Agenda

- Introduction
- Treatment goals
- Review of ADA-EASD guideline 2018-Insulin therapy

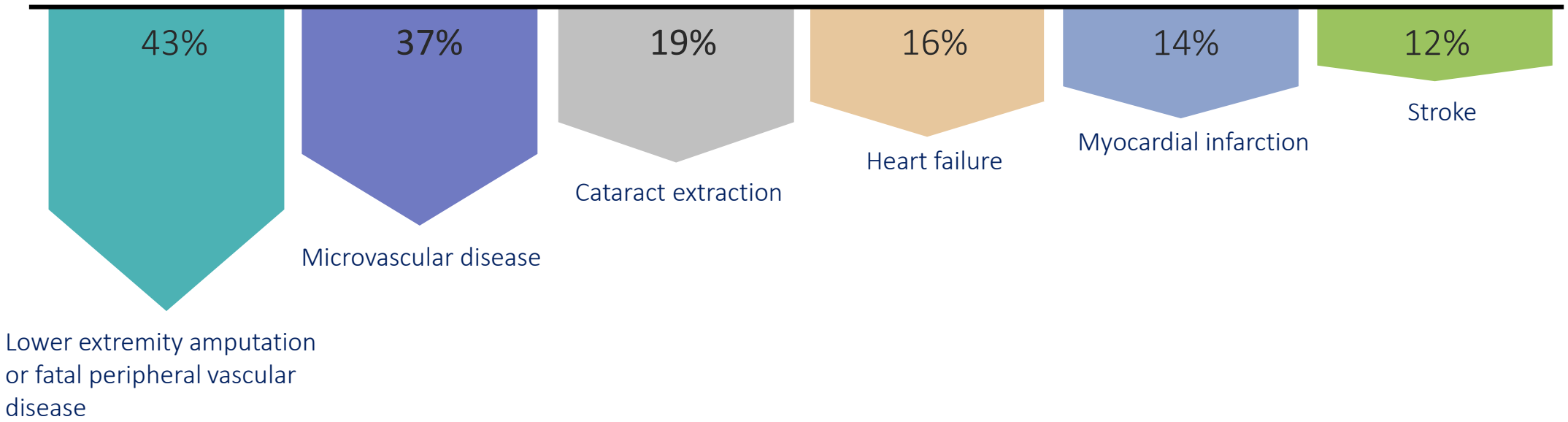
Introduction

Prevalence of DM

Dramatically rise over the past two decades, from an estimated 30 million cases in 1985 to 415 million in 2015 and that 642 million individuals will have diabetes by the year 2040.

Improving control reduces risks of long-term complications

Every 1% drop in HbA_{1c} can reduce long-term diabetes complications



UKPDS 35: Stratton et al. BMJ 2000;321:405–12.

Treatment goals

The Goals of Therapy

Eliminate symptoms related to hyperglycemia.

Reduce or eliminate the long-term microvascular and macrovascular complications.

Allow the patient to achieve as normal a lifestyle as possible.

The care of an individual with either type 1 or type 2 DM requires a multidisciplinary team:

Endocrinologist or diabetologist, a certified diabetes educator, a nutritionist, and a psychologist, neurologists, nephrologists, vascular surgeons, cardiologists, ophthalmologists, and podiatrists.

ADA / EASD 2018 consensus
Patient based Approach

"The selection of glycaemic targets and glucose-lowering treatments should be individualised on the basis of patient specific factors (age, stage of diabetes, cardiovascular risk factors, weight, risk associated with hypoglycaemia, etc.) and of effects on multiple pathophysiological aspects of type 2 diabetes"

Diabetes care 2015; 35:1364 -1379

Current glycaemic targets

Current HbA_{1c} goals include:

- ADA, EASD: **<7%**
- AACE, JDS **≤6.5%**

Current pre- and postprandial glucose goals include:

ADA

- Pre-meal: 80–130 mg/dL (5.0–7.2 mmol/L)
- Peak: <180 mg/dL (<10 mmol/L)

IDF

- Pre-meal: <110 mg/dL (<6.0 mmol/L)
- 1–2-h peak: <160 mg/dL (<9.0 mmol/L)

AACE, American Association of Clinical. Endocrinologists; JDS, Japan Diabetes Society

More Stringent HbA1c Targets <6.5%

Short disease duration.

