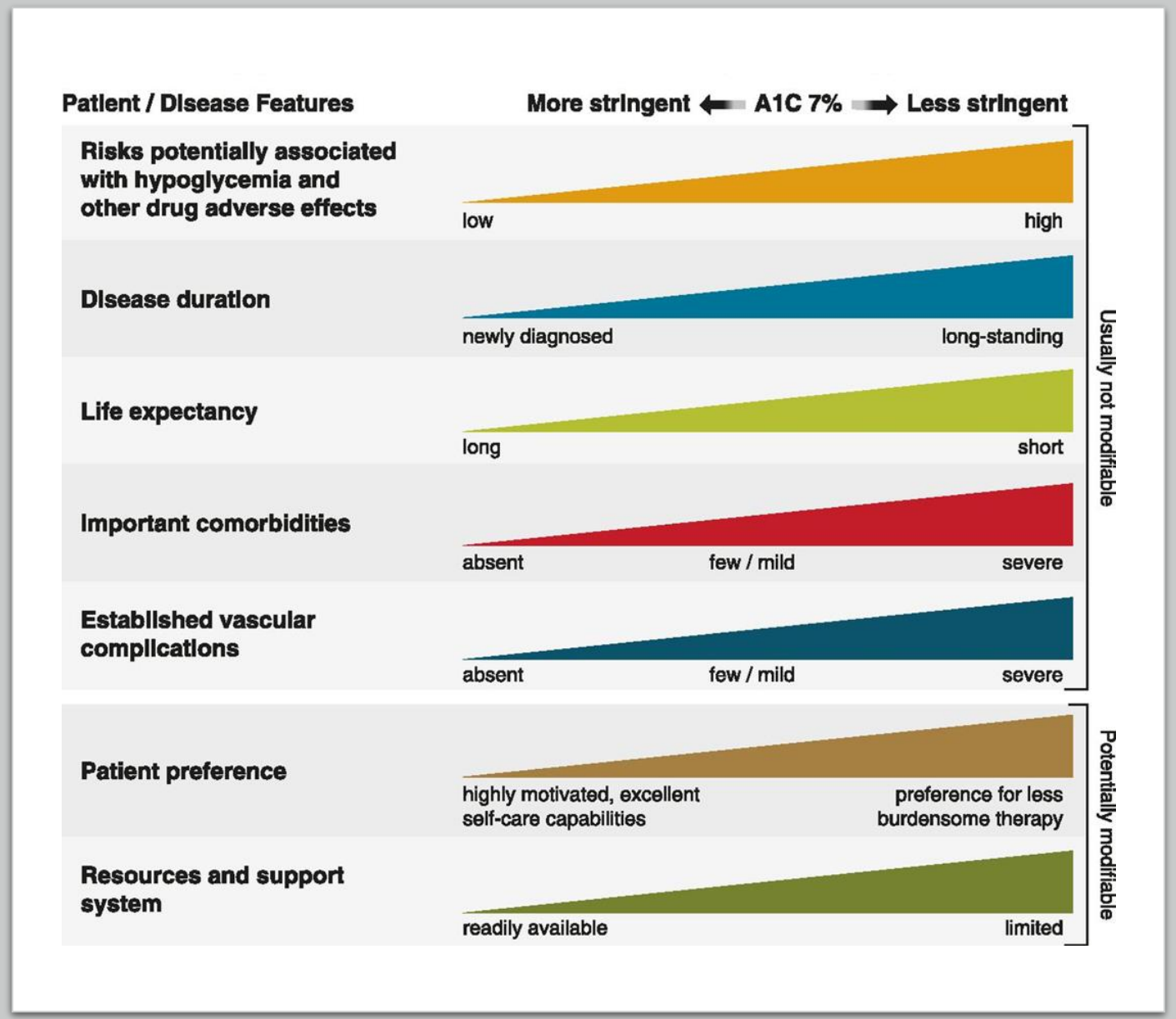
Approach to Individualization of Glycemic Targets



American Diabetes Association Diabetes Care 2021;44:S73-S84

Glycemic Recommendations for Many Non-Pregnant Adults With Diabetes

A1c	<7%*
Preprandial capillary plasma glucose	80-130 mg/dl*
Peak postprandial plasma glucose^	<180 mg/dl*

- *More stringent glycemic goals maybe appropriate for individual patients
- ^Postprandial glucose measurements should be made 1-2 hours after the beginning of the meal, generally peak levels in patients with diabetes.

AACE Glycemic Control Algorithm: When to Consider Insulin Therapy in Patients with T2DM

Strong recommendation to initiate 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

Choice of treatment depends on patient and medication

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

Therapeutic inertia in the treatment of hyperglycemia in patients with type 2 diabetes: A systematic review

