PRACTICAL MANAGEMENT OF DIABETES MELLITUS : WHAT'S WRONG WITH US?

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- Wrong diagnosis
- Wrong concepts in the control of diabetes
- Wrong management concepts
- Wrong choice of patients
- Wrong dosage
- Wrong combination of OHAs
- Wrong information/beliefs – metformin and renal damage

- End stage of DM
- No other treatment options that lower the damage to eyes, kidneys, etc
- Barriers like unaffordable, no refrigeration, painful and no capacity for injection
- Hypoglycemia
- Hyperinsulinaemia

SELECTION OF PATIENT

- Type 1 DM patients
- Type 2 DM patients
- MODY
- LADA
- GDM
- SECONDARY DIABETES

DIAGNOSIS OF DM (WHO CRITERIA)

- **Symptoms of hyperglycaemia** (eg polyuria, polydipsia, unexplained weight loss, visual blurring, genital thrush, lethargy) AND raised venous glucose detected once—fasting ≥7mmol/L or random ≥11.1mmol/L OR

- **Raised venous glucose on 2 separate occasions**—
  - ✓ fasting ≥7mmol/L,
  - ✓ random ≥11.1mmol/L or
  - ✓ oral glucose tolerance test (**OGTT**)—2h value ≥11.1mmol/L

- **HbA1c ≥48mmol/L (6.5%),** but below doesn't exclude DM. Avoid in pregnancy, children and type 1 DM.

- Whenever you have a needle in a vein, do a blood glucose (unless recently done); note if fasting or after food. Non-systematic, but better than urine tests (too many false negatives). In one UK GP trial, 5% of those screened aged 40–69 had new DM.

SMBG (SELF MONITORING BLOOD GLUCOSE)

For Out Patients :

- FBS : 80-120 mg/dl
- 2HPPL / 2HPPD : <180 mg/dl

For Inpatients

- FBS :
- 2HPPL / 2HPPD :

Spectrum of DM Type I and Type II

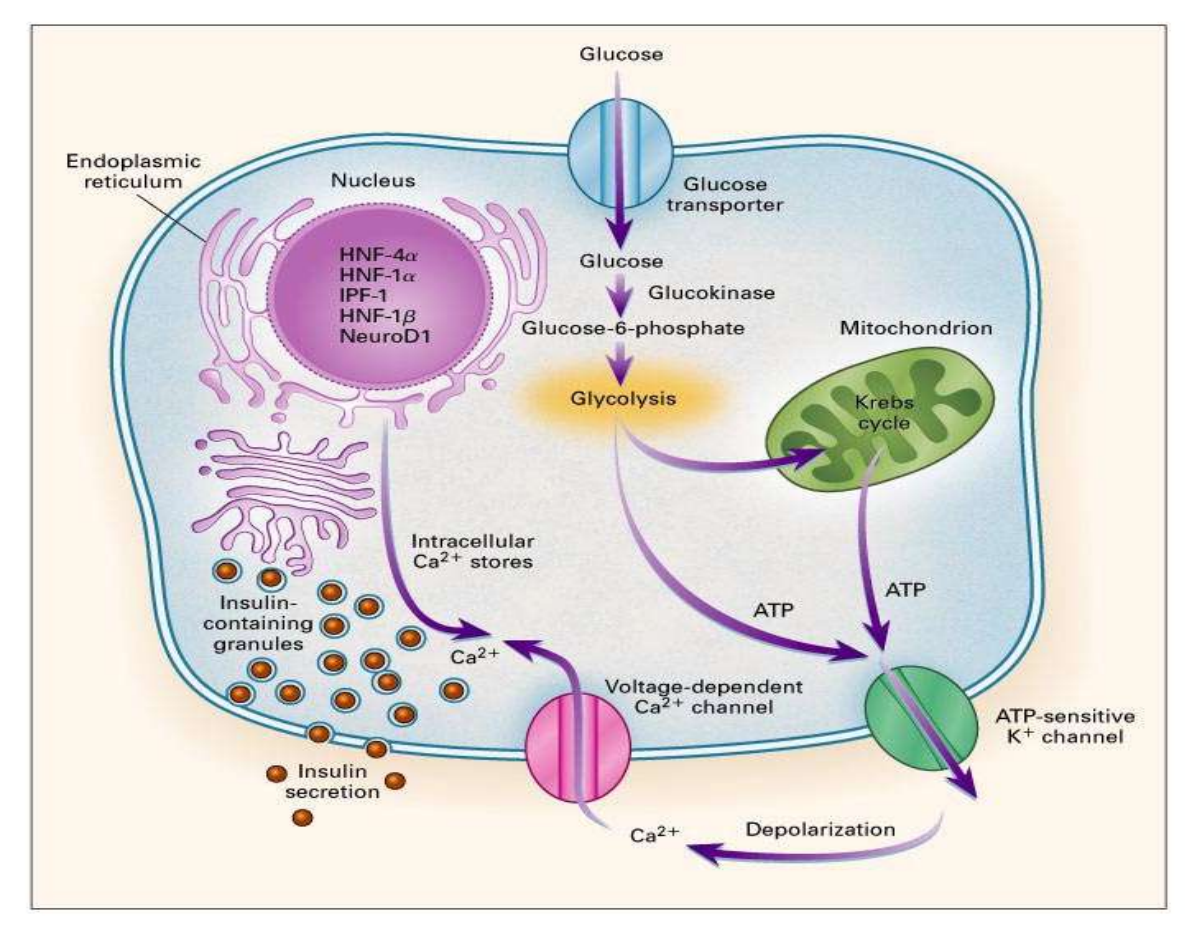
	Type 1	Type 2
Age	Younger (usually <30)	Older (usually >30)
Weight	Lean	Overweight
Symptom duration	Weeks	Months/years
Higher risk ethnicity	Northern European	Asian, African, Polynesian and American-Indian
Seasonal onset	Yes	No
Heredity	HLA-DR3 or DR4 in >90%	No HLA links
Pathogenesis	Autoimmune disease	No immune disturbance
Ketonuria	Yes	No
Clinical	Insulin deficiency ± ketoacidosis Always need insulin	Partial insulin deficiency initially ± hyperosmolar state Need insulin when beta cells fail over time
Biochemical	C-peptide disappears	C-peptide persists

MATURITY-ONSET DIABETES OF THE YOUNG (MODY)

- Maturity-onset diabetes of the Young(MODY) is a genetically and clinically heterogeneous group of disorders
- Characterized by nonketotic diabetes mellitus
- Autosomal dominant – (+) Family history
- Onset usually before 25 years of age
- Resulting from a primary defect in pancreatic beta-cell function (6 causative gene mutations in insulin and glucose regulation)
- Account for 1-5% of all cases of diabetes
- Most common clinical presentation is a mild, asymptomatic increase in blood glucose in a child, adolescent, or young adult with a prominent family history of diabetes
- Resembles with Type 2 DM and relatively mind but the patient are not obese and not insulin resistant

GENETIC DEFECTS OF BETA-CELL FUNCTION

Type	Gene mutated	Chromosome no.
MODY 1	Hepatocyte nuclear factor 4A (*HNF4A*)	20
MODY 2	Glucokinase (GCK)	7
MODY 3	Hepatocyte nuclear factor 1A (HNF1A)	12
MODY 4	Insulin promoter factor 1 (ING1)	13
MODY 5	Hepatocyte nuclear factor 1B(HNF 1B)	17
MODY 6	Neuro 1/ BETA2	2



Model of a Pancreatic Beta Cell and the Proteins Implicated in Maturity-Onset Diabetes of the Young (MODY).

- **LADA** : Latent autoimmune diabetes of adults

A form of type I DM, with slower progression to insulin dependence in later life.

- **GDM** : Gestational DM

21.23 Identifying patients with gestational diabetes

sma glucose (after glucose load) ≥ 8 mmol/L (144 mg/dL)

- Consider testing high-risk women at first booking visit with an HbA_{1c} or fasting blood glucose

- The aim is to normalise the maternal blood glucose and thereby reduce excessive fetal growth.
- Dietary modification
- Regular pre- and post-prandial self-monitoring of blood glucose, aiming for pre-meal blood glucose levels of <5.5 mmol/L (100 mg/dL) or post- meal blood glucose levels of <7.0 mmol/L (125 mg/dL)
- **Metformin or Glibenclamide** is considered safe to use in pregnancy.
- **Insulin** may be required, especially in the **later stages of pregnancy**.
- After delivery, maternal glucose usually rapidly returns to pre-pregnancy levels. Woman should be tested at least 6 weeks post-partum with an oral glucose tolerance test

Secondary Diabetes Mellitus

- Pancreatic disease (e.g. pancreatitis, pancreatectomy, neoplastic disease, cystic fibrosis, haemochromatosis, fibrocalculous pancreatopathy)

- Excess endogenous production of hormonal antagonists to insulin, e.g.
  - ✓ Growth hormone – acromegaly
  - ✓ Glucocorticoids – Cushing's syndrome
  - ✓ Glucagon – glucagonoma
  - ✓ Catecholamines – phaeochromocytoma
  - ✓ Thyroid hormones – thyrotoxicosis

- Drug-induced (e.g. corticosteroids, thiazide diuretics, phenytoin)

- Uncommon forms of immune-mediated diabetes (e.g. IPEX (immunodysregulation polyendocrinopathy X) syndrome)

- Associated with genetic syndromes (e.g. Down's syndrome; Klinefelter's syndrome; Turner's syndrome; DIDMOAD (Wolfram's syndrome) – diabetes insipidus, diabetes mellitus, optic atrophy, nerve deafness; Friedreich's ataxia; myotonic dystrophy)

GLYCEMIC TARGET FOR OUT-PATIENTS

HbA1C Goals	
Nonpregnant adult	<7%(53mmol/mol)
Patients with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease	<6.5(48mmol/mol)
Patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-lasting diabetes	<8%(64mmol/mol)

GLYCEMIC TARGETS IN HOSPITALIZED PATIENTS

Standard definition of glucose abnormalities	
Hyperglycemia	>140mg/dl(7.8mmol/L)
Admission HbA1c value	≥6.5%(suggests that diabetes preceded hospitalization)
Hypoglycemia	previously defined as blood glucose <70mg/dl(3.9mg/L), and now define clinically significant hypoglycemia as blood glucose <54mg/dl (3.0mg/L)
Severe hypoglycemia	previously <40mg/dl (2.2mmol/L), and now it is defined as that associated with severe cognitive impairment regardless of blood glucose level

GLYCEMIC TARGET IN PREGNANCY

Glucose monitoring

- Fasting ≤95mg/dl (5.3mmol/L) and either
- One-hour postprandial ≤140mg/dl (7.8mmol/L) or
- Two-hour postprandial ≤120mg/dl (6.7mmol/L)

BEDSIDE BLOOD GLUCOSE MONITORING

- In the patients with regular meal, glucose monitoring should be performed before meal.
- In the patients with enteral/parenteral nutrition, glucose monitoring is advised every 4-6 hours.
- More frequent blood glucose testing will range from every 30minutes to 2 hours in the patient with IV insulin infusion.

INSULIN THERAPY IN HOSPITALIZED PATIENTS

Type of patients	Insulin therapy
Critical care setting	Continuous IV insulin infusion
Outside of critical care units	Scheduled insulin regimens (regimens using insulin analogue and human insulin result in similar glycemic control)
With no meal or continuous enteral/parenteral nutrition	Rapid- or short-acting insulin before meals or every 4-6 hours
Noncritically ill patients with poor oral intake or those who are taking nothing by mouth	Basal insulin or a basal plus bolus correction insulin regimen
Noncritically ill patients with good nutritional intake	An insulin regimen with basal, nutritional, and correction components

MODERATE VERSUS TIGHT GLYCEMIC CONTROL

- Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold **≥180mg/dl (10.0mmol/L)**.
- Once insulin therapy is started, a target glucose range of **140-180mg/dl (7.8-10.0mmol/L)** is recommended for the majority of critically ill and noncritically ill patients.
- More significant goals, such as **<140mg/dl (7.8mmol/L)**, may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia.
- Conversely, higher glucose ranges may be acceptable in terminally ill patients, those with severe comorbidities, and in inpatient care setting where frequent glucose monitoring or close nursing supervisions not feasible.

ANTIHYPERGLYCEMIC AGENTS IN HOSPITALIZED PATIENTS

- In most instances in the hospital setting, insulin is the preferred treatment for glycemic control.
- However,, in certain circumstances, it may be appropriate to continue home regimens including oral antihyperglycemic medications.
- If oral medications are held in the hospital, there should be a protocol for resuming them 1-2days before discharge.

CHOICE OF TYPE OF INSULIN

Types of Insulin

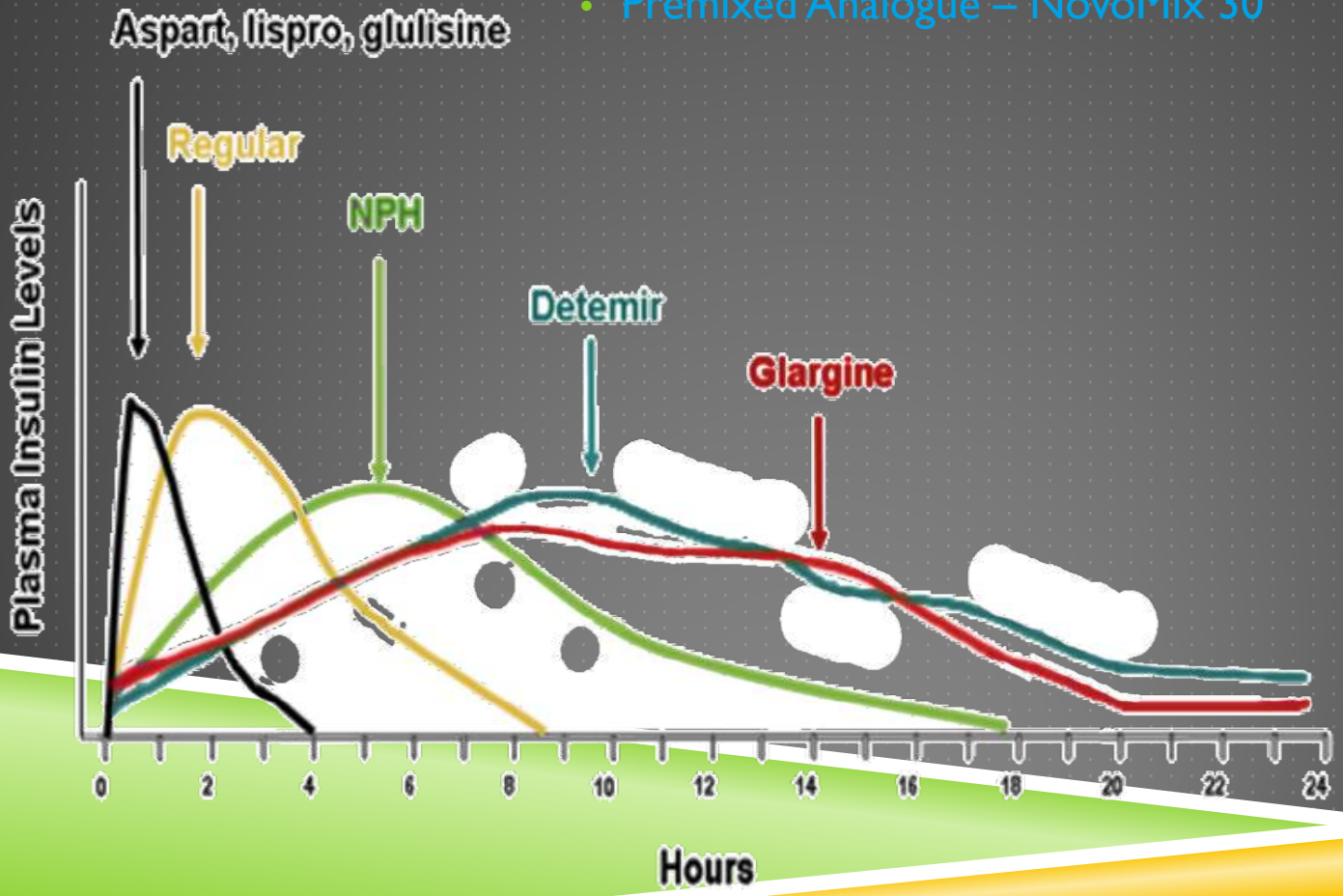
Classified on the basis of

- Species - Bovine/Porcine/Human
- Purity – Human Monocomponent
- Action Profile - short, intermediate & long acting
- Strength - 100 i.u/ml & 300 i.u/ml

Species and purity - the most important determinants of antigenicity

Types of Insulin

- Short-acting – Regular (Actrapid)
- Intermediate – NPH
- Premixed – Mixtard 30
- Rapid-acting - Humalog®, NovoRapid®, Apidra
- Long-acting - Glargine (Lantus), Detemir (Levemir)
- Premixed Analogue – NovoMix 30



SO.....WHAT ARE INSULIN ANALOGUES??

