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Management of Hyperglycemia in T2DM: A Patient-Centered Approach

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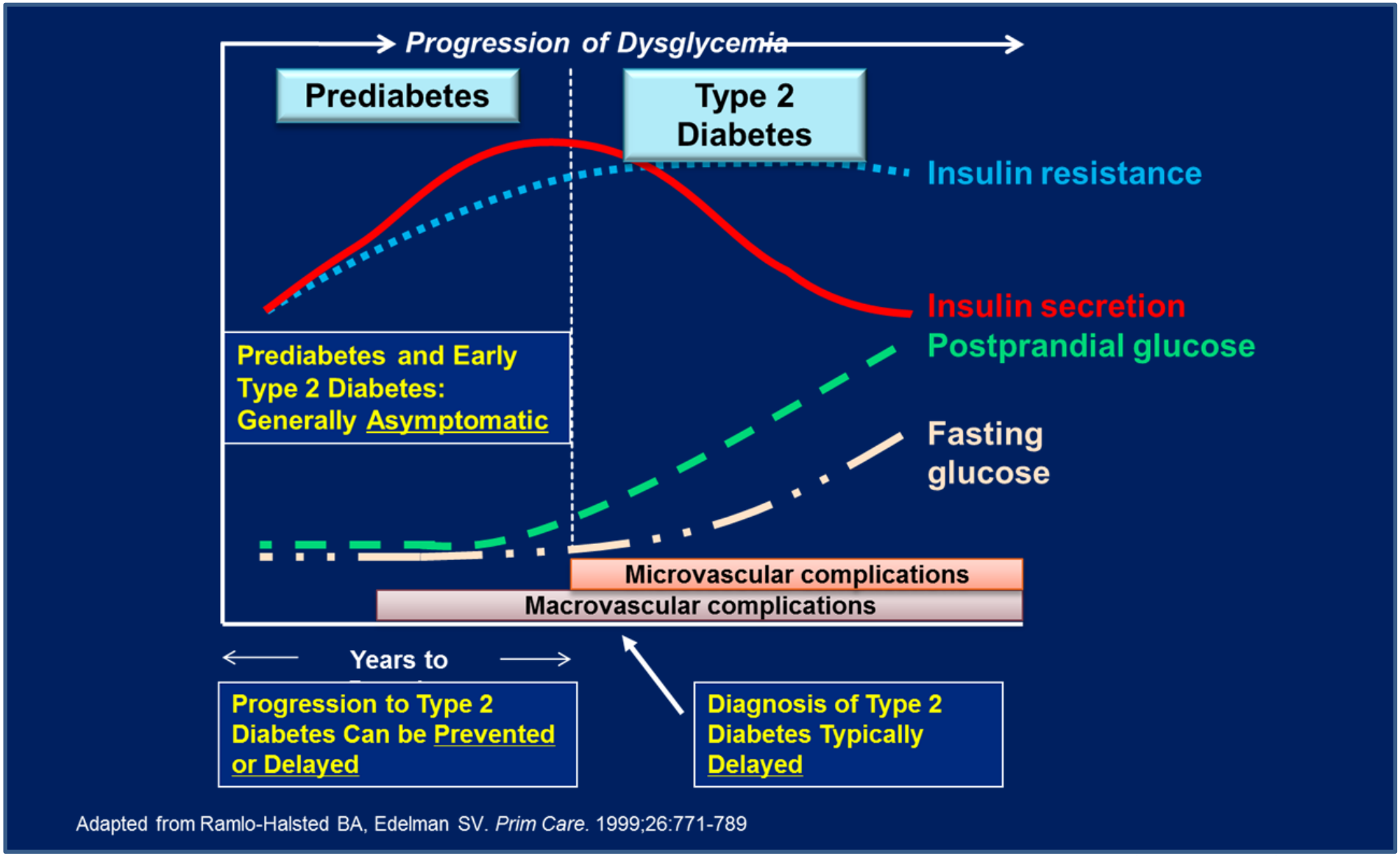
Johnson & Johnson Diabetes Care Companies, Wayne PA

Natural History of Type 2 Diabetes



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

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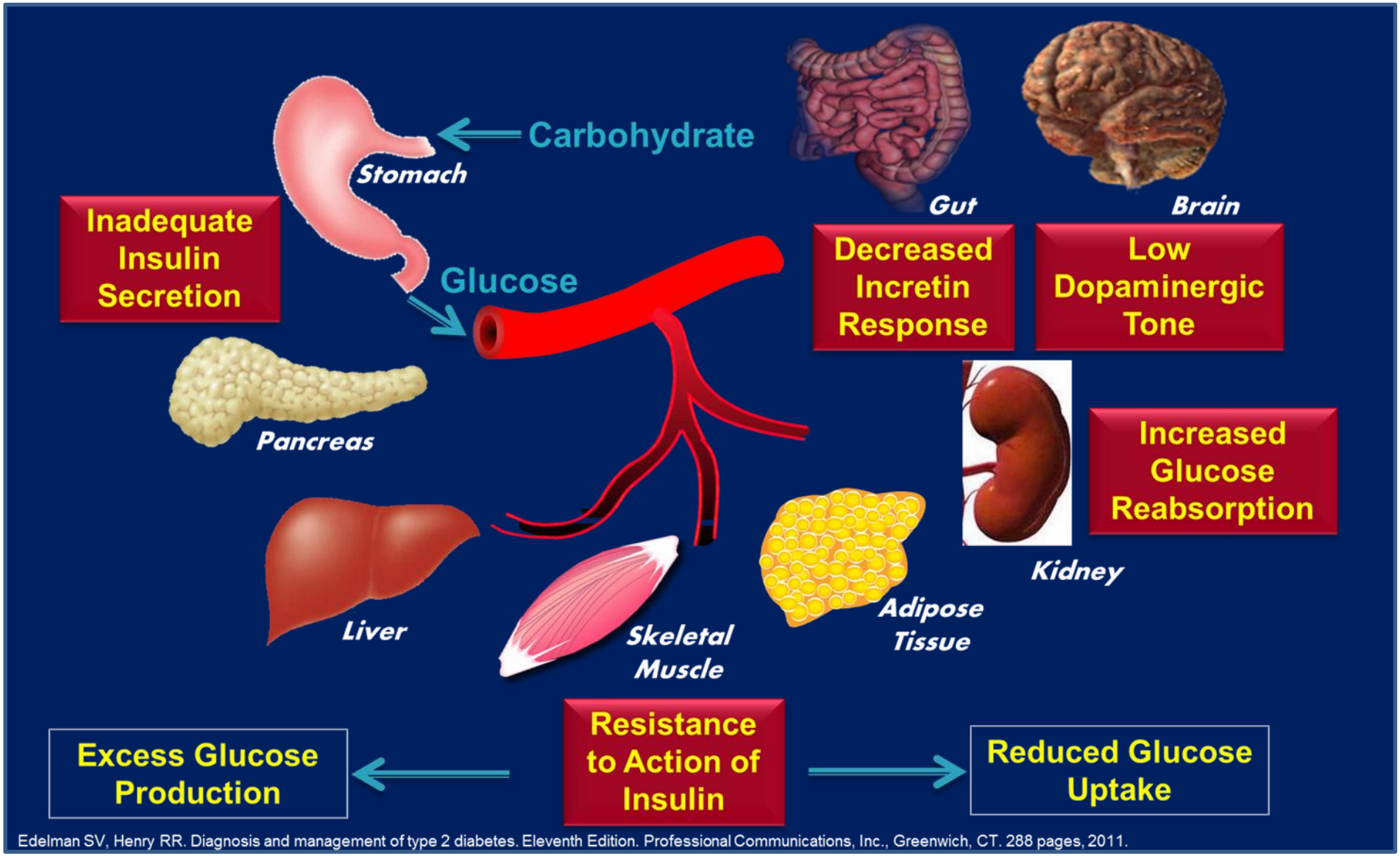
Pathophysiology of Type 2 Diabetes



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

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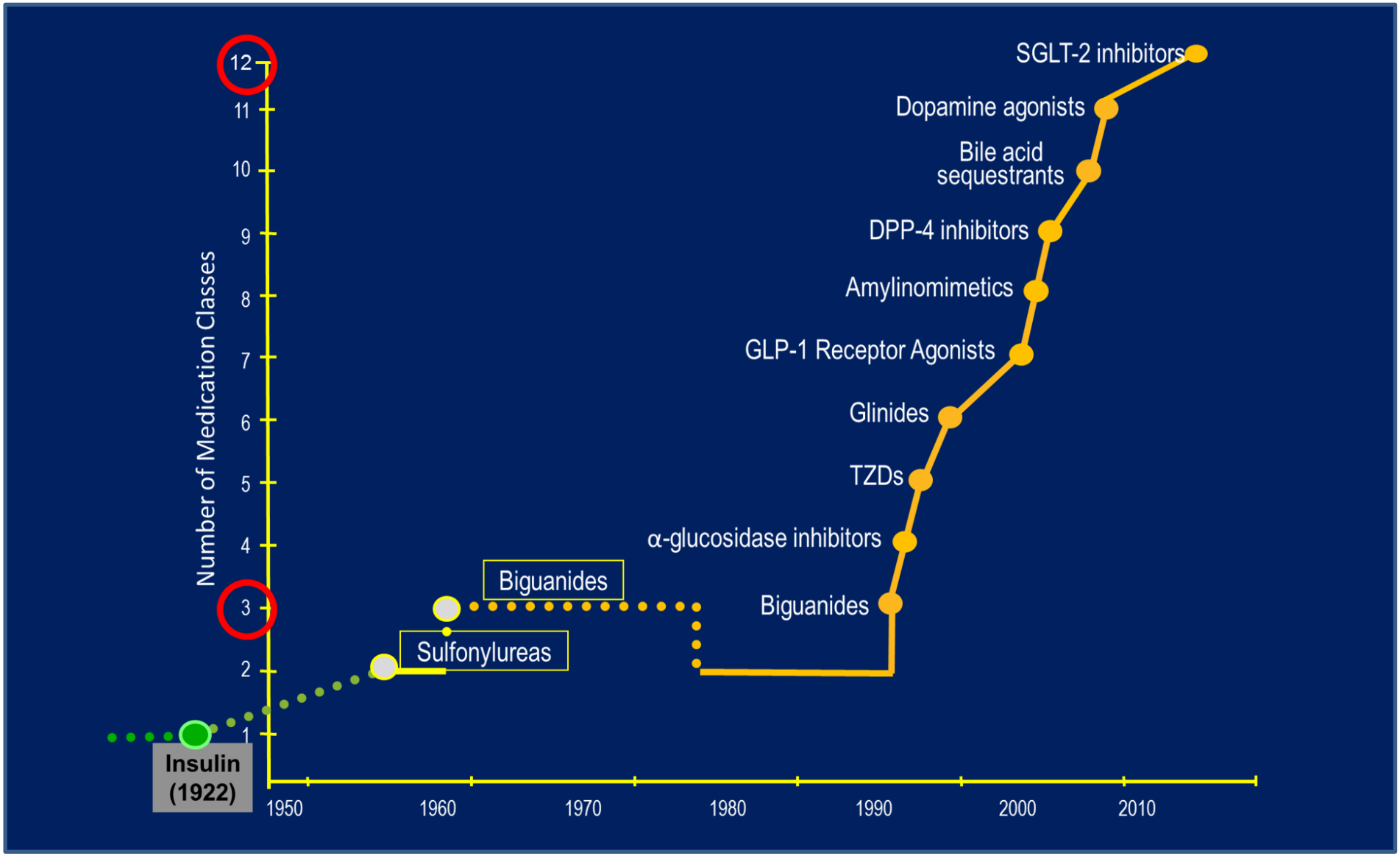
Polling Question