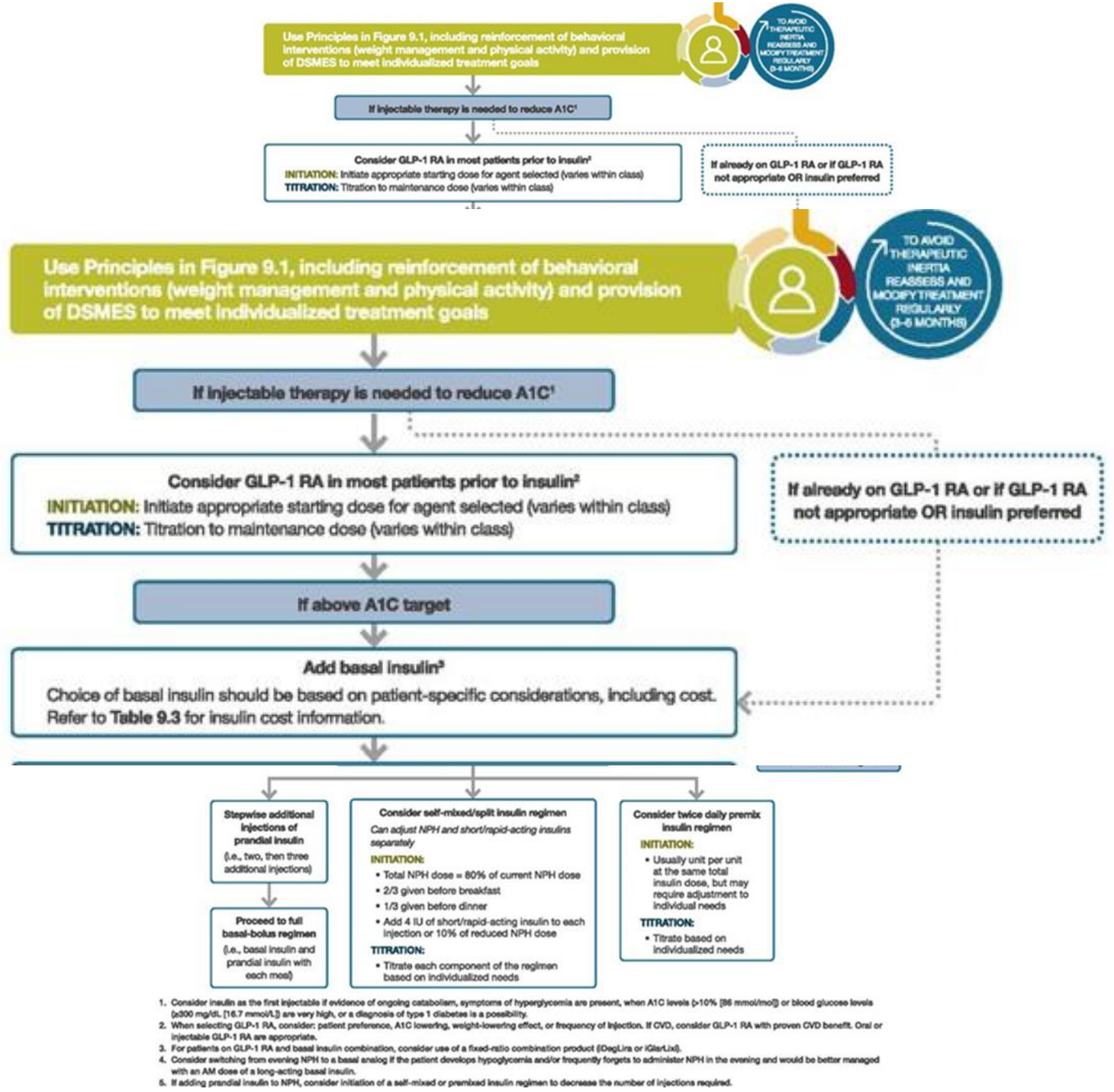
First author, year	Country	Study period	N*	Index treatment	TI (addition to index treatment)	Patients who received TI, %†	HbA1c threshold‡	Mean glycaemic burden, years
Brown, 2004[16]	USA	1994–2002	7,208	Diet and exercise	Change of therapy	Not reported	>7.0%	1.9
				Metformin			>7.0%	3.5
				Sulfonylurea			>7.0%	2.8
				Metformin + sulfonylurea			>7.0%	4.9
				Diet and exercise		67	>8.0%	0.7
				Metformin		35	>8.0%	1.6
				Sulfonylurea		45	>8.0%	1.4
				Metformin + sulfonylurea		19	>8.0%	2.5
Halimi, 2012[34]	France	2010	702	≥1 OAD	1 drug or dose increase	7§	Variable‖	1.2
				1 OAD		7§	≥6.5%	1.2
				2 OADs		7§	≥7.0%	1.2
				≥3 OADs		0§	≥8.0%	0.9
Khunti, 2013[39]	UK	2004–2011	62,896	1 OAD	OAD	65	≥7.0%	2.9#
						67	≥7.5%	1.9#
						67	≥8.0%	1.6#
					Insulin	7	≥7.0%	>7.2#,**
						8	≥7.5%	>7.1#,**
						9	≥8.0%	>6.9#,**
					OAD or insulin	72	≥7.0%	2.2#
						75	≥7.5%	1.5#
						76	≥8.0%	1.1#
				2 OADs	OAD	32	≥7.0%	>7.2#,**
						32	≥7.5%	>7.2#,**
						30	≥8.0%	>6.9
					Insulin	14	≥7.0%	>7.2#,**
						17	≥7.5%	>7.2#,**
						20	≥8.0%	>6.9#,**
					OAD or insulin	45	≥7.0%	>7.2#,**
						49	≥7.5%	>7.2#,**
						50	≥8.0%	6.3#
				3 OADs	Insulin	18	≥7.0%	>7.1#,**
						21	≥7.5%	>6.1#,**
						22	≥8.0%	>6.0#,**
Zografou, 2014[69]	UK	2002–2011	509	Not insulin	Initiation of insulin	100¶	>7.0%	4.1#,††
							>8.0%	2.1#,††
							>9.0%	0.8#,††
Hugie, 2016[36]	USA	2009–2013	90,497	1 OAD	Initiation of insulin	100¶	>8.0%	0.4
				2 OADs			>8.0%	0.9
				3 OADs			>8.0%	1.2
				>3 OADs			>8.0%	1.3

0.0 2.0 4.0 6.0 8.0

Mean glycaemic burden, years

Khunti K, et al. Diabetes Obes Metab. 2018;20:427-437.

Is A1c above target despite dual/triple therapy? What's next?



American Diabetes Association Dia Care 2021;44:S111-S124

The Treat-to-Target Trial

Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients

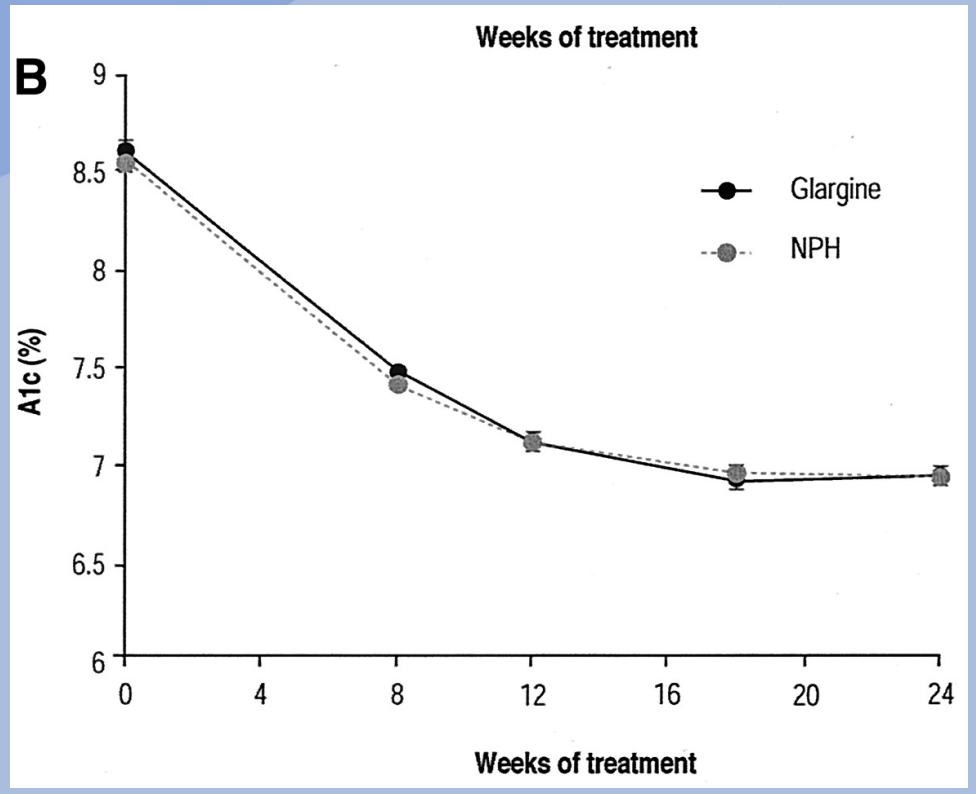
MATTHEW C. RIDDLE, MD[1]
JULIO ROSENSTOCK, MD[2]
JOHN GERICH, MD[3]

