



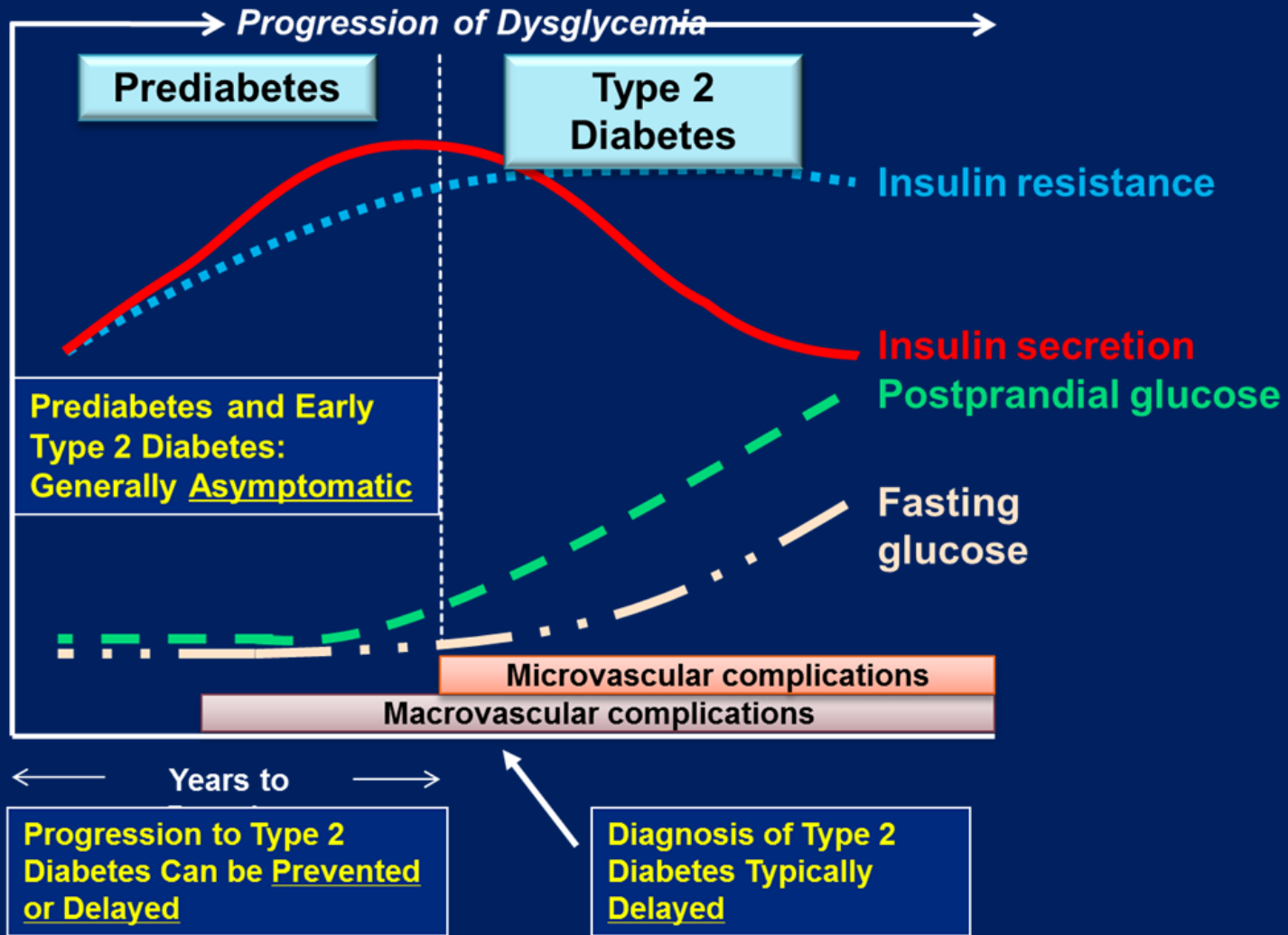
Management of Hyperglycemia in T2DM: A Patient-Centered Approach

Ramachandra G. Naik, MD

Senior Medical Director, Worldwide Clinical Affairs

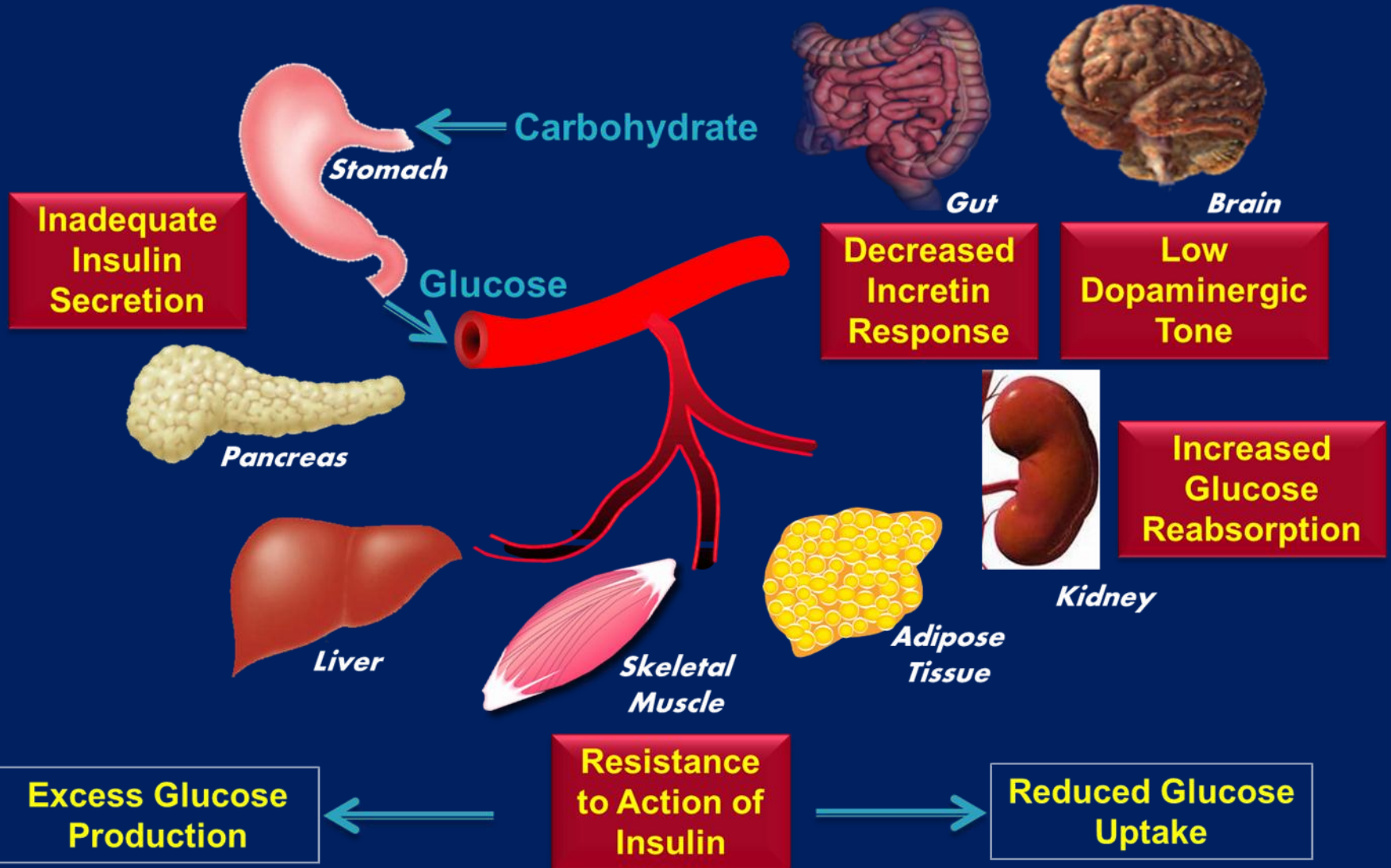
Johnson & Johnson Diabetes Care Companies, Wayne PA

Natural History of Type 2 Diabetes



Adapted from Ramlo-Halsted BA, Edelman SV. *Prim Care*. 1999;26:771-789

Pathophysiology of Type 2 Diabetes



Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. Eleventh Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2011.

