Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Diabetes Care 2015;38:140–149
Diabetologia 2015;58:429–442

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Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

1. PATIENT-CENTERED CARE

2. BACKGROUND

- Epidemiology and health care impact
- Relationship of glycemic control to outcomes
- Overview of the pathogenesis of Type 2 diabetes

3. ANTI-HYPERGLYCEMIC THERAPY

- Glycemic targets
- Therapeutic options
  - Lifestyle
  - UPDATED - Oral agents & non-insulin injectables
  - Insulin

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

3. ANTIHYPERGLYCEMIC THERAPY

- Implementation Strategies
  - Initial drug therapy
  - UPDATED - Advancing to dual combination therapy
  - UPDATED - Advancing to triple combination therapy
  - UPDATED - Transitions to and titrations of insulin

4. OTHER CONSIDERATIONS

- Age
- Weight
- Sex/racial/ethnic/genetic differences
- Comorbidities *(CAD, HF, CKD, Liver disease, Hypoglycemia-prone)*

5. FUTURE DIRECTIONS / RESEARCH NEEDS

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

1. 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.**
- **<u>Shared Decision Making</u> – 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.**

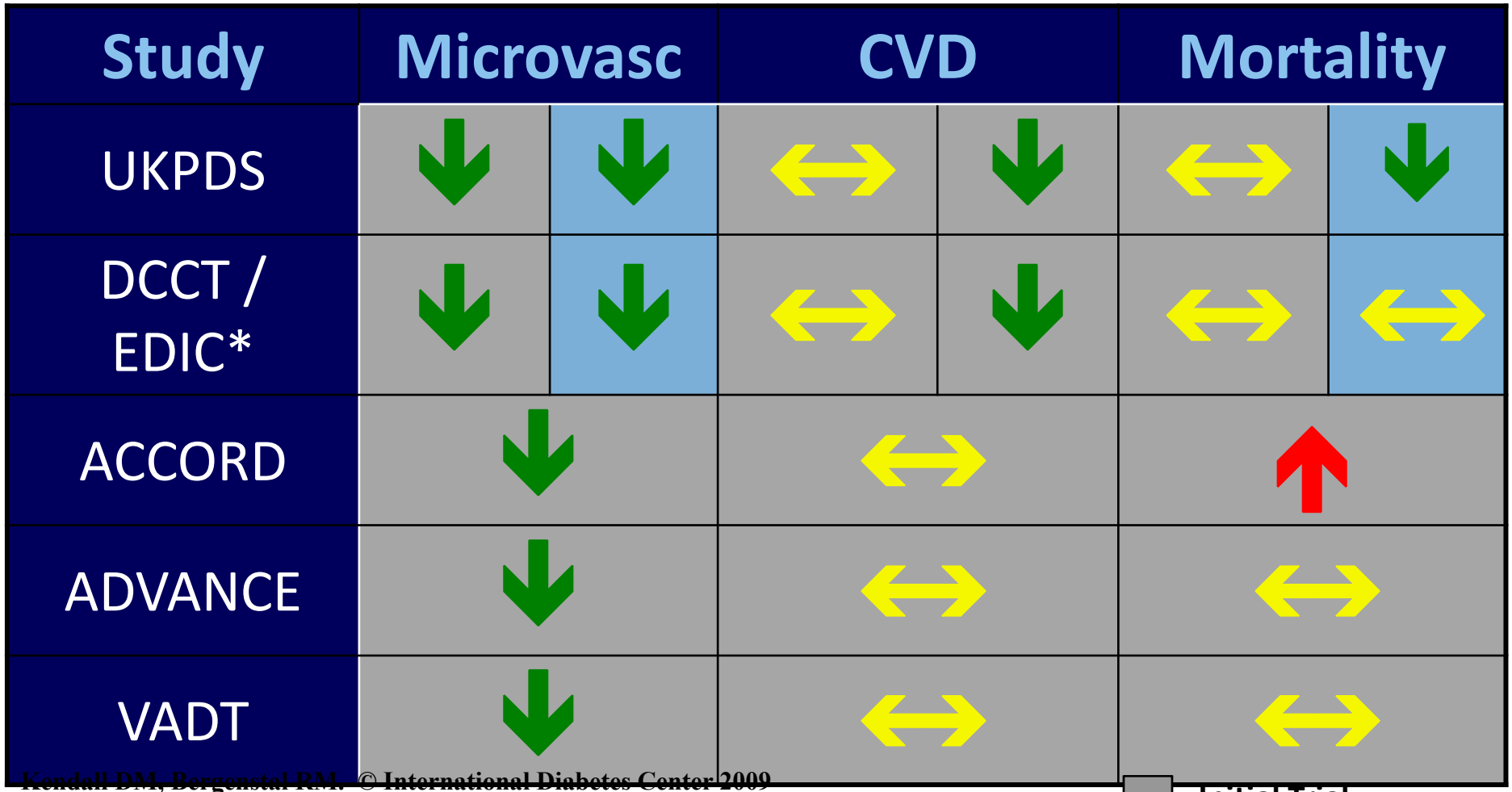
Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596

2. BACKGROUND

- Relationship of glycemic control to microvascular and macrovascular outcomes.

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

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



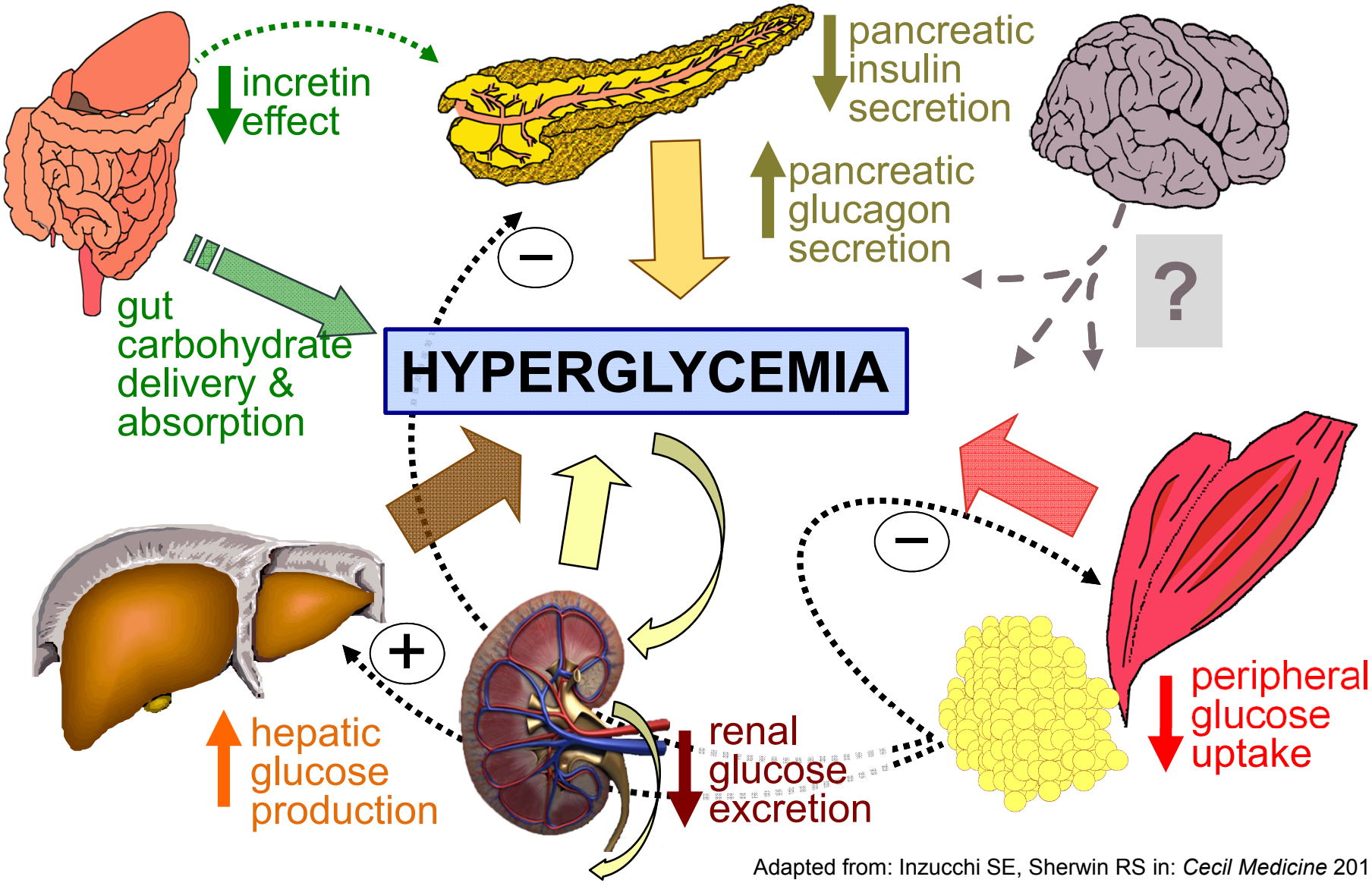
UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)

2. BACKGROUND

- **Overview of the pathogenesis of T2DM**
  - Insulin secretory dysfunction
  - Insulin resistance (muscle, fat, liver)
  - Increased endogenous glucose production
  - Decreased incretin effect
  - Deranged adipocyte biology