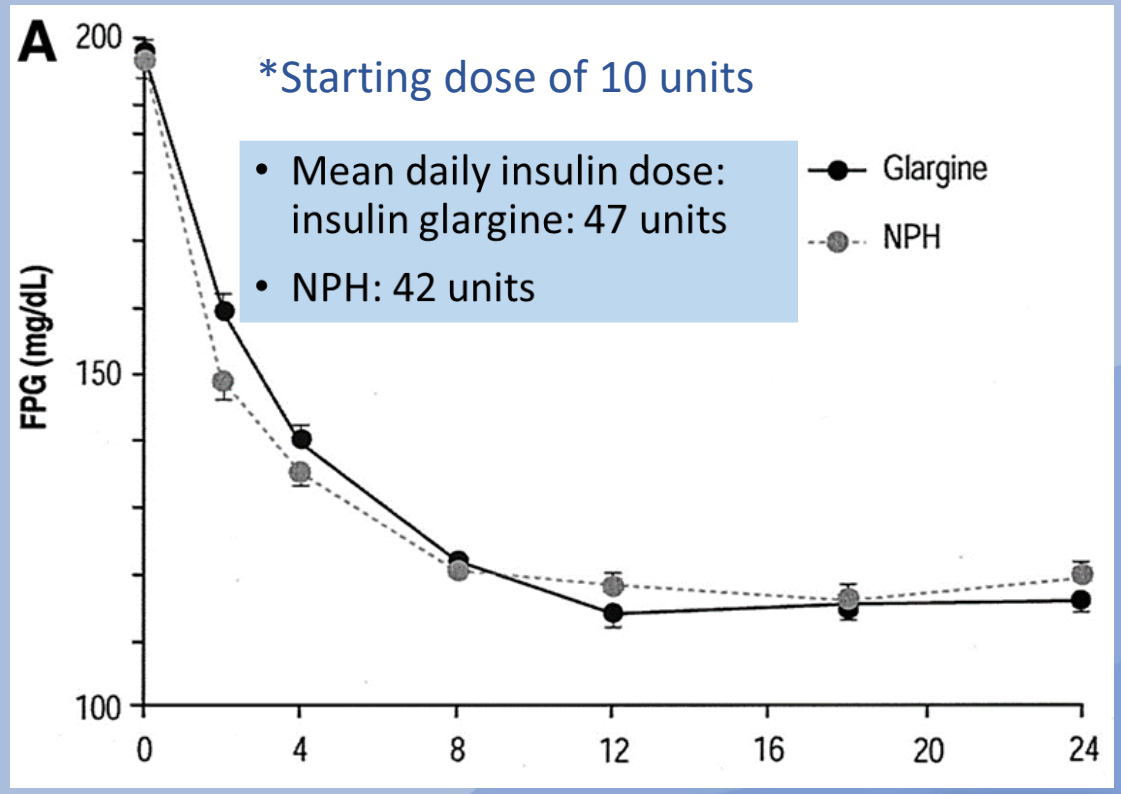
ON BEHALF OF THE INSULIN GLARGINE 4002 STUDY INVESTIGATORS*

The first study to force-titrate insulin dosages to achieve a prespecified treatment goal; enabled comparison of safety endpoints to establish risk-benefit of a newer basal insulin

Matthew C. Riddle et al. Dia Care 2003;26:3080-3086

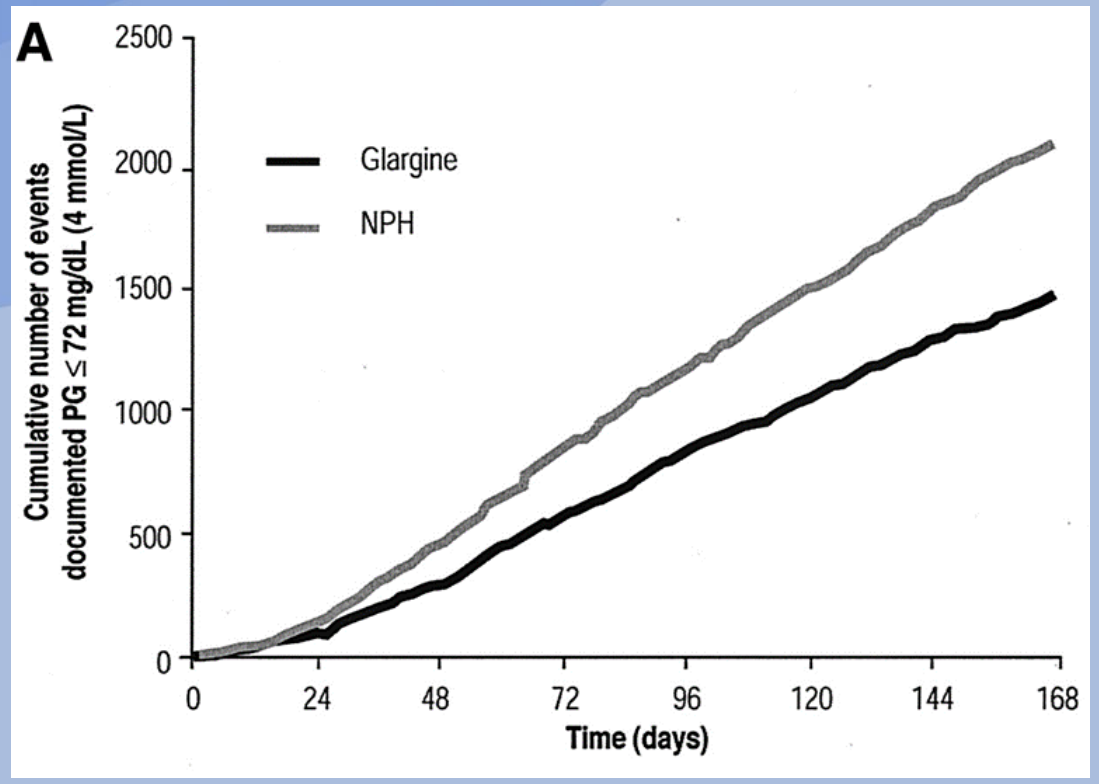
Effects on glycemic parameters of adding insulin to patients previously treated with 1-2 oral agents with A1c >7.5% *(n=756)*