Johnson & Johnson

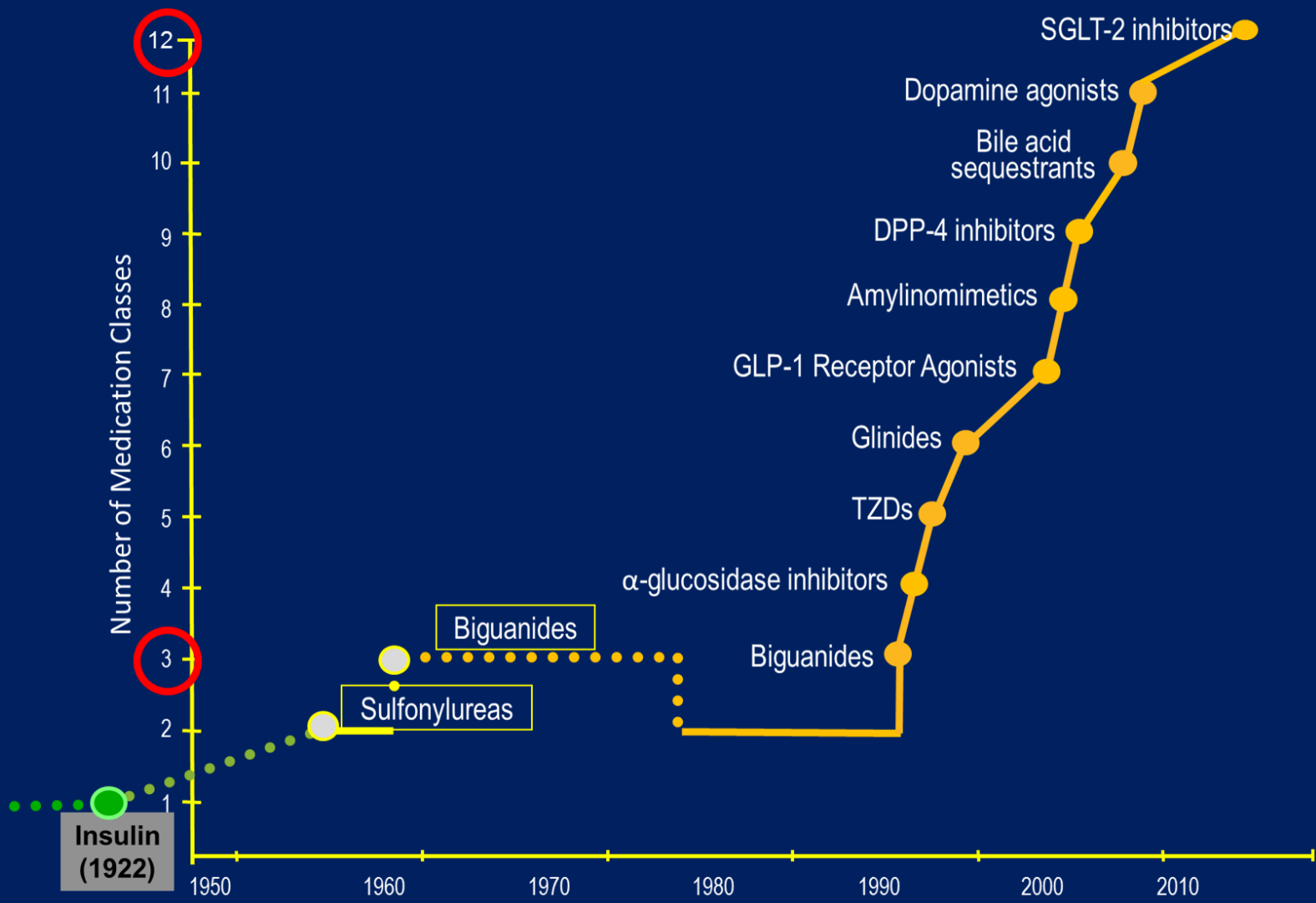
DIABETES INSTITUTE, LLC

Polling Question

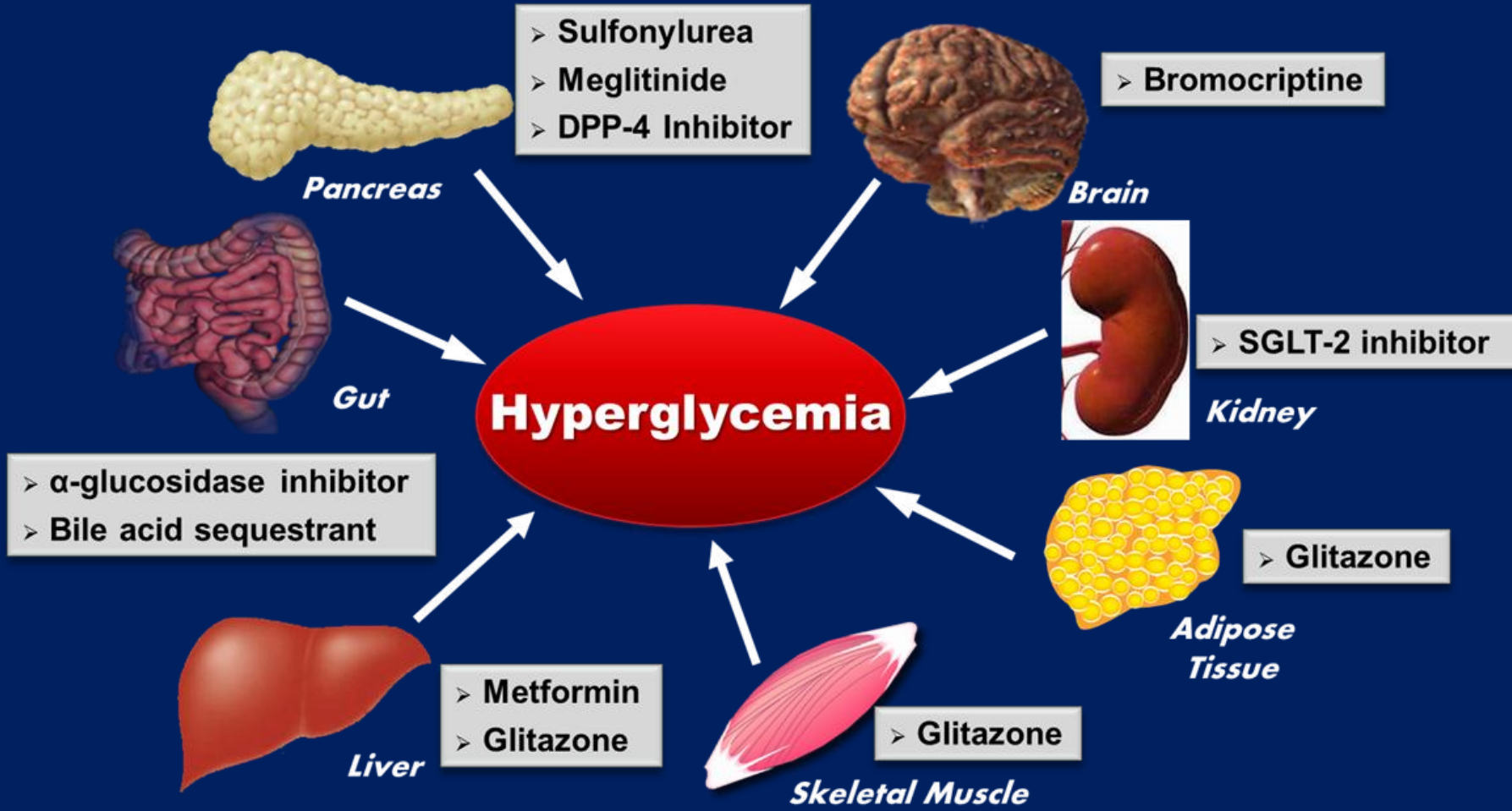
More than 50% of all non-insulin medications currently used to treat T2DM have been approved since 2000.

- A. True**
- B. False**

Diabetes Drug Classes Increasing Rapidly



Type 2 Diabetes Therapy: Sites of Action



Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. Eleventh Edition. Professional Communications, Inc., Greenwich, CT. 288 pages, 2011.

Patient-Centered Approach

“...providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions.”

- Gauge patient’s preferred level of involvement.
- Explore, where possible, therapeutic choices. Consider using decision aids.
- Shared Decision Making – a collaborative process between patient and clinician, using best available evidence and taking into account the patient’s preferences and values
- Final decisions regarding lifestyle choices ultimately lie with the patient.

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

Study	Microvasc		CVD		Mortality	
	Initial Trial	Long Term Follow-up	Initial Trial	Long Term Follow-up	Initial Trial	Long Term Follow-up
UKPDS	↓	↓	↔	↓	↔	↓
DCCT / EDIC*	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

Kendall DM, Bergenstal RM. © International Diabetes Center 2009

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.

Holman RR et al. *N Engl J Med.* 2008;359:1577. DCCT Research Group. *N Engl J Med* 1993;329:977.

Nathan DM et al. *N Engl J Med.* 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.