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



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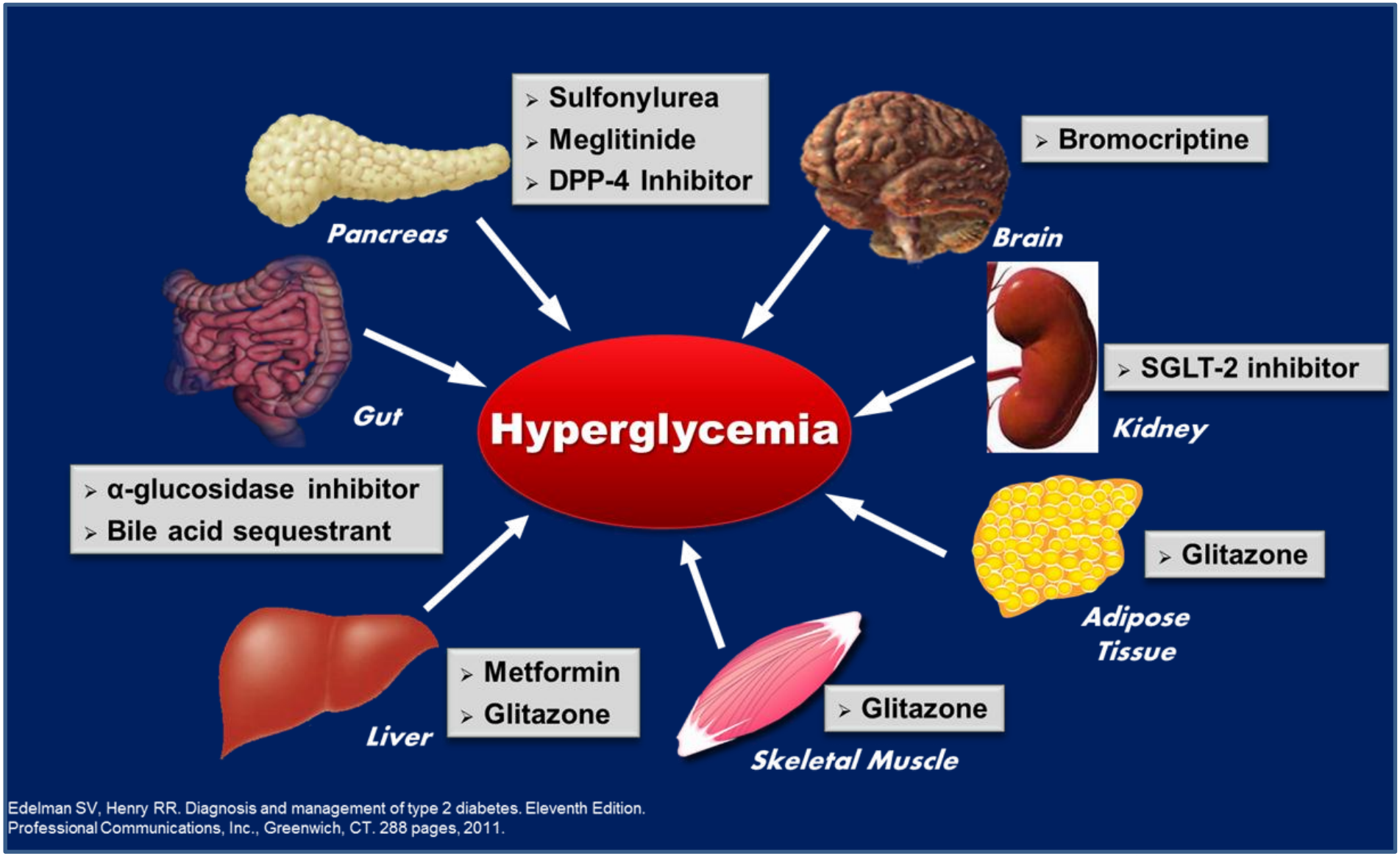
Type 2 Diabetes Therapy: Sites of Action



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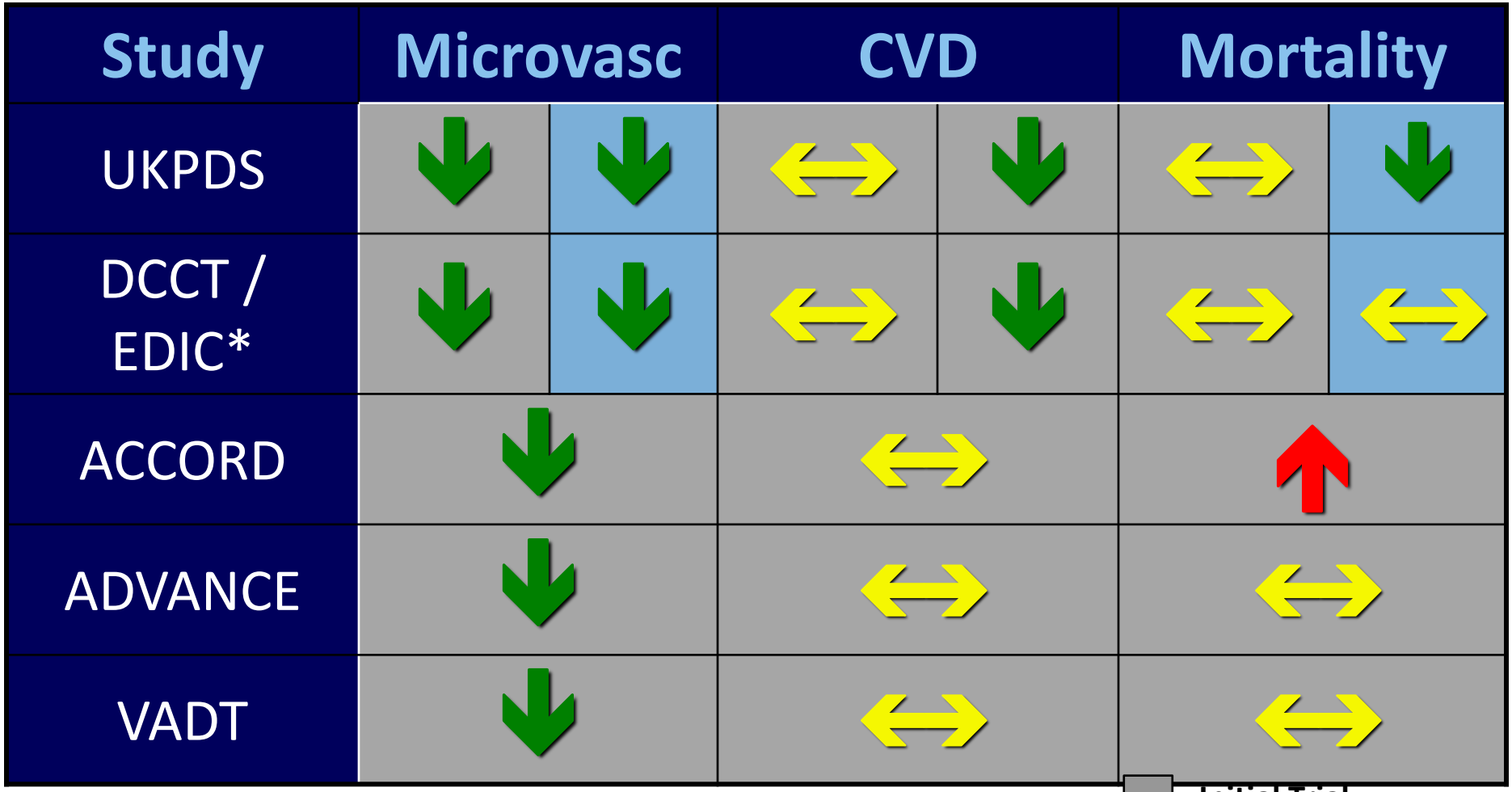
Patient-Centered Approach

"…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.**

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596

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



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)

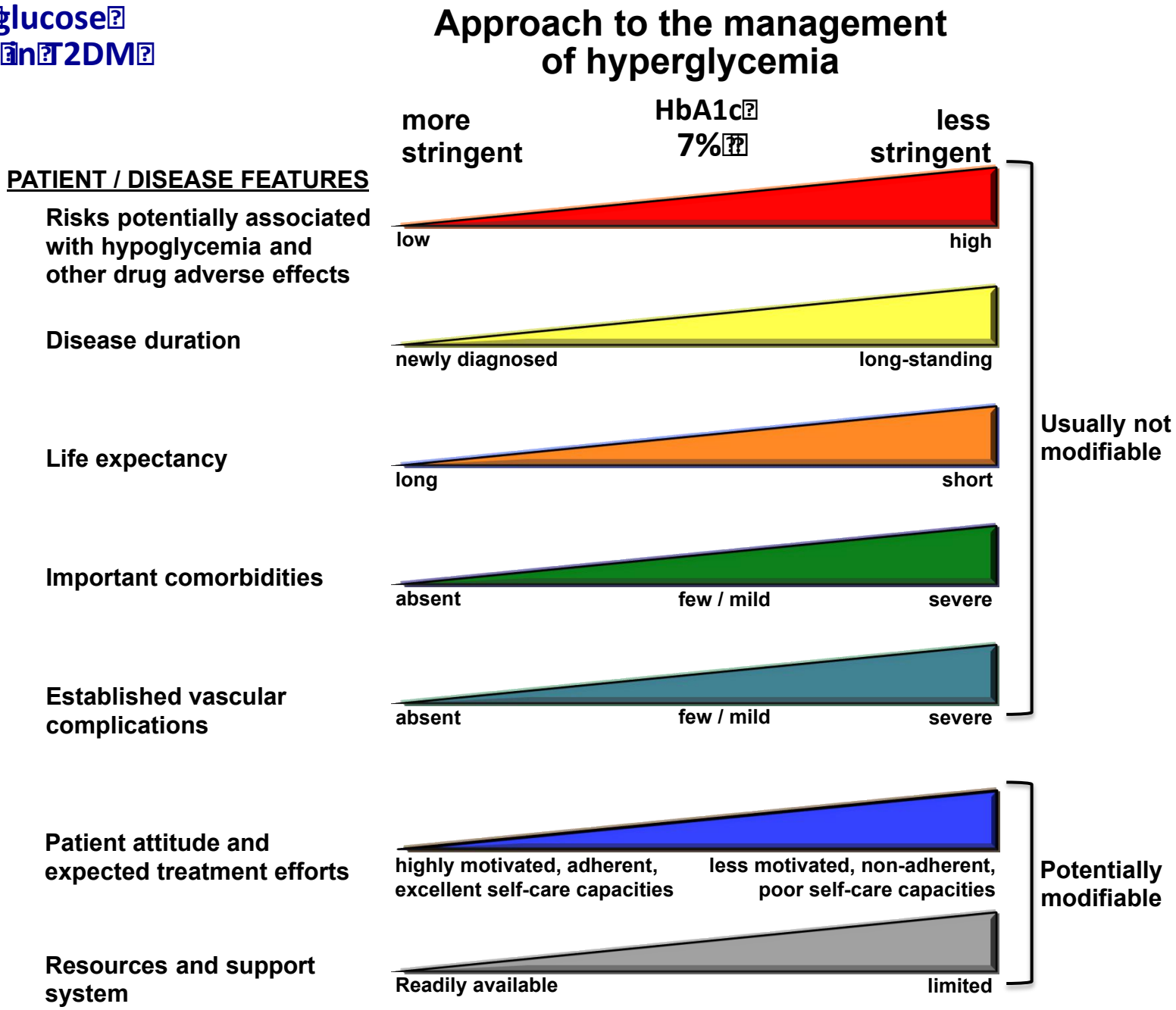
ANTI-HYPERGLYCEMIC THERAPY

- **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

PG = plasma glucose

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596

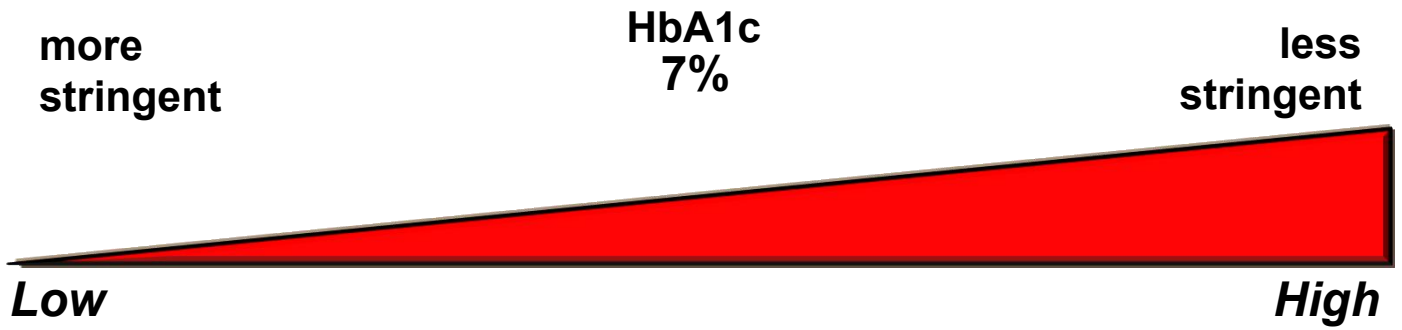
Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM



Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

Approach to the Management of Hyperglycemia

Risks potentially associated with hypoglycemia, other drug adverse effects



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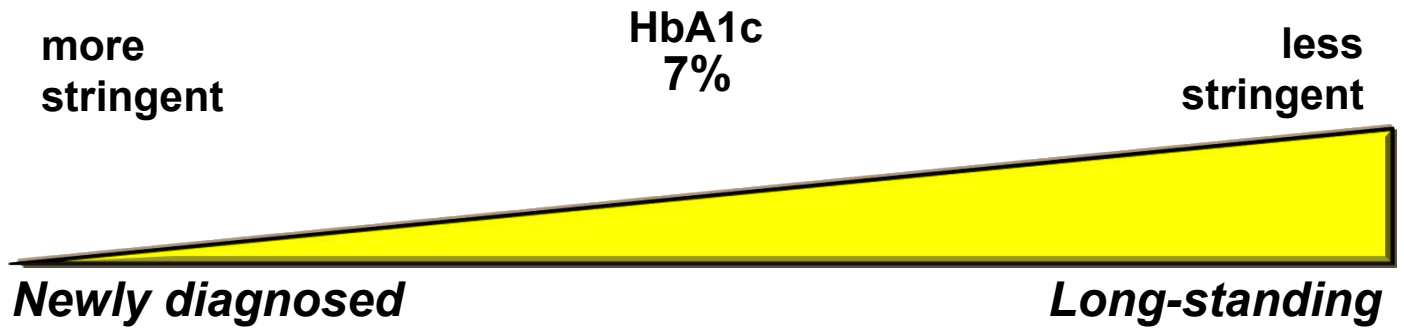
Approach to the Management of Hyperglycemia



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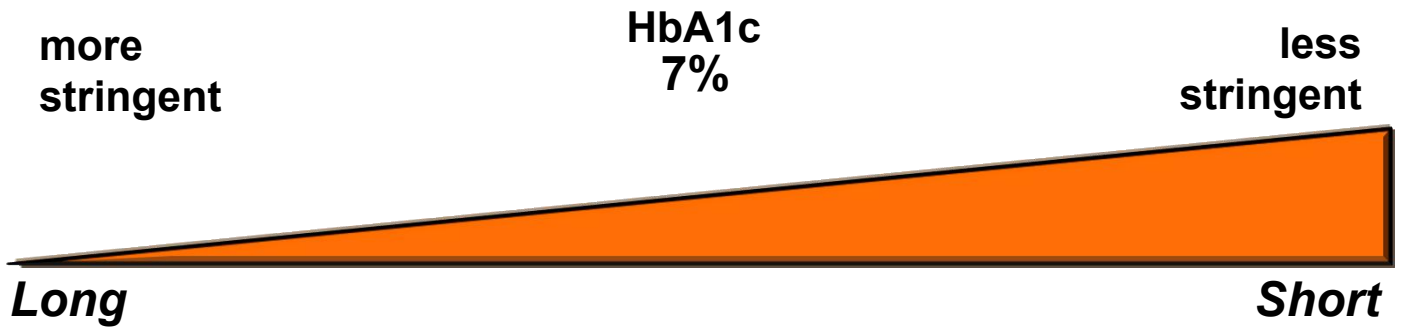

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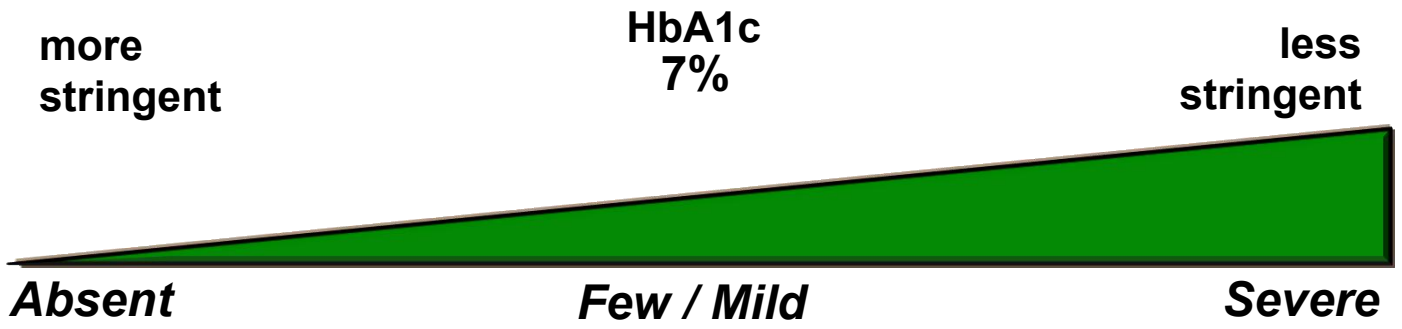


Important comorbidities

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

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

Approach to the Management of Hyperglycemia

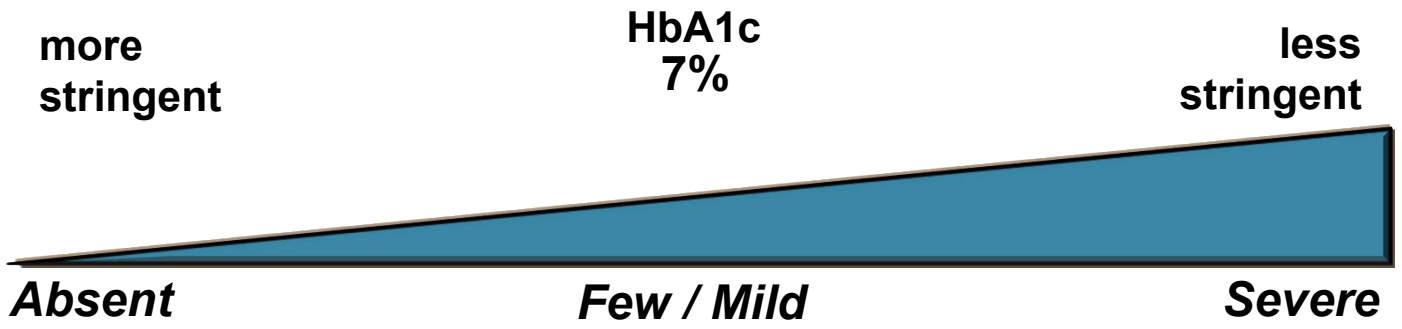
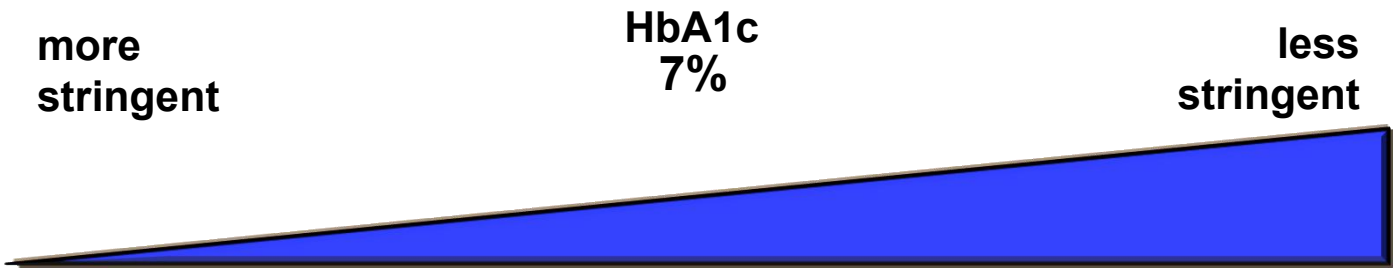


Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

Approach to the Management of Hyperglycemia

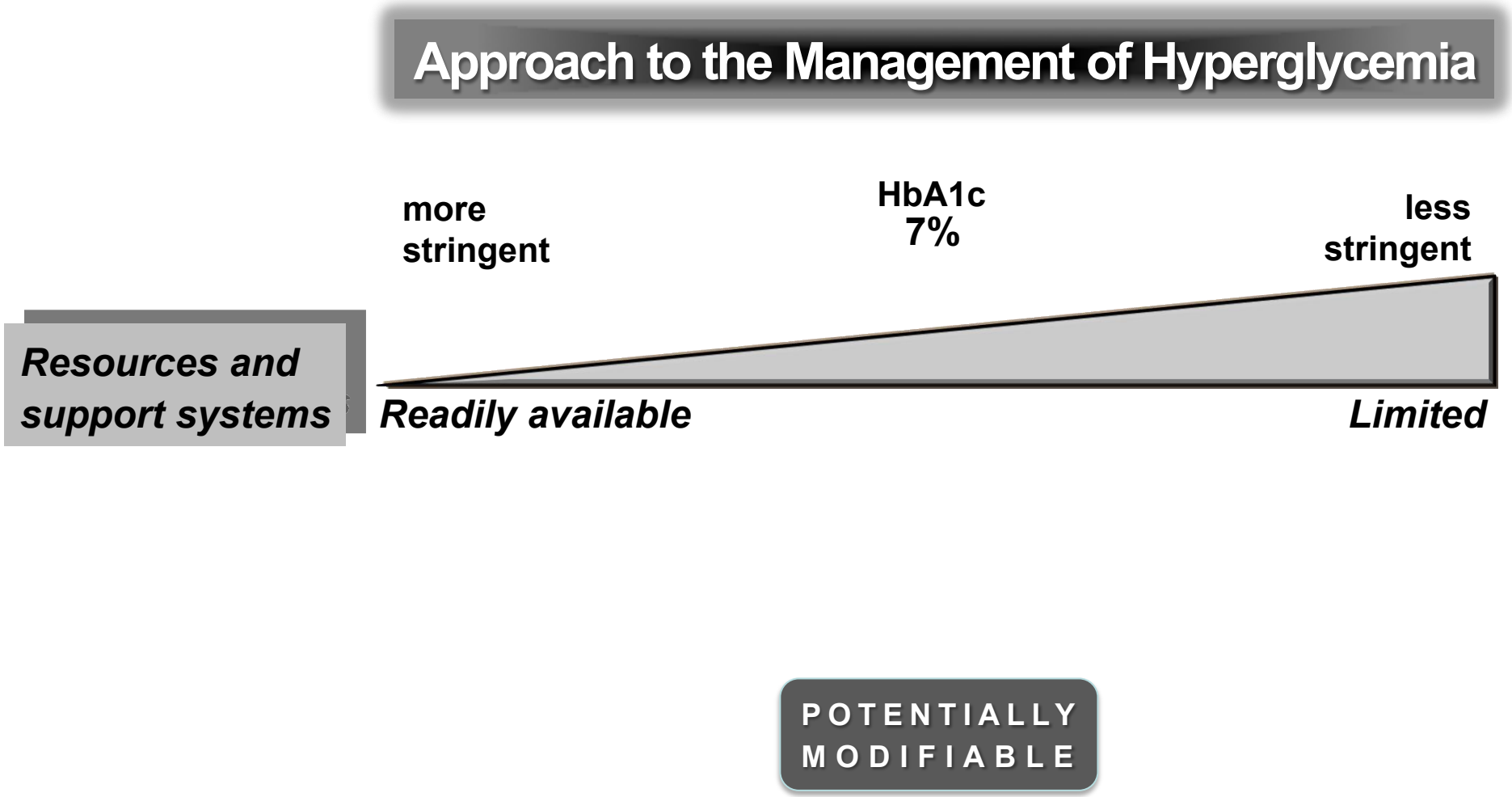
Patient attitude & expected treatment efforts