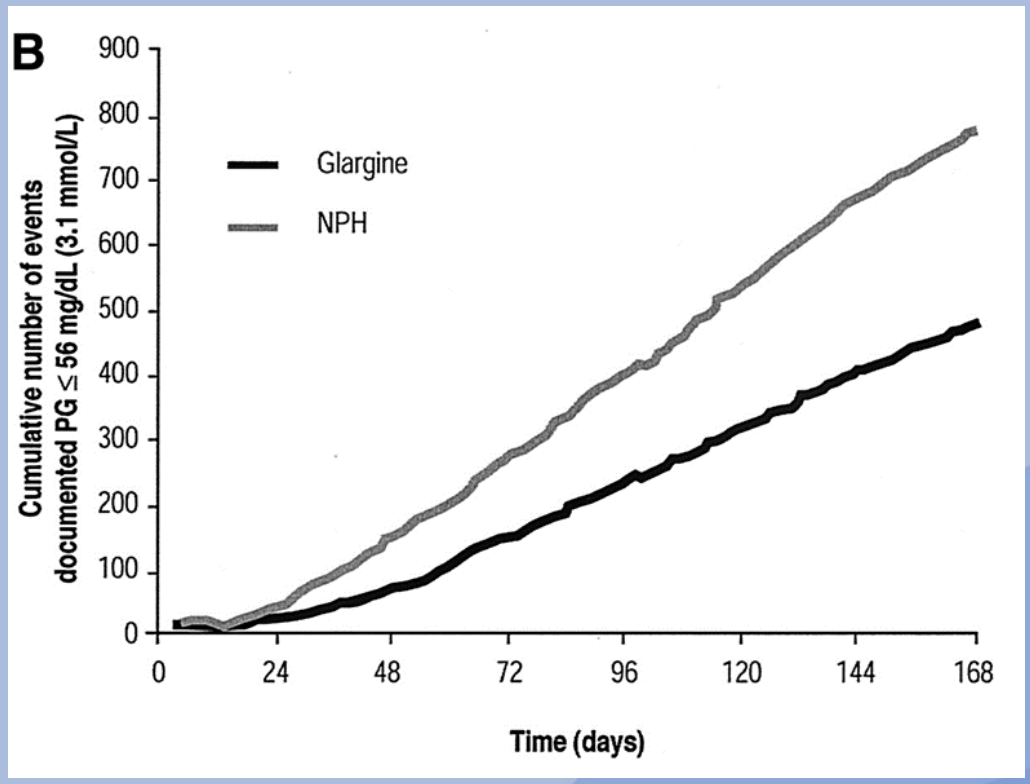




Matthew C. Riddle et al. Dia Care 2003;26:3080-3086

Cumulative Number of Hypoglycemia Events: The Treat-to-Target Trial

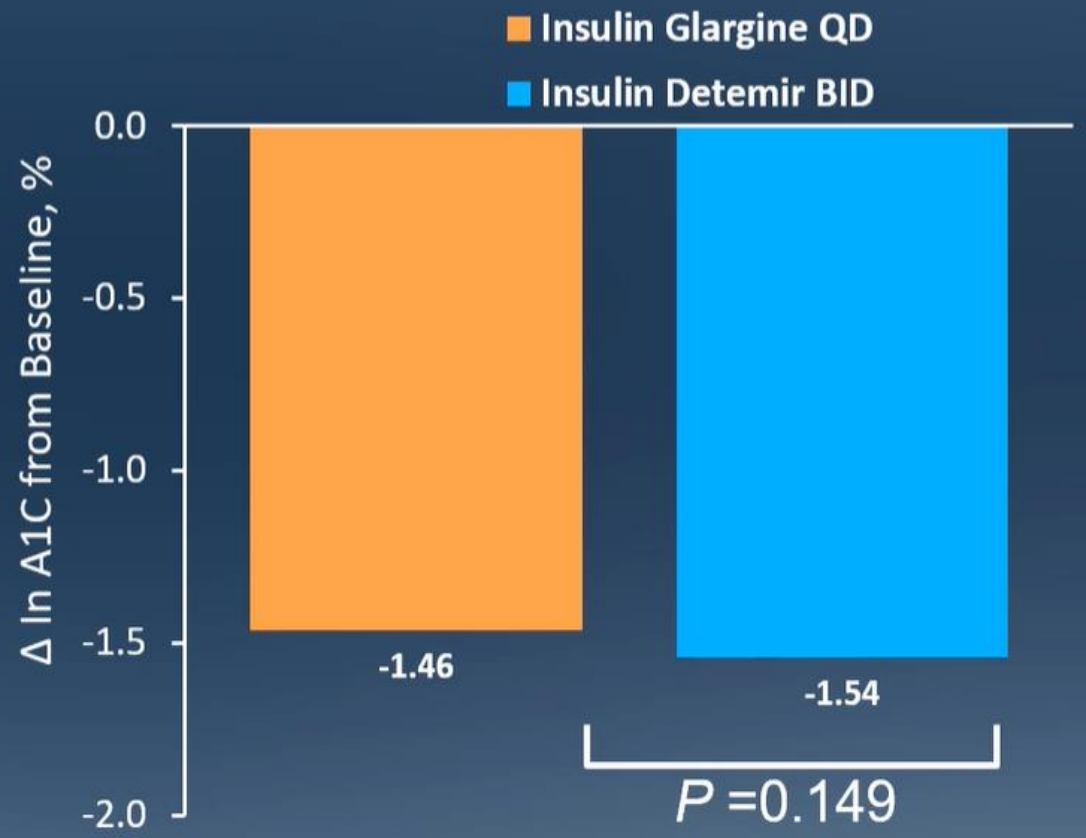




Matthew C. Riddle et al. Dia Care 2003;26:3080-3086

Basal Insulin Added to Oral Agents Improves Glycemic Control

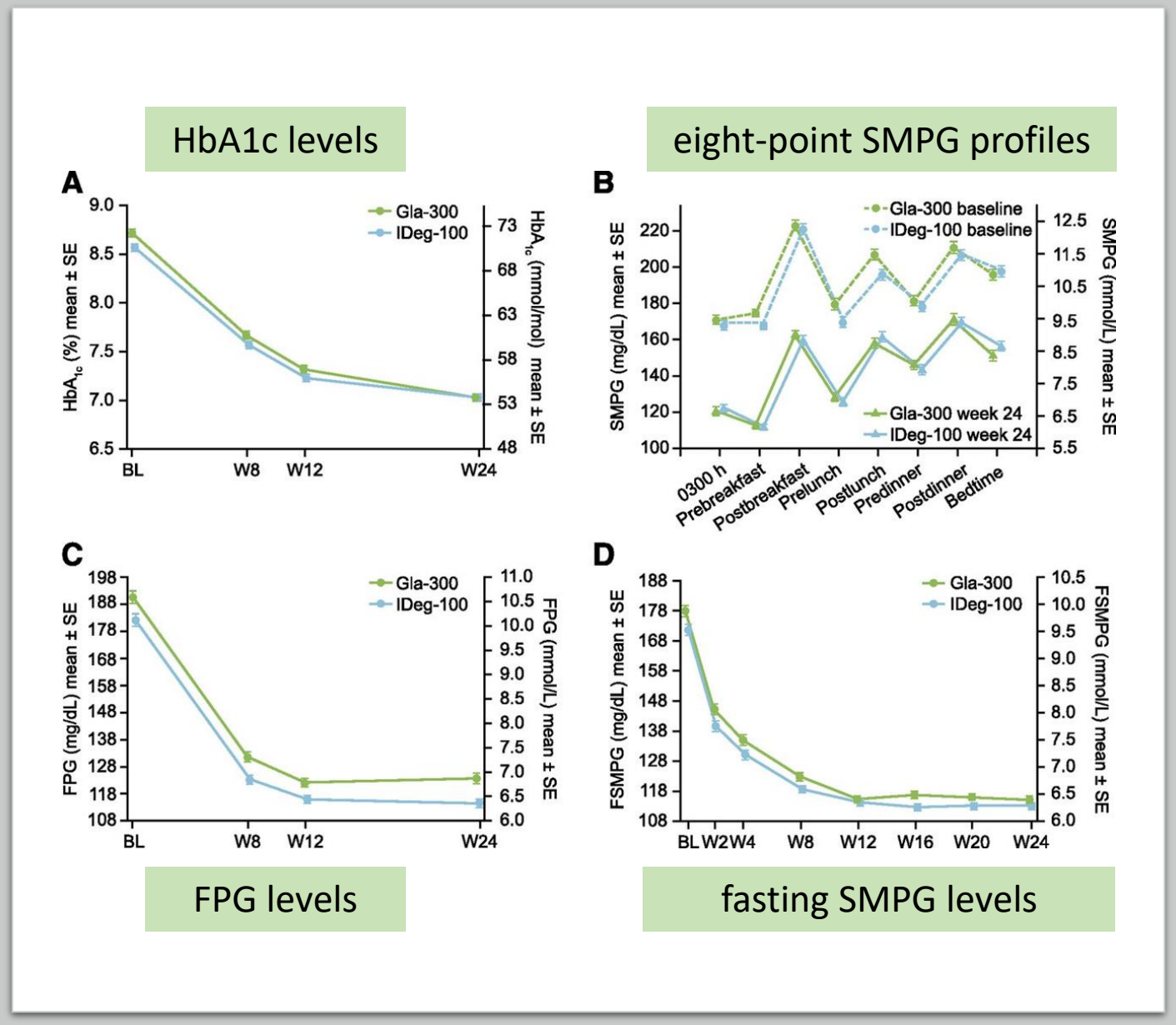
24-week noninferiority trial of 973 insulin-naive patients with type 2 diabetes inadequately controlled on oral antidiabetic drugs