Patel A et al. *N Engl J Med* 2008;358:2560. Duckworth W et al. *N Engl J Med* 2009;360:129. (erratum:

Moritz T. *N Engl J Med* 2009;361:1024)



Initial Trial



Long Term Follow-up

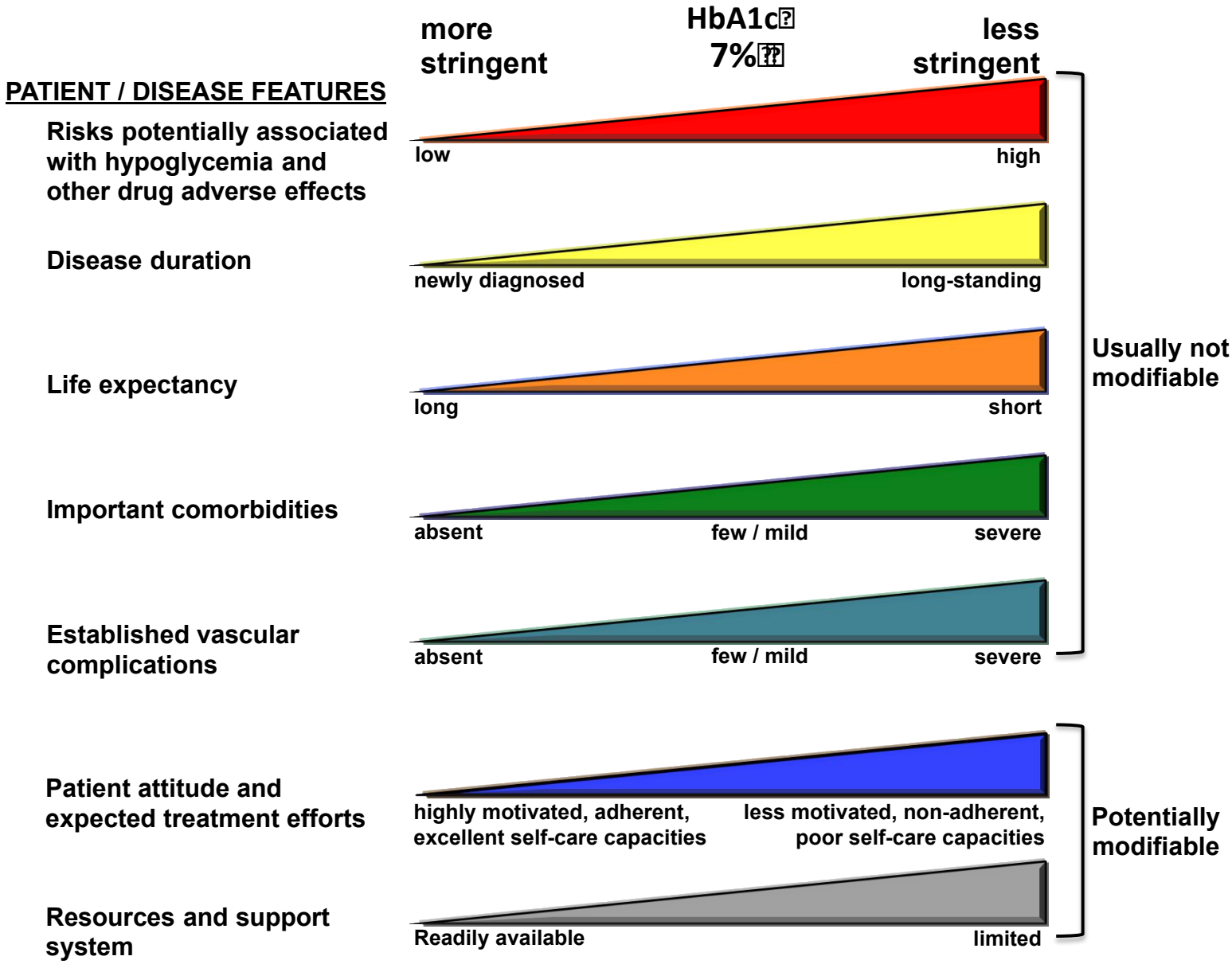
* in T1DM

ANTI-HYPERGLYCEMIC THERAPY

- **Glycemic targets**
 - **HbA1c < 7.0%** (mean PG ~150-160 mg/dl)
 - Pre-prandial PG <130 mg/dl
 - Post-prandial PG <180 mg/dl
 - ***Individualization*** is key:
 - Tighter targets (6.0 - 6.5%) - younger, healthier
 - Looser targets (7.5 - 8.0%⁺) - older, comorbidities, hypoglycemia prone, etc.
 - Avoidance of hypoglycemia

Figure 1. Modulation of the intensiveness of glucose lowering therapy in 2DM

Approach to the management of hyperglycemia



Approach to the Management of Hyperglycemia

**Risks
potentially
associated with
hypoglycemia,
other drug
adverse effects**

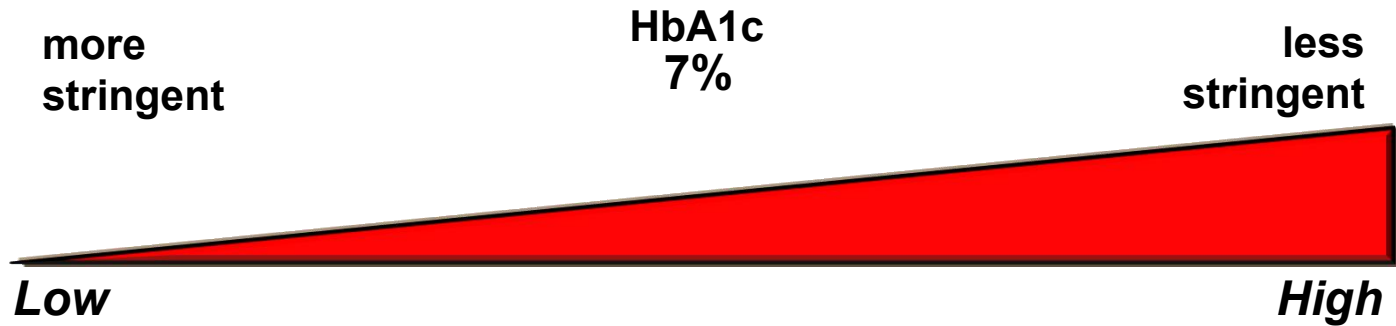
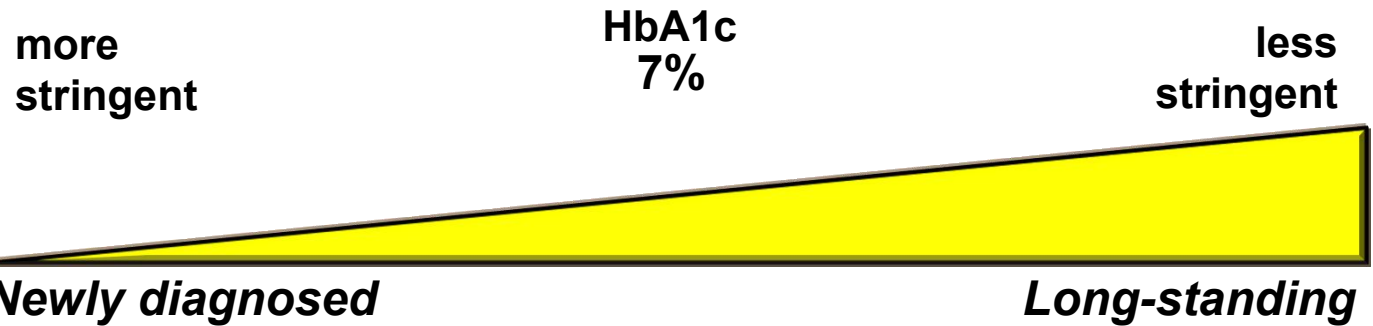


Figure 1. Modulation of the Intensiveness of Glucose Lowering Therapy in T2DM

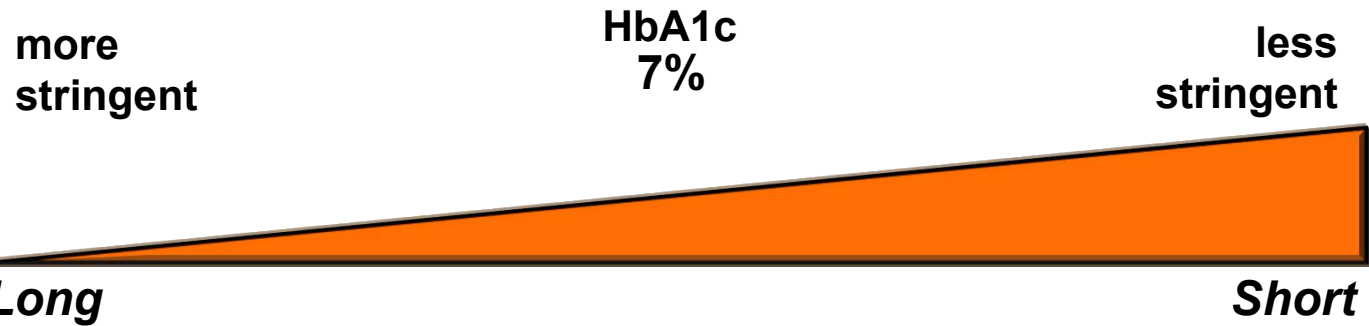
Approach to the Management of Hyperglycemia