POTENTIALLY MODIFIABLE

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

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0



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Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

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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ENDOCRINE PRACTICE Vol 21 No. 4 April 2015

GOALS FOR GLYCEMIC CONTROL

INDIVIDUALIZE GOALS

A1c ≤ 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

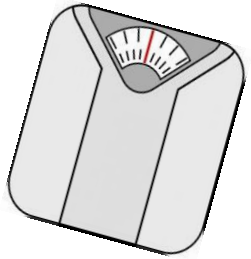
Which of the following statement(s) about individualization of pharmacotherapy is consistent with 2015 ADA EASD Position statement update?

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**

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596

Noninsulin Agents Available for T2D

Class	Primary Mechanism of Action	Agent(s)	Available as
α-Glucosidase inhibitors	• Delay carbohydrate absorption from intestine	Acarbose Miglitol	Precose or generic Glyset
Amylin analogue	• Decrease glucagon secretion • Slow gastric emptying • Increase satiety	Pramlintide	Symlin
Biguanide	• Decrease HGP • Increase glucose uptake in muscle	Metformin	Glucophage or generic
Bile acid sequestrant	• Decrease HGP? • Increase incretin levels?	Colesevelam	WelChol
DPP-4 inhibitors	• Increase glucose-dependent insulin secretion • Decrease glucagon secretion	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tradjenta Onglyza Januvia
Dopamine-2 agonist	• Activates dopaminergic receptors	Bromocriptine	Cycloset
Glinides	• 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	• 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	• Increase urinary excretion of glucose	Canagliflozin Dapagliflozin Empagliflozin	Invokana Farxiga Jardiance
Sulfonylureas	• Increase insulin secretion	Glimepiride Glipizide Glyburide	Amaryl or generic Glucotrol or generic Diaβeta, Glynase, Micronase, or generic
Thiazolidinediones	• 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

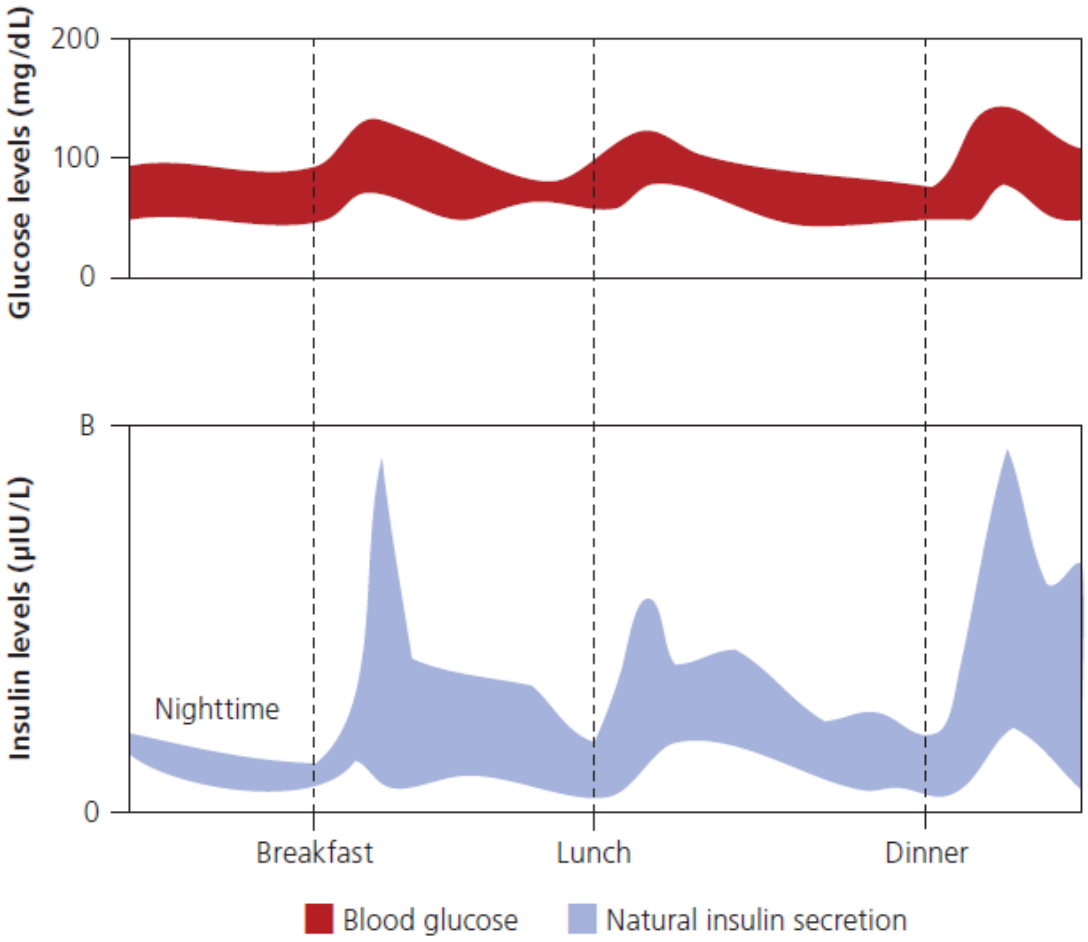
- **Neutral protamine Hagedorn (NPH)**
- **Regular human insulin**
- **Pre-mixed formulations**