- Similar hypoglycemia rates (<30% symptomatic)
- Changes in body weight (kg):
  - Insulin glargine: 1.4
  - Insulin detemir: 0.6 (*P* <0.001)
- Final insulin doses (units/day):
  - Insulin glargine: 43.5
  - Insulin detemir: 76.5 (*P* <0.001)

Swinnen, SG, et al. Diabetes Care 2010 Jun; 33(6): 1176-1178.

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



Julio Rosenstock et al. Dia Care 2018;41:2147-2154

Initiation of basal insulin

If A1c >8%
consider starting
dose 0.2-0.3 units/kg

Initiate insulin with a single injection of a basal insulin

Bedtime or morning long-acting insulin or bedtime intermediate-acting insulin

Daily dose: 10 units or 0.1-0.2 units/Kg

American Diabetes Association Dia Care 2021;44:S111-S124.
Garber A J, et al. Endocr Pract. 2020;26(1):107-139

Titration of Basal Insulin

START

Basal Insulin

Daily dose: 10 units *or* 0.1-0.2 units/kg

Check FPG daily with SMBG

ADJUST

Choose evidence-based titration algorithm (e.g., increase 2 units every 3 days) to reach FPG target without hypoglycemia

If signs/symptoms of hypoglycemia, address cause and reduce insulin dose by 10-20%

Continue regimen and check A1c every 3 months

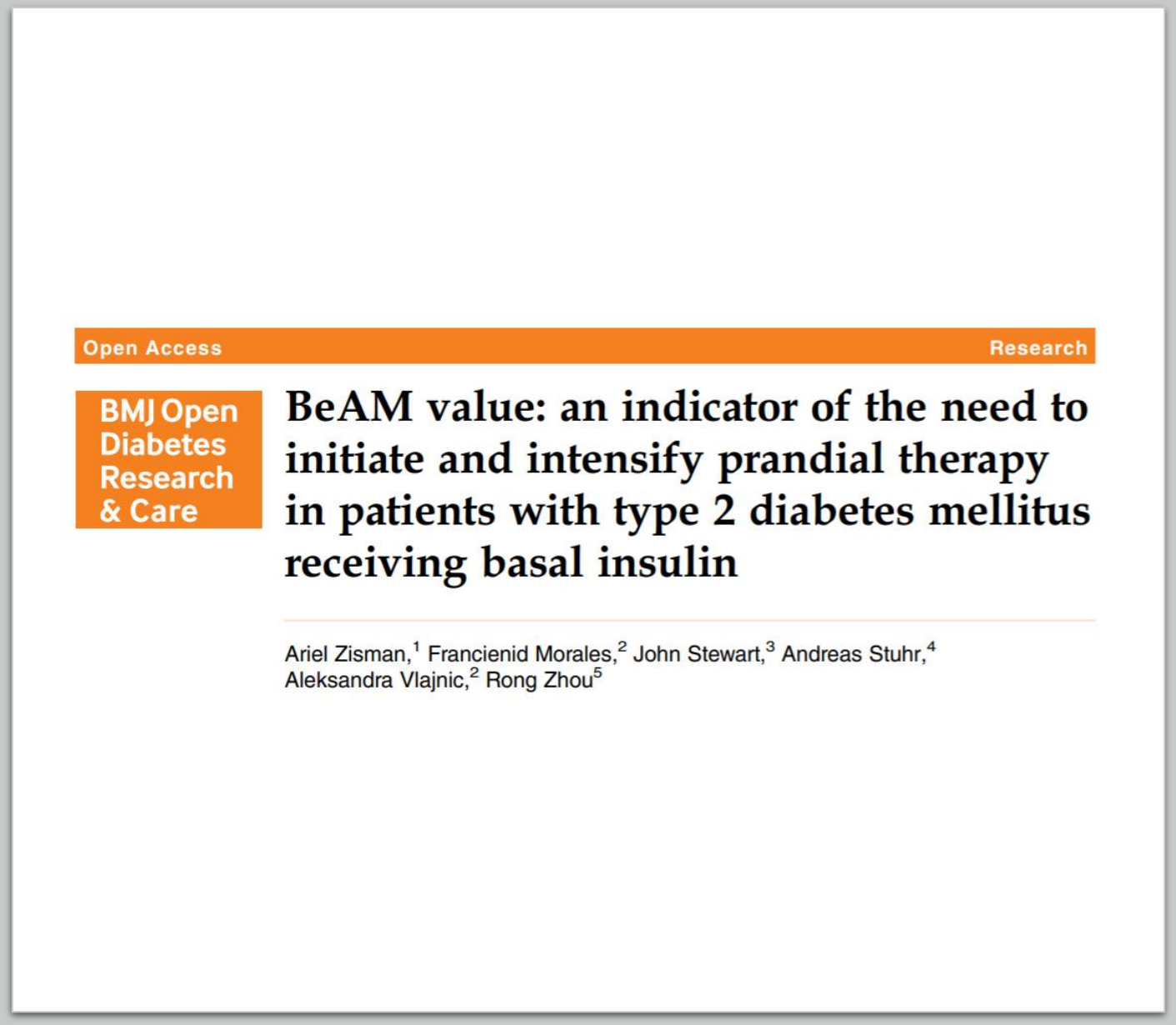
- **Patient self-titration is more effective**
- **Set FPG target that correlates to A1c target**

American Diabetes Association Dia Care 2021;44:S111-S124.
Inzucchi, SE, et al. Dia Care 2015;38:140-149

Assess Adequacy of Basal Insulin Dose

Overbasalization? Need to consider adjunctive therapies?