Disease duration

Figure 1. Modulation of the Intensiveness of glucose-lowering therapy in T2DM

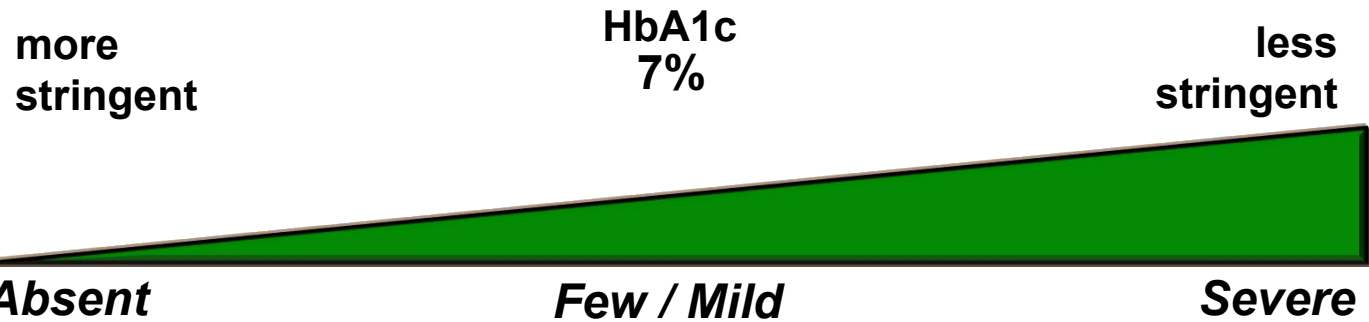
Approach to the Management of Hyperglycemia



Life expectancy

Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM

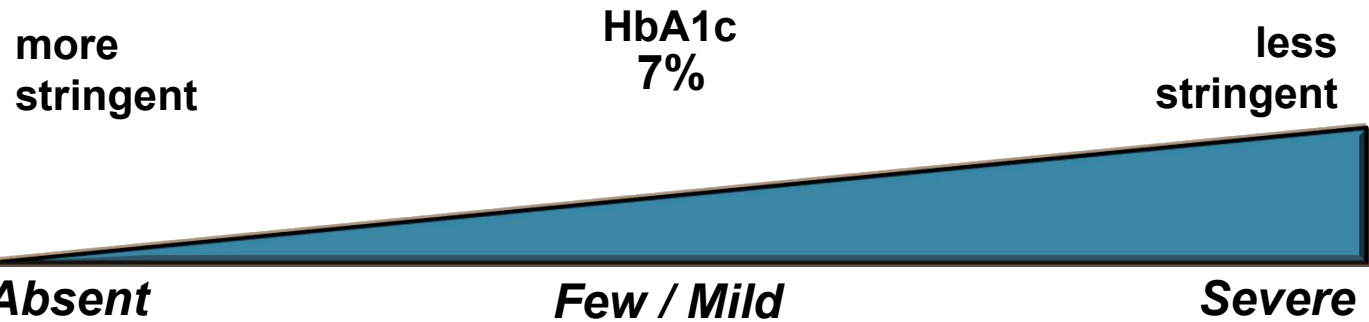
Approach to the Management of Hyperglycemia



**Important
comorbidities**

Figure 1. Modulation of the Intensiveness of glucose-lowering therapy in T2DM

Approach to the Management of Hyperglycemia



Established vascular complications

Figure 1. Modulation of the Intensiveness of glucose lowering therapy in T2DM

Approach to the Management of Hyperglycemia

more stringent

HbA1c
7%

less stringent

Patient attitude & expected treatment efforts

Highly motivated, adherent, excellent self-care capacities

Less motivated, non-adherent, poor self-care capacities

POTENTIALLY MODIFIABLE

Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM

Approach to the Management of Hyperglycemia

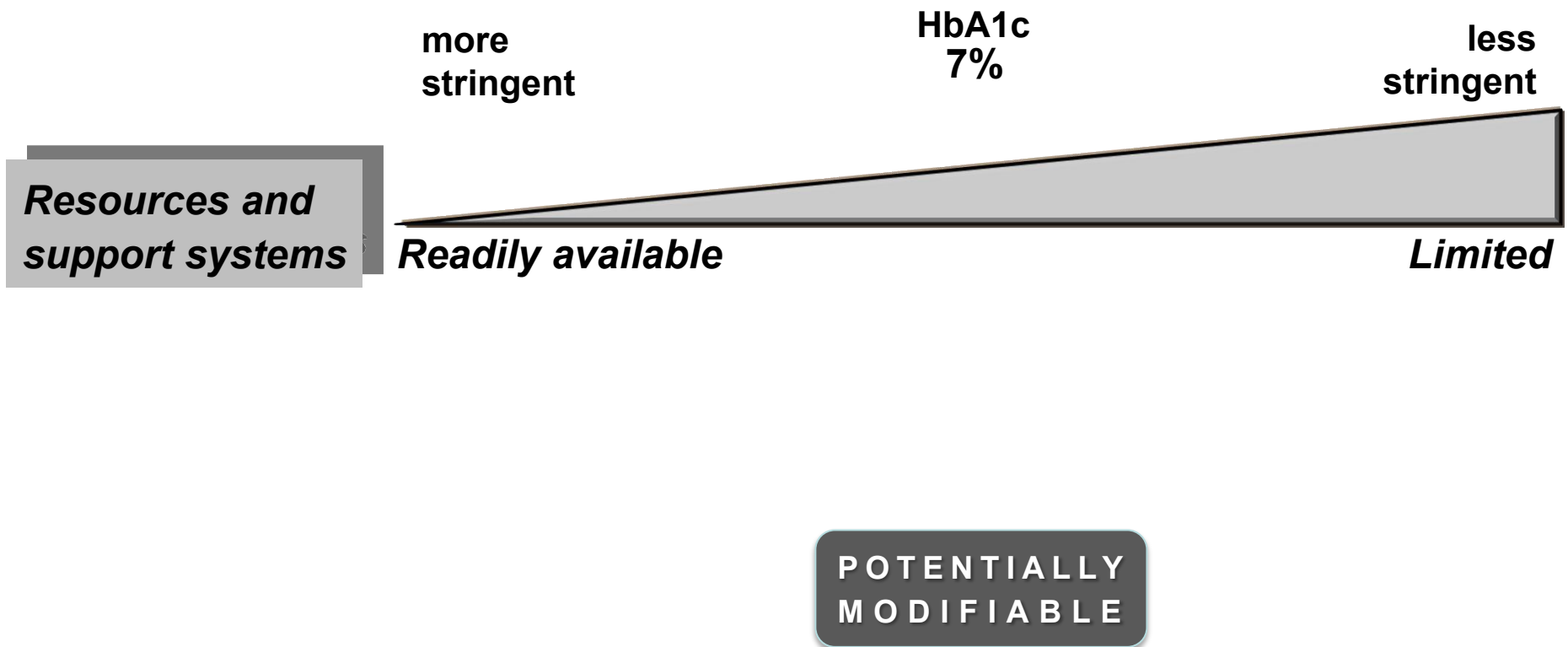


Figure 1. Modulation of the intensiveness of glucose-lowering therapy in T2DM

American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan

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INDIVIDUALIZE GOALS

$A1c \leq 6.5\%$

For patients without
concurrent serious
illness and at low
hypoglycemic risk

$A1c > 6.5\%$

For patients with
concurrent serious
illness and at risk
for hypoglycemia

Polling Question

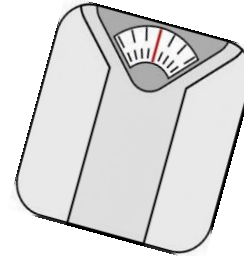
Which of the following statement(s) about individualization of pharmacotherapy is consistent with 2015 ADA EASD Position statement update?