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

Multiple, Complex Pathophysiological Abnormalities in T2DM



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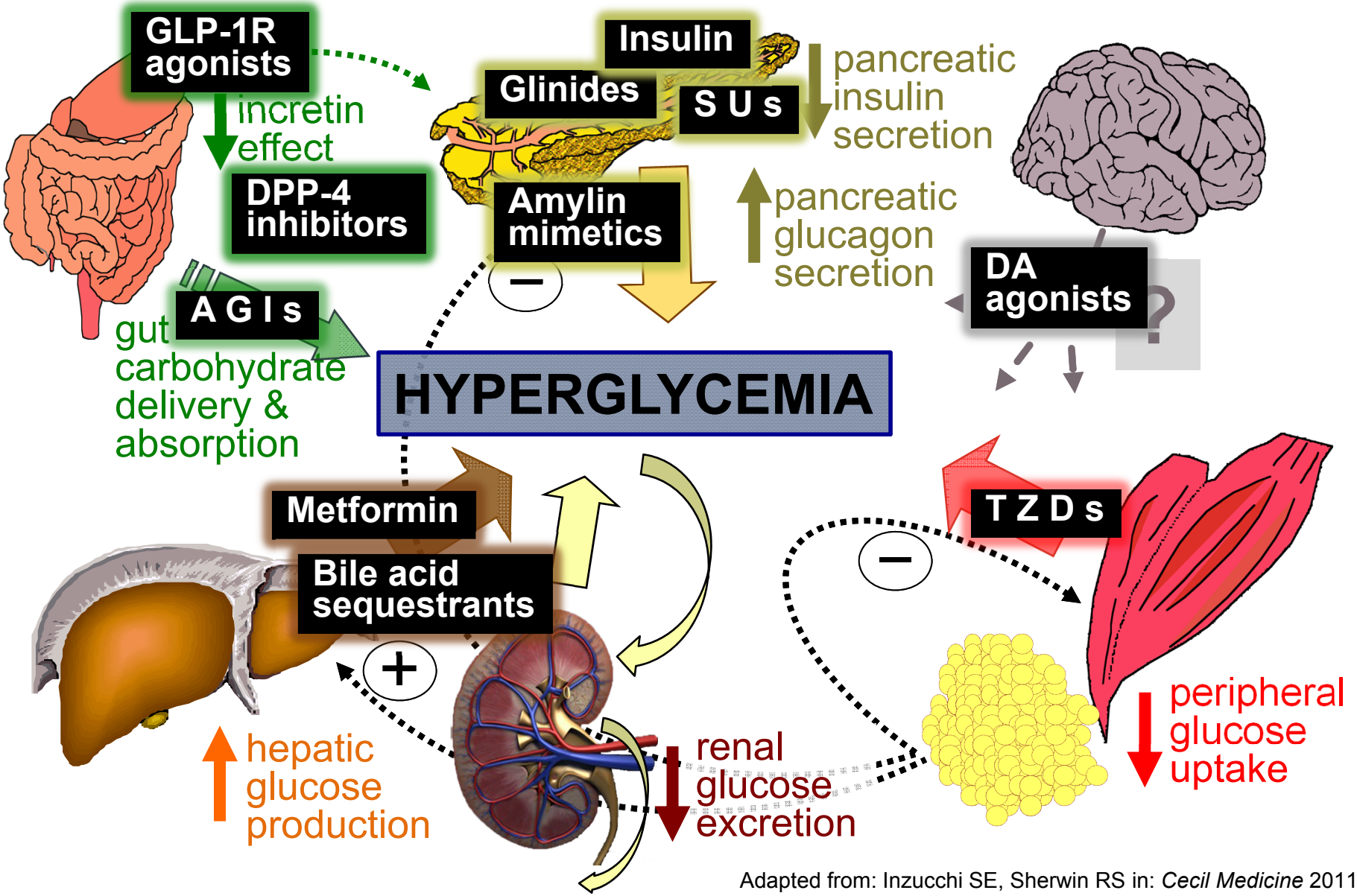

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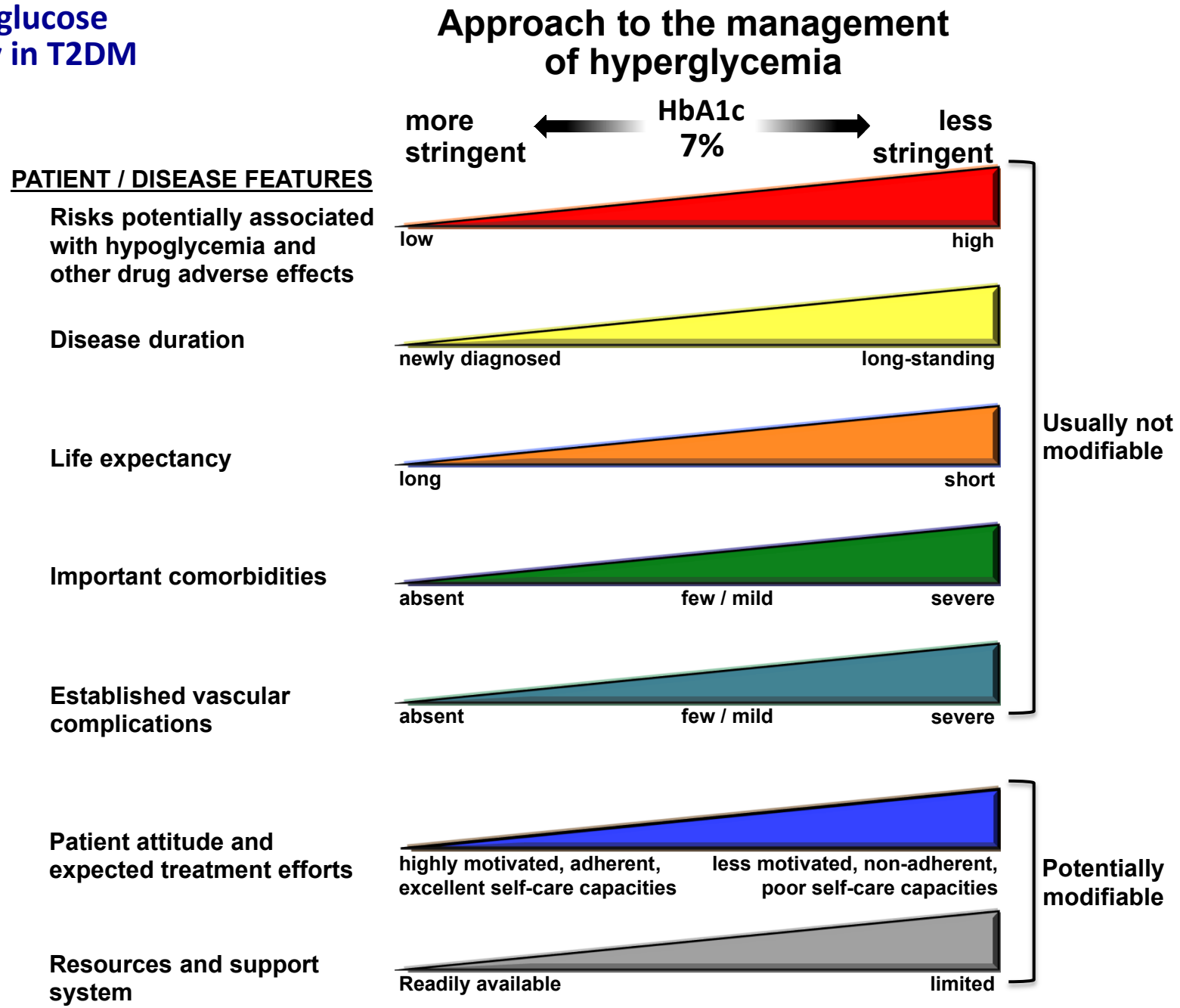
3. ANTI-HYPERGLYCEMIC THERAPY

- **Glycemic targets**
  - **HbA1c < 7.0%** (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)
  - ***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
Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

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



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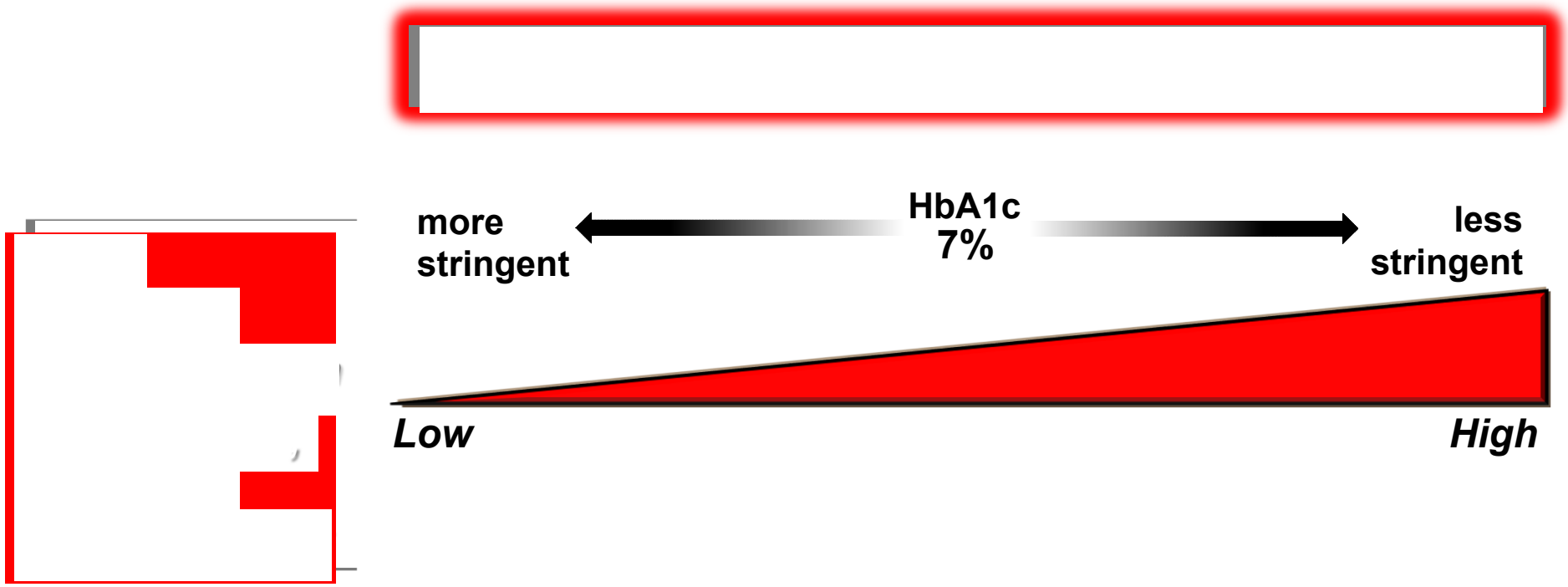