Molecules produced by genetic engineering wherein the amino acid sequence in human insulin is changed to alter its pharmacokinetics. However, they bind to insulin receptors in the same way as human insulin and produce similar effects

Also termed as:

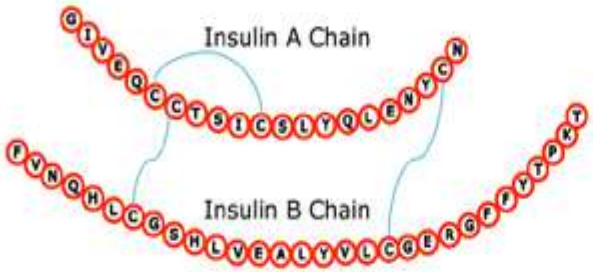
Designer Insulins

Insulin receptor ligands

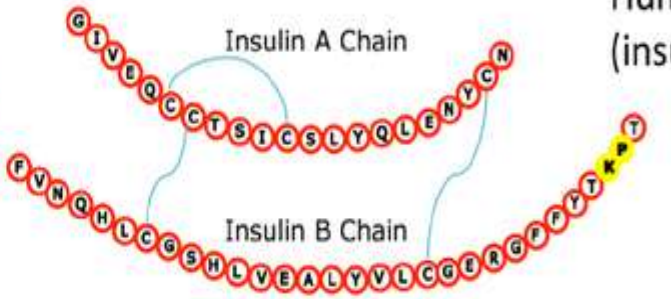
Democratic insulins

ARTS OF INSULIN ANALOGUE

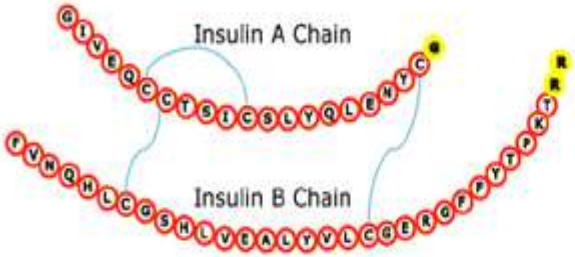
Human Insulin
MW 5808



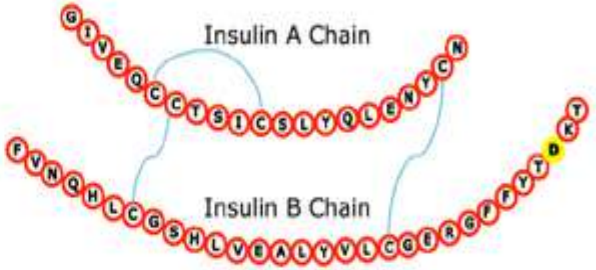
Humalog
(insulin lispro)



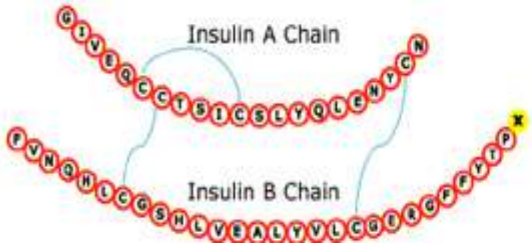
Insulin glargine
(Lantus®)
Avg MW 6063



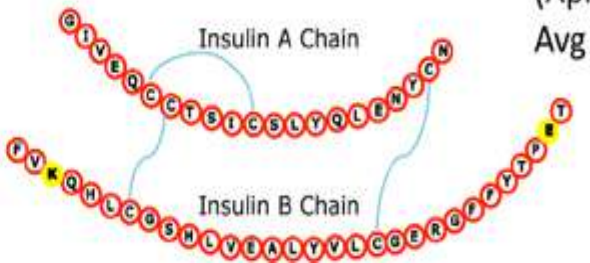
Insulin aspart
(NovoRapid)
Avg MW 5826



Insulin detemir
(Levemir®)
Avg MW 5917



Insulin glulisine
(Apidra®)
Avg MW 5823



PK/PD OF ANALOGUE INSULIN

Insulin	Onset Time (min)	Duration of Action (h)	Pregnancy Category
			Rapid-Acting (
Insulin lispro	10-15	4-6	B
Insulin aspart	10-15	4-6	B
Insulin glulisine	10-15	4-6	C
			Long-Acting
Insulin glargine	30-90	24-26	C
Insulin detemir	30-90	Up to 24	B
Insulin degludec	60	>42	C

min: minute; NA: not applicable; NPH: neutral protamine Hagedorn;
Source: References 9, 12-17.

INSULIN DEFICIENCY & DIABETES

- Type 1-absolute deficiency-insulin therapy essential to survive
- Type 2 DM-relative deficiency
  - loss of first phase
  - sluggish second phase

ABSOLUTE INDICATIONS FOR INSULIN

Regular or continuous Use

* Type 1 Diabetes
* Type 2 Diabetes with OAD failure
  - Primary
  - Secondary

Intermittent Use

* Type 2 diabetes during
  - major surgery
  - pregnancy, labour and delivery
  - myocardial infarction
  - acute infections
  - acute metabolic crisis like hyperosmolar coma and lactic acidosis
* Gestational diabetes mellitus

Life-saving in T1DM

Essential in T2DM

PHARMACOLOGICAL PROFILE OF DIFFERENT BASAL INSULINS

Basal insulin classification	Insulin preparation	Onset (hours)*	Peak (hours)	Duration (hours)	Within subject variability (CV%)	Timing of administration
Intermediate or long-acting	NPH	1-3	4-6	12-16	68	Usually taken once or twice daily
Long-acting analog	Glargine	0.5-2	Flat, no peak	~24	32-82	Usually taken once-daily at the same time every day
	Detemir	0.5-2	Flat, no peak	~20	27	Usually taken once or twice daily
	Degludec	NR	Flat, no peak	>42	20	Once-daily, any time of the daily
	LY2605541	NR	Flat, no peak	>36	<18	Once-daily
	U300	NR	Flat, no peak	>36	NR	Once-daily

Basal insulin regimen

Treatment	Dose
Initiation	10 Units or 0.2 U/kg/day at bed time
Monitoring	Fasting Plasma Glucose (FPG/FBS)
Optimization	Adjust insulin dose after 3 consecutive FBS (every 3-7 days) <80 mg% → reduce dose by 2 unit 80-110 mg% → maintain current dose >110 mg% → increase dose by 2 units

TIMING OF INJECTION IN ONCE DAILY BASAL INSULIN REGIMEN

- Administration of **NPH** in the evening appears to be superior to morning injection.(1,2)
- Studies examining the injection time of the **long-acting insulin analogs** showed conflicting results.
- One study conducted with **insulin glargine** found greater reductions in A1C and nocturnal hypoglycemia with morning compared with evening injection.(3)
- whereas a larger comparison of morning versus evening **glargine** with an identical study design did not find any difference (both studies investigated this issue against a background of glimepiride once daily).(4)
- A morning administration of **insulin detemir** was associated with lower glucose levels during the day and a trend toward a reduced risk of nocturnal hypoglycemia compared with evening injection.(5)

1. Hirsch IB. Insulin analogues. N Engl J Med 2005;352:174 –183.
2. N Engl J Med 1992;327:1426 –1433.
3. Ann Intern Med 2003;138:952–959.
4. Horm Metab Res 2006;38:172–177.
5. Clin Ther 2006;28:1569 –1581.

OTHER OPTIONS FOR THE INITIATION OF INSULIN THERAPY

Treating to Targets in Type 2 diabetes (4-T) study

- The **biphasic** and **prandial insulin** regimens provided better glycemic control than **once-daily basal insulin** (escalated to twice daily in 34% of patients) but at the expense of increased risks of hypoglycemia and weight gain.
- **Biphasic** insulin reduced A1C levels to the same extent as **prandial** insulin, the latter regimen was associated with the most hypoglycemic episodes and the highest weight gain (1).

1. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, Levy JC, Group TS. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med 2007;357:1716–1730.

INITIATION WITH PRANDIAL INSULIN IS GENERALLY NOT A FIRST-CHOICE APPROACH WHEN STARTING INSULIN IN TYPE 2 DIABETIC PATIENTS.

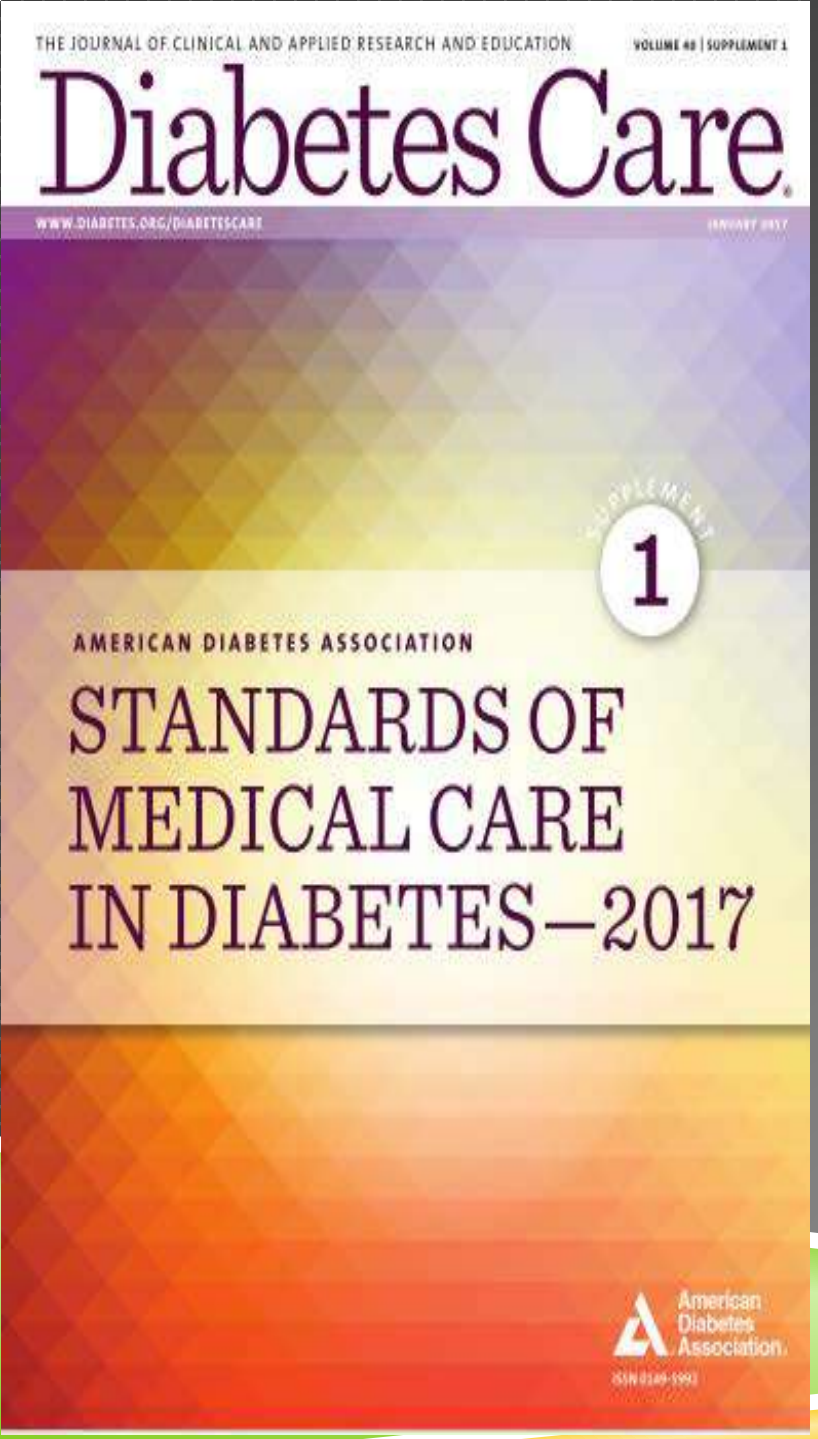
- To date there is no clinical trial evidence supporting the specific lowering of postprandial glucose levels when aiming to lower cardiovascular risk in type 2 diabetes. (1)
- A therapeutic regimen involving the addition of either basal or prandial insulin analogue is equally effective in lowering haemoglobin A1C.(2)