Insulin Analogues

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

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

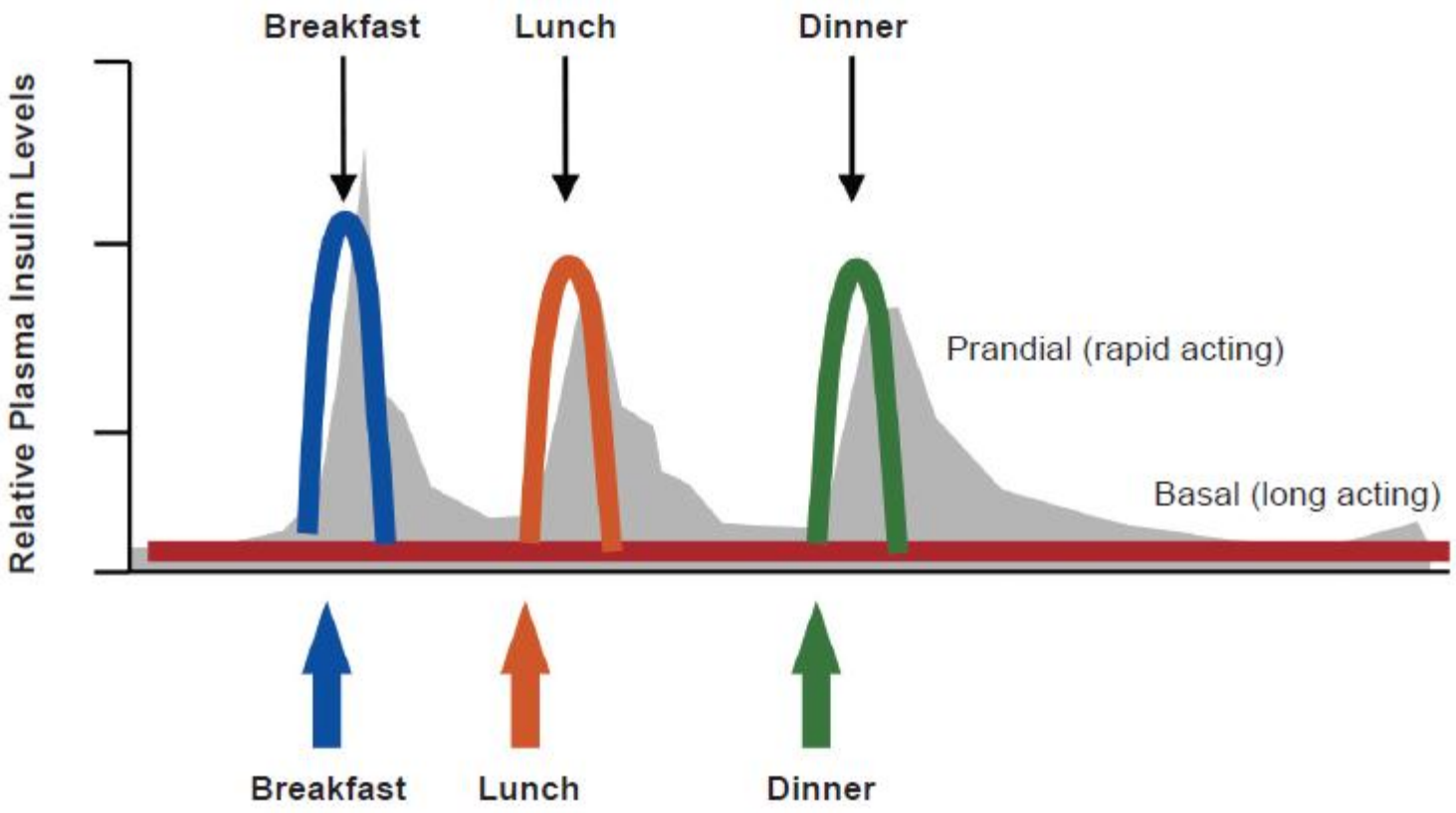
Insulin Secretion



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

Am Fam Physician. 2011;84(2):183-190

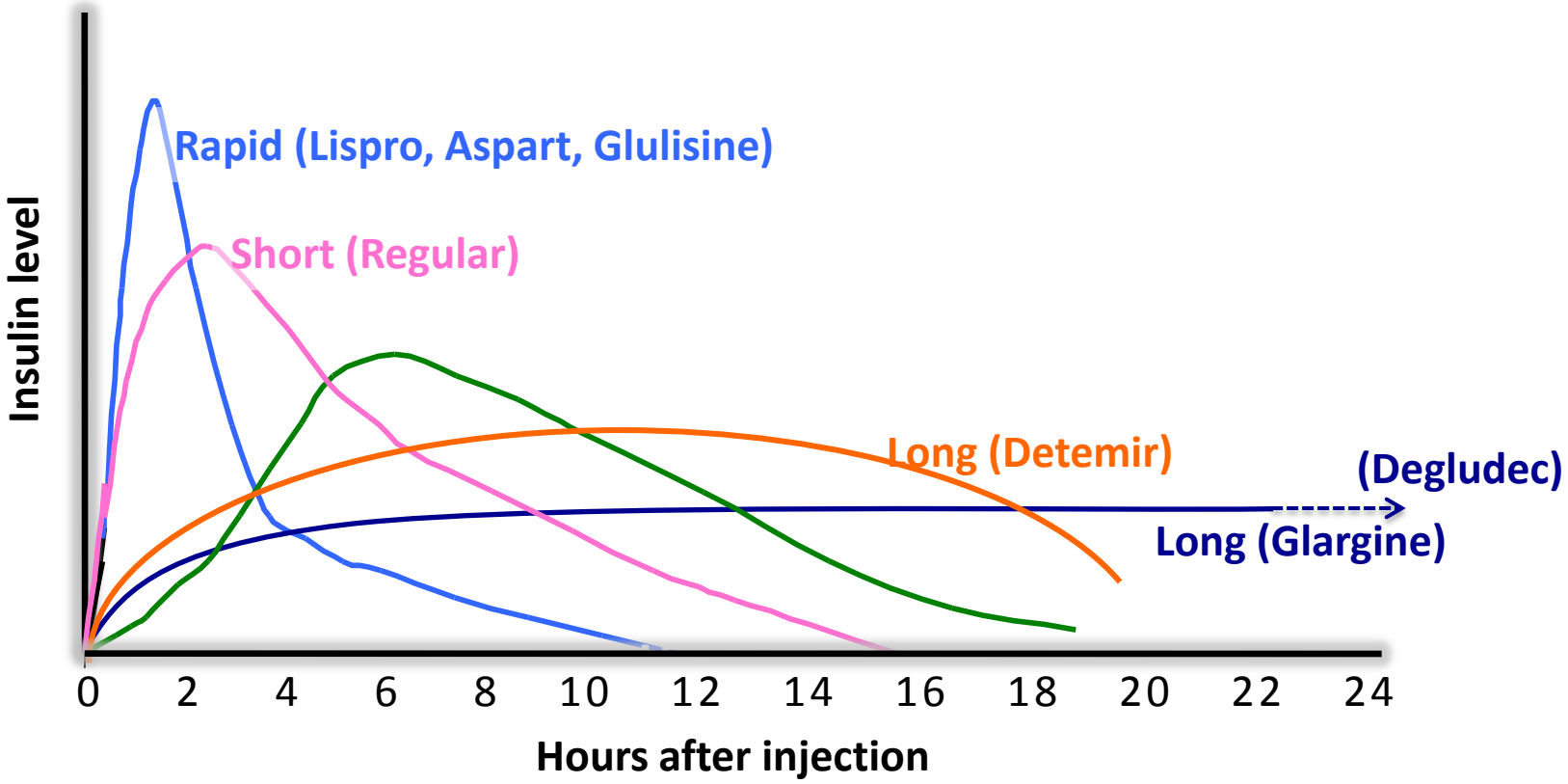
Insulin Mimics Normal Physiologic Profile



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

Supplement to The Journal of the American Osteopathic Association April 2013;113(4): Supplement 2: S6–S16

Pharmacokinetic Profiles of Human Insulin and Insulin Analogs



PROFILES OF ANTIDIABETIC MEDICATIONS

	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	?		Safe		
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

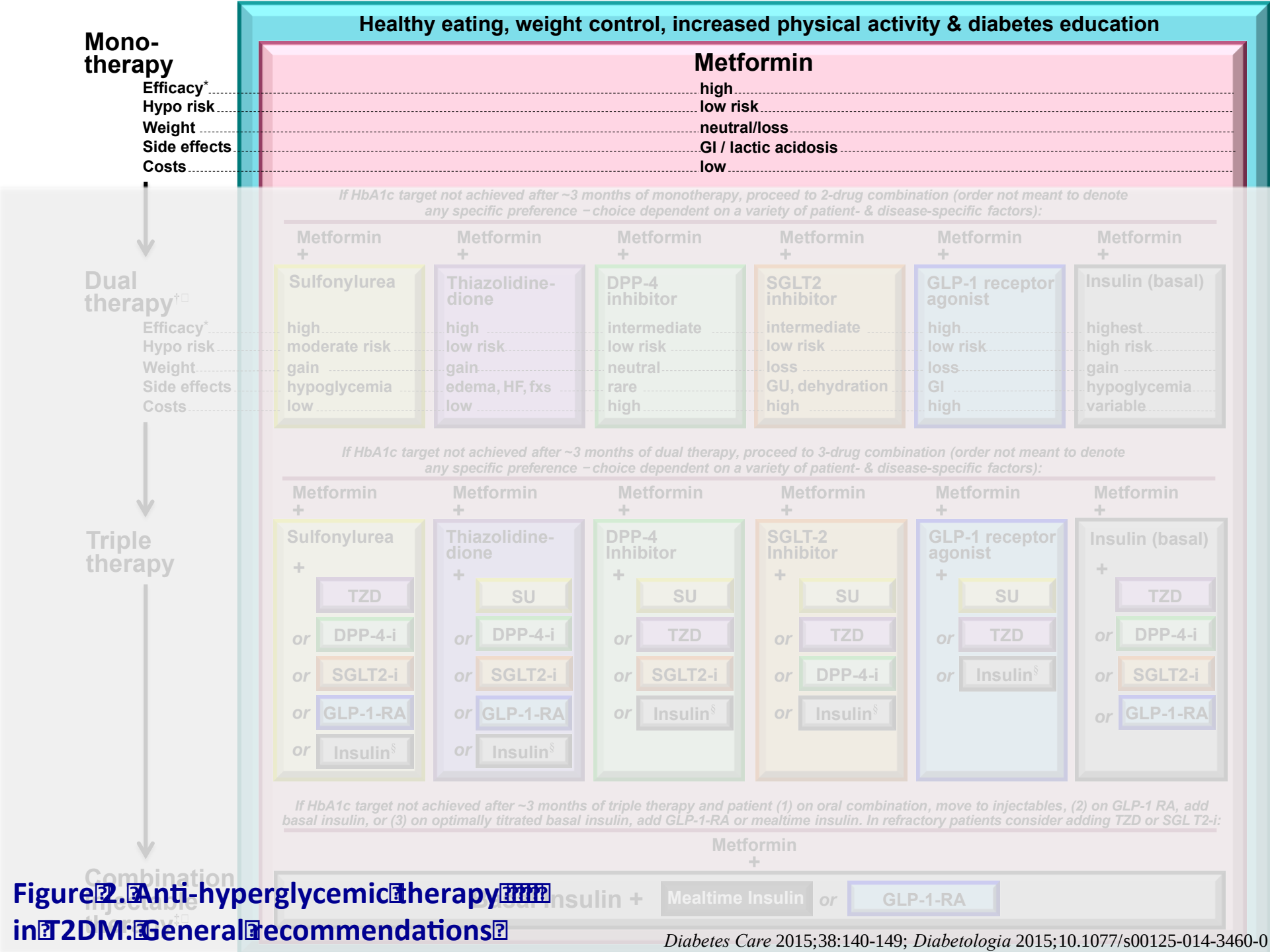


Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations

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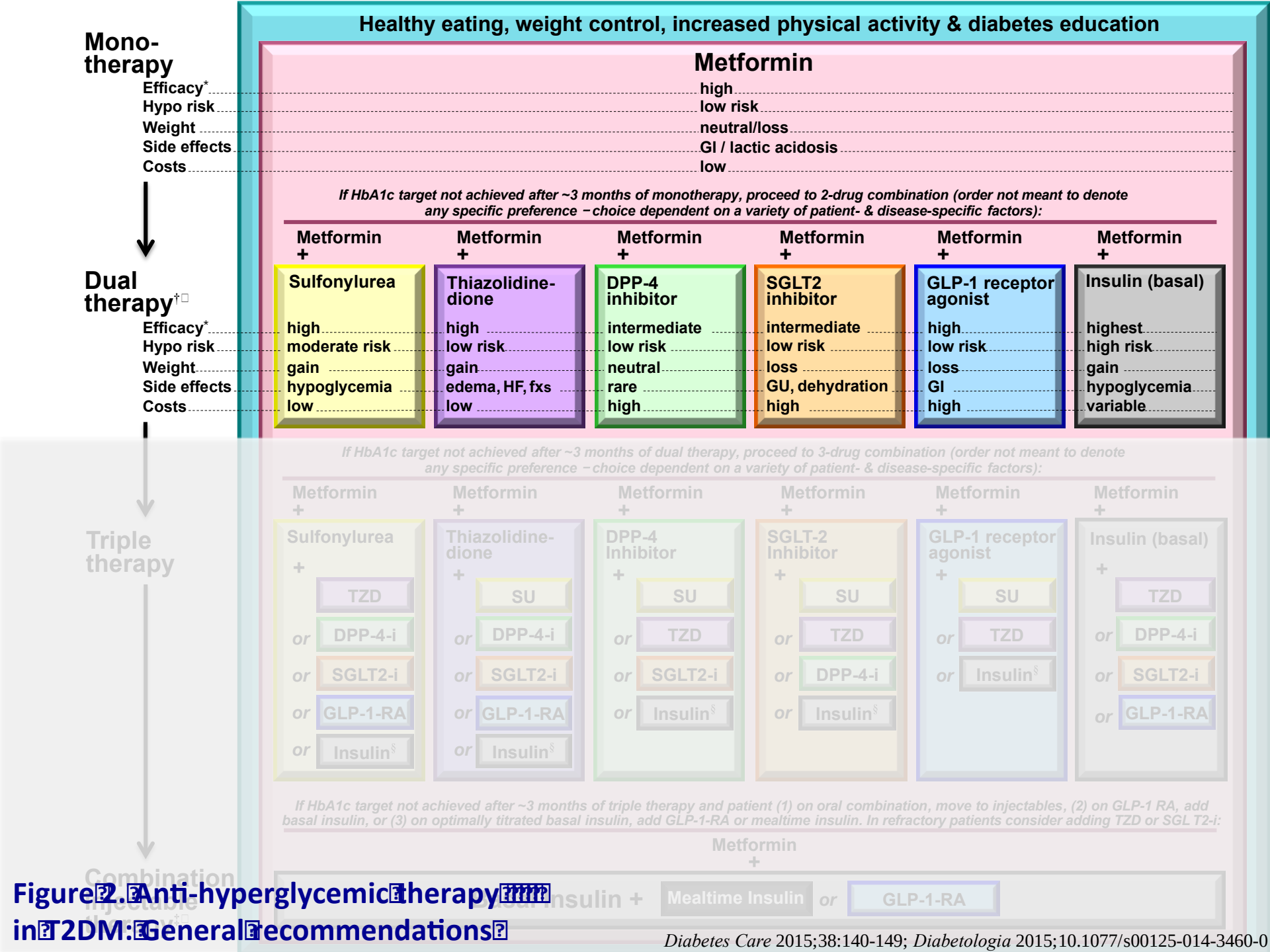