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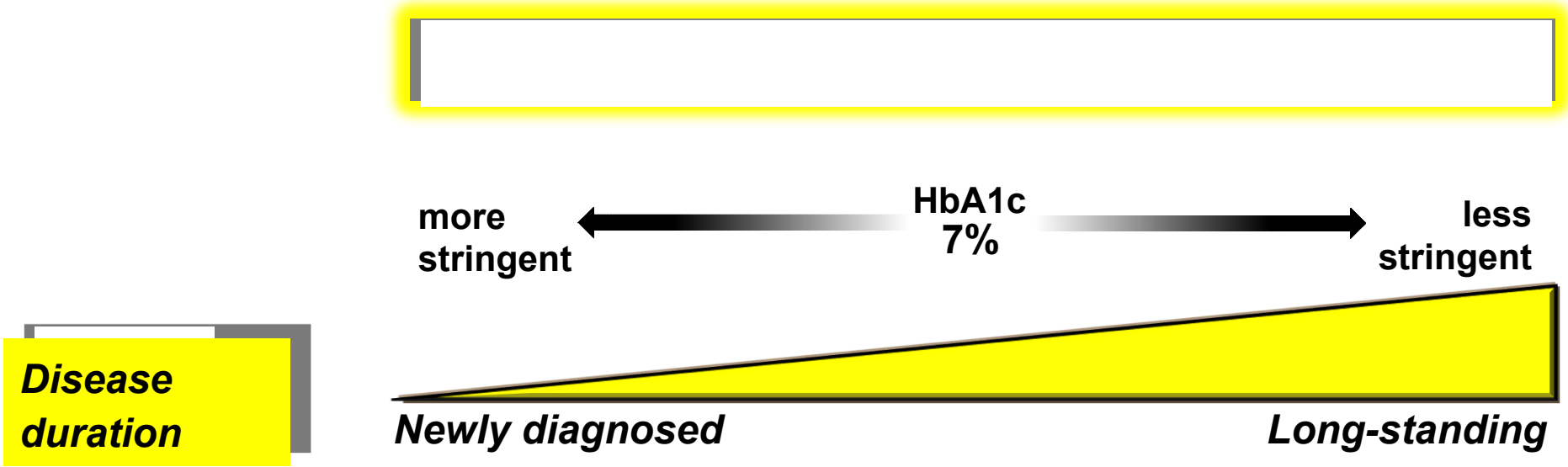

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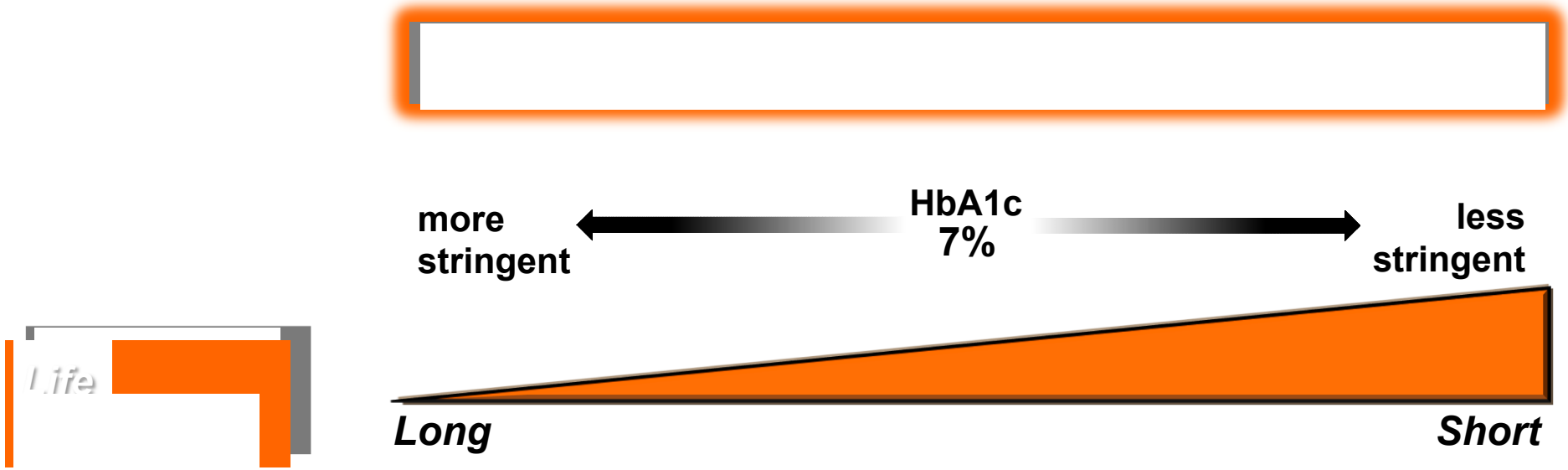

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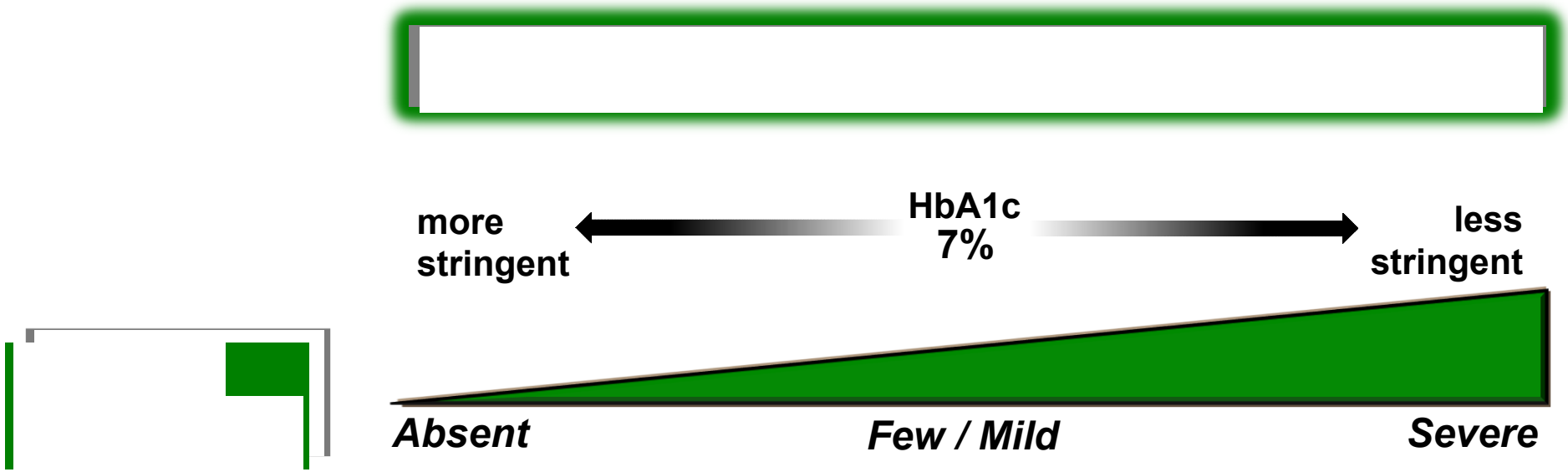

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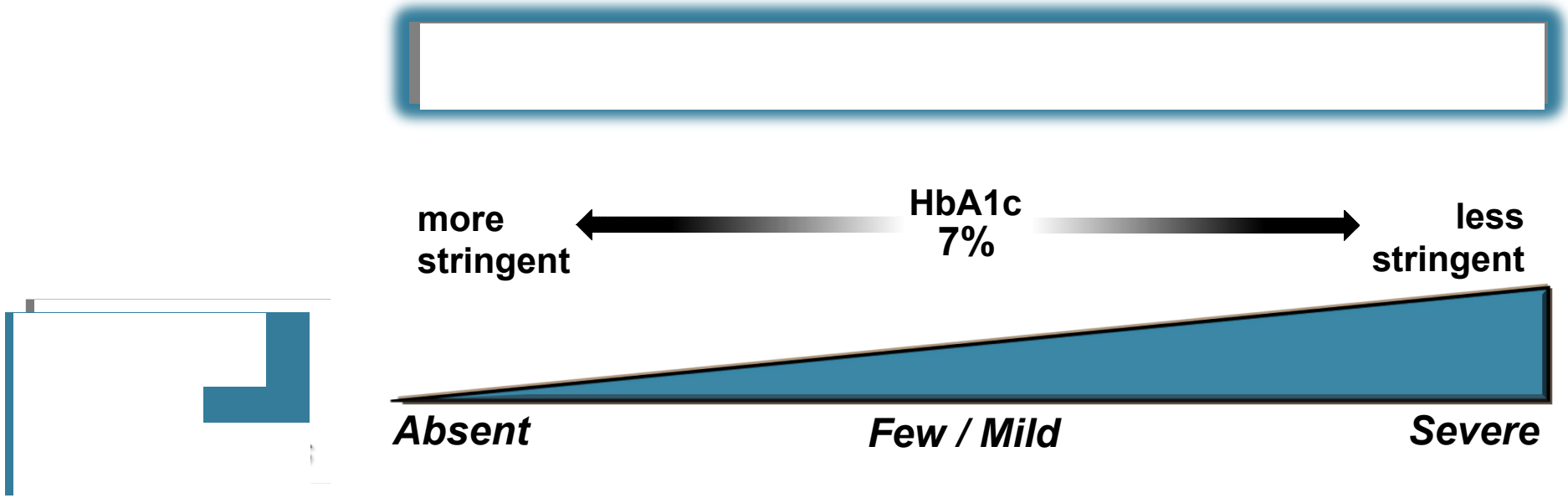