1. DIABETES CARE, VOLUME 32, SUPPLEMENT 2, NOVEMBER 2009.
2. Lancet 2008;371:1073–1084.

INITIATION WITH BIPHASIC INSULIN VS ONCE DAILY BASAL INSULIN

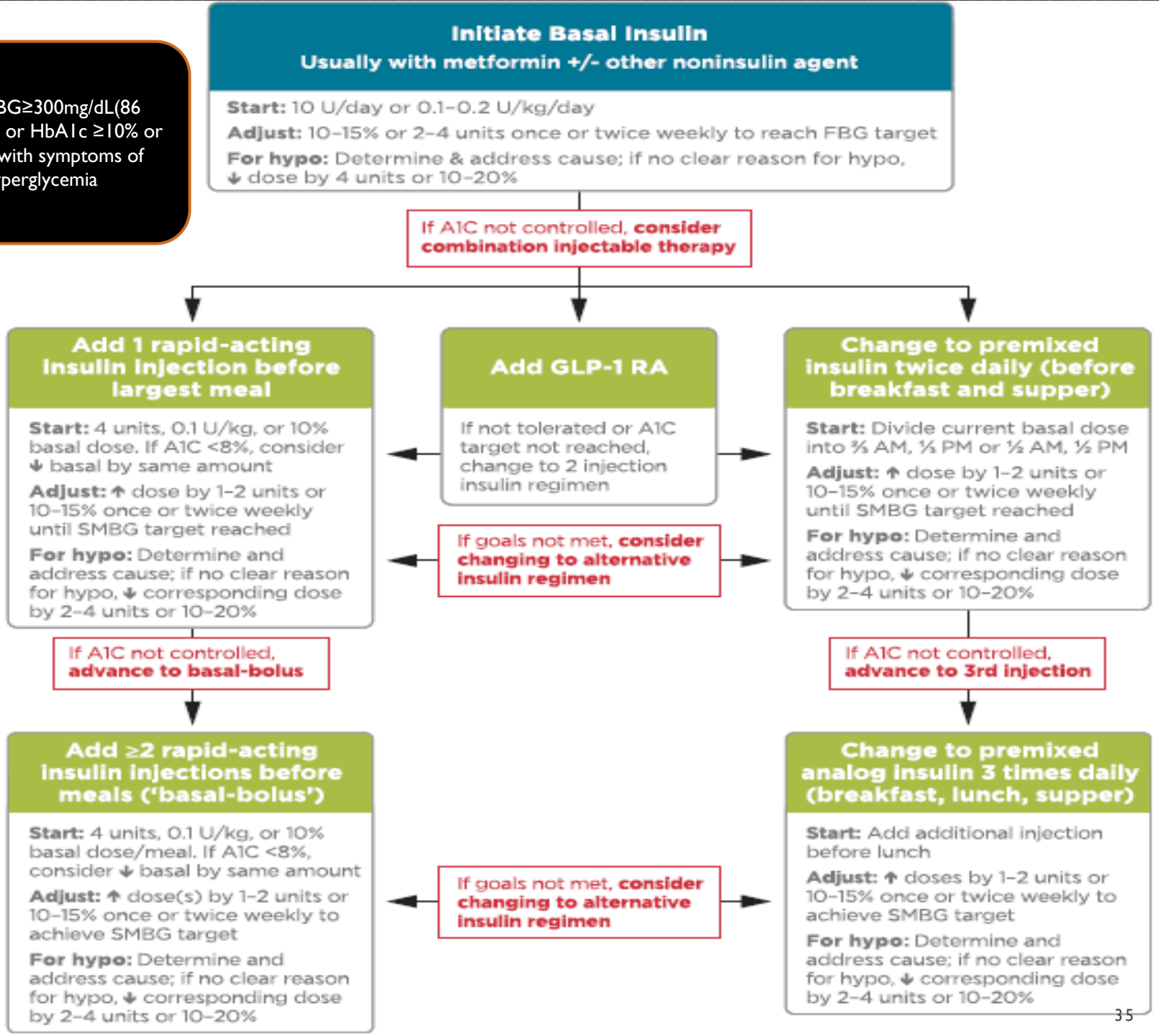
- The lower A1C levels reached with biphasic insulin comes at the expense of increased risks of hypoglycemia and weight gain.(1,2)
- Trials with systematic dose titration demonstrated that once-daily basal insulin achieves the currently recommended glycemic levels in many patients with type 2 diabetes. (3)
- LANMET study proved that A1C levels decreased from 9.1% at baseline to 7.1% with combination therapy of bedtime insulin glargine or NPH insulin and metformin.(4)
- Finally, it seems likely that insulin initiation by means of one (basal) injection may also facilitate patients' acceptance of insulin initiation.(5)

1. N Engl J Med 2007;357:1716– 1730.
2. Diabetes Care 2005;28:260 –265.
3. Diabetes Care 2003;26:3080 –3086
4. Diabetologia 2006;49:442– 451.
5. DIABETES CARE, VOLUME 32, SUPPLEMENT 2, NOVEMBER 2009.



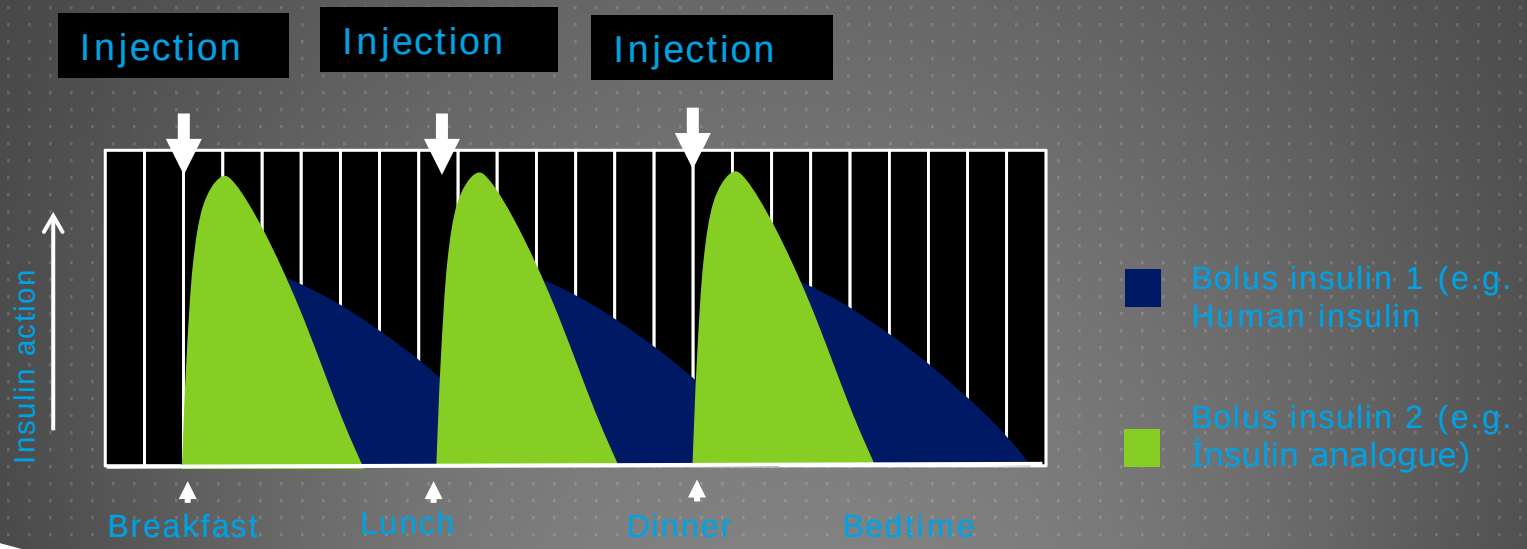
- Consider initiating combination insulin injectable therapy when blood glucose is ≥300 mg/dL (16.7 mmol/L) or A1C is ≥10% (86 mmol/mol) or if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia).
- As the patient's glucose toxicity resolves, the regimen may, potentially, be simplified.

When BG≥300mg/dL(86 mmol/mol or HbA1c ≥10% or patient with symptoms of hyperglycemia



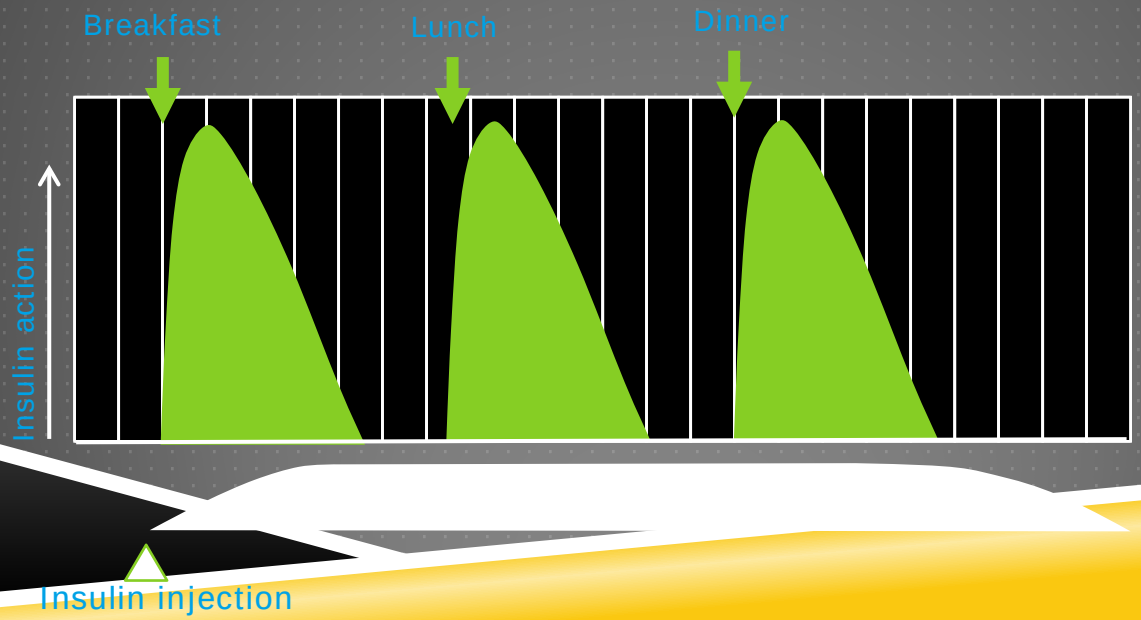
BOLUS INSULIN REGIMEN

- Short-acting: prandial blood glucose control
- Profile depends on insulin used



BASAL–BOLUS REGIMEN

- Short- *and* long- (intermediate-) acting components to control prandial and between-meal blood glucose
- Four or five daily injections
  - Short-acting: one at each of three mealtimes
  - Long-acting: one or two for control between meals
- Used by few type 2 patients, mostly those with severe β-cell failure
- Typical regimen for type 1 patients

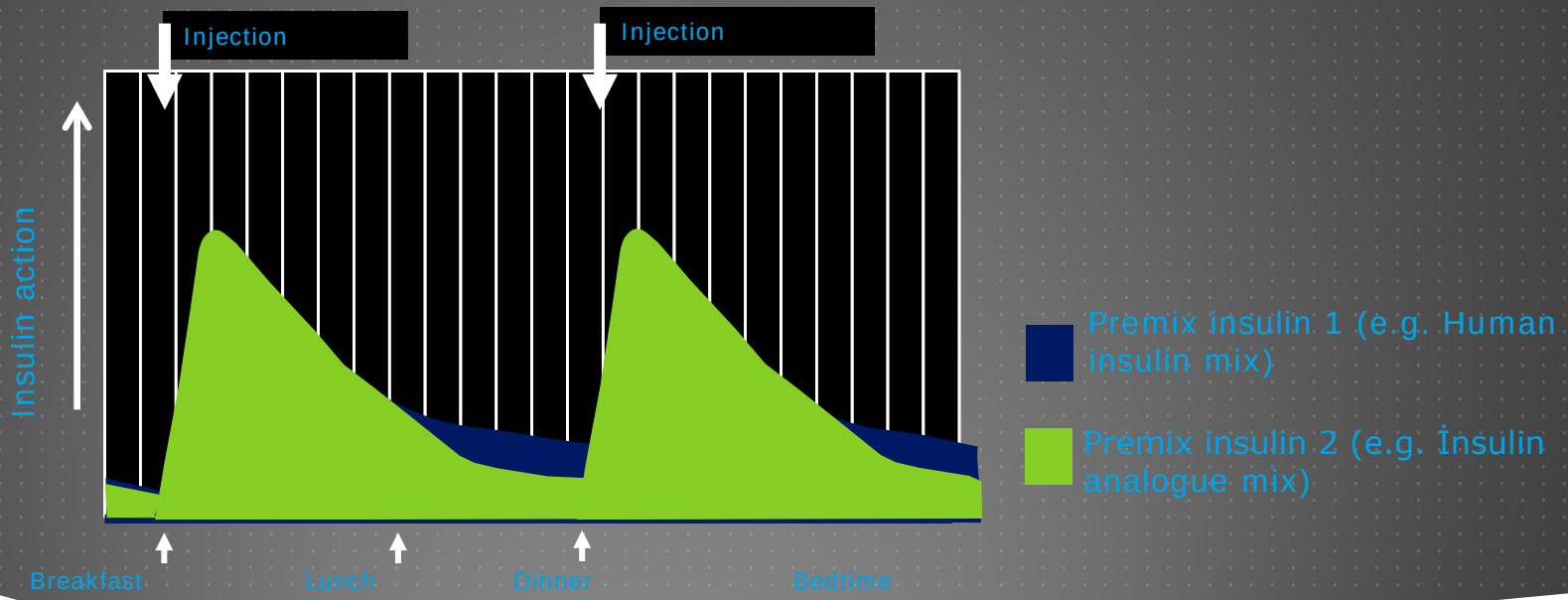


Basal-Bolus insulin regimen

Treatment	Dose
Initiation	60% of TDD is Regular and 40% of TDD is Basal 20% of TDD for each meal and 40% at Pre-Dinner or Bed-time
Monitoring	4-5 times Self Monitoring of Blood Glucose (SMBG)
Optimization	Depends on SMBG and dose adjustment should be individualized
Intensification	Basal-Bolus regimen

PREMIXED INSULIN REGIMEN

- A mix of short- *and* long- (intermediate-) acting insulins: control prandial and between-meal blood glucose
- Profile depends on insulins used and the proportions



Premixed insulin regimen

Treatment	Dose
Initiation	10 Units or 0.2 U/kg/day at pre-dinner (OD) and divide the total daily dose 2/3 in the morning and 1/3 in the evening for human insulin and 50:50 of the dose for modern insulin
Monitoring	Fasting Plasma Glucose (FPG/FBS) (OD) Pre-Breakfast & Pre-Dinner glucose (BD)
Optimization	Adjust insulin dose after 3 consecutive Pre-Breakfast glucose (OD) Adjust morning dose with Pre-Dinner glucose and evening dose with Pre-Breakfast glucose → <80 mg% → reduce dose by 2 unit 80-130 mg% → maintain current dose >130 mg% increase dose by 2 units
Intensification	Basal-Bolus regimen

PATIENT CONCERNS ABOUT INSULIN

- Fear of injections
- Perceived significance of need for insulin
- Worries that insulin could worsen diabetes
- Concerns about hypoglycemia
- Complexity of regimens

DRAWBACKS OF INSULIN

1. Hypoglycaemia
2. Weight gain
3. Allergic Reactions –
   - Local redness, itching – self limiting, disappears with continuation of therapy
   - Systemic allergy – angioedema, anaphylaxis-rare, requires desensitization
4. Insulin lipoatrophy
5. Insulin Edema

BARRIERS

- Unaffordable
- Painful
- No capacity for injection
- No refrigerator

COMBINATION WITH ORAL ANTI-DIABETES

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

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PRINCIPLES OF THE AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

1.	Lifestyle therapy, including medically supervised weight loss, is key to managing type 2 diabetes.
2.	The A1C target must be individualized.
3.	Glycemic control targets include fasting and postprandial glucoses.
4.	The choice of therapies must be individualized on basis of patient characteristics, impact of net cost to patient, formulary restrictions, personal preferences, etc.
5.	Minimizing risk of hypoglycemia is a priority.
6.	Minimizing risk of weight gain is a priority.
7.	Initial acquisition cost of medications is only a part of the total cost of care which includes monitoring requirements, risk of hypoglycemia, weight gain, safety, etc.
8.	This algorithm stratifies choice of therapies based on initial A1C.
9.	Combination therapy is usually required and should involve agents with complementary actions.
10.	Comprehensive management includes lipid and blood pressure therapies and related comorbidities.
11.	Therapy must be evaluated frequently until stable (e.g., every 3 months) and then less often.
12.	The therapeutic regimen should be as simple as possible to optimize adherence.
13.	This algorithm includes every FDA-approved class of medications for diabetes.