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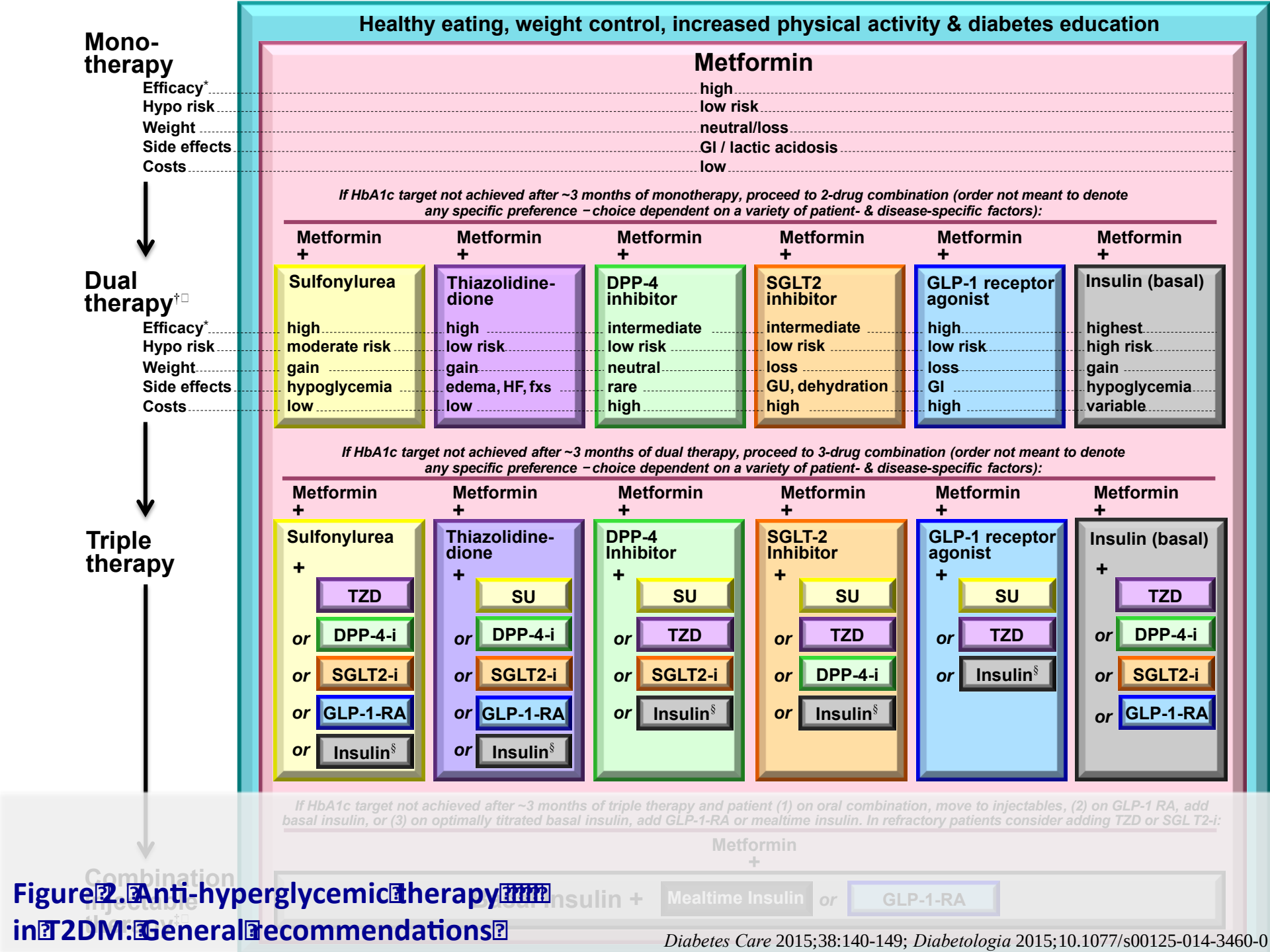

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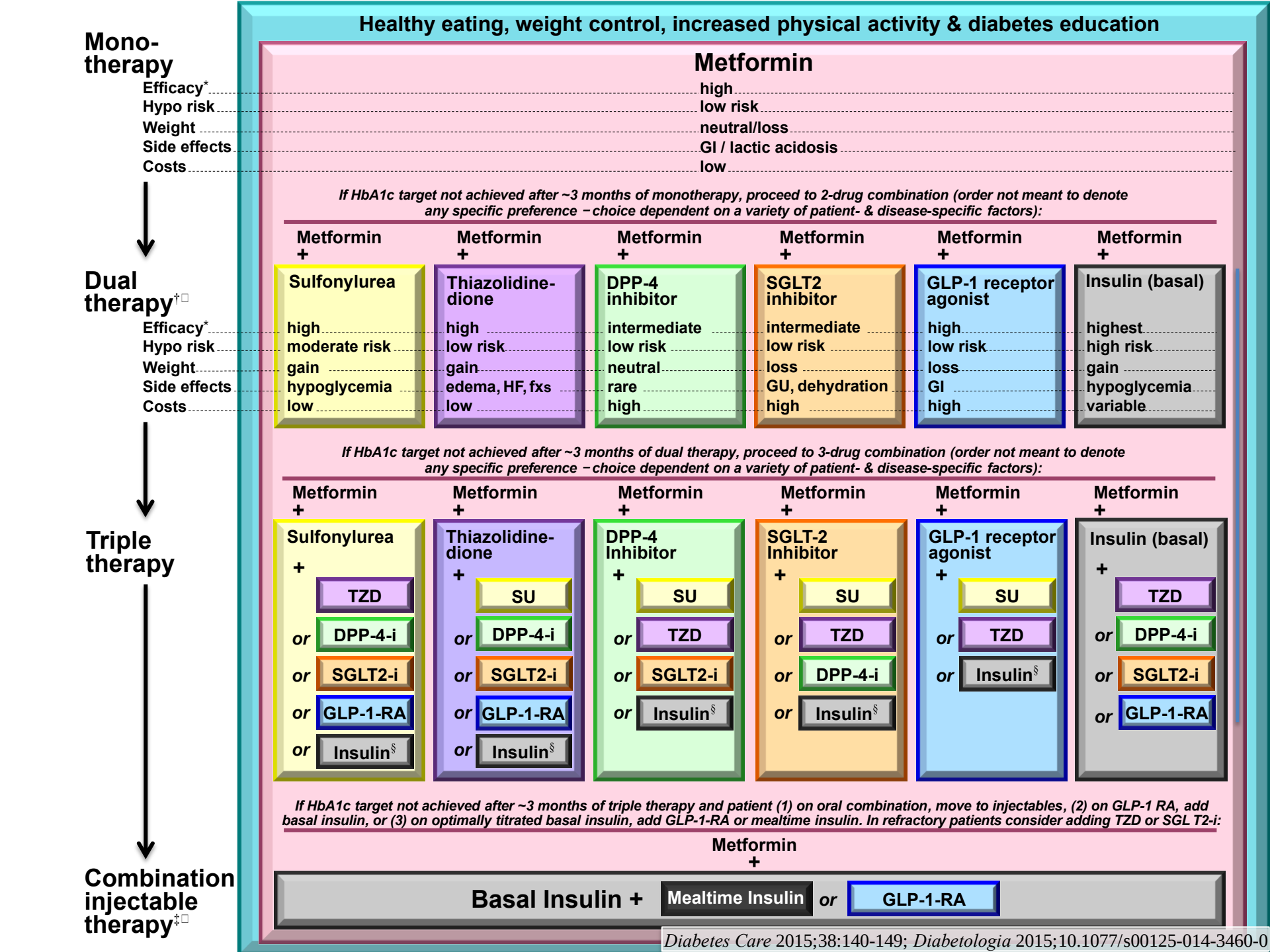

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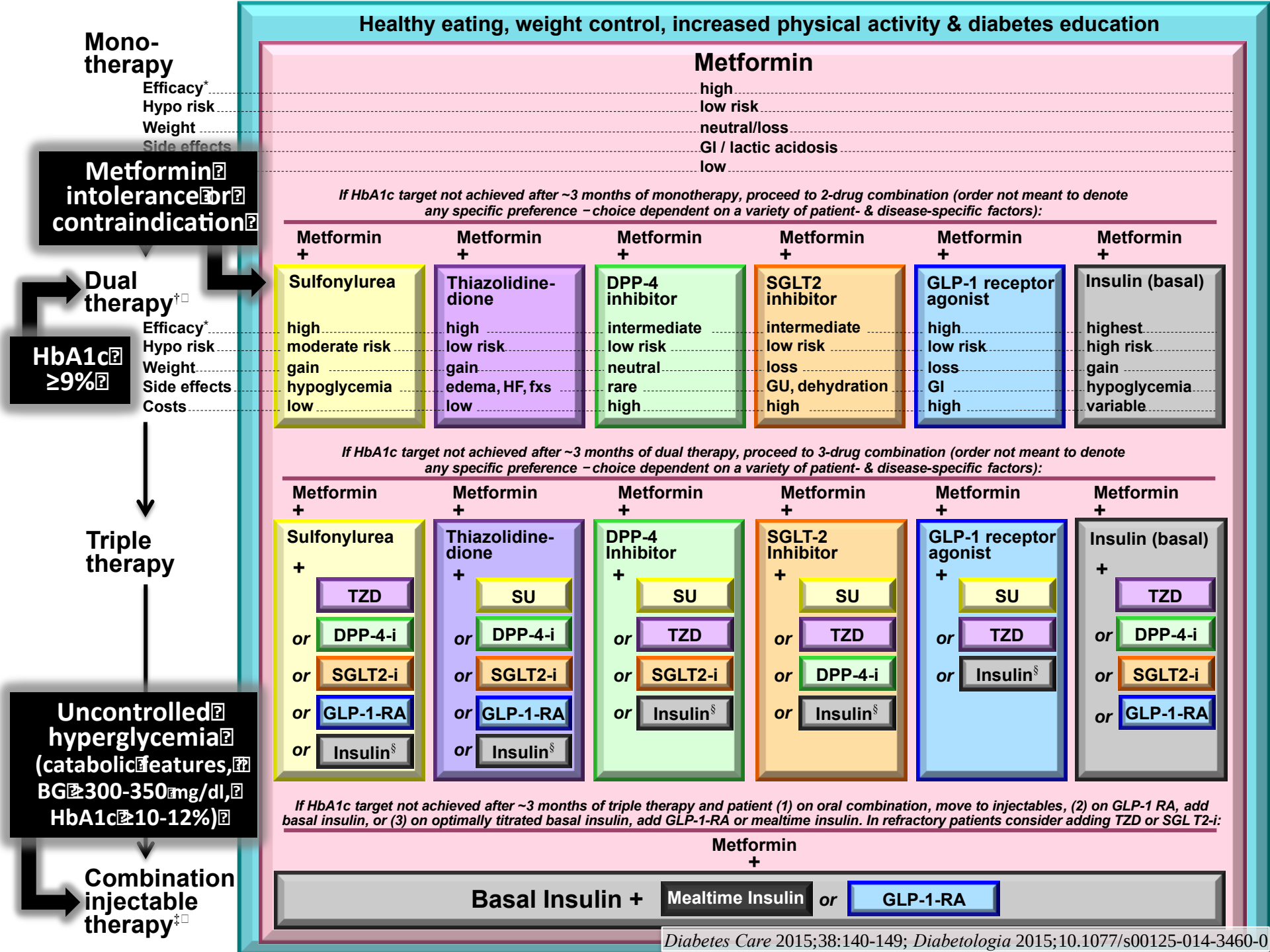