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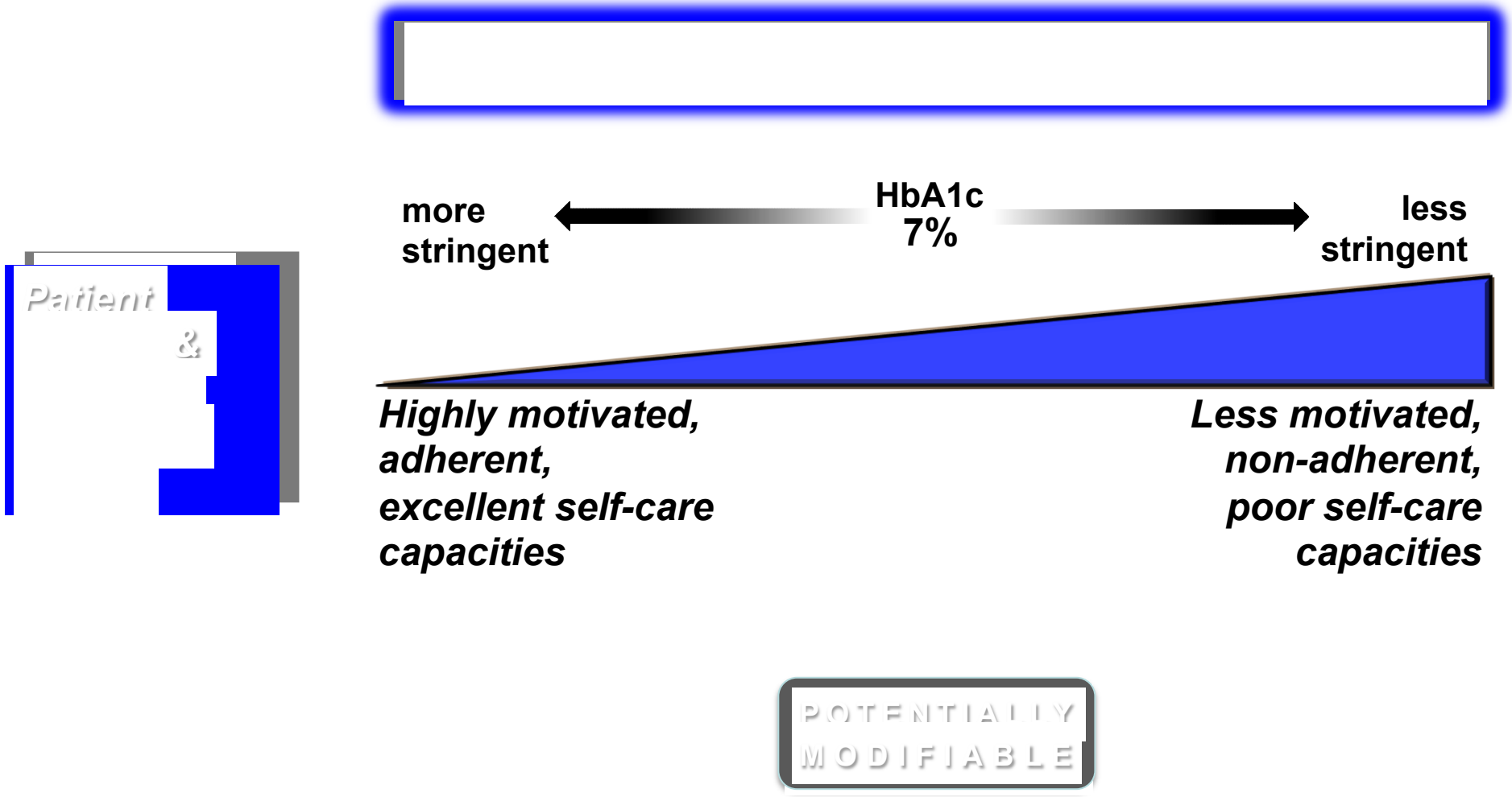

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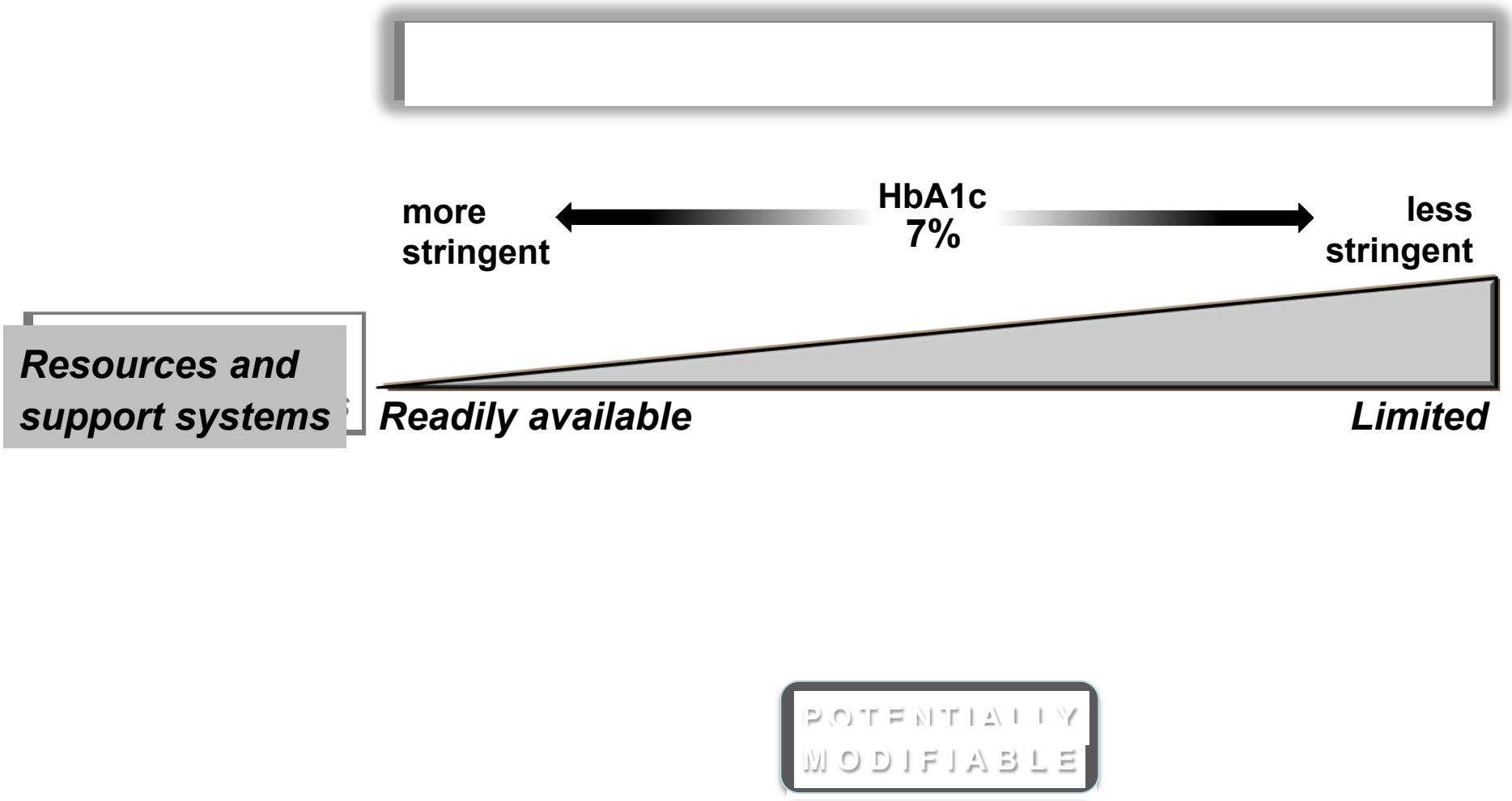

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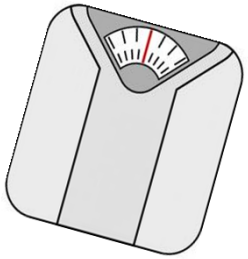
Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

3. ANTI-HYPERGLYCEMIC THERAPY

- **Therapeutic options: Lifestyle**

  - **Weight optimization**



  - **Healthy diet**

  - **Increased activity level**

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

3. ANTI-HYPERGLYCEMIC THERAPY

- **Therapeutic options:**

  Oral agents & non-insulin injectables

  - **Metformin**
  - **Sulfonylureas**
  - **Thiazolidinediones**
  - **DPP-4 inhibitors**
  - **SGLT-2 inhibitors**
  - **GLP-1 receptor agonists**
  - Meglitinides
  - α-glucosidase inhibitors
  - Colesevelam
  - Dopamine-2 agonists
  - Amylin mimetics

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

Oral Class	Mechanism	Advantages	Disadvantages	Cost
Biguanides	• Activates AMP-kinase (?other) • ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • Weight neutral • ? ↓ CVD	• Gastrointestinal • Lactic acidosis (rare) • B-12 deficiency • Contraindications	Low
Sulfonylureas	• Closes K_{ATP} channels • ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk	• Hypoglycemia • ↑ Weight • Low durability • ? Blunts ischemic preconditioning	Low
Meglitinides	• Closes K_{ATP} channels • ↑ Insulin secretion	• ↓ Postprandial glucose • Dosing flexibility	• Hypoglycemia • ↑ Weight • ? Blunts ischemic preconditioning • Dosing frequency	Mod.
TZDs	• PPAR-γ activator • ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↓ TGs (pio) • ↑ HDL-C • ? ↓ CVD events (pio)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosi) • ? ↑ MI (rosi)	Low

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Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2015;38:140-149;
Diabetologia 2015;58:429-442

Oral Class	Mechanism	Advantages	Disadvantages	Cost
α-Glucosidase inhibitors	• Inhibits α-glucosidase • Slows carbohydrate digestion / absorption	• No hypoglycemia • Nonsystemic • ↓ Postprandial glucose • ? ↓ CVD events	• Gastrointestinal • Dosing frequency • Modest ↓ A1c	Mod.
DPP-4 inhibitors	• Inhibits DPP-4 • Increases incretin (GLP-1, GIP) levels	• No hypoglycemia • Well tolerated	• Angioedema / urticaria • ? Pancreatitis • ? ↑ Heart failure	High
Bile acid sequestrants	• Bind bile acids • ? ↓ Hepatic glucose production	• No hypoglycemia • ↓ LDL-C	• Gastrointestinal • Modest ↓ A1c • Dosing frequency	High
Dopamine-2 agonists	• Activates DA receptor • Alters hypothalamic control of metabolism • ↑ insulin sensitivity	• No hypoglyemia • **?** ↓ CVD events	• Modest ↓ A1c • Dizziness, fatigue • Nausea • Rhinitis	High
SGLT2 inhibitors	• Inhibits SGLT2 in proximal nephron • Increases glucosuria	•↓ Weight • No hypoglycemia • ↓ BP • Effective at all stages	• GU infections • Polyuria • Volume depletion • ↑ LDL-C • ↑Cr (transient)	High

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2015;38:140-149;
Diabetologia 2015;58:429-442

Injectable Class	Mechanism	Advantages	Disadvantages	Cost
Amylin mimetics	• Activates amylin receptor • ↓ glucagon • ↓ gastric emptying • ↑ satiety	• ↓ Weight • ↓ Postprandial glucose	• Gastrointestinal • Modest ↓ A1c • Injectable • Hypo if insulin dose not reduced • Dosing frequency • Training requirements	High
GLP-1 receptor agonists	• Activates GLP-1 R • ↑ Insulin, ↓ glucagon • ↓ gastric emptying • ↑ satiety	• ↓ Weight • No hypoglycemia • ↓ Postprandial glucose • ↓ Some CV risk factors	• Gastrointestinal • ? Pancreatitis • ↑ Heart rate • Medullary ca (rodents) • Injectable • Training requirements	High
Insulin	• Activates insulin receptor • Myriad	• Universally effective • Unlimited efficacy • ↓ Microvascular risk	• Hypoglycemia • Weight gain • ? Mitogenicity • Injectable • Patient reluctance • Training requirements	Variable

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2015;38:140-149;
Diabetologia 2015;58:429-442

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

Mono-therapy	Metformin
Efficacy*	high
Hypo risk	low risk
Weight	neutral/loss
Side effects	GI / lactic acidosis
Costs	low