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	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 Not Indicated CrCl < 30	Not Effective with eGFR < 45 / Genital Mycotic Infections	Dose Adjustment Necessary (Except Linagliptin)	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Possible Benefit	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
CARDIAC ASCVD	Benefit					Neutral	?		Safe		
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

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

If not at goal in 3 months proceed to Dual 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 and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

 DOI 10.4158/EP161682.CS

ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

A1C < 8%

TDD 0.1–0.2 U/kg

A1C > 8%

TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - **FBG** > 180 mg/dL: add 20% of TDD
  - **FBG** 140–180 mg/dL: add 10% of TDD
  - **FBG** 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - **BG** < 70 mg/dL: 10% – 20%
  - **BG** < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

***Glycemic Goal:**

- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

Glycemic Control Not at Goal*

INTENSIFY (Prandial Control)

Add GLP-1 RA

Or SGLT-2i
Or DPP-4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals
- Start: 10% of basal dose or 5 units

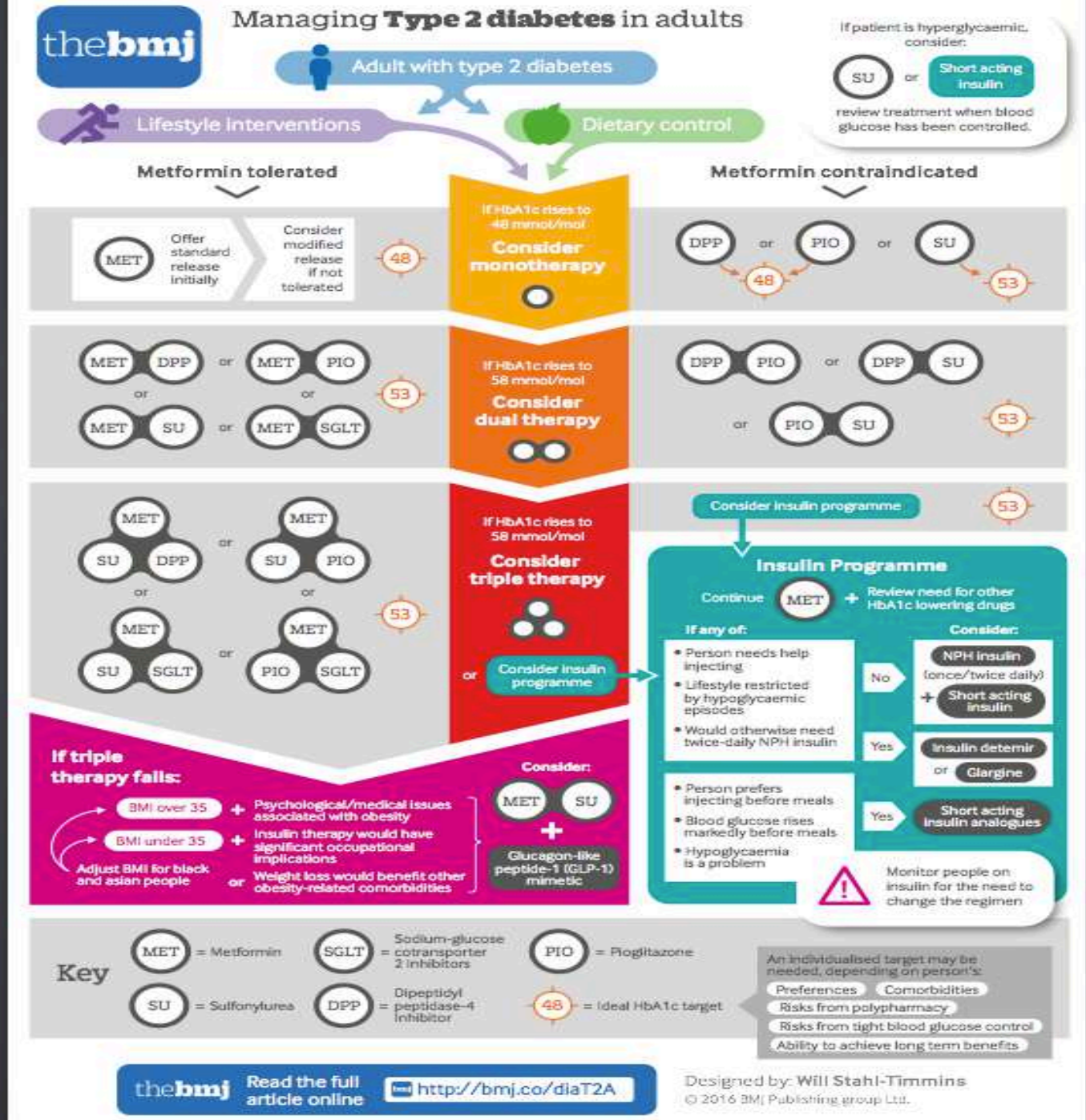
Basal Bolus

- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
- Start: 50% of TDD in three doses before meals

Insulin titration every 2–3 days to reach glycemic goal:

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%

 DOI 10.4158/EP161682.CS


thebmj
Managing Type 2 diabetes in adults
Adult with type 2 diabetes
Lifestyle interventions
Dietary control
If patient is hyperglycaemic, consider:
SU or Short acting insulin
review treatment when blood glucose has been controlled.
Metformin tolerated
Metformin contraindicated
MET
Offer standard release initially
Consider modified release if not tolerated
48
If HbA1c rises to 48 mmol/mol
Consider monotherapy
DPP or PIO or SU
MET DPP or MET PIO or MET SU or MET SGLT
53
If HbA1c rises to 58 mmol/mol
Consider dual therapy
DPP PIO or DPP SU or PIO SU
MET SU DPP or MET SU PIO or MET SU SGLT or MET PIO SGLT
If HbA1c rises to 58 mmol/mol
Consider triple therapy
or Consider insulin programme
Consider insulin programme
Insulin Programme
Continue MET + Review need for other HbA1c lowering drugs
If any of:
• Person needs help injecting
• Lifestyle restricted by hypoglycaemic episodes
• Would otherwise need twice-daily NPH insulin
Consider:
No
NPH insulin (once/twice daily) + Short acting insulin
Yes
Insulin determir or Glargine
• Person prefers injecting before meals
• Blood glucose rises markedly before meals
• Hypoglycaemia is a problem
Yes
Short acting insulin analogues
Monitor people on insulin for the need to change the regimen
If triple therapy fails:
BMI over 35 + Psychological/medical issues associated with obesity
BMI under 35 + Insulin therapy would have significant occupational implications
Adjust BMI for black and asian people
or Weight loss would benefit other obesity-related comorbidities
Consider:
MET SU + Glucagon-like peptide-1 (GLP-1) mimetic
Key
MET = Metformin
SGLT = Sodium-glucose cotransporter 2 inhibitors
PIO = Pioglitazone
SU = Sulfonylurea
DPP = Dipeptidyl peptidase-4 inhibitor
48 = Ideal HbA1c target
An individualised target may be needed, depending on person's:
Preferences
Comorbidities
Risks from polypharmacy
Risks from tight blood glucose control
Ability to achieve long term benefits
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Designed by: Will Stahl-Timmins
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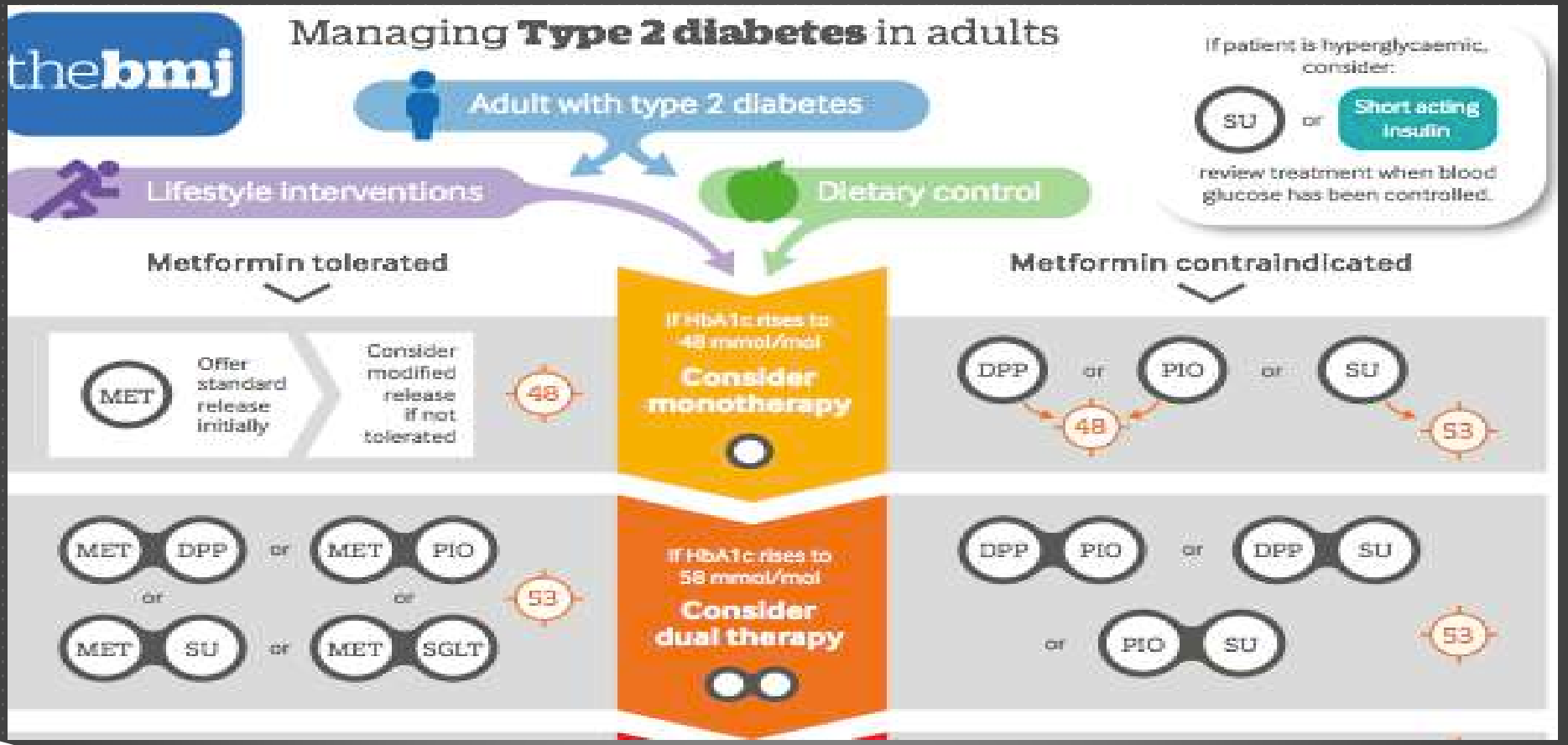
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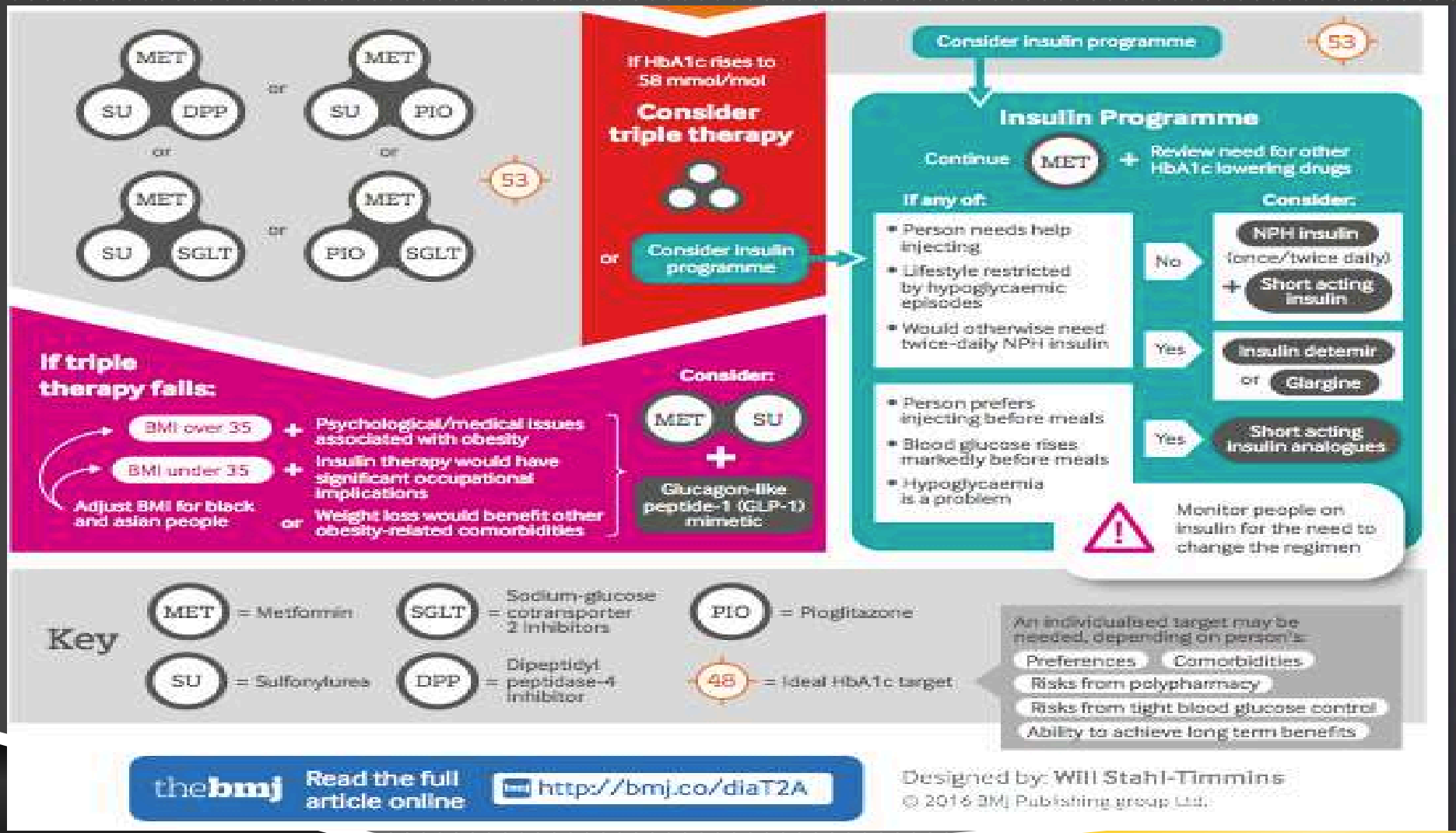
or
MET PIO
or
MET SU
or
MET SGLT
53
If HbA1c rises to 58 mmol/mol
Consider dual therapy
DPP PIO
or
DPP SU
or
PIO SU
53



GLYCEMIC MANAGEMENT(INITIAL)

Mild	Moderate	Severe
Mild or no symptoms	Hyperglycemia (FPG >150, RPG>250mg/dl)	Marked hyperglycemia(FPG> 250, RPG > 350mg/dl)
Negative ketones AND	HbA1c >7.0%	Significant weight loss
No acute concurrent illlness AND	Does not meet criteria for mild or severe	Severe/significant symptoms
HbA1c < 7.0%		DKA or Hyperosmolar state
		Severe intercurrent illness or surgery
Diet + PA	Metformin or other OHA	Insulin