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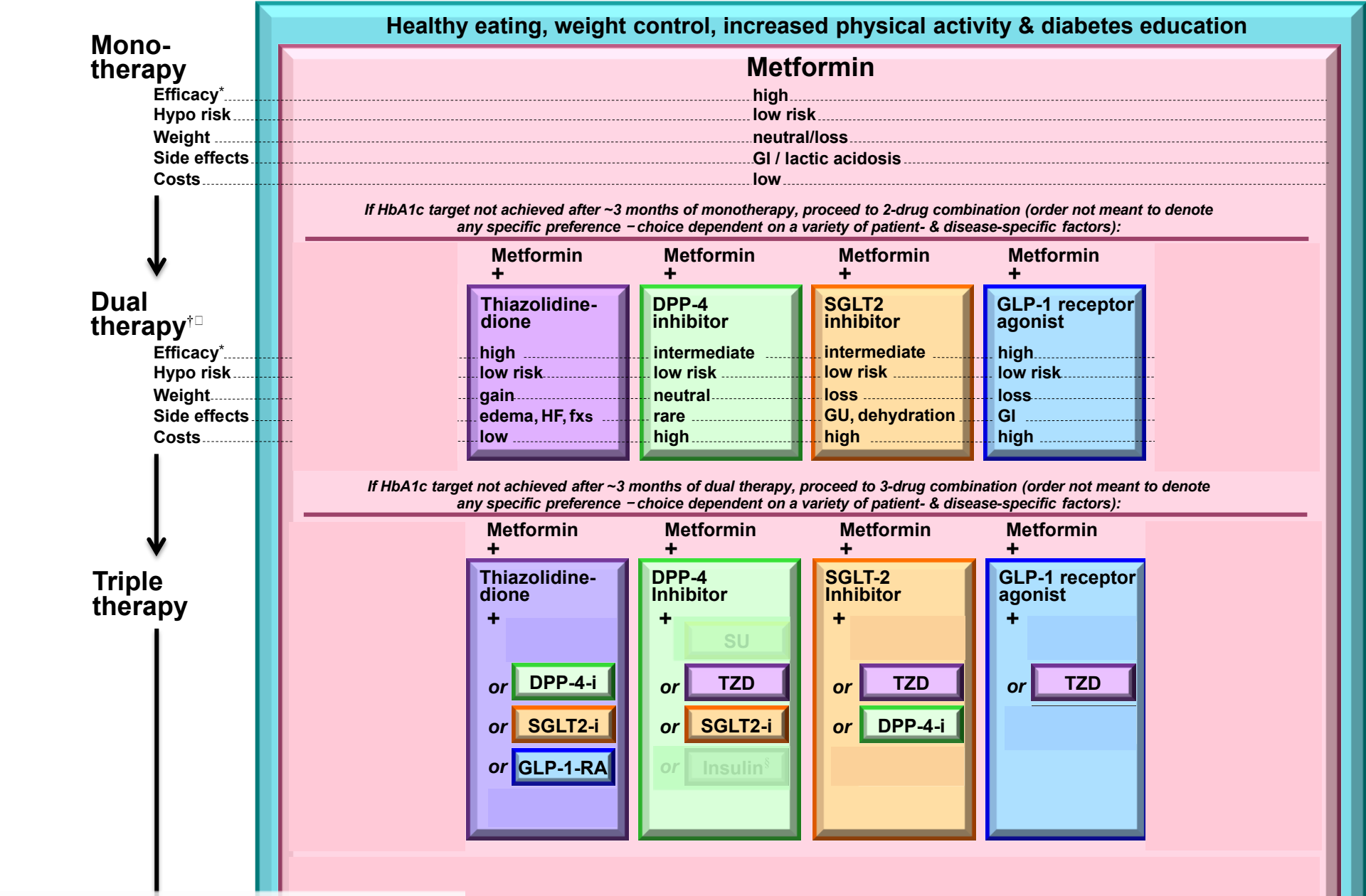


Figure 2A. Anti-hyperglycemic therapy in T2DM: *Avoidance of hypoglycemia*

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

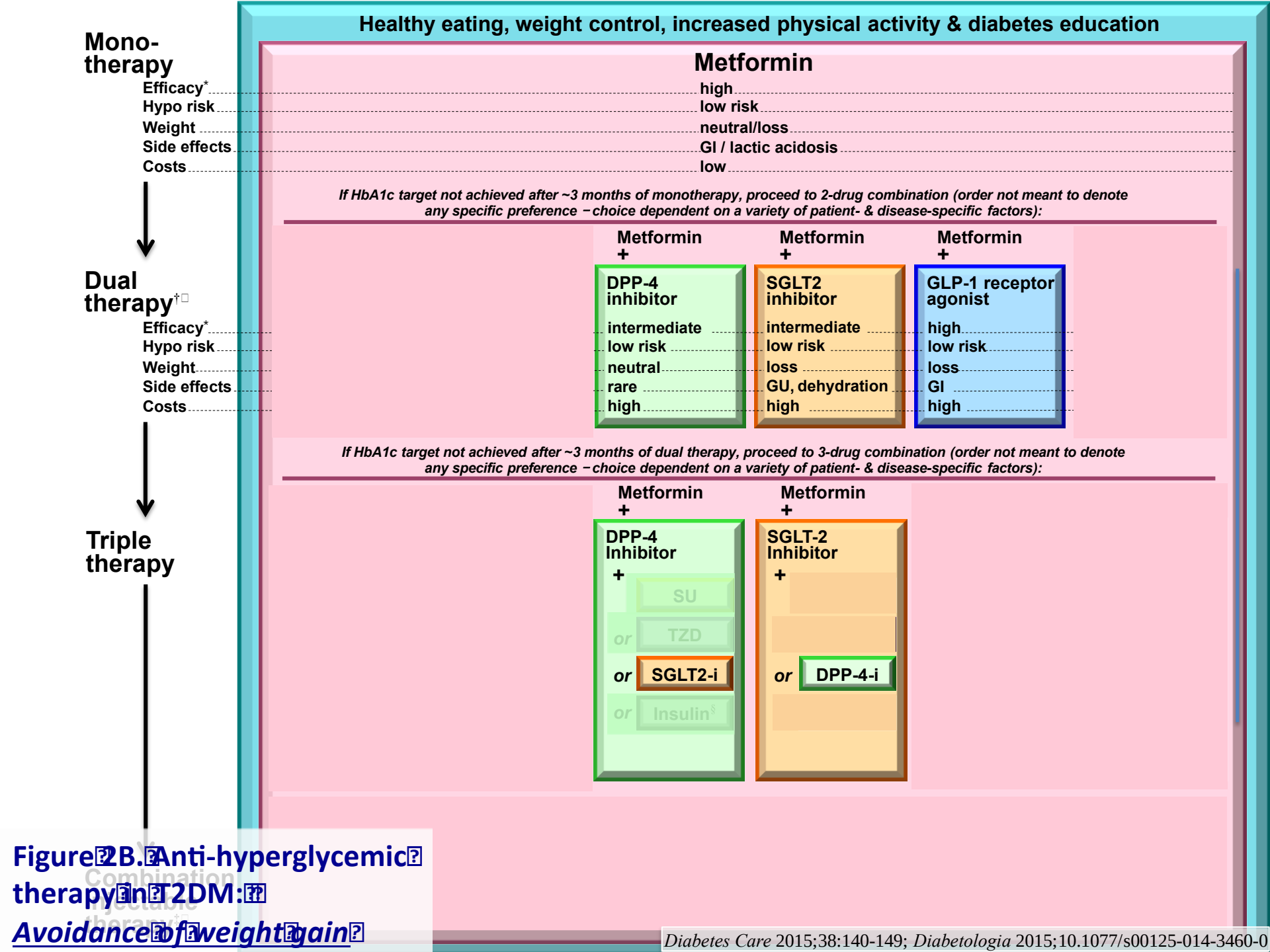


Figure 2B. Anti-hyperglycemic therapy in T2DM: *Avoidance of weight gain*

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1007/s00125-014-3460-0

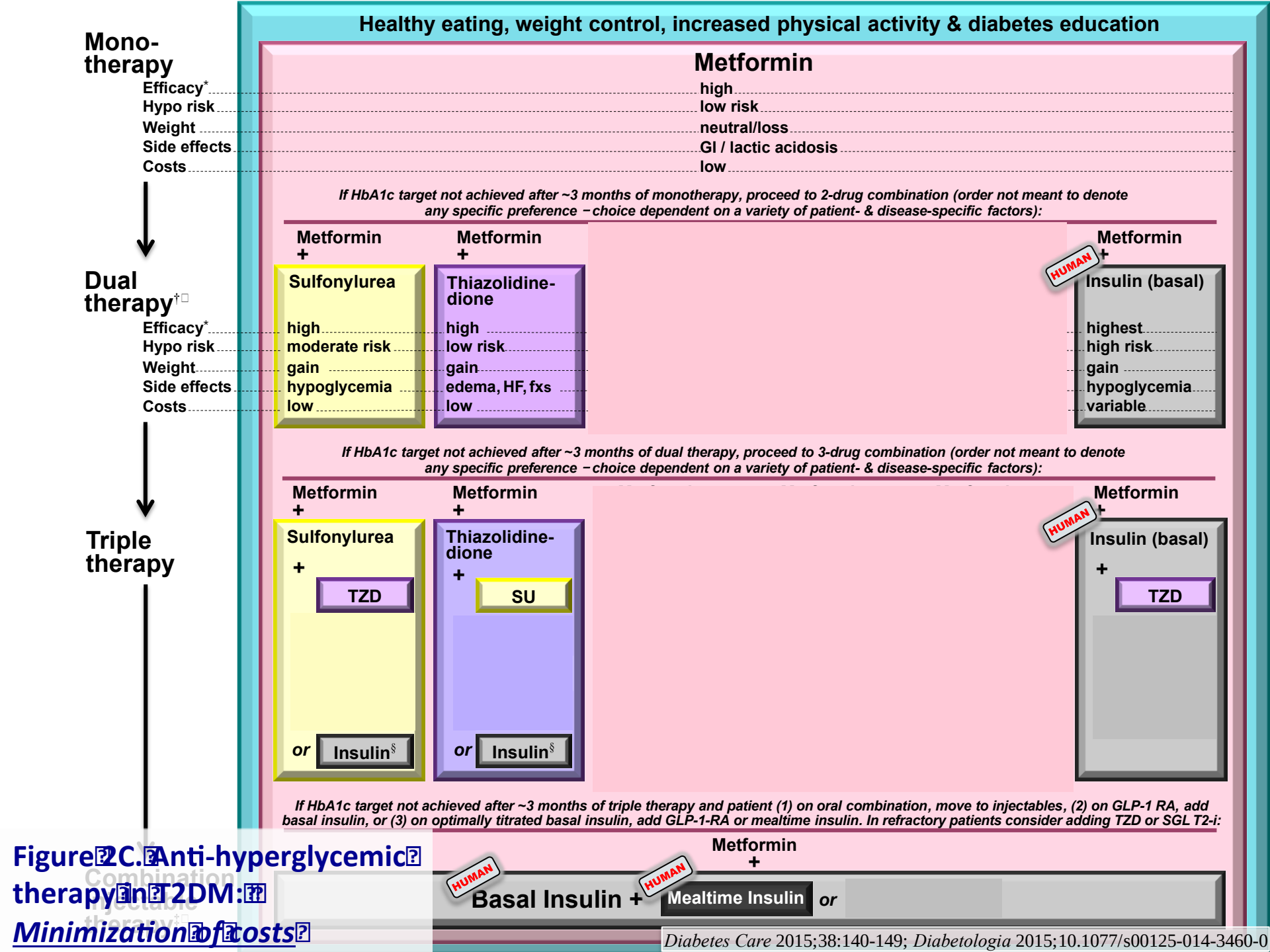
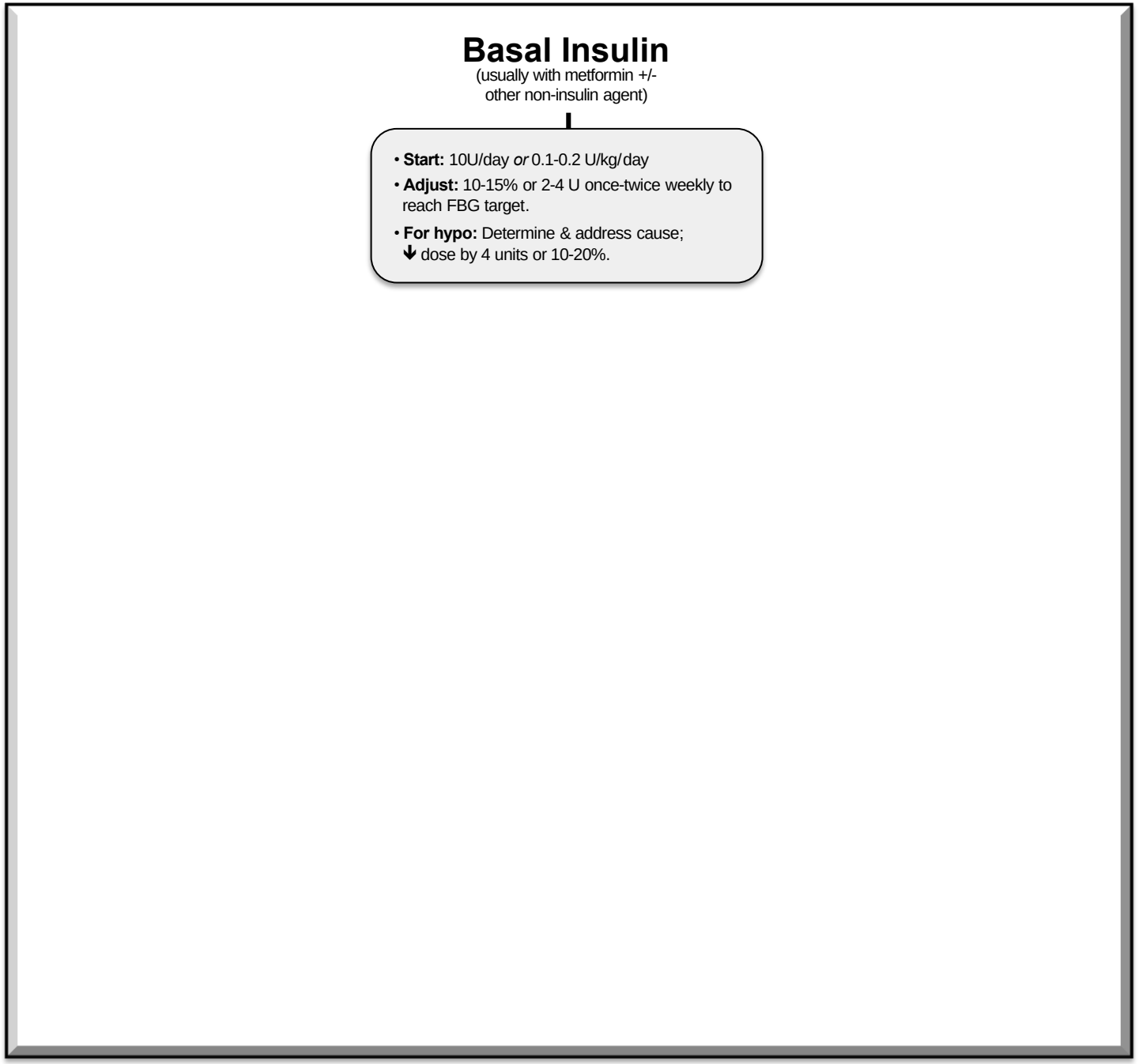