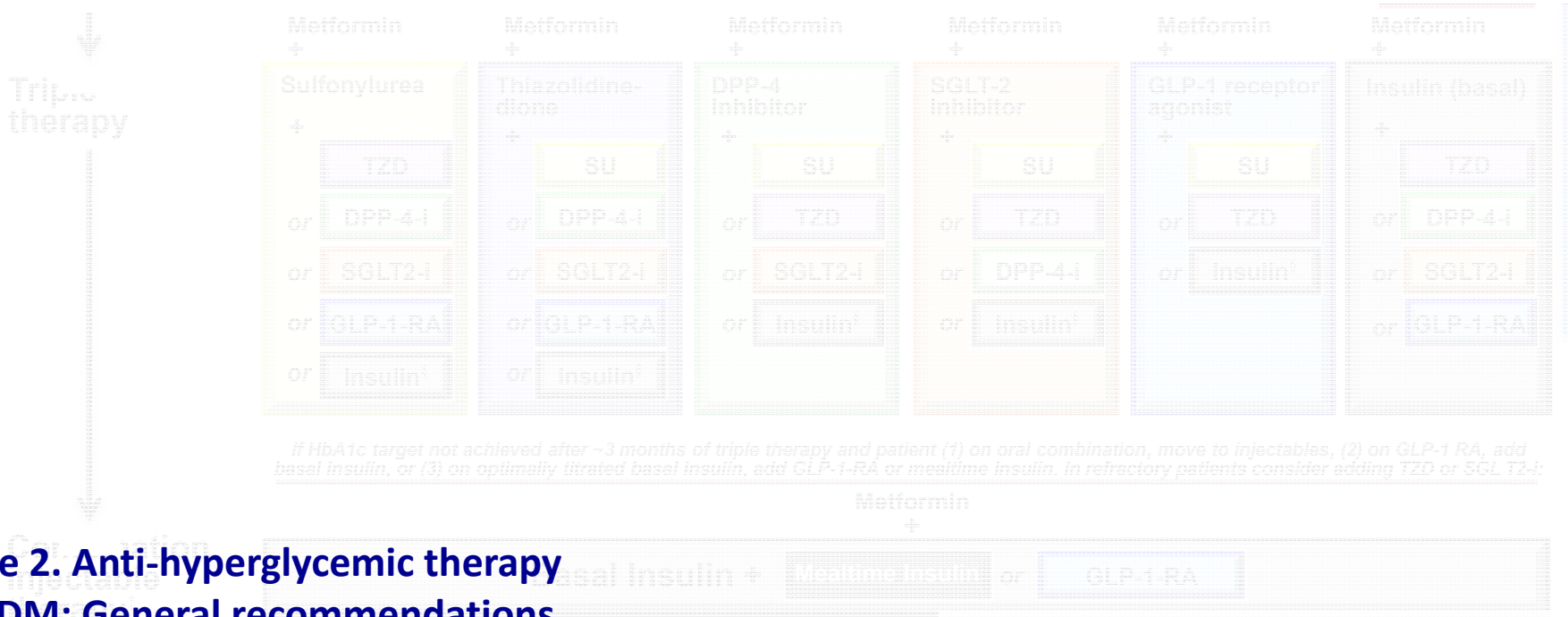
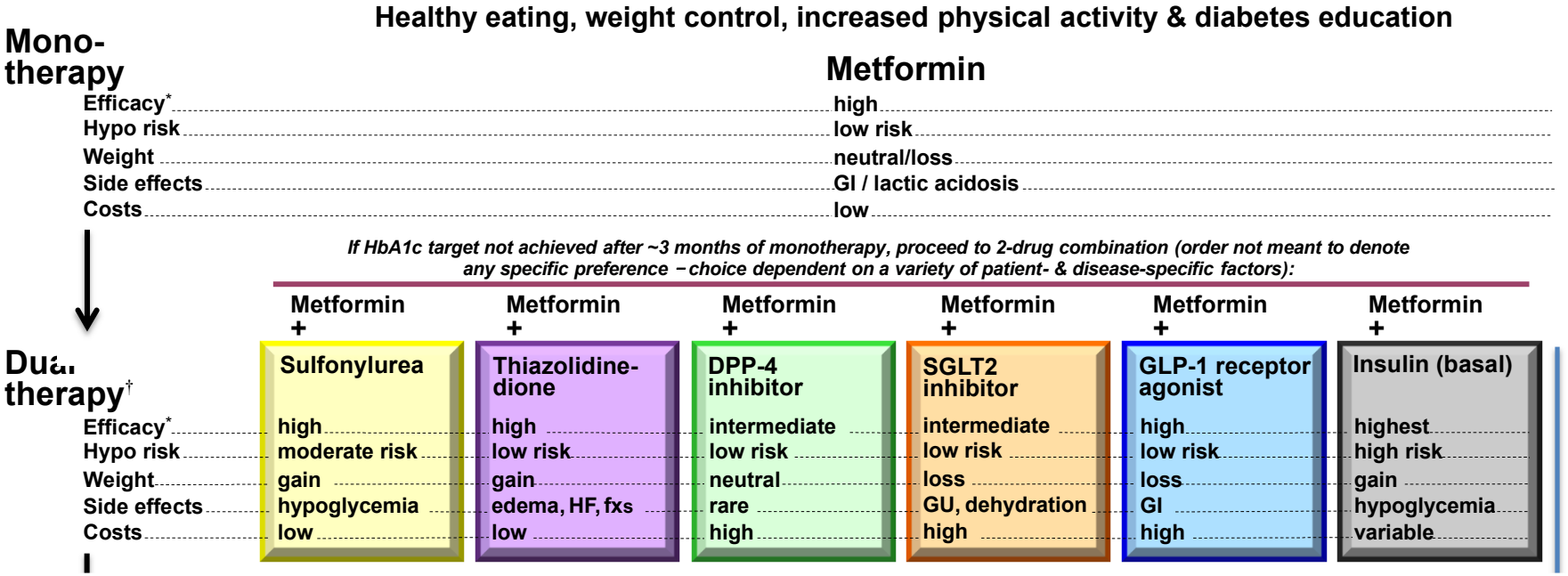


Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442



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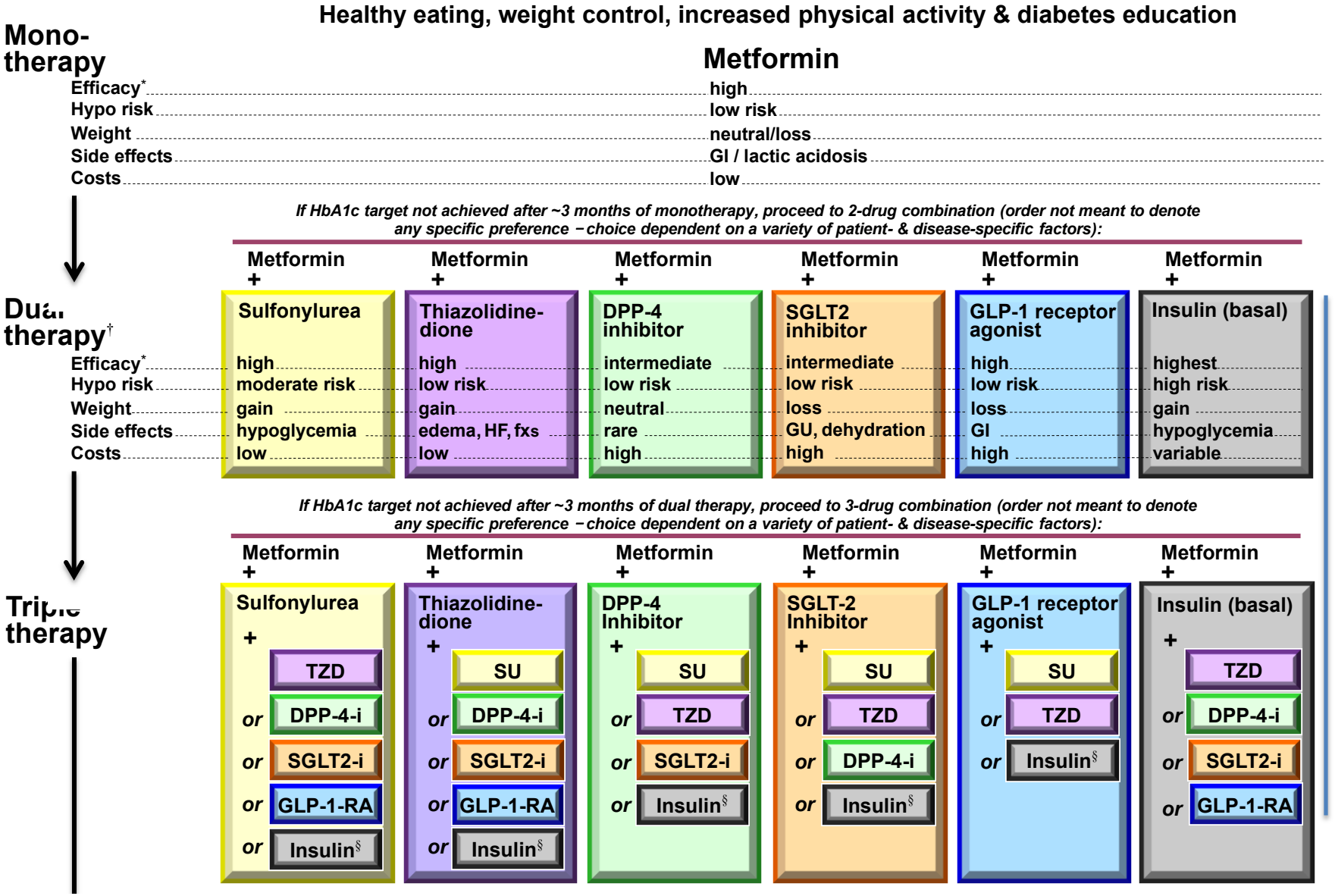