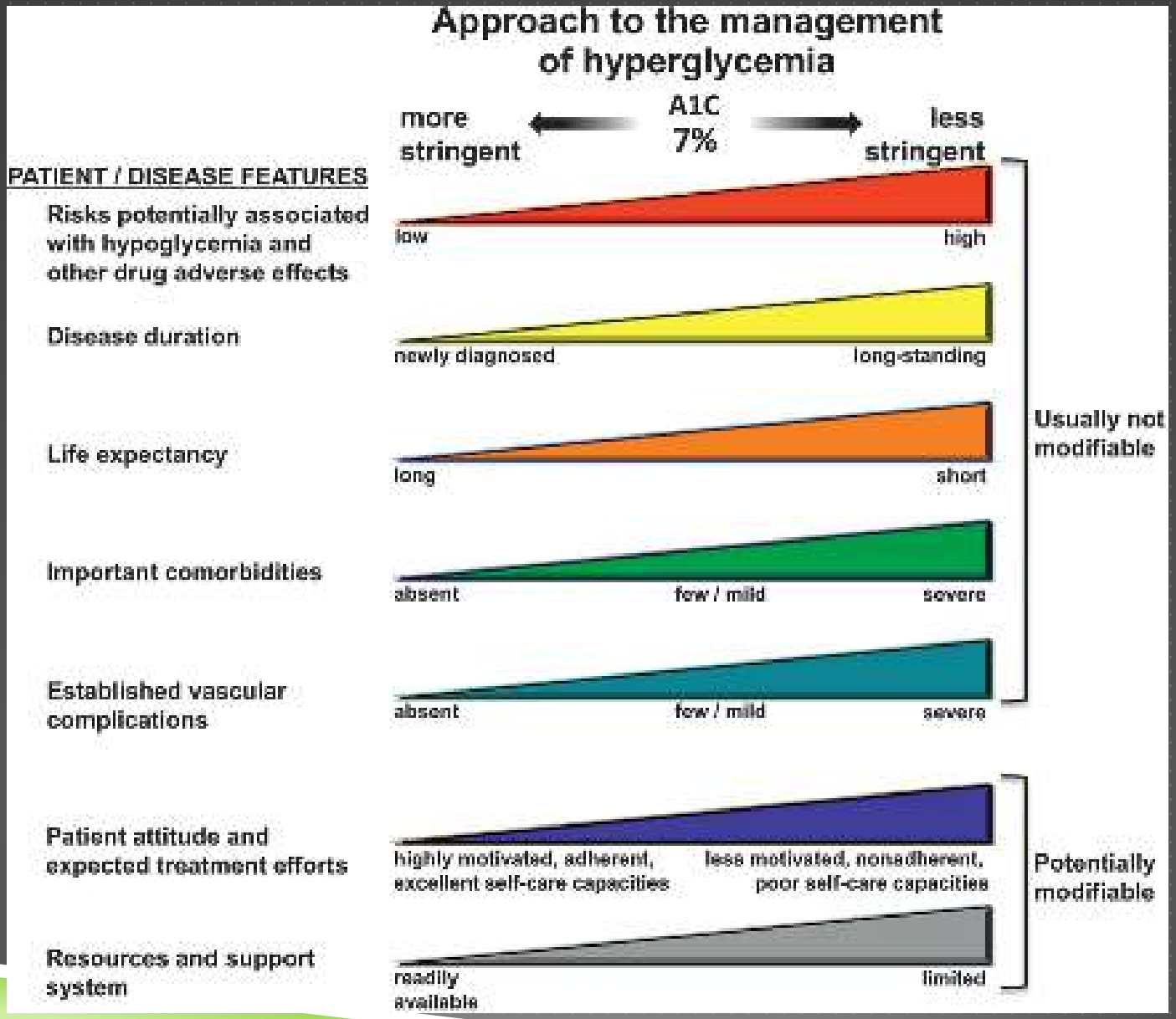


Figure —Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. Adapted with permission from Inzucchi et al. (53).

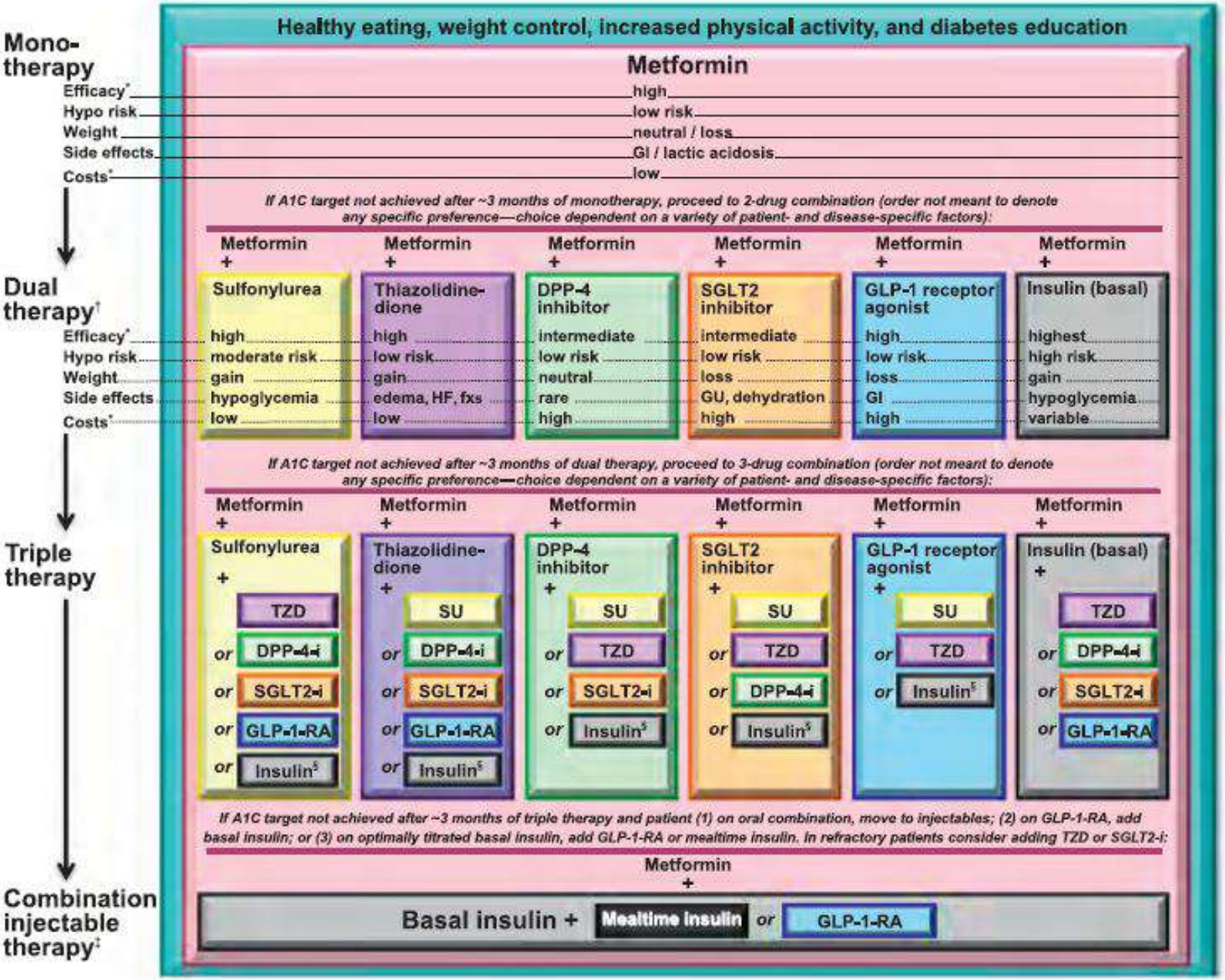


Figure — Antihyperglycemic therapy in type 2 diabetes: general recommendations .

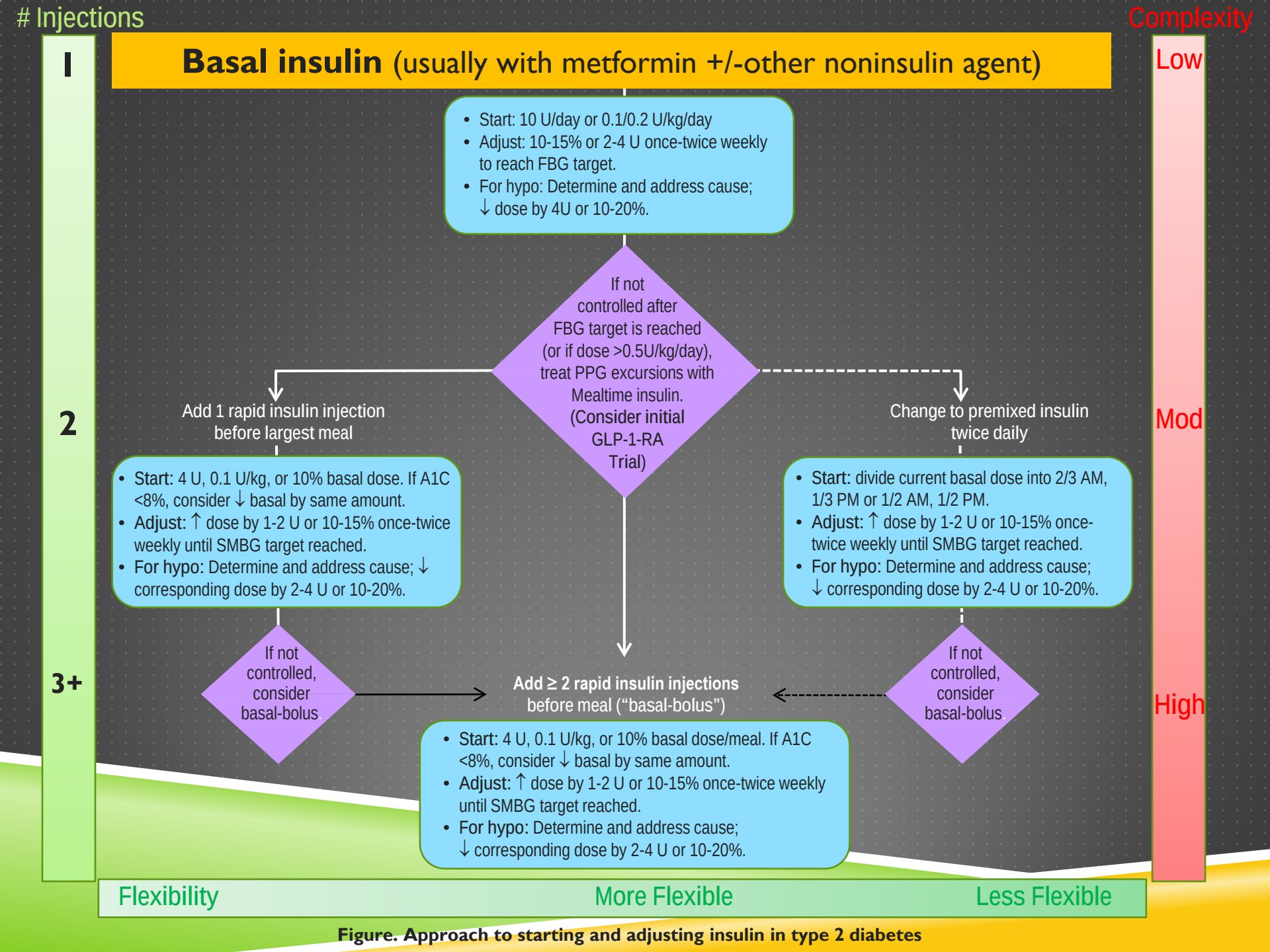
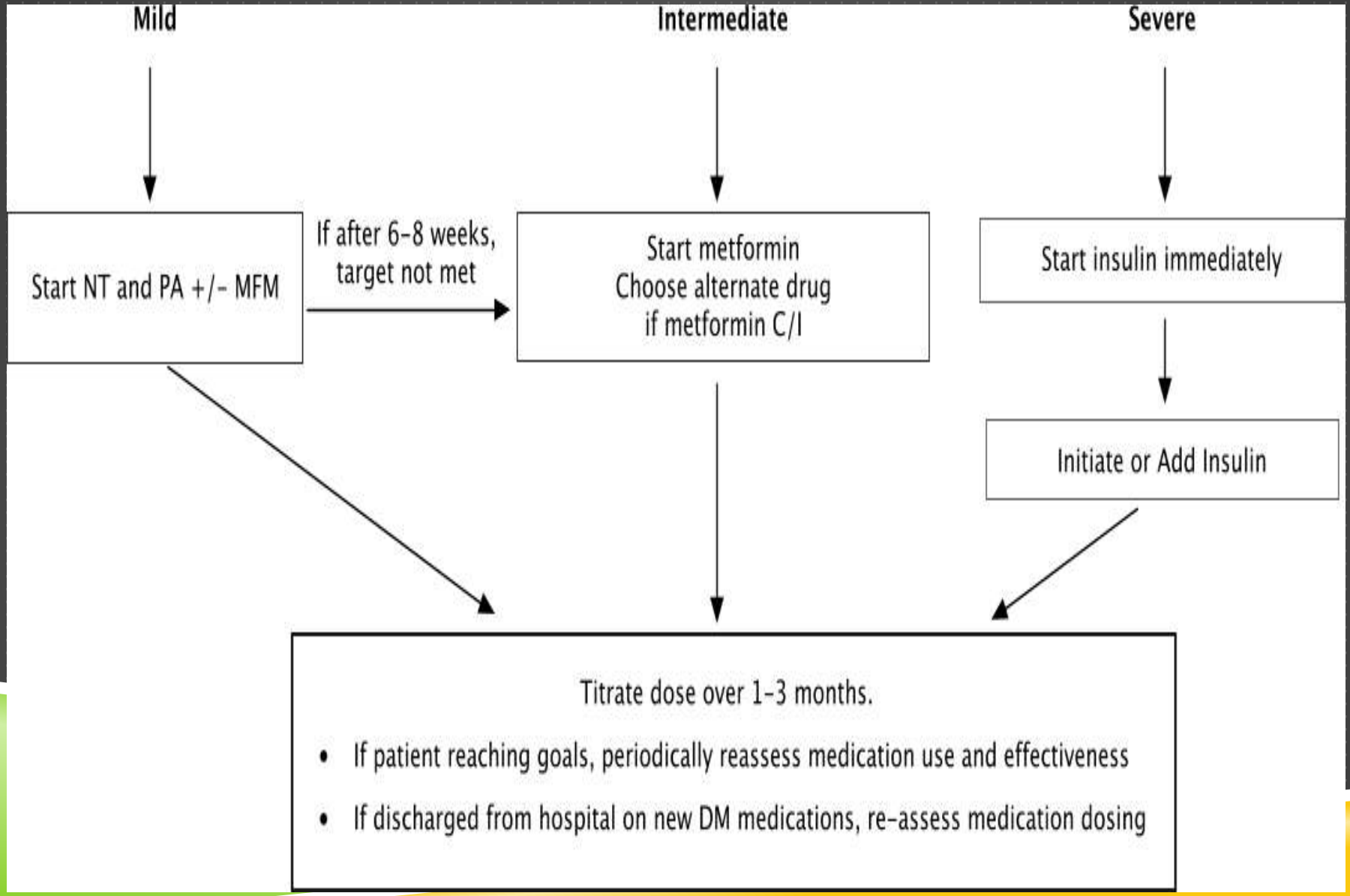


Figure. Approach to starting and adjusting insulin in type 2 diabetes

Initial Treatment Strategy

Joslin Diabetes Center & Joslin Clinic
Clinical Guideline for Pharmacological Management of Adults with Type 2 Diabetes
10/08/2016



INITIAL TREATMENT STRATEGY

INITIAL TREATMENT STRATEGY

Nutrition therapy (NT), physical activity, blood glucose monitoring and patient education are the cornerstones of diabetes management for all patients. Pharmacological management should be used in combination with nutrition therapy and physical activity. Current weight status and lifestyle should be considered when choosing initial pharmacological therapy.