- Basal dose >0.5 IU/kg
- Elevated bedtime-morning
- Hypoglycemia
- High variability



Open Access Research

BMJ Open Diabetes Research & Care

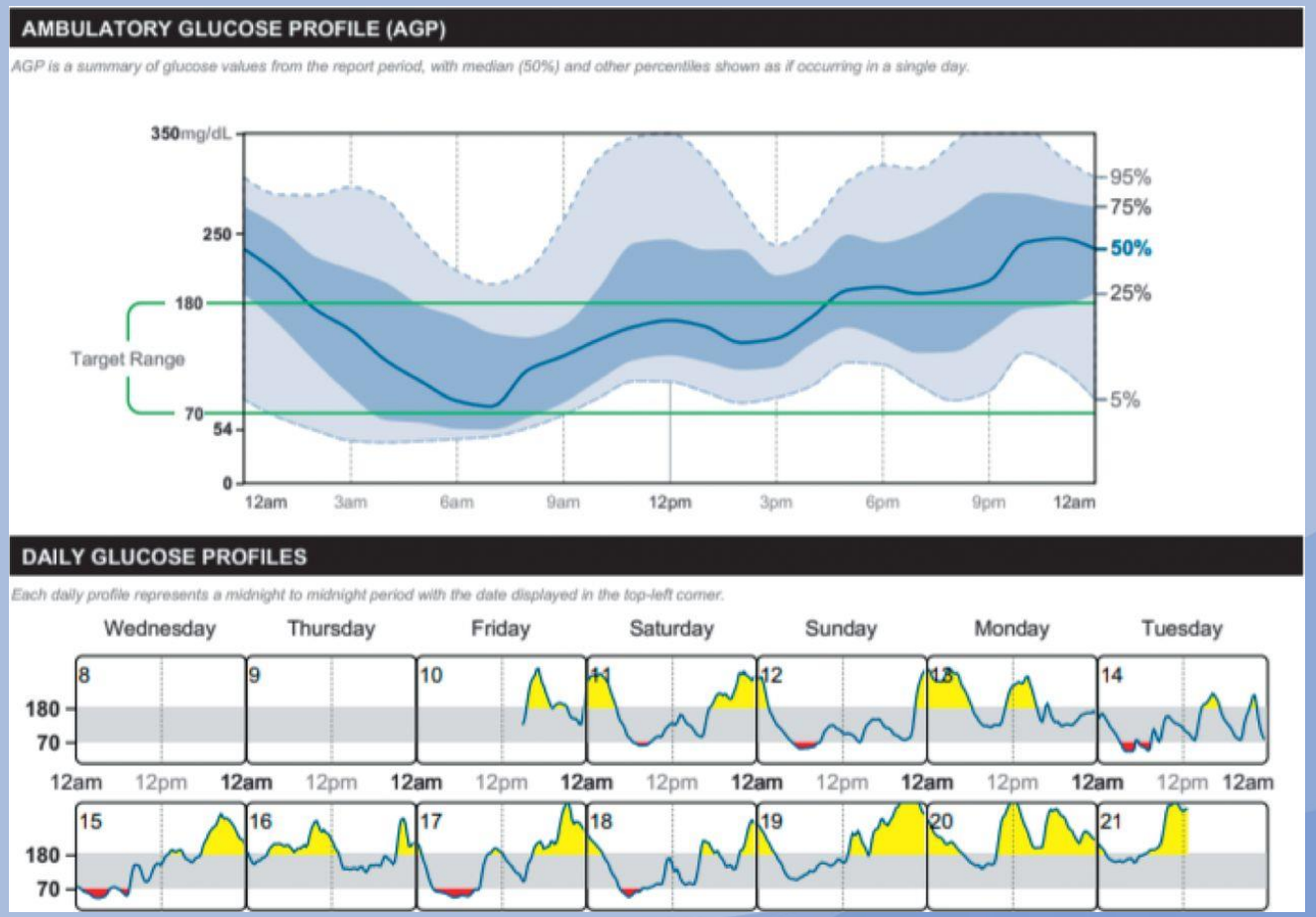
BeAM value: an indicator of the need to initiate and intensify prandial therapy in patients with type 2 diabetes mellitus receiving basal insulin

Ariel Zisman,[1] Francienid Morales,[2] John Stewart,[3] Andreas Stuhr,[4] Aleksandra Vlajnic,[2] Rong Zhou[5]

Zisman A, et al.BMJ Open Diabetes Research and Care 2016;4:e000171.

Assess Adequacy of Basal Insulin Dose

Date	Fasting	Bedtime
Mon	100 mg/dl	180 mg/dl
Tue	95 mg/dl	175mg/dl
Wed	80 mg/dl	168 mg/dl
Thu	110 mg/dl	200 mg/dl
Fri	105 mg/dl	190 mg/dl
Sat	99 mg/dl	170 mg/dl



100 Years of Insulin Therapy: A long Successful Path

Prandial Insulin Intensification

If above A1C target

Consider GLP-1 RA if not already in regimen

For addition of GLP-1 RA, consider lowering insulin dose dependent on current glycemic assessment and patient factors

Add prandial insulin[5]

Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

INITIATION:

- 4 IU a day or 10% of basal insulin dose
- If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 IU a day or 10% of basal dose

TITRATION:

- Increase dose by 1-2 IU or 10-15% twice weekly
- For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10-20%

If on bedtime NPH, consider converting to twice-daily NPH regimen

Conversion based on individual needs and current glycemic control. The following is one possible approach:

INITIATION:

- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION:

- Titrate based on individualized needs

If above A1C target

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American Diabetes Association Dia Care 2021;44:S111-S124.

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[1,2]

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

Premixed
Combination short and intermediate acting insulin[2]

1. Garber A J, et al. Endocr Pract. 2020;26(1):107-139. 2. American Diabetes Association Dia Care 2021;44:S111-S124.

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American Diabetes Association.