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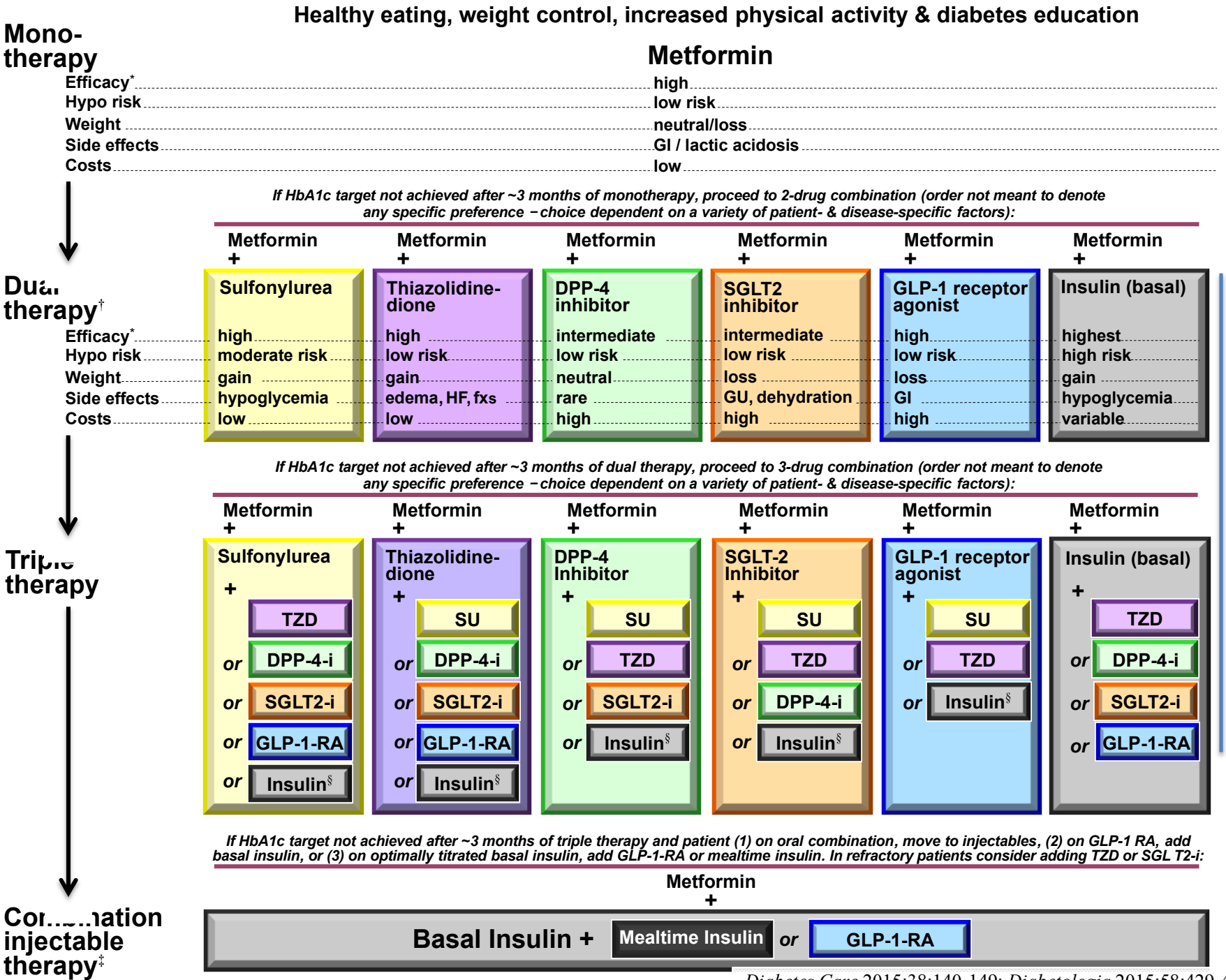

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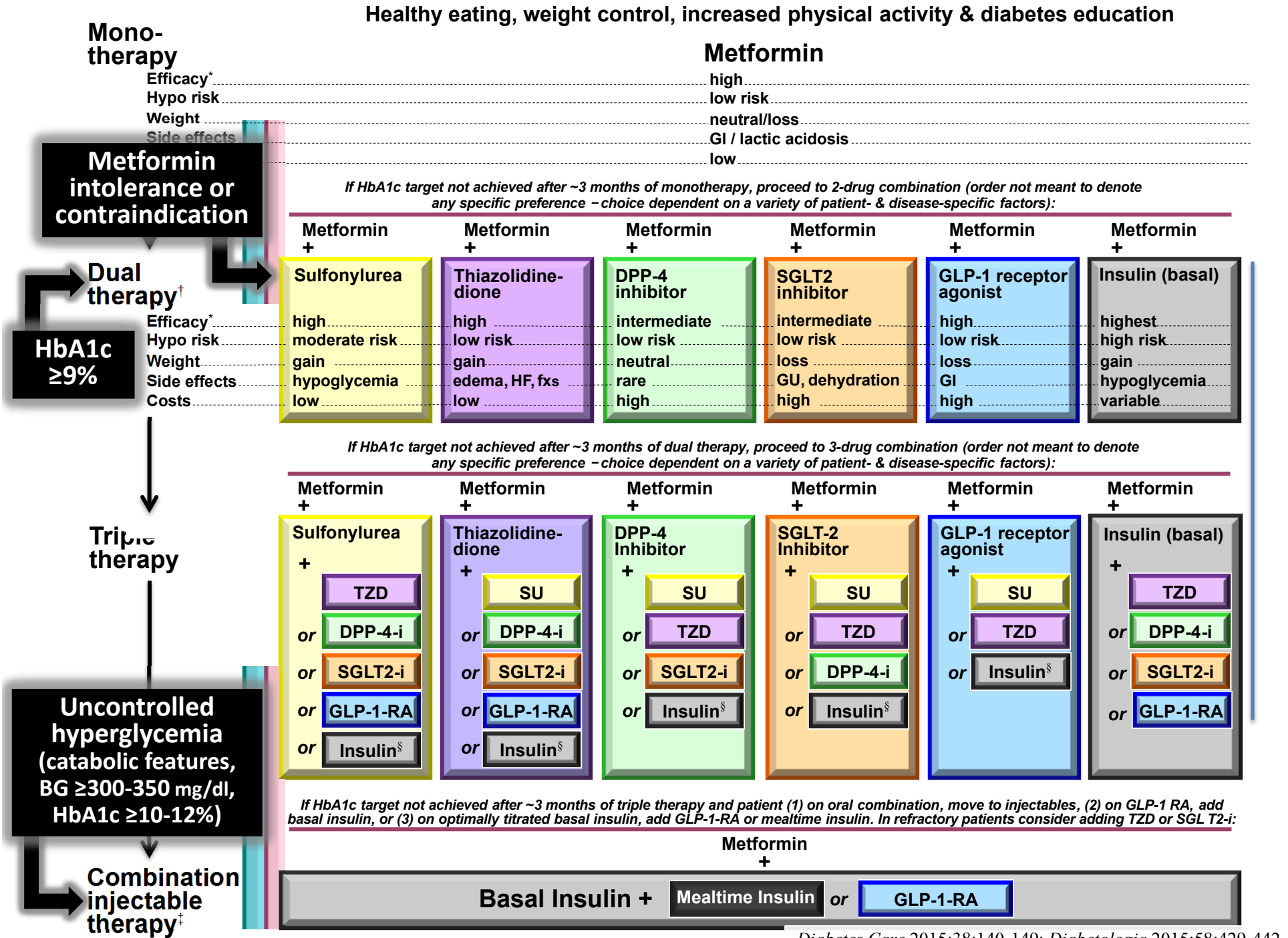

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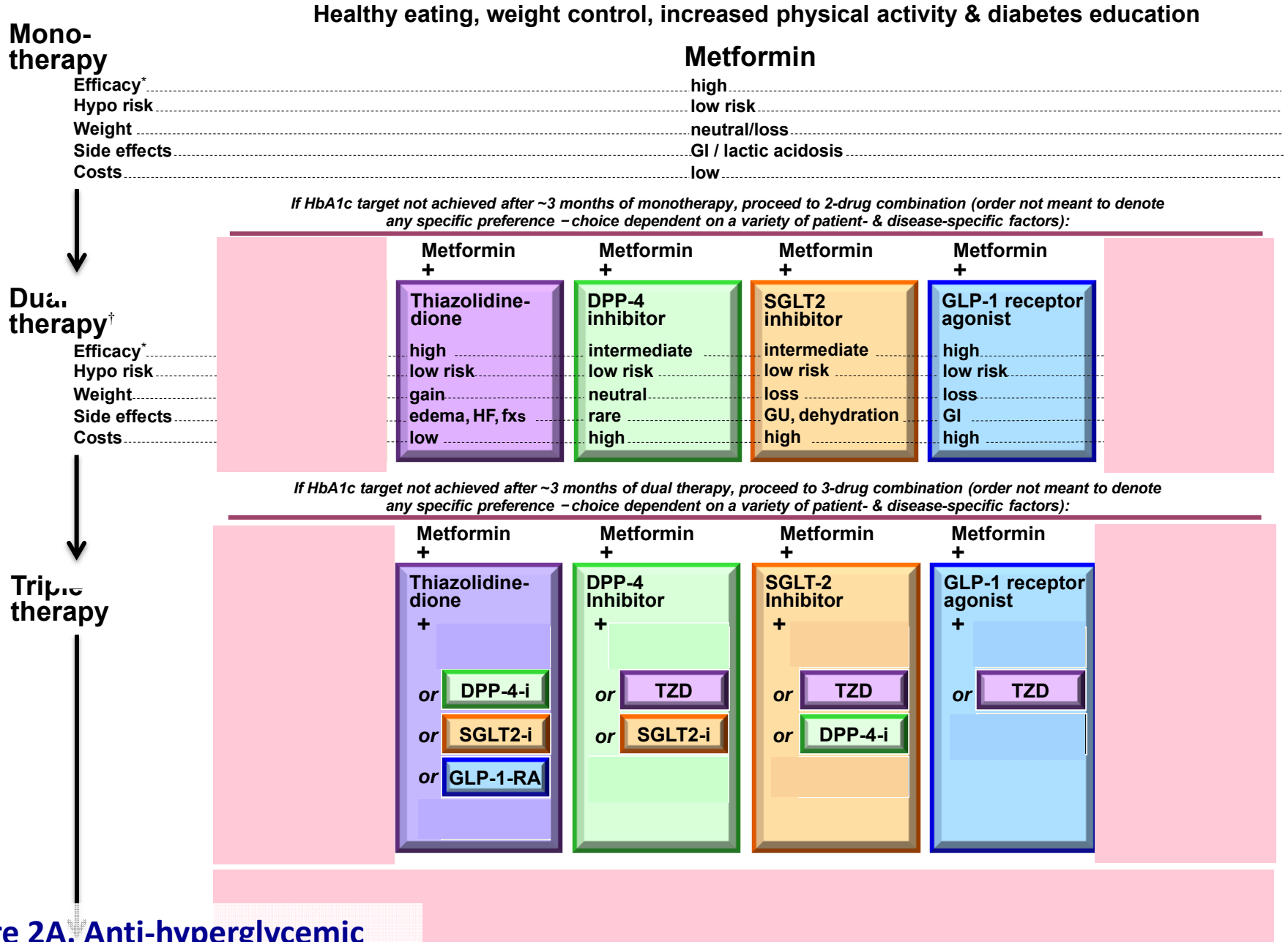