Figure 2C. Anti-hyperglycemic therapy in T2DM: *Minimization of costs*

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

Figure 3. Approach to starting & adjusting insulin in T2DM



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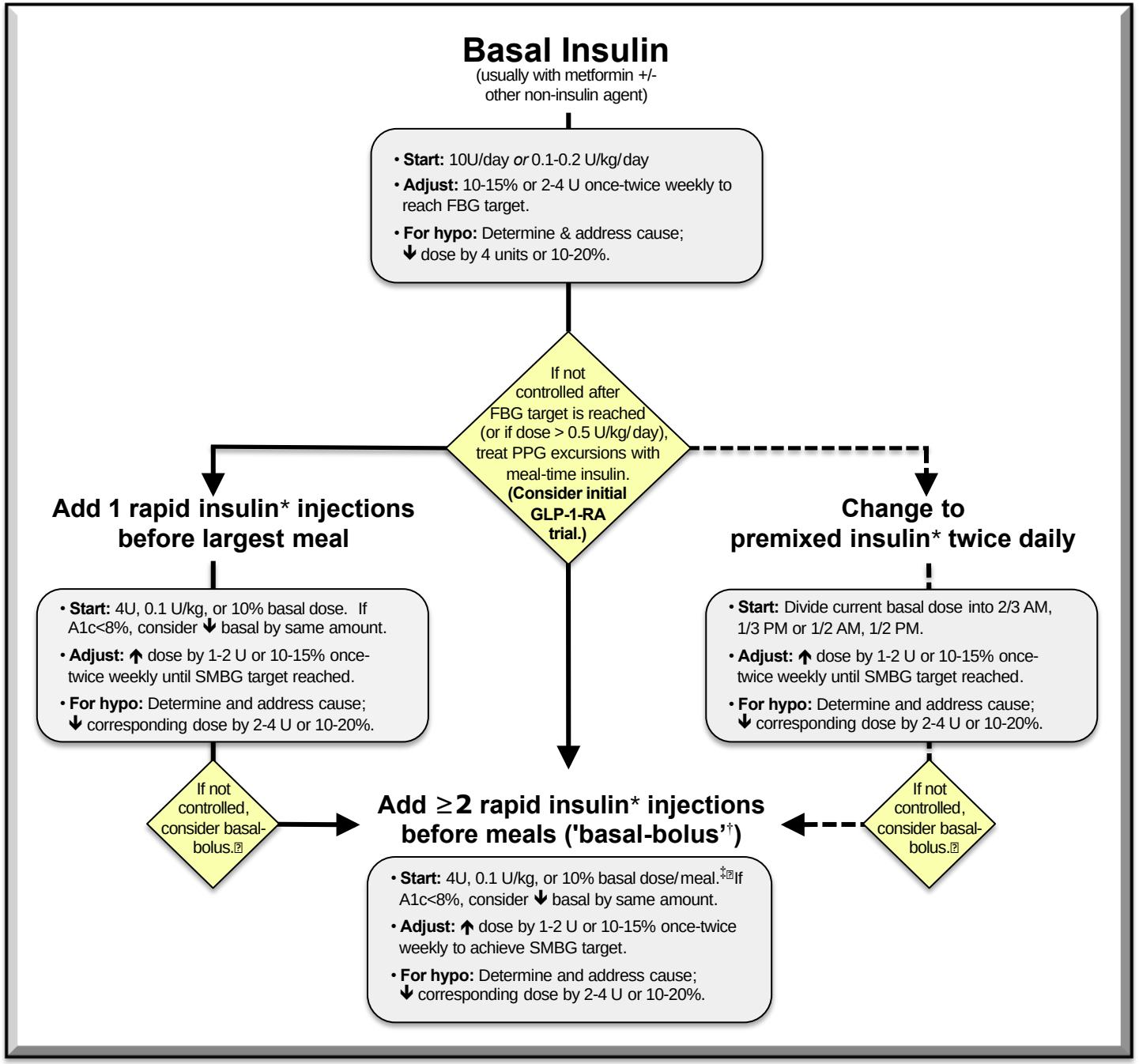

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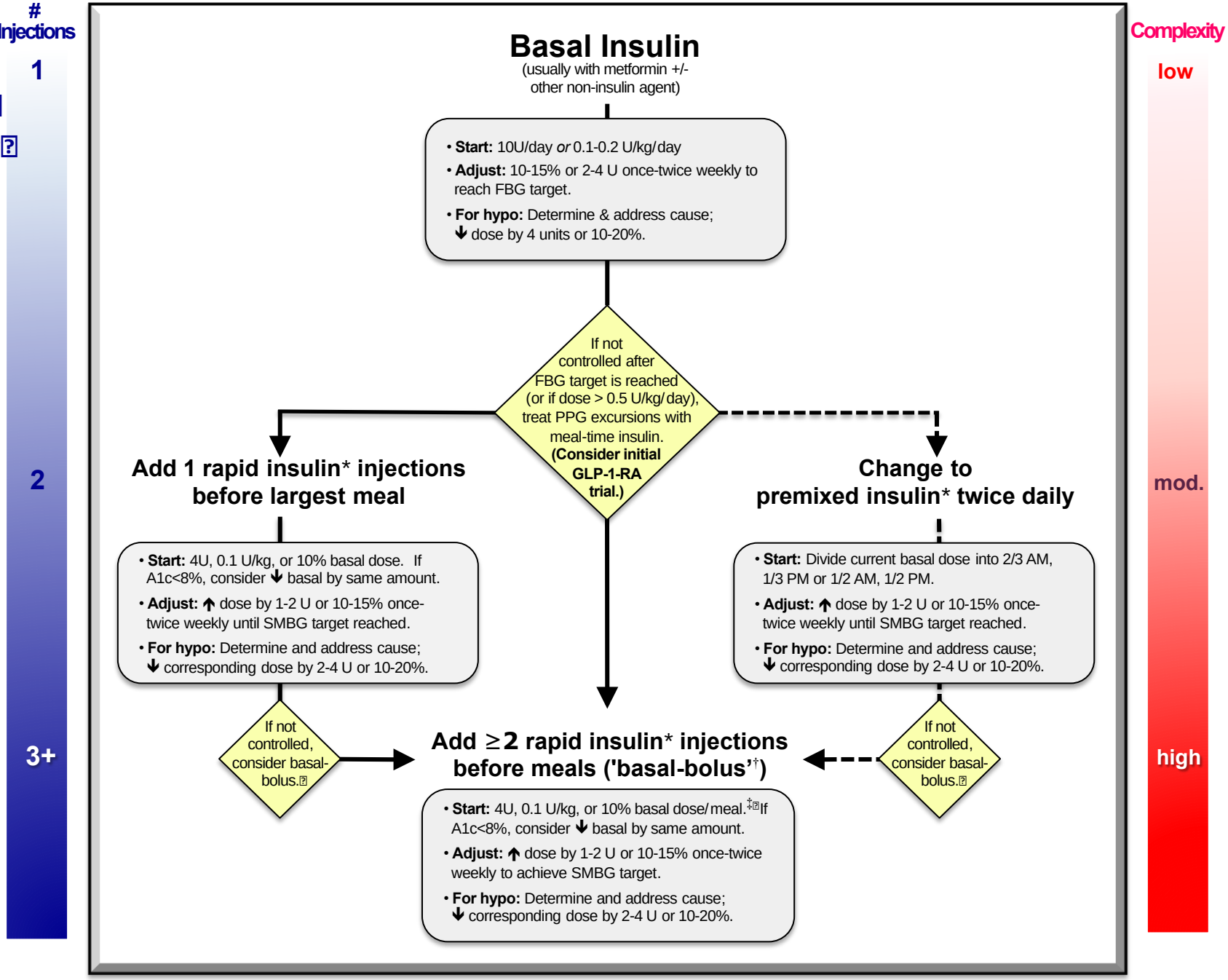

Diabetes Care 2015;38:140; *Diabetologia* 2015;10.1077/s00125-014-3460-0

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

Glycemic Control Algorithm

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

Entry A1c < 7.5%

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

If not at goal in 3 months proceed to Double Therapy

Entry A1c ≥ 7.5%

DUAL THERAPY*
MET or other 1st-line agent +
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*
MET or other 1st-line agent + 2nd-line agent +
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

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

Entry A1c > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND
- ✓ Few adverse events 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

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596

FUTURE DIRECTIONS / RESEARCH NEEDS

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

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596

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

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

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