Initial Presentation (Based on characteristics listed within each box)

Mild

- Mild or no symptoms *AND*
- Negative ketones *AND*
- No acute concurrent illness *AND*
- A1C ≤ 7.0%

→ Start NT and physical activity and consider addition of metformin

If after 6-8 weeks, target not met →

Intermediate

- Hyperglycemia (e.g. FPG > 150 mg/dl[2] or elevated random glucose > 250 mg/dl[2] AND/OR
- A1C > 7.0%[2]
- Does not meet criteria for mild or severe

→ Start metformin. Choose alternate drug if metformin is contraindicated

Severe

- Marked hyperglycemia (e.g. if FPG > 250 mg/dl, A1C >10%, random glucose >350 mg/dl) OR
- Significant weight loss *OR*
- Severe/significant symptoms *OR*
- 2+ or greater ketonuria *OR*
- DKA/ hyperosmolar state OR
- Severe intercurrent illness or surgery

→ Start insulin immediately [3]

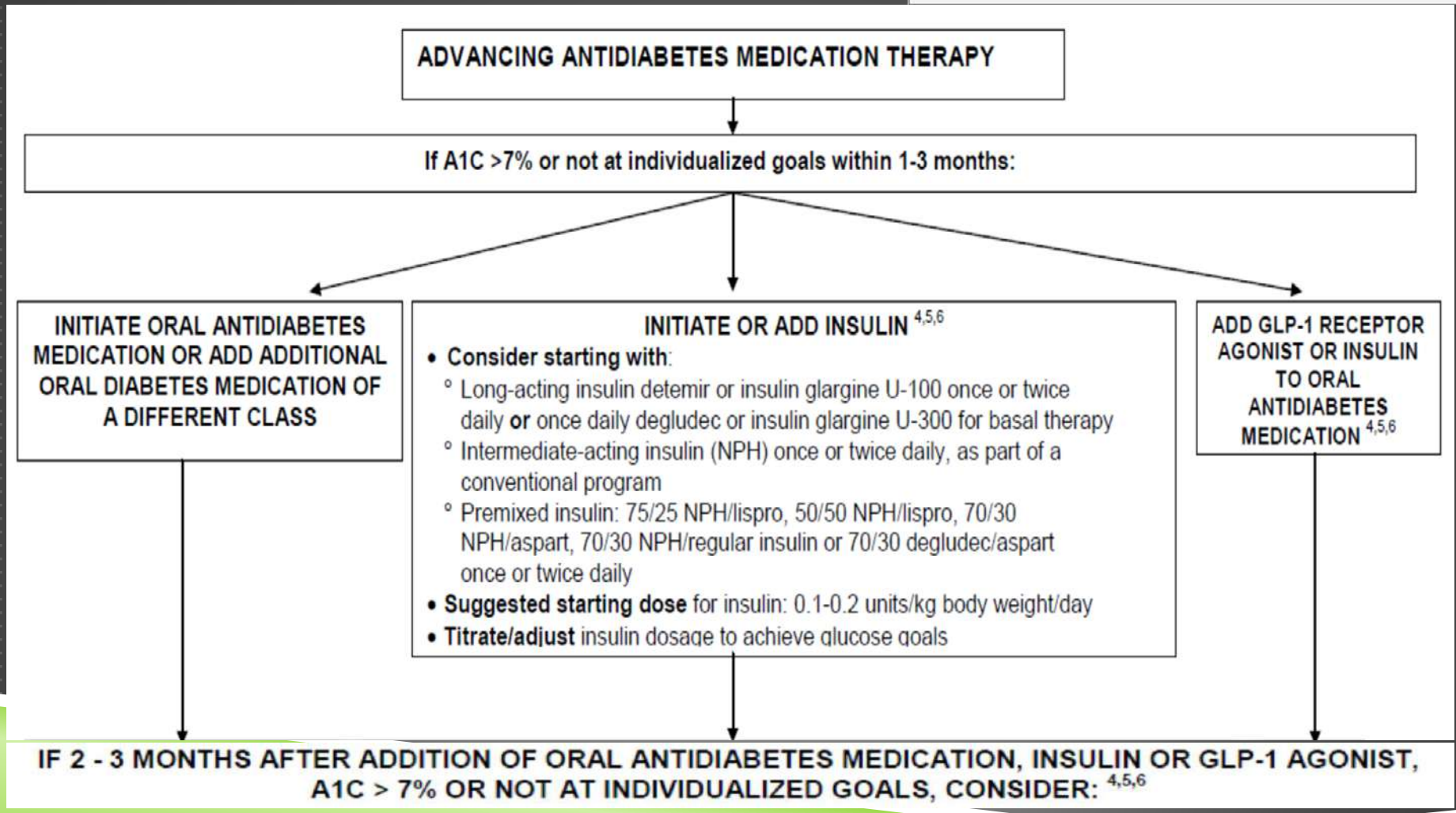
→ See page 3 section on "INITIATE OR ADD INSULIN"

Titrate dose over 1-3 months. Reinforce NT and physical activity

- If initial therapy results in the patient reaching goals, periodically reassess medication use and effectiveness
- If patient discharged from hospital on new diabetes medications, re-assess medication choices and dosing

See next page: ADVANCING ANTIDIABETES MEDICATION THERAPY

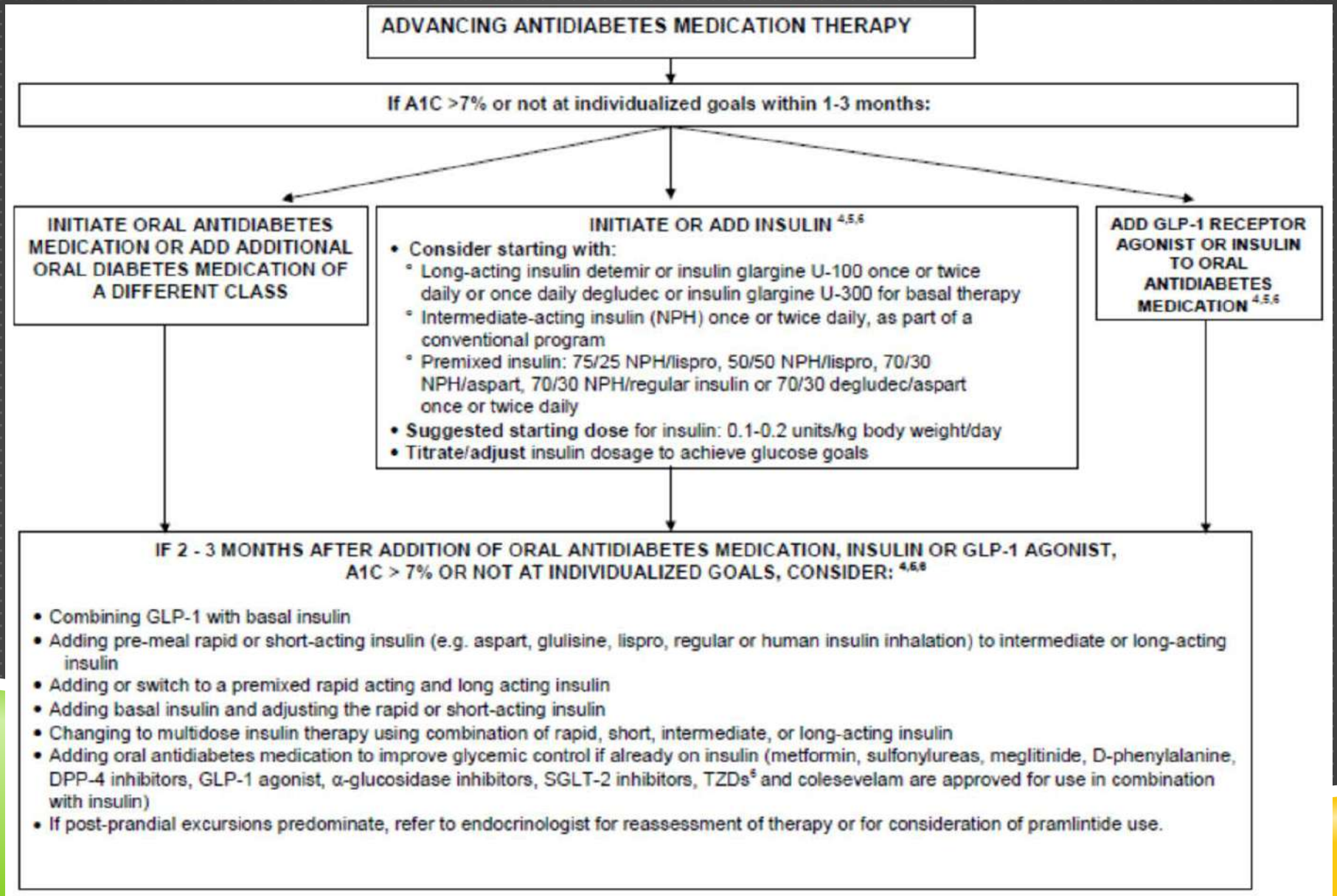
ADVANCED ANTIDIABETES MEDICATION THERAPY



- Combining GLP-1 with basal insulin
- Adding pre-meal rapid or short-acting insulin (e.g. aspart, glulisine, lispro, regular or human insulin inhalation) to intermediate or long-acting insulin
- Adding or switch to a premixed rapid acting and long acting insulin
- Adding basal insulin and adjusting the rapid or short-acting insulin
- Changing to multidose insulin therapy using combination of rapid, short, intermediate, or long-acting insulin
- Adding oral antidiabetes medication to improve glycemic control if already on insulin (metformin, sulfonylureas, meglitinide, D-phenylalanine, DPP-4 inhibitors, GLP-1 agonist, α-glucosidase inhibitors, SGLT-2 inhibitors, TZDs6 and colesevelam are approved for use in combination with insulin)
- If post-prandial excursions predominate, refer to endocrinologist for reassessment of therapy or for consideration of pramlintide use.

ADVANCED ANTIDIABETES MEDICATION THERAPY

Joslin Diabetes Center & Joslin Clinic
Clinical Guideline for Pharmacological Management of Adults with Type 2 Diabetes
10/08/2016



WRONG COMBINATION OF OHAS

- Same mechanism of action
- Same receptors
- More than one agent from the same class of drugs
- More than three agents simultaneously

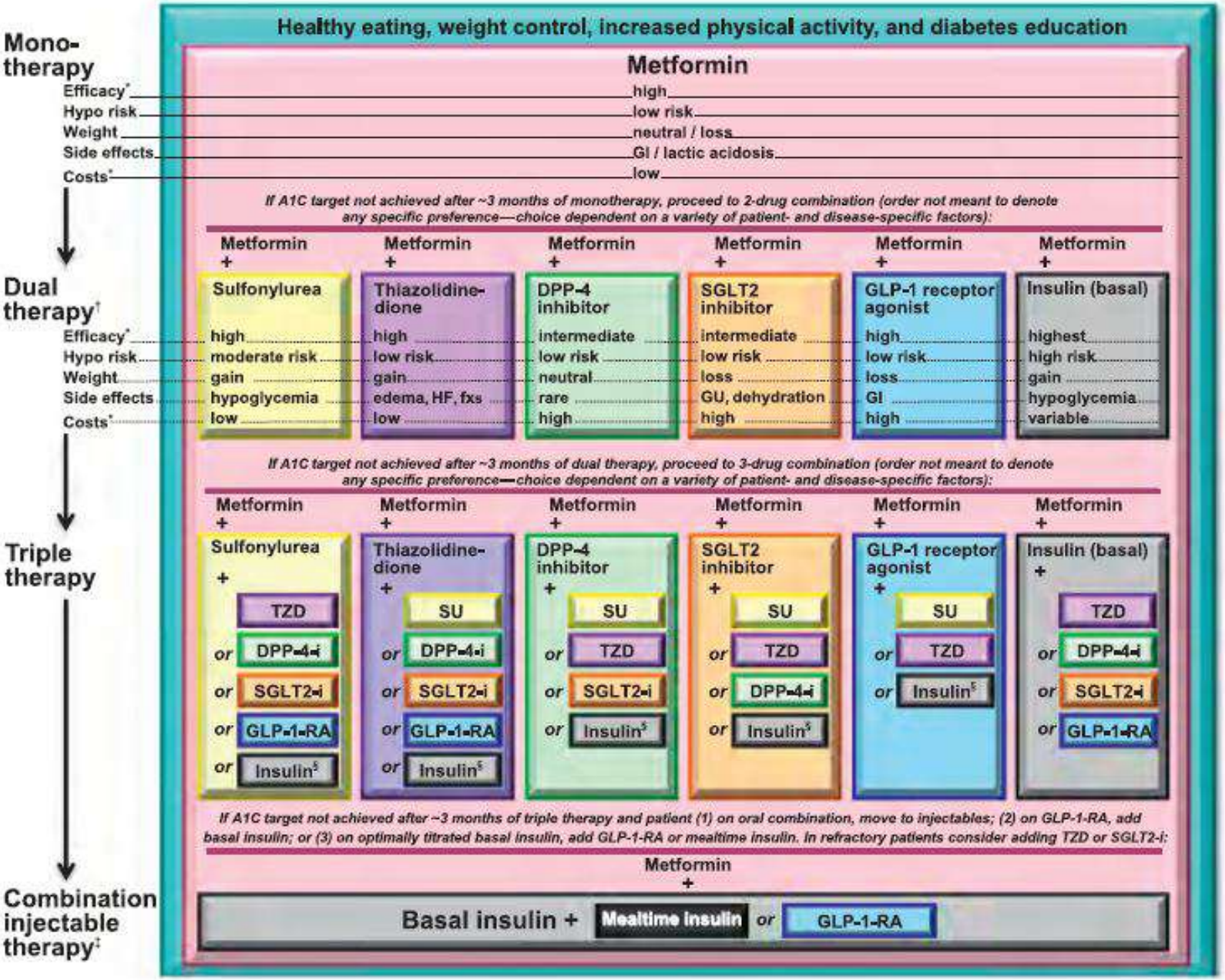


Figure — Antihyperglycemic therapy in type 2 diabetes: general recommendations .

WRONG INFORMATION OR BELIEFS

- Wrong belief about metformin
- Wrong belief about renal damage

THE HIGHER THE DOSAGE THE MORE EFFECTIVE THE TREATMENT

METFORMIN AND LACTIC ACIDOSIS

- With long-term use, fear of metformin-associated lactic acidosis initially blighted the use of metformin in some countries.