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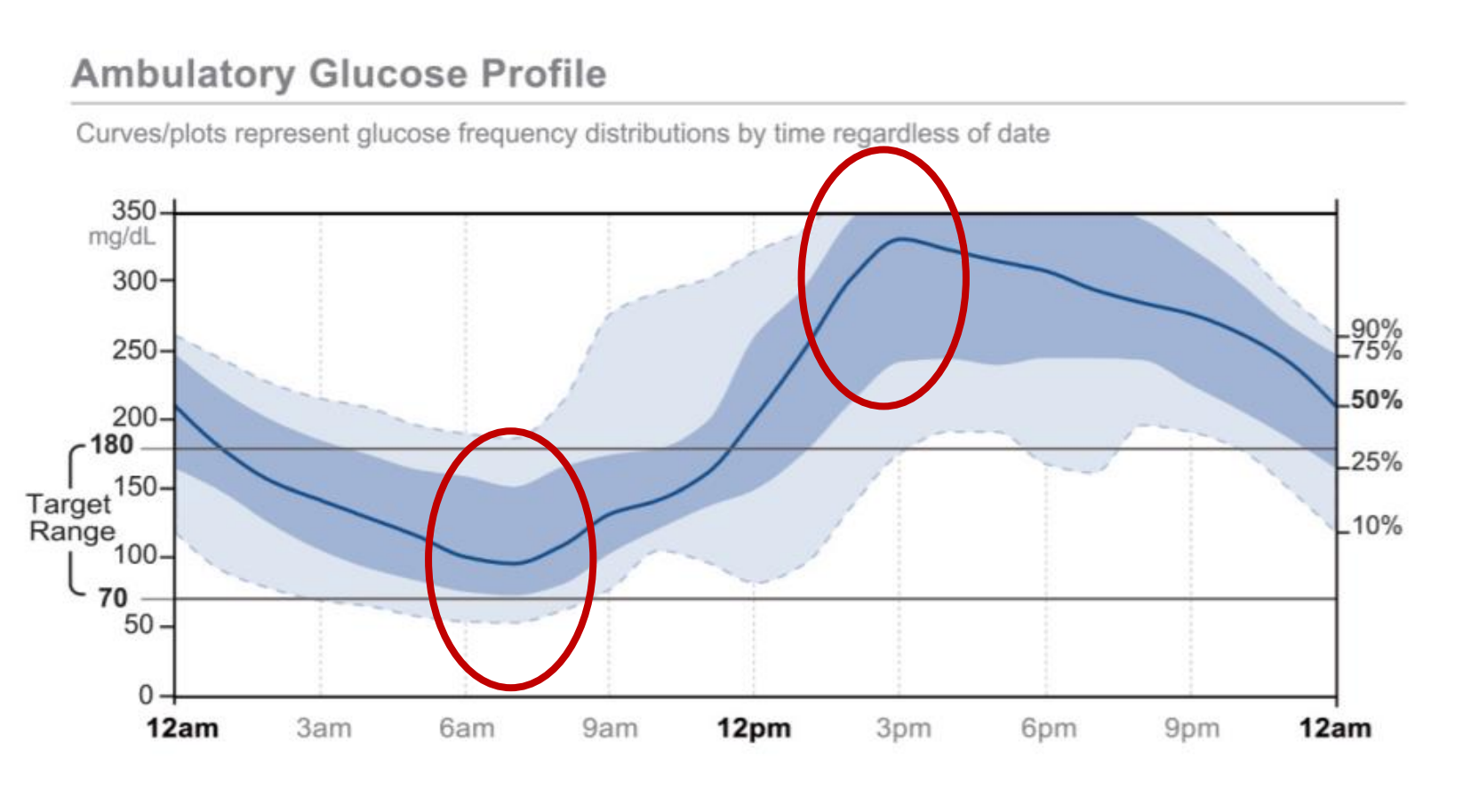

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Prandial Insulin Intensification

	Breakfast		Lunch		Dinner		Bedtime
	Pre	Post	Pre	Post	Pre	Post	
Mon	130	160	146	200	180	200	190
Tue	110	140	150	220	190	210	200
Wed	105	145	143	199	178	220	180
Thu	125	158	138	198	170	190	174
Fri	113	161	130	190	168	185	185
Sat	108	149	147	207	191	210	192
Sun	129	165	138	198	178	187	210

BeAm = >60 mg/dl
Reduced Basal Insulin by 4 U or 10%

Add 4 U lispro before lunch

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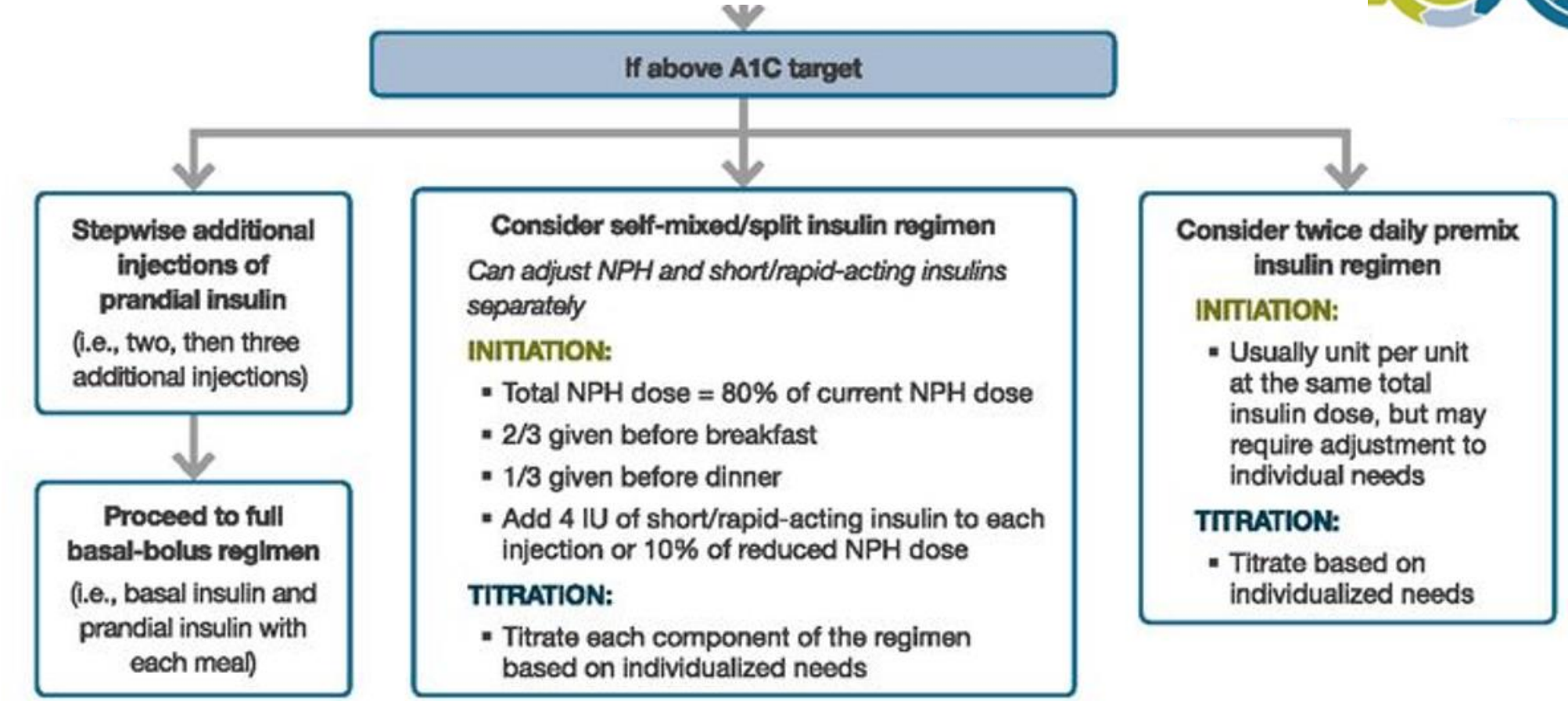
Prandial Insulin Intensification



American Diabetes Association.