Figure 2A. Anti-hyperglycemic therapy in T2DM:
Avoidance of hypoglycemia

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

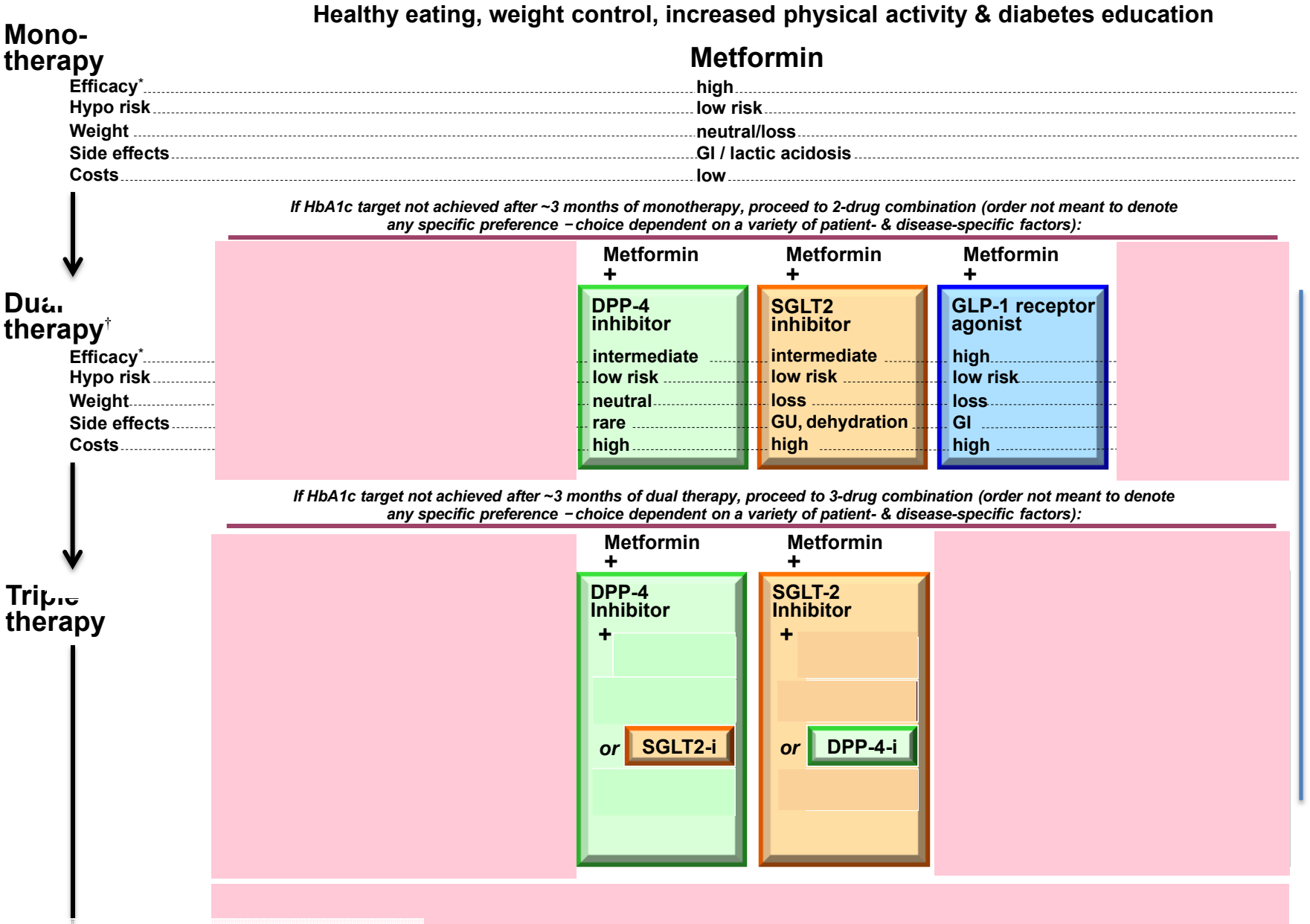

Figure 2B. Anti-hyperglycemic therapy in T2DM:
Avoidance of weight gain

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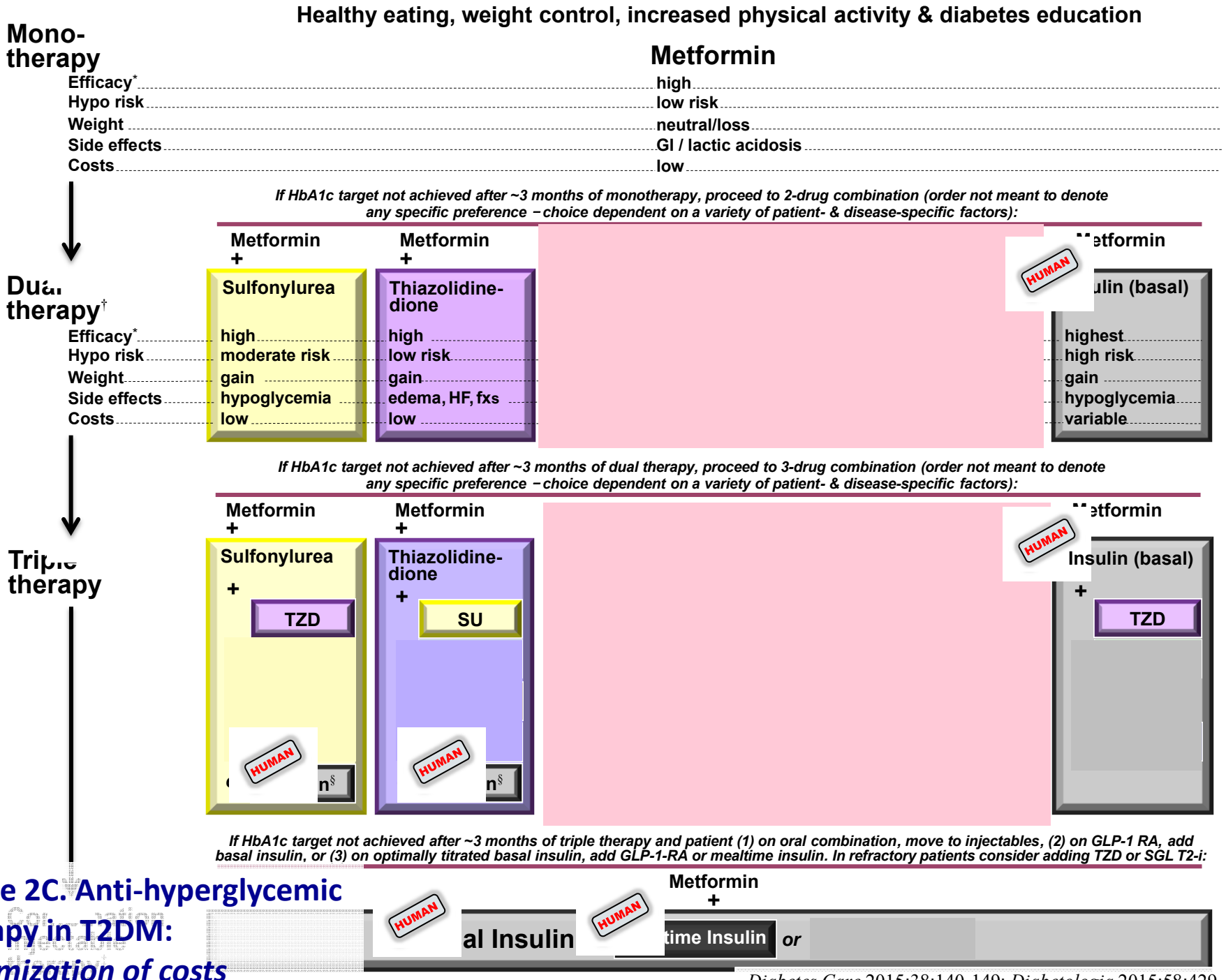
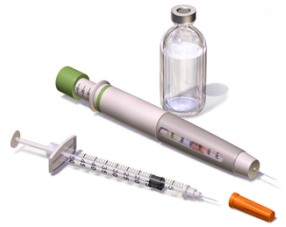


Figure 2C. Anti-hyperglycemic therapy in T2DM: *Minimization of costs*

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

3. ANTI-HYPERGLYCEMIC THERAPY



- **Therapeutic options*: 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
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3. ANTI-HYPERGLYCEMIC THERAPY