- However, a recent systematic review of prospective comparator trials and observational cohorts suggests that lactic acidosis is extremely rare, with a similar incidence in people with diabetes taking metformin or other glucose-lowering agents

METFORMIN AND RENAL DAMAGE

- Indeed, many people have suggested that the contraindication of metformin use in chronic kidney disease stage 3 and beyond (estimated GFR [eGFR] <60 ml min−1 [1.73 m]−2) is too restrictive.

- A further meta-analysis, however, supports the cautious use of metformin in individuals with chronic kidney disease with an eGFR as low as 30 ml min−1 [1.73 m]−2, with appropriate dose reductions and meticulous ongoing measurement of renal function

END STAGE OF DIABETES

Complications :

- DKA
- HONK

- Microvascular :
  - ✓ Retinopathy, cataract
  - ✓ Nephropathy
  - ✓ Peripheral neuropathy
  - ✓ Autonomic neuropathy
  - ✓ Foot disease

- Macrovascular :
  - ✓ Coronary circulation
  - ✓ Cerebral circulation
  - ✓ Peripheral circulation

No other treatment options that lower the damage to eye, kidney, etc.

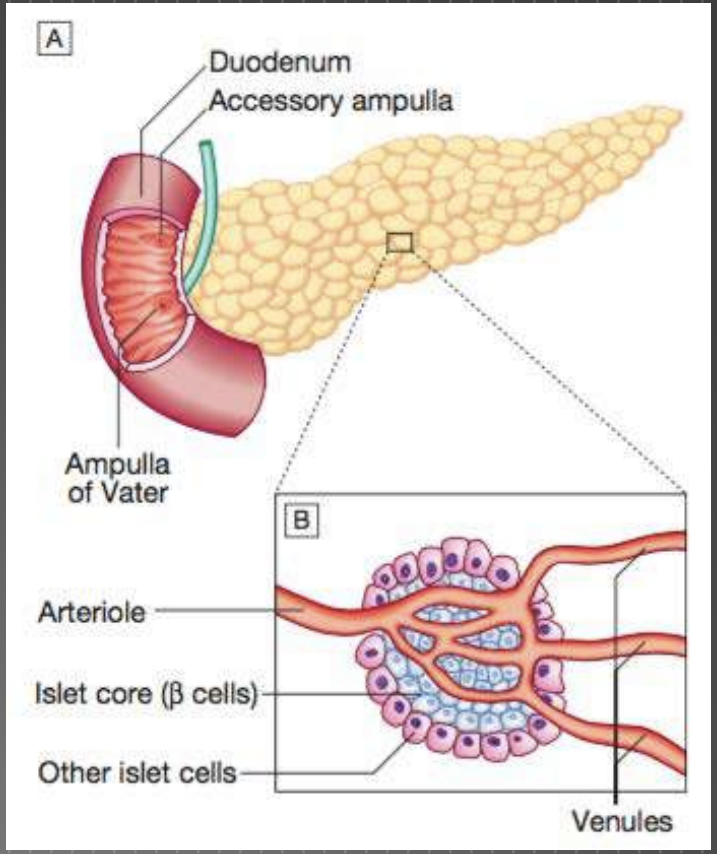
- **Renal disease** : End-stage renal failure (ESRF) **:** GFR <15 mL/min/1.73m^2 or need for renal replacement therapy (RRT—dialysis or transplant)

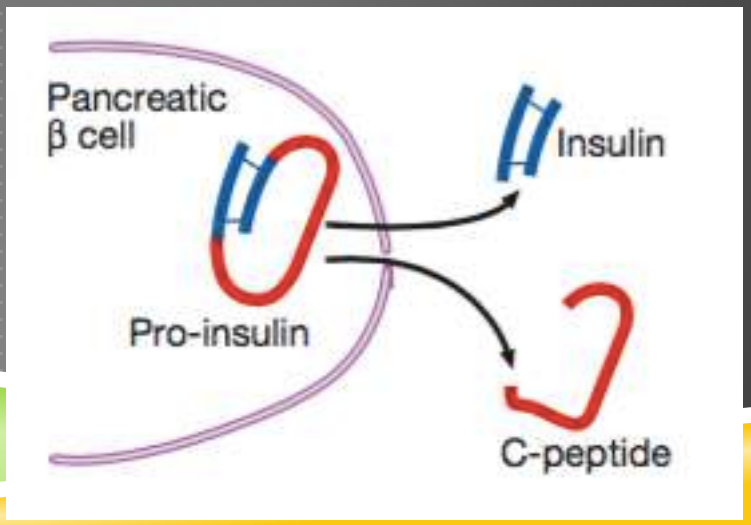
- **Liver Diseases** : Liver Transplant is required for
  - ✓ Acute fulminant hepatic failure of any cause, including acute viral hepatitis.
  - ✓ Chronic liver disease **:** usually for complications of cirrhosis, no longer responsive to therapy.
  - ✓ *Primary biliary cirrhosis* : Need transplant when serum bilirubin is persistently >100 µmol/L or symptoms such as itching are intolerable.
  - ✓ *Chronic hepatitis B if HBV DNA negative* or levels falling under therapy
  - ✓ *Chronic hepatitis C*

- **Heart disease** : Cardiac transplant for Stage D heart failure (Refractory symptoms requiring special intervention)

- **Lung disease** : *Single lung transplantation* is used for end-stage emphysema , Pulmonary fibrosis , Primary pulmonary hypertension, Cystic fibrosis, Bronchiectasis, Emphysema – particularly α1-antitrypsin inhibitor deficiency, Eisenmenger's syndrome.

- **Pancreas disease** :
- ✓ **Type I diabetes** is a T cell-mediated autoimmune disease involving destruction of the insulin-secreting β cells in the pancreatic islets. Progressive loss of β cell function takes place over a prolonged period (months to years), but marked hyperglycaemia, accompanied by the classical symptoms of diabetes, occurs only when **80–90% of the functional capacity of β cells has been lost.**
- ✓ Insulin treatment
- ✓ No need to do pancreas transplant





HYPOGLYCEMIA

- Plasma glucose ≤3mmol/L.

- Threshold for symptoms varies.

- **Symptoms :**

•*Autonomic*—Sweating, anxiety, hunger, tremor, palpitations, dizziness.

•*Neuroglycopenic*—Confusion, drowsiness, visual trouble, seizures, coma. Rarely focal symptoms, eg transient hemiplegia. Mutism, personality change, restlessness and incoherence may lead to misdiagnosis of alcohol intoxication or even psychosis.

Fasting Hypoglycemia

- **Ex**ogenous drugs, eg *insulin*, *oral hypoglycaemics*. Does she have access to these (diabetic in the family)? Body-builders may misuse insulin to help stamina. Also: *alcohol*, eg a binge with no food; *aspirin poisoning*; *ACE-i*; β-*blockers*; *pentamidine*; *quinine sulfate*; *aminoglutethamide*; insulin-like growth factor.
- **P**ituitary insuciency.
  Liver failure, plus some rare inherited enzyme defects.
  Addison's disease.
  Islet cell tumours (insulinoma) and immune hypoglycaemia (eg anti-insulin receptor antibodies in Hodgkin's disease).
  Non-pancreatic neoplasms, eg fibrosarcomas and haemangiopericytomas.

Post-prandial Hypoglycemia

- after gastric/bariatric surgery ('dumping'), and
- in type **2 DM**

Insulinoma :

Often benign (**90**–**95**%) pancreatic islet cell tumour is sporadic or seen with **MEN-1**. It presents as fasting hypoglycaemia, with Whipple's triad: **1** Symptoms associated with fasting or exercise **2** Recorded hypoglycaemia with symptoms **3** Symptoms relieved with glucose.

Other causes of hypoglycemia :

- Hypoglycaemia with other tumours
- Hepatic and renal causes of hypoglycaemia
- Endocrine causes of hypoglycaemia
- Drug-induced hypoglycaemia
- Alcohol-induced hypoglycaemia
- Factitious hypoglycaemia

HYPERINSULINAEMIA

- Due to insulin resistance associated with obesity, PCOS and the metabolic syndrome
- One of the diabetic risk factors for macrovascular complications

SOMOGYI AND DAWN PHENOMENON

- The somogyi effect (first discovered my Dr. Michael Somogyi) is caused by nighttime hypoglycemia, which leads to a rebound hyperglycemia in the early morning hours.
- When blood glucose drops during the night, hormones are released which trigger the liver to release stored glucose. This normally results in a high-fasting glucose reading the next morning.
- The Somogyi effect is a result of having extra insulin the body before bedtime, either from not having a bedtime snack, or from having your long-acting insulin not at the proper dose.
- The Somogyi effect occurs mainly with type 1 diabetics.

SOMOGYI PHENOMONON

SOMOgyi = **SO MO**ch insulin

Dawn = **Down** insulin

Normal glucose at night

↓

High Insulin given at 9pm

↓

Leads to hypoglycemia
At around 2-3pm

↓

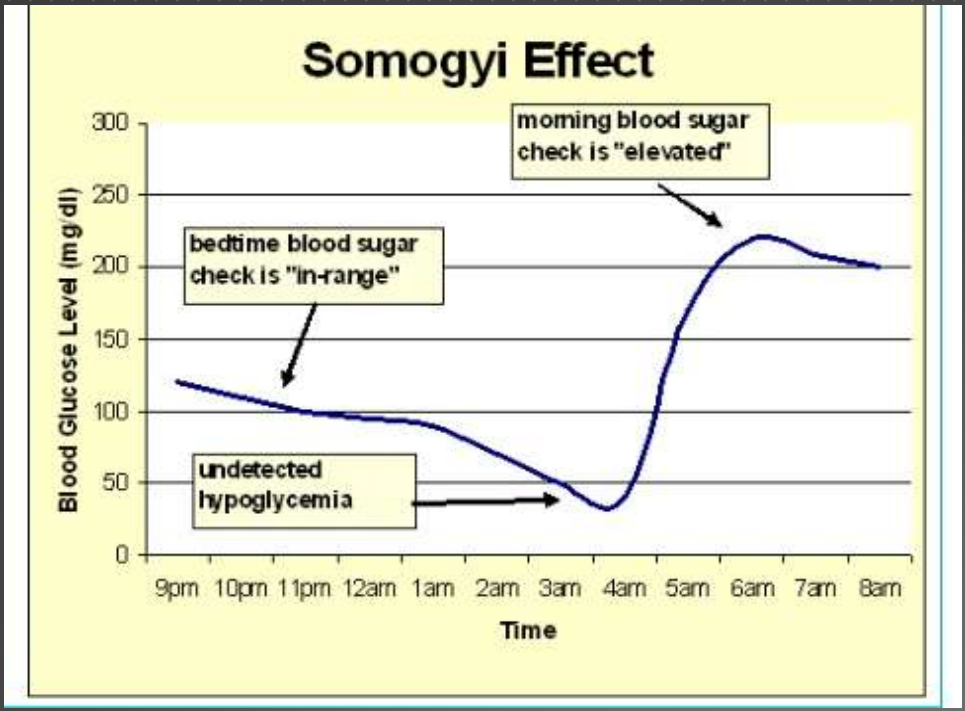
Due to hypoglycemic stress

↓

Glucagon and other stress
hormones are released

↓

Leads to hyperglycemia
In morning



- It is **similar to the dawn phenomenon** in that both lead to high morning blood glucose readings as a result of a hormone release that causes the liver to release glucose into the blood.
- **The difference is that dawn phenomenon is not caused by hypoglycemia, but by a random release of the triggering hormones.**

-Early morning (3-4am) hypoglycemia due to excess administration of Insulin at night but again at morning around 6-7am there will be hyperglycemia.

Explanation of 6am hyperglycemia is given below

When the blood glucose level falls below normal, the body responds by releasing the endocrine hormone glucagon as well as the stress hormones epinephrine, cortisol and growth hormone.

- Glucagon facilitates release of glucose from the liver that raises the blood glucose immediately, and
- the stress hormones cause insulin resistance for several hours, sustaining the elevated blood sugar.

TREATMENT OF SOMOGYI OR DAWN PHENOMENON

- Check blood glucose level at 2-3 am to identify whether it is Somogyi or Dawn effect (hypoglycemia in Somogyi and hyperglycemia in Dawn)
- Time for taking long-acting insulin is changed
- Consume extra dosage of insulin if there is a symptom of Dawn phenomenon

CONSIDERATION TO LIFE STYLE MODIFICATION

CONSIDERATION TO QUALITY OF LIFE AND DDS17

DIABETES DISTRESS SCALE (DDS17)

- Living with diabetes can sometimes be tough.
- There may be many problems and hassles concerning diabetes and they can vary greatly in severity.
- Problems may range from minor hassles to major life difficulties.
- Listed below are **17 potential problem areas that people with diabetes may experience.**
- Consider the degree to which each of the 17 items may have distressed or bothered **DURING THE PAST MONTH** and circle the appropriate number.

1. Polonsky, W.H., Fisher, L., Esarles, J., Dudl, R.J., Lees, J., Mullan, J.T., Jackson, R. (2005). Assessing psychosocial distress in diabetes: Development of the Diabetes Distress Scale. Diabetes Care, 28, 626-631.
2. Fisher, L., Hessler, D.M., Polonsky, W.H., Mullan, J. (2012). When is diabetes distress clinically meaningful? Establishing cut-points for the Diabetes Distress Scale. Diabetes Care, 35, 259-264.

	Not a Problem	A Slight Problem	A Moderate Problem	Somewhat Serious Problem	A Serious Problem	A Very Serious Problem
1. Feeling that my doctor doesn't know enough about diabetes and diabetes care.	1	2	3	4	5	6
2. Feeling that diabetes is taking up too much of my mental and physical energy every day.	1	2	3	4	5	6
3. Not feeling confident in my day-to-day ability to manage diabetes.	1	2	3	4	5	6
4. Feeling angry, scared and/or depressed when I think about living with diabetes.	1	2	3	4	5	6
5. Feeling that my doctor doesn't give me clear enough directions on how to manage my diabetes.	1	2	3	4	5	6
6. Feeling that I am not testing my blood sugars frequently enough.	1	2	3	4	5	6
7. Feeling that I will end up with serious long-term complications, no matter what I do.	1	2	3	4	5	6
8. Feeling that I am often failing with my diabetes routine.	1	2	3	4	5	6

	Not a Problem	A Slight Problem	A Moderate Problem	Somewhat Serious Problem	A Serious Problem	A Very Serious Problem
9. Feeling that friends or family are not supportive enough of self-care efforts (e.g. planning activities that conflict with my schedule, encouraging me to eat the "wrong" foods).	1	2	3	4	5	6
10. Feeling that diabetes controls my life.	1	2	3	4	5	6
11. Feeling that my doctor doesn't take my concerns seriously enough.	1	2	3	4	5	6
12. Feeling that I am not sticking closely enough to a good meal plan.	1	2	3	4	5	6
13. Feeling that friends or family don't appreciate how difficult living with diabetes can be.	1	2	3	4	5	6
14. Feeling overwhelmed by the demands of living with diabetes.	1	2	3	4	5	6
15. Feeling that I don't have a doctor who I can see regularly enough about my diabetes.	1	2	3	4	5	6
16. Not feeling motivated to keep up my diabetes self management.	1	2	3	4	5	6
17. Feeling that friends or family don't give me the emotional support that I would like.	1	2	3	4	5	6

DDS17 SCORING SHEET

The DDS17 yields a **total diabetes distress score plus 4 subscale scores**, each addressing a different kind of distress.1 To score, simply sum the patient's responses to the appropriate items and divide by the number of items in that scale.