- A. Anti-hyperglycemic therapy includes increased activity levels**
- B. Insulin used to treat T2DM includes both human insulin and insulin analogues**
- C. Consider sex, racial, ethnic and genetic differences in management of T2DM**
- D. All of the above**

ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options: Lifestyle

- Weight optimization



- Healthy diet

- Increased activity level



Noninsulin Agents Available for T2D

Class	Primary Mechanism of Action	Agent(s)	Available as
α -Glucosidase inhibitors	<ul style="list-style-type: none"> • Delay carbohydrate absorption from intestine 	Acarbose Miglitol	Precose or generic Glyset
Amylin analogue	<ul style="list-style-type: none"> • Decrease glucagon secretion • Slow gastric emptying • Increase satiety 	Pramlintide	Symlin
Biguanide	<ul style="list-style-type: none"> • Decrease HGP • Increase glucose uptake in muscle 	Metformin	Glucophage or generic
Bile acid sequestrant	<ul style="list-style-type: none"> • Decrease HGP? • Increase incretin levels? 	Colesevelam	WelChol
DPP-4 inhibitors	<ul style="list-style-type: none"> • Increase glucose-dependent insulin secretion • Decrease glucagon secretion 	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tadjenta Onglyza Januvia
Dopamine-2 agonist	<ul style="list-style-type: none"> • Activates dopaminergic receptors 	Bromocriptine	Cycloset
Glinides	<ul style="list-style-type: none"> • Increase insulin secretion 	Nateglinide Repaglinide	Starlix or generic Prandin

DPP-4 = dipeptidyl peptidase; HGP = hepatic glucose production.

Garber AJ, et al. *Endocr Pract.* 2013;19(suppl 2):1-48. Inzucchi SE, et al. *Diabetes Care.* 2012;35:1364-1379.

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Noninsulin Agents Available for T2D

Class	Primary Mechanism of Action	Agent(s)	Available as
GLP-1 receptor agonists	<ul style="list-style-type: none"> • Increase glucose-dependent insulin secretion • Decrease glucagon secretion • Slow gastric emptying • Increase satiety 	Albiglutide Dulaglutide Exenatide Exenatide XR Liraglutide	Tanzeum Trulicity Byetta Bydureon Victoza
SGLT2 inhibitors	<ul style="list-style-type: none"> • Increase urinary excretion of glucose 	Canagliflozin Dapagliflozin Empagliflozin	Invokana Farxiga Jardiance
Sulfonylureas	<ul style="list-style-type: none"> • Increase insulin secretion 	Glimepiride Glipizide Glyburide	Amaryl or generic Glucotrol or generic DiaBeta, Glynase, Micronase, or generic
Thiazolidinediones	<ul style="list-style-type: none"> • Increase glucose uptake in muscle and fat • Decrease HGP 	Pioglitazone Rosiglitazone	Actos Avandia

GLP-1 = glucagon-like peptide; HGP = hepatic glucose production; SGLT2 = sodium glucose cotransporter 2.

Garber AJ, et al. *Endocr Pract.* 2013;19(suppl 2):1-48. Inzucchi SE, et al. *Diabetes Care.* 2012;35:1364-1379.

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ANTI-HYPERGLYCEMIC THERAPY



- ***Insulins***

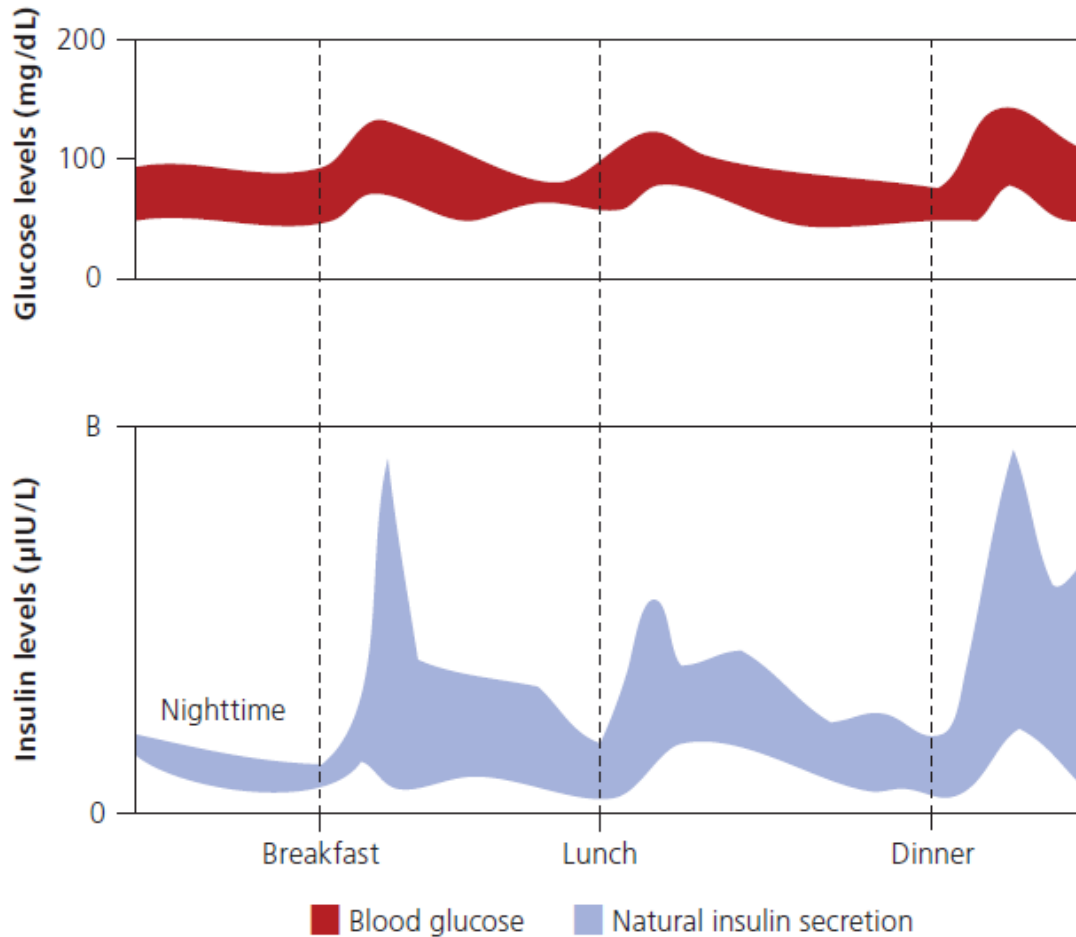
Human Insulins

- Neutral protamine Hagedorn (NPH)
- Regular human insulin
- Pre-mixed formulations

Insulin Analogues

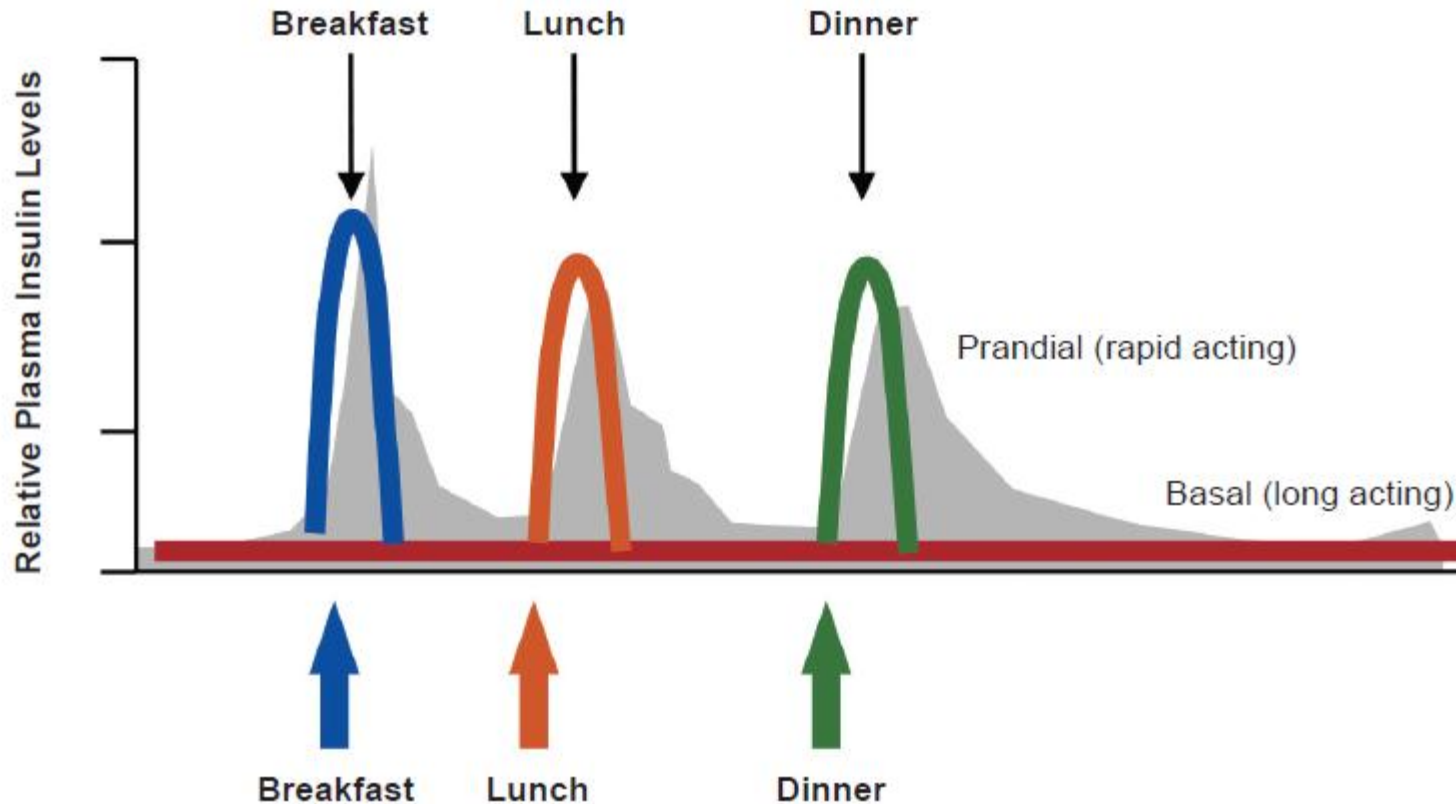
- Basal analogues (glargine, detemir, degludec)
- Rapid analogues (lispro, aspart, glulisine)
- Pre-mixed formulations