American Diabetes Association Dia Care 2021;44:S111-S124.

Using Premixed Insulin

Pros	Cons
• Only one co-pay • Patient with a predictable schedule with regular meals and with a lower risk of hypoglycemia. • Patients often need fewer shots (1-2 per day) • Premixed R & N has the lowest cost. • Premixed Humalog 50/50 for patients with high carbohydrate meals.	• Patients must eat regular meals or they will be at a greater risk for hypoglycemia. • More nocturnal hypoglycemia • Premixed Regular & NPH has a greater risk for hypoglycemia. • There is an increased need for between meal snacks.

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AID™
ACCURATE INSULIN DECISIONS

STARTING PREMIXED ANALOG INSULIN:
WHEN TO TEST AND HOW TO ADJUST YOUR DOSE

(USING HUMALOG MIX 75/25%* OR NOVOLOG MIX 70/30%* | For Patients Who Are Not On Basal Insulin)

HOW TO START PREMIXED INSULIN

The first dose should be 10% of the patient's weight in pounds (i.e. 220 lbs = 22 units) taken once daily at the largest meal.

When Premixed Insulin Is Taken:	When To Test Blood Sugar:	If The Blood Sugar Results Are:	Then You Should:
At Breakfast	Before Dinner	Under 80	Subtract 2 Units Every 3-5 Days Until Blood Sugar is 80–130 Before Dinner
		80–130	Do Not Adjust
		Over 130	Add 2 Units Every 3-5 Days Until Blood Sugar is 80–130 Before Dinner
At Dinner	Before Bed	80–130	Eat a Small Snack
		130–180	For Most People on Premixed Insulin, This is a Good Blood Sugar Goal to Have in Order to Avoid Hypoglycemia During the Night.
	Before Breakfast	Under 80	Subtract 2 Units Every 3–5 Days Until Blood Sugar is 80–130 Before Breakfast
		80–130	Do Not Adjust Dose
		Over 130	Add 2 Units Every 3–5 Days Until Blood Sugar is 80–130 Before Breakfast

If blood sugar is under 70, drink 1/2 cup of juice or soda or eat something that contains sugar. You can also take glucose tablets to bring your blood sugar into normal range. Let your physician/care team know that you had low blood sugar.

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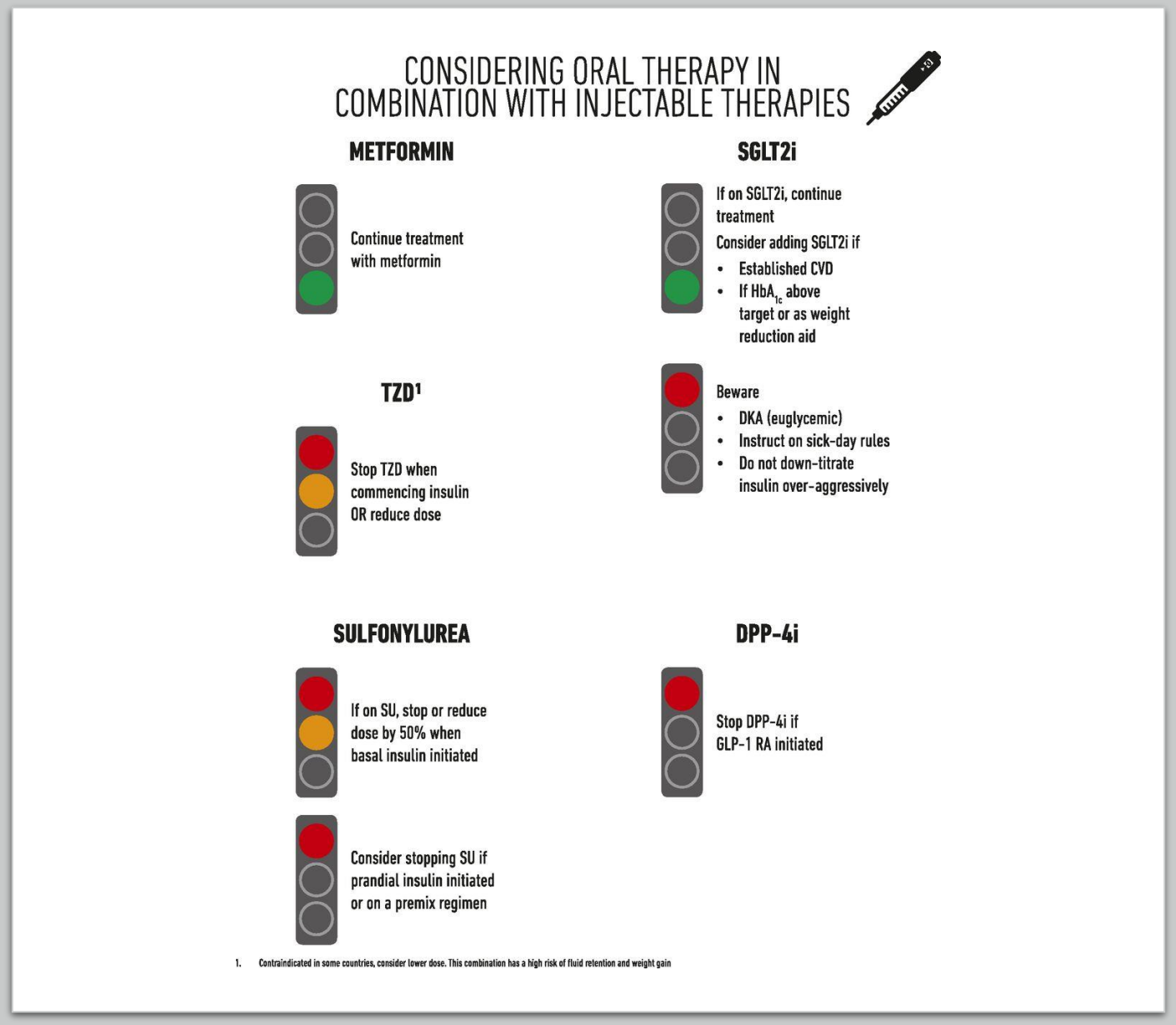
Considering oral therapy in combination with injectable therapies.



Melanie J. Davies et al. Dia Care 2018;41:2669-2701

Summary

- Type 2 diabetes is a progressive disease.
- Individualize your patients' glycemic target based on patient and disease characteristics.
- Provide patient-centered care and use shared decision-making to overcome barriers to injectable therapy.
- Consider GLP-1 RA as the first injectable before insulin.
- Initiate appropriate basal insulin based in the individual patient's hypoglycemia risk, weight concerns, and cost considerations.

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Summary

- Basal insulin have a physiological maximum benefit around 0.8 units per Kg/day and prescribers should look beyond basal to prandial intervention.
- Intensification of therapy beyond basal can be accomplished through addition of GLP-1 RA or SGLT2 inhibitors.
- Addition of prandial insulin can be simplified by stepwise approach with close follow up and titration.
- Professional or intermittent CGM can illuminate need for intensification or directional changes in therapy.

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“Insulin is not the enemy it is the misuse of insulin that is the enemy.”

Richard Aguilar