Current research2 suggests that

- a mean item score 2.0 – 2.9 should be considered 'moderate distress,'
- a mean item score > 3.0 should be considered 'high distress.'
- Current research also indicates that associations between DDS scores and behavioral management and biological variables (e.g., A1C) occur with DDS scores of > 2.0.
- Clinicians may consider moderate or high distress worthy of **clinical attention, depending on the clinical context.**

1. Polonsky, W.H., Fisher, L., Esarles, J., Dudl, R.J., Lees, J., Mullan, J.T., Jackson, R. (2005). Assessing psychosocial distress in diabetes: Development of the Diabetes Distress Scale. Diabetes Care, 28, 626-631.
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Total DDS Score:	a. Sum of 17 item scores.	_____
	b. Divide by:	_____17_____
	c. Mean item score:	_____
	Moderate distress or greater? (mean item score > 2)	yes__ no__
A. Emotional Burden:	a. Sum of 5 items (2, 4, 7, 10, 14)	_____
	b. Divide by:	_____5_____
	c. Mean item score:	_____
	Moderate distress or greater? (mean item score > 2)	yes__ no__
B. Physician Distress:	a. Sum of 4 items (1, 5, 11, 15)	_____
	b. Divide by:	_____4_____
	c. Mean item score:	_____
	Moderate distress or greater? (mean item score > 2)	yes__ no__
C. Regimen Distress:	a. Sum of 5 items (6, 8, 3, 12, 16)	_____
	b. Divide by:	_____5_____
	c. Mean item score:	_____
	Moderate distress or greater? (mean item score > 2)	yes__ no__
D. Interpersonal Distress:	a. Sum of 3 items (9, 13, 17)	_____
	b. Divide by:	_____3_____
	c. Mean item score:	_____
	Moderate distress or greater? (mean item score ≥ 2)	yes__ no__

1. Polonsky, W.H., Fisher, L., Esarles, J., Dudl, R.J., Lees, J., Mullan, J.T., Jackson, R. (2005). Assessing psychosocial distress in diabetes: Development of the Diabetes Distress Scale. Diabetes Care, 28, 626-631.
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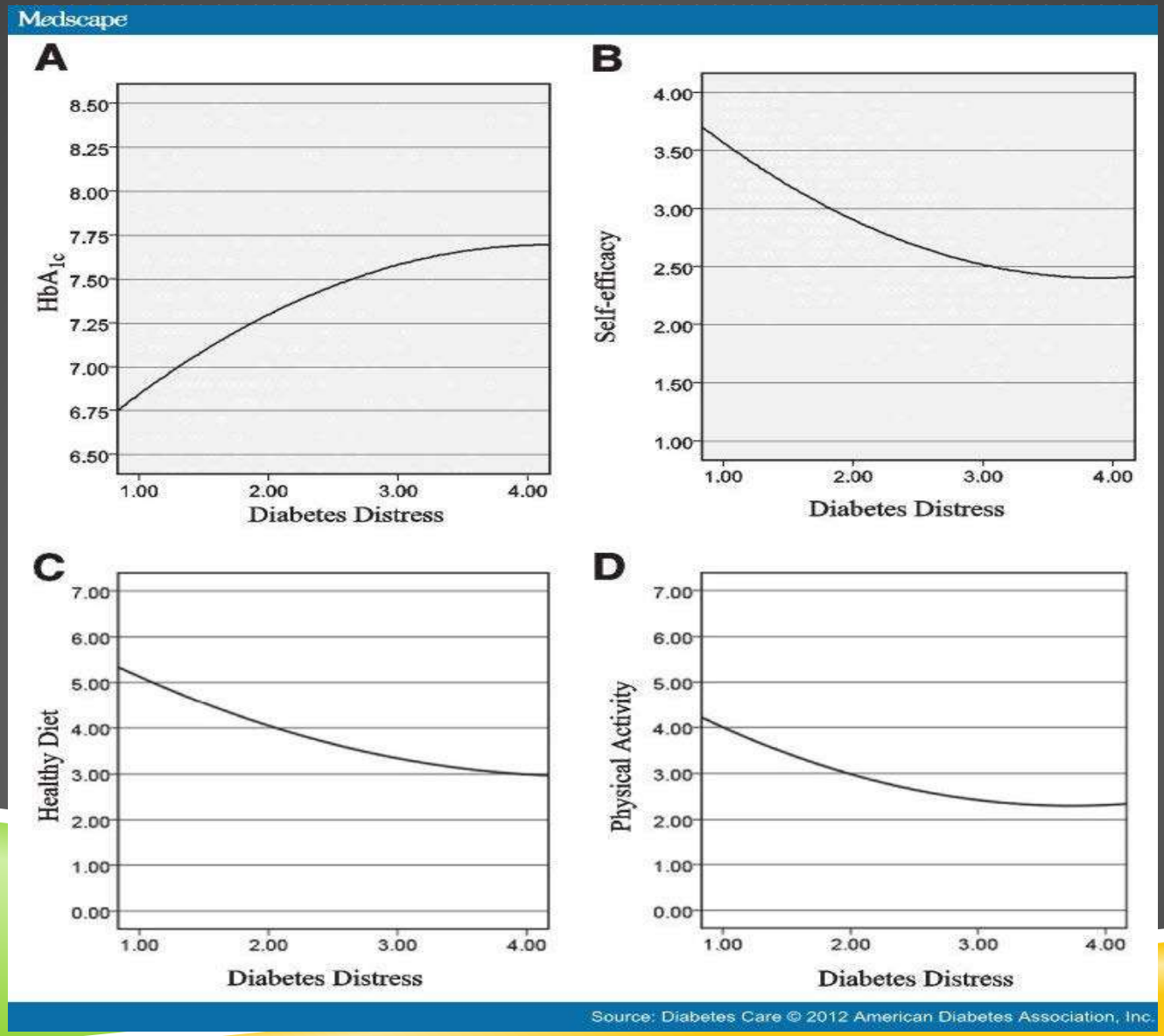
ASSOCIATIONS BETWEEN DDS17 SCORES AND KEY DIABETES VARIABLES



Quality of life

8+1 DIMENSION OF QUALITY OF LIFE

- Material living conditions
- Productive or main activity
- Health
- Education
- Leisure and social interaction
- Economic and physical safety
- Governance and basic rights
- Natural and living environment
- Overall experience of life

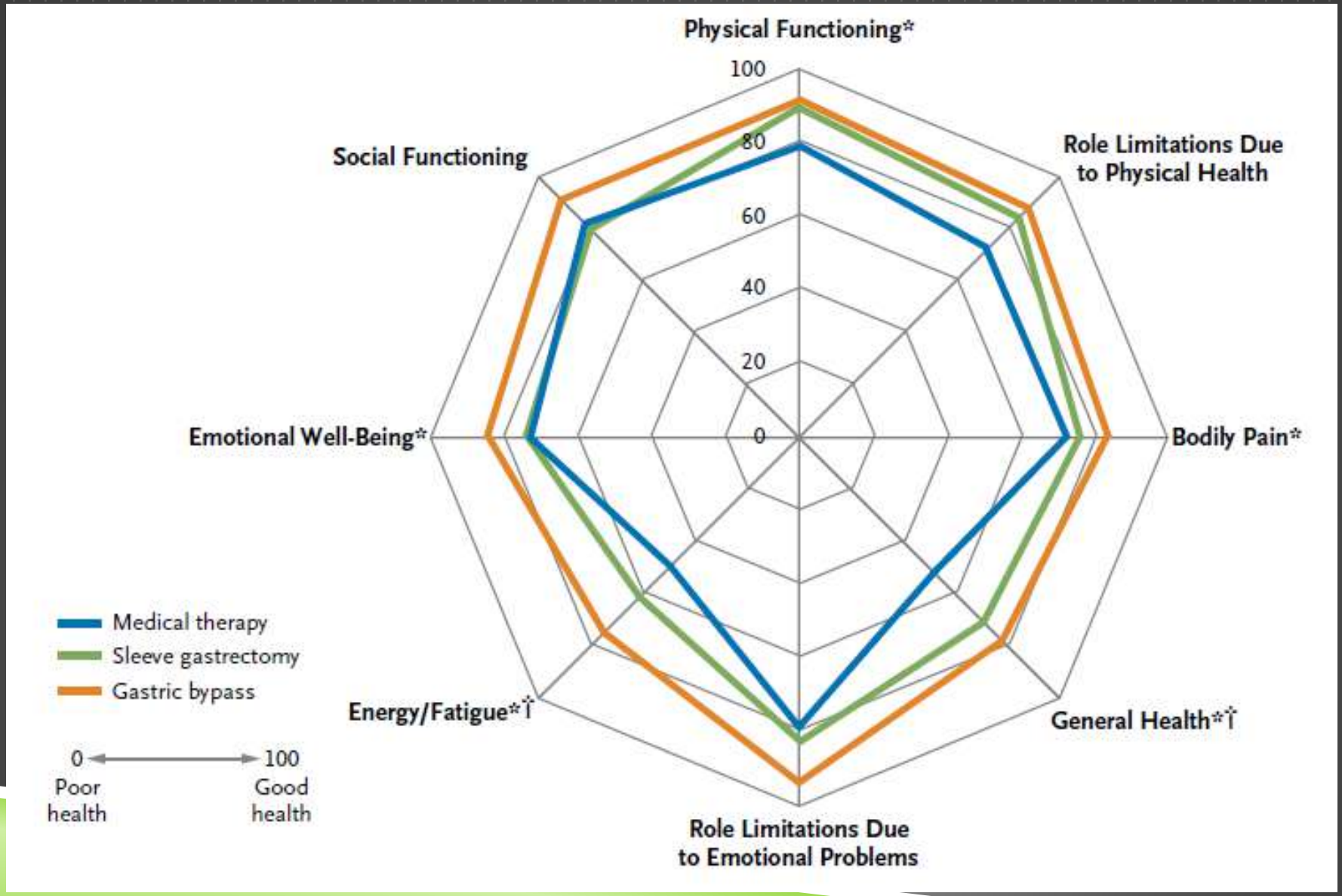
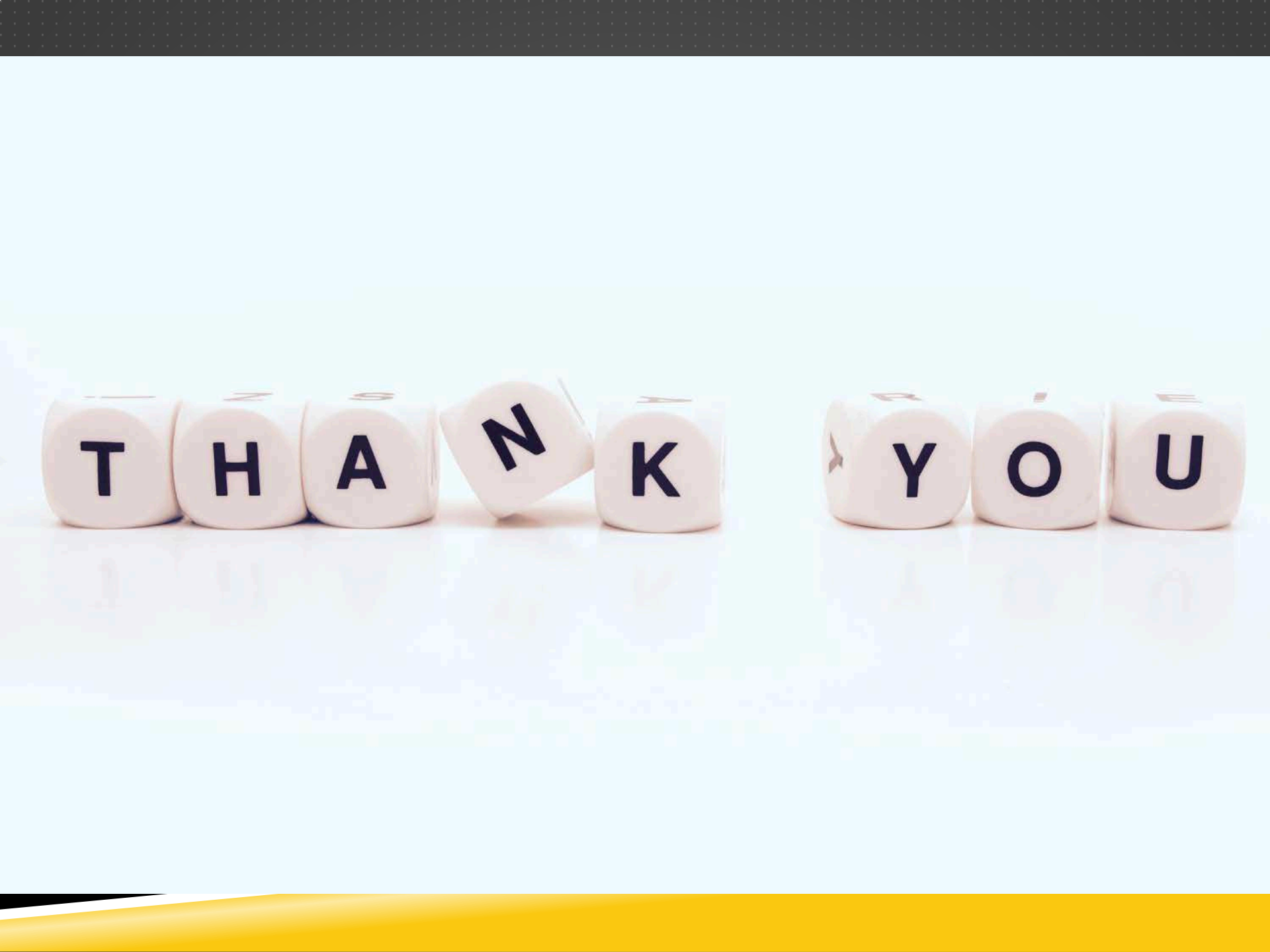


Fig (5): Other secondary end points favoring surgery over medical treatment.

DIABETES-RELATED DISTRESS


THANK YOU

HOW TO TREAT THE DAWN EFFECT

- Take long-acting insulin in the evening so its peak action happens when the blood sugars start rising.
- Change the type of insulin taken in the evening.
- Start incorporating a continuous glucose monitor (CGM) to avoid the dawn phenomenon
- Take a small amount of insulin overnight if blood sugar goes up during the night.
- Switch to an insulin pump, which can be programmed to automatically increase basal rates in the morning.

Sates and regions	Male	Female	Total
Yangon	3,769,778	4,166,859	7,936,637
Mandalay	3,021,814	3,367,577	6,389,391
Ayeyarwaddy	3,045,040	3,226,030	6,271,070
Shan	3,087,257	3,101,432	6,188,689
Sagai	2,590,664	2,900,506	5,491,170
Bago	2,336,464	2,582,357	4,918,821
Magway	1,814,230	2,127,009	3,941,239
Rakhine	1,572,956	1,727,083	3,300,039
Mon	955,744	1,055,683	2,011,427
Kachin	951,283	878,611	1,829,849
Taninthayi	724,536	735,417	1,459,953
Nay-pyi-daw	601,072	636,966	1,2388,038
Chin	243,326	265,033	508,359
Kayar	154,330	155,883	310,213
Total	**25,647,847**	**27,740,101**	**53,387,948**