Insulin Secretion



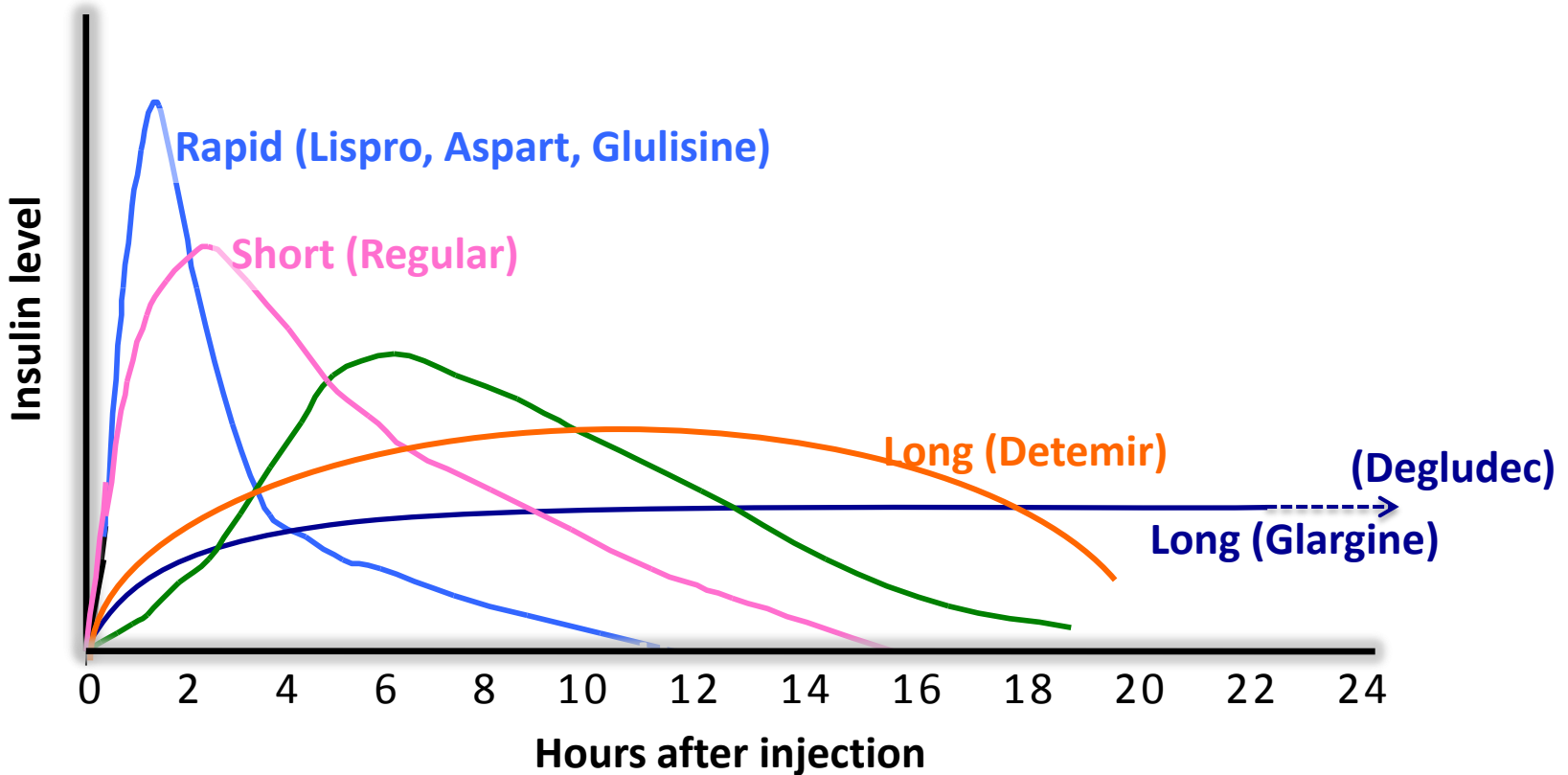
Insulin is secreted by the pancreas in a glucose-dependent manner continuously throughout the day, as well as in response to oral carbohydrate loads

Insulin Mimics Normal Physiologic Profile



Principle of insulin use - to create as normal a glycemic profile as possible without causing unacceptable weight gain or hypoglycemia

Pharmacokinetic Profiles of Human Insulin and Insulin Analogs



	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD	SU GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL/ GU	Contra- indicated CKD Stage 3B,4,5	Exenatide Contra- indicated CrCl < 30	Genital Mycotic Infections	Dose Adjustment May be Necessary (Except Linagliptin)	Neutral	May Worsen Fluid Retention	More Hypo Risk	Neutral	Neutral	More Hypo Risk & Fluid Retention	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit		Increased LDL			Neutral	?				
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral

■ Few adverse events or possible benefits
 ■ Use with caution
 ■ Likelihood of adverse effects

Mono-therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs

Healthy eating, weight control, increased physical activity & diabetes education

Metformin

high
low risk
neutral/loss
GI / lactic acidosis
low

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference - choice dependent on a variety of patient- & disease-specific factors):

Dual therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
high efficacy moderate risk weight gain hypoglycemia low costs	high efficacy low risk weight gain edema, HF, fxs low costs	intermediate efficacy low risk neutral weight rare side effects high costs	intermediate efficacy low risk weight loss GI dehydration high costs	high efficacy low risk weight loss GI side effects high costs	highest efficacy high risk weight gain hypoglycemia variable costs

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference - choice dependent on a variety of patient- & disease-specific factors):

Triple therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea +	Thiazolidinedione +	DPP-4 Inhibitor +	SGLT-2 Inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
or TZD	or SU	or SU	or SU	or SU	or TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or Insulin [§]	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin [§]	or Insulin [§]		or GLP-1-RA
or Insulin [§]	or Insulin [§]				

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2-i:

Metformin +

Basal Insulin +	Mealtime Insulin	or	GLP-1-RA
-----------------	------------------	----	----------

Combination therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs

Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations

Mono-therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs

Healthy eating, weight control, increased physical activity & diabetes education

Metformin

high
low risk
neutral/loss
GI / lactic acidosis
low

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Dual therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
high efficacy moderate risk weight gain hypoglycemia low costs	high efficacy low risk weight gain edema, HF, fxs low costs	intermediate efficacy low risk neutral weight rare side effects high costs	intermediate efficacy low risk weight loss GI, dehydration high costs	high efficacy low risk weight loss GI side effects high costs	highest efficacy high risk weight gain hypoglycemia variable costs

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Triple therapy

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea +	Thiazolidinedione +	DPP-4 Inhibitor +	SGLT-2 Inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
or TZD	or SU	or SU	or SU	or SU	or TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or Insulin [§]	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin [§]	or Insulin [§]		or GLP-1-RA
or Insulin [§]	or Insulin [§]				

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2-i:

Combination therapy

Metformin +	Metformin +
Basal Insulin +	Mealt ime Insulin or GLP-1-RA

Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations

Mono-therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs

Healthy eating, weight control, increased physical activity & diabetes education

Metformin

high
low risk
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GI / lactic acidosis
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If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Dual therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
high efficacy moderate risk weight gain hypoglycemia low costs	high efficacy low risk weight gain edema, HF, fxs low costs	intermediate efficacy low risk neutral weight rare side effects high costs	intermediate efficacy low risk weight loss GI, dehydration high costs	high efficacy low risk weight loss GI side effects high costs	highest efficacy high risk weight gain hypoglycemia variable costs

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Triple therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 receptor agonist	Insulin (basal)
+ or or or or	+ or or or or	+ or or or or	+ or or or or	+ or or or or	+ or or or or
TZD	SU	SU	SU	SU	TZD
DPP-4-i	DPP-4-i	TZD	TZD	TZD	DPP-4-i
SGLT2-i	SGLT2-i	SGLT2-i	DPP-4-i	Insulin[§]	SGLT2-i
GLP-1-RA	GLP-1-RA	Insulin[§]	Insulin[§]	Insulin[§]	GLP-1-RA
Insulin[§]	Insulin[§]				

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2-i:

Metformin +

Combination therapy

Basal Insulin +	Mealtime Insulin	or	GLP-1-RA
-----------------	------------------	----	----------

Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations

Healthy eating, weight control, increased physical activity & diabetes education

Mono-therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs

Metformin

high
low risk
neutral/loss
GI / lactic acidosis
low

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Dual therapy^{†□}

Efficacy*
Hypo risk
Weight
Side effects
Costs

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
high efficacy moderate risk weight gain hypoglycemia low costs	high efficacy low risk weight gain edema, HF, fxs low costs	intermediate efficacy low risk neutral weight rare side effects high costs	intermediate efficacy low risk weight loss GI, dehydration high costs	high efficacy low risk weight loss GI side effects high costs	highest efficacy high risk weight gain hypoglycemia variable costs

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Triple therapy

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 receptor agonist	Insulin (basal)
+ or or or or	+ or or or or	+ or or or or	+ or or or or	+ or or or or	+ or or or or
TZD DPP-4-i SGLT2-i GLP-1-RA Insulin [§]	SU DPP-4-i SGLT2-i GLP-1-RA Insulin [§]	SU TZD SGLT2-i Insulin [§]	SU TZD DPP-4-i Insulin [§]	SU TZD Insulin [§]	TZD DPP-4-i SGLT2-i GLP-1-RA

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2-i:

Combination injectable therapy^{†□}

Metformin +	Basal Insulin + Mealtime Insulin or GLP-1-RA
-------------	--

Healthy eating, weight control, increased physical activity & diabetes education

Mono-therapy

Efficacy*
Hypo risk
Weight
Side effects

Metformin

high
low risk
neutral/loss
GI / lactic acidosis
low

Metformin intolerance or contraindication

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Dual therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs

HbA1c ≥9%

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
high efficacy moderate risk weight gain hypoglycemia low costs	high efficacy low risk weight gain edema, HF, fxs low costs	intermediate efficacy low risk neutral weight rare side effects high costs	intermediate efficacy low risk weight loss GI, dehydration high costs	high efficacy low risk weight loss GI side effects high costs	highest efficacy high risk weight gain hypoglycemia variable costs

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Triple therapy

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 receptor agonist	Insulin (basal)
+ or or or or	+ or or or or	+ or or or or	+ or or or or	+ or or or or	+ or or or or
TZD	SU	SU	SU	SU	TZD
DPP-4-i	DPP-4-i	TZD	TZD	TZD	DPP-4-i
SGLT2-i	SGLT2-i	SGLT2-i	DPP-4-i	Insulin [§]	SGLT2-i
GLP-1-RA	GLP-1-RA	Insulin [§]	Insulin [§]	Insulin [§]	GLP-1-RA
Insulin [§]	Insulin [§]				

Uncontrolled hyperglycemia (catabolic features, BG 300-350 mg/dl, HbA1c 10-12%)

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2-i:

Combination injectable therapy

Metformin +	Basal Insulin +	Mealtime Insulin	or	GLP-1-RA
-------------	-----------------	------------------	----	----------

Mono-therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs



Dual therapy

Efficacy*
Hypo risk
Weight
Side effects
Costs



Triple therapy

Healthy eating, weight control, increased physical activity & diabetes education

Metformin

high
low risk
neutral/loss
GI / lactic acidosis
low

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Metformin +	Metformin +	Metformin +	Metformin +
Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist
high	intermediate	intermediate	high
low risk	low risk	low risk	low risk
gain	neutral	loss	loss
edema, HF, fxs	rare	GU, dehydration	GI
low	high	high	high

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Metformin +	Metformin +	Metformin +	Metformin +
Thiazolidinedione	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 receptor agonist
+	+	+	+
or	or	or	or
DPP-4-i	SU	TZD	TZD
or	or	or	or
SGLT2-i	TZD	DPP-4-i	
or	or		
GLP-1-RA	SGLT2-i		
	or		
	Insulin [§]		

Figure 2A. Anti-hyperglycemic therapy in T2DM: Avoidance of hypoglycemia

Mono-therapy

- Efficacy*
- Hypo risk
- Weight
- Side effects
- Costs



Dual therapy^{†□}

- Efficacy*
- Hypo risk
- Weight
- Side effects
- Costs



Triple therapy

Healthy eating, weight control, increased physical activity & diabetes education

Metformin

- high
- low risk
- neutral/loss
- GI / lactic acidosis
- low

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Metformin +	Metformin +	Metformin +
DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist
intermediate	intermediate	high
low risk	low risk	low risk
neutral	loss	loss
rare	GU, dehydration	GI
high	high	high

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Metformin +	Metformin +
DPP-4 Inhibitor	SGLT-2 Inhibitor
+	+
SU	
or TZD	
or SGLT2-i	or DPP-4-i
or Insulin [§]	

Figure 2B. Anti-hyperglycemic therapy in T2DM: Avoidance of weight gain

Mono-therapy

- Efficacy*
- Hypo risk
- Weight
- Side effects
- Costs

Healthy eating, weight control, increased physical activity & diabetes education

Metformin

- high
- low risk
- neutral/loss
- GI / lactic acidosis
- low

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Dual therapy

- Efficacy*
- Hypo risk
- Weight
- Side effects
- Costs

Metformin +

Sulfonylurea

- high
- moderate risk
- gain
- hypoglycemia
- low

Metformin +

Thiazolidinedione

- high
- low risk
- gain
- edema, HF, fxs
- low

Metformin +

Insulin (basal)

- highest
- high risk
- gain
- hypoglycemia
- variable

HUMAN

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Triple therapy

Metformin +

Sulfonylurea

+

TZD

or Insulin[§]

Metformin +

Thiazolidinedione

+

SU

or Insulin[§]

Metformin +

Insulin (basal)

+

TZD

HUMAN

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2-i:

Metformin +

HUMAN

Basal Insulin +

HUMAN

Mealtime Insulin or

Figure 2C. Anti-hyperglycemic therapy in 2DM: Minimization of costs

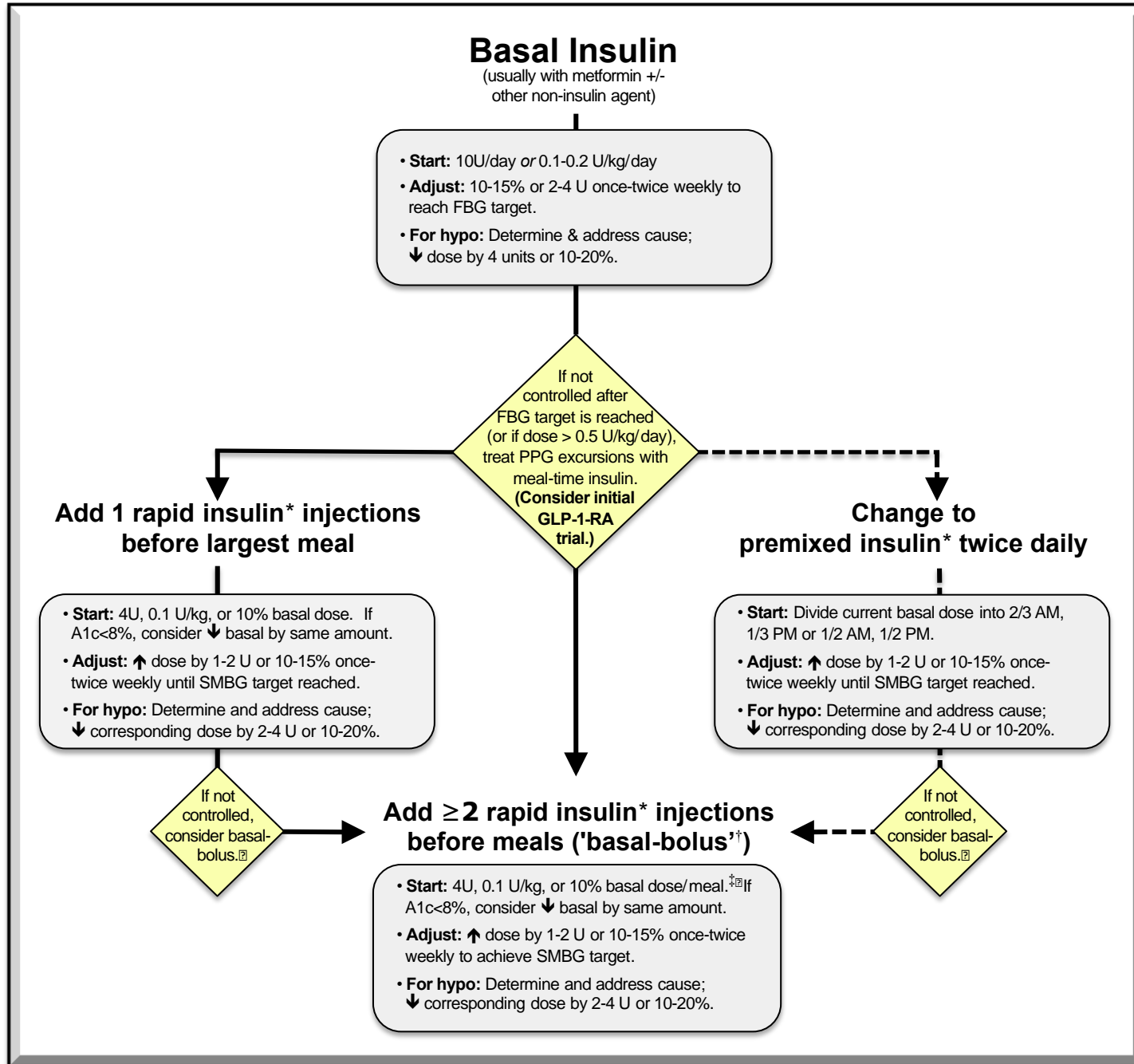
Figure 3.11
Approach to starting & adjusting insulin in T2DM

Basal Insulin

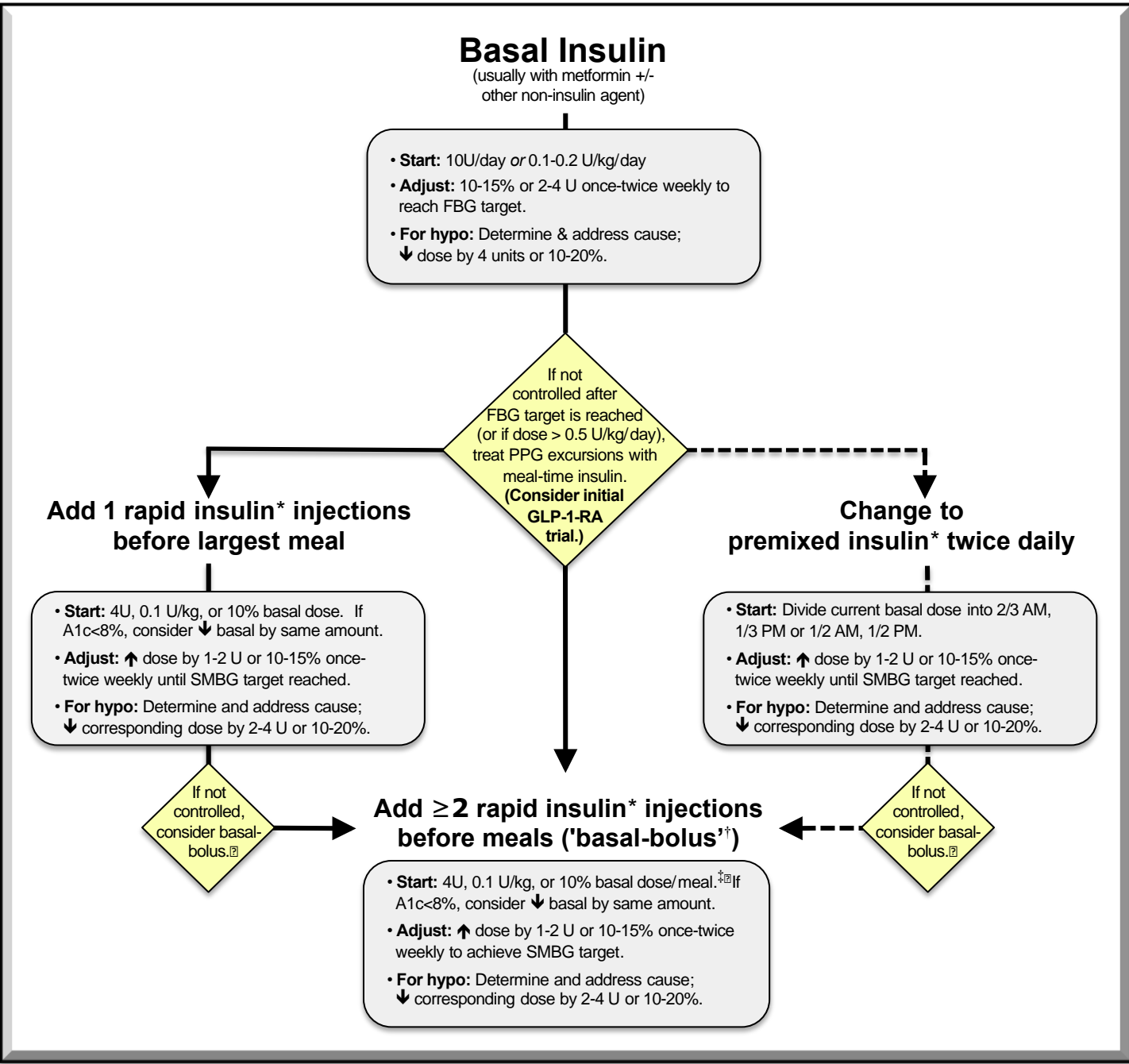
(usually with metformin +/-
other non-insulin agent)

- **Start:** 10U/day or 0.1-0.2 U/kg/day
- **Adjust:** 10-15% or 2-4 U once-twice weekly to reach FBG target.
- **For hypo:** Determine & address cause;
↓ dose by 4 units or 10-20%.

Figure 3.17
Approach to starting & adjusting insulin in T2DM



2
3+



Complexity
 low
 mod.
 high

Flexibility

more flexible

less flexible

Polling Question

American Association of Clinical Endocrinologists (AACE) Treatment Guidelines are based on the A1c at initial entry into treatment and at all follow-up visits.

- A. True**
- B. False**

LIFESTYLE MODIFICATION

(Including Medically Assisted Weight Loss)

Entry A1c < 7.5%

Entry A1c ≥ 7.5%

Entry A1c > 9.0%

MONOTHERAPY*

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

If not at goal in 3 months proceed to Double Therapy

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

SYMPTOMS

NO

YES

DUAL
Therapy

OR

TRIPLE
Therapy

INSULIN
±
Other
Agents

**ADD OR INTENSIFY
INSULIN**

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events or possible benefits
- ⚠ Use with caution

* Order of medications listed represents a suggested hierarchy of usage

PROGRESSION OF DISEASE →

OTHER CONSIDERATIONS

- Age
- Weight
- Sex / racial / ethnic / genetic differences
- Co-morbidities
 - Coronary artery disease
 - Heart Failure
 - Chronic kidney disease
 - Liver dysfunction
 - Hypoglycemia-prone

FUTURE DIRECTIONS / RESEARCH NEEDS

- **Comparative effectiveness research**
 - Focus on important clinical outcomes
- **Contributions of genomic research**
- **Perpetual need for clinical judgment!**

ADA-EASD Position Statement Update: Management of Hyperglycemia in T2DM, 2015

KEY POINTS

- Glycemic targets & BG-lowering therapies must be individualized, based on a variety of patient and disease characteristics.
- Diet, exercise, & education: foundation of any T2DM therapy program
- Unless contraindicated, metformin remains the optimal first-line drug.
- After metformin, data are limited. Combination therapy with 1-2 other oral / injectable agents is reasonable. Try to minimize side effects.
- Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain BG control.
- All treatment decisions should be made in conjunction with the patient (focusing on his or her preferences, needs & values.)
- Comprehensive CV risk reduction - a major focus of therapy

Johnson & Johnson
INSTITUTE