- **Therapeutic options*: Insulins***

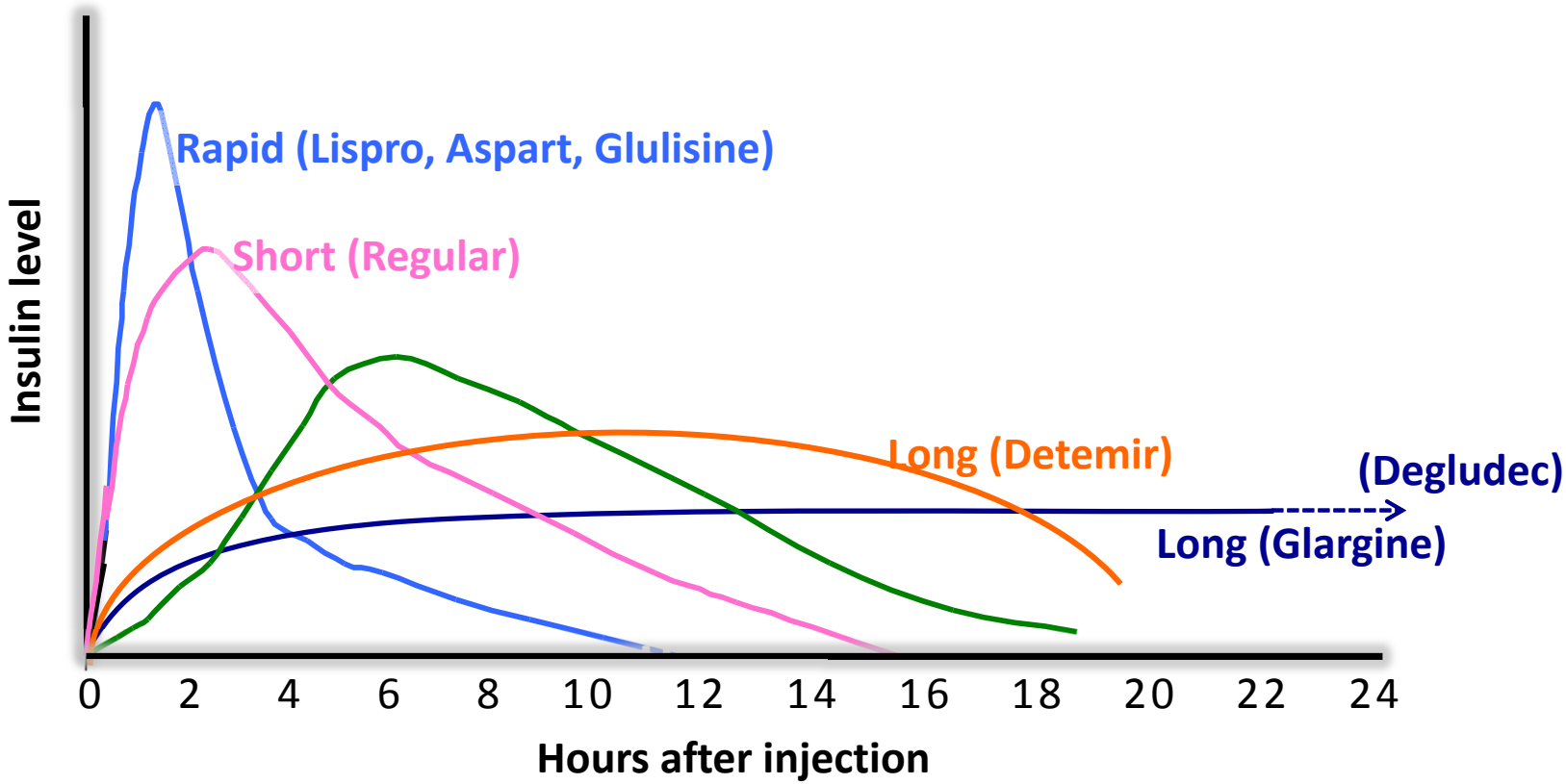
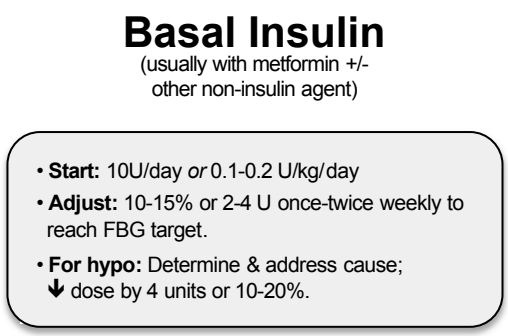


Figure 3. Approach to starting & adjusting insulin in T2DM



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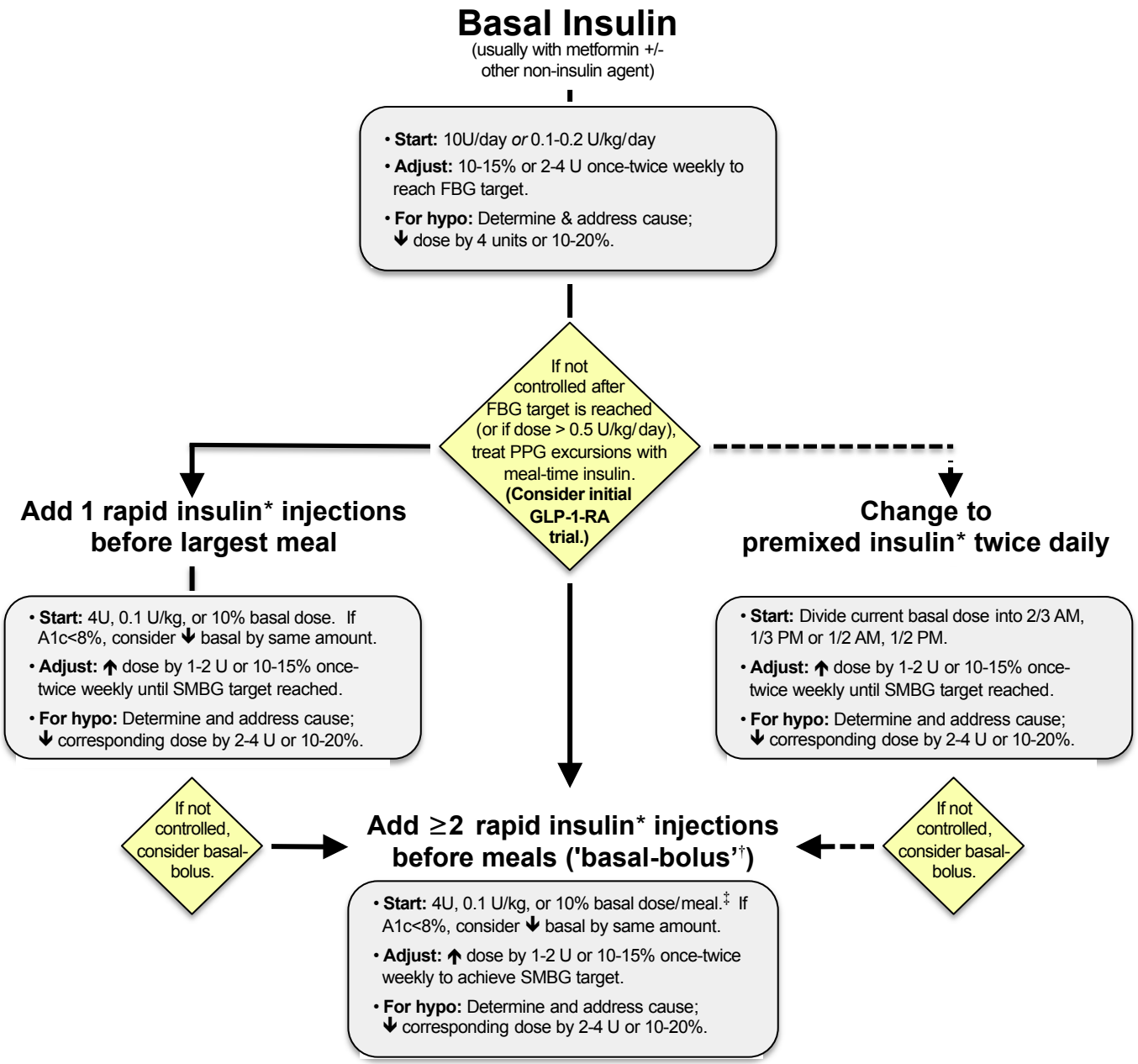

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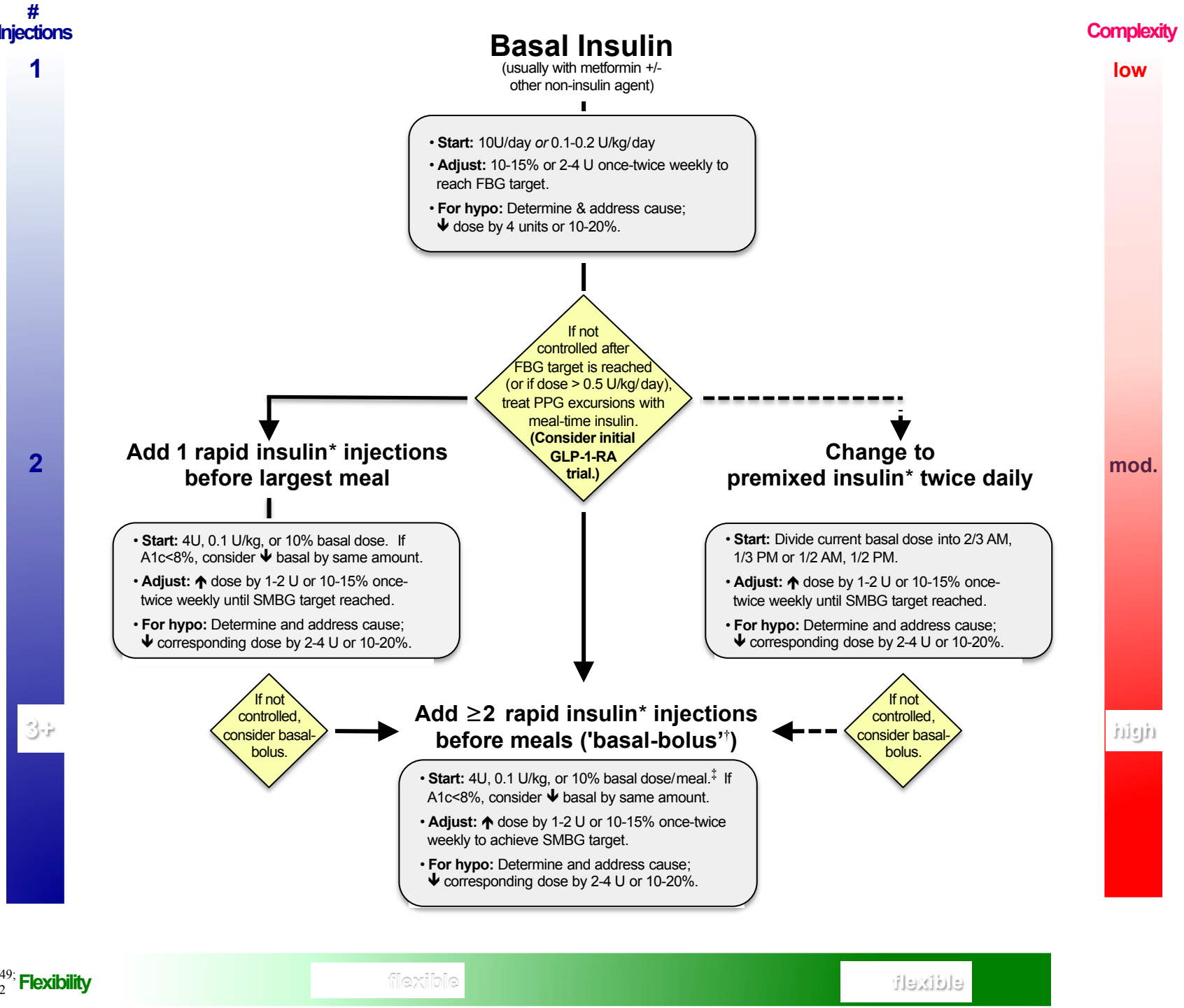

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4. OTHER CONSIDERATIONS

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

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

4. 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

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.

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