Long life expectancy.

No significant CVD .

Type 2 diabetes treated with lifestyle or metformin only.

Less Stringent HbA1c Targets < 8.0

History of severe hypoglycemia.

Limited life expectancy.

Advanced complications.

Extensive comorbid conditions.

Guidelines:
ADA –EASD 2018

Diabetes Care 1

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

https://doi.org/10.2337/dci18-0033

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Despite over 200 years of research on lifestyle management of diabetes and more than 50 years of comparative effectiveness research in diabetes, in numerable un anaswerecd questions regarding the management of type 2 diabetes remain

Lifestyle interventions, including MNT and physical activity:

Effective and safe

for improving glucose control in type 2 diabetes

Medical Nutrition Therapy goals:

is to manage:

Blood glucose and cardiovascular risk factors

to reduce

Risk for diabetes-related complications

While

Preserving the pleasure of eating .

Two basic dimensions of MNT include:

Dietary quality

And

Energy restriction.

Dietary Quality and Eating Patterns

There is no single ratio of carbohydrate, proteins, and fat intake that is optimal for every person with type 2 diabetes.

Three trials of a

Mediterranean eating pattern

reported modest weight loss and improved glycemic control.

In one of these

People with new-onset diabetes

assigned to a

low carbohydrate Mediterranean eating pattern

were **37%** less likely to require glucose-lowering medications over 4 years

compared

with patients assigned to a low-fat diet

Low-carbohydrate diets (26% of total energy)

produce

substantial reductions in HbA1c at 3months and 6months .

no benefit of

moderate carbohydrate restriction (26–45%) was observed.

Two basic dimensions of MNT include:

Dietary quality

And

Energy restriction.

Energy restriction

The most effective

nonsurgical strategies for weight reduction

involve

food substitution and intensive, sustained counseling

(e.g., 12–26 individual counseling sessions over 6–12 months).

Energy restriction

Among adults with type 2 diabetes,

meal replacement

(825–853 kcal/day formula diet for 3–5 months)

resulted in 9-kg placebo-adjusted weight loss at 1 year

and high rates of diabetes remission compared with best usual practice .

Physical Activity

Aerobic exercise, resistance training, and the combination of

the two are effective in reducing HbA1c by about 0.6%.

Special considerations are required for individuals with

CVD, uncontrolled retinopathy or nephropathy, and severe neuropathy.

A wide range of physical activity,

including

leisure time activities

(e.g., walking, swimming, gardening, jogging, and yoga)

can significantly reduce HbA1c

In general,

supervision of exercise and motivational strategies,

such as monitoring using a step counter, can improve the effect of exercise on HbA1c compared with advice alone .

Medications for Lowering Glucose

Metformin

Dosages of

immediate release metformin

start at 500 mg once or twice a day with meals

and

should be increased as tolerated to a target dosage of 1,000 mg twice a day.

The doses above 2,000 mg are generally associated with little additional efficacy and poorer tolerability.

Gastrointestinal symptoms are common and dose dependent, and may improve over time or with dose reduction.

Metformin should not be used

in patients with

an GFR<30

and dose reduction

when the GFR is 45 mL min.

Rare cases of lactic acidosis

have been reported,

usually in the setting of severe illness or acute kidney injury.

Therefore, metformin should be omitted in the setting of severe illness, vomiting, or dehydration.

Metformin may result in lower serum vitamin B12 concentration;

therefore, periodic monitoring and supplementation is generally recommended if levels are deficient, particularly in those with anemia or neuropathy .

Because of its high efficacy in lowering HbA1c, good safety profile, and low cost,

metformin

remains the first-line medication for management of type 2 diabetes.

Choice of Glucose-Lowering Medication After Metformin

The selection of medication added to metformin is based on:

Patient preference

and

Clinical characteristics.

Important clinical characteristics include

the presence of established
comorbidities such as ASCVD, HF or CKD
; the risk for specific adverse medication effects,
particularly hypoglycemia and weight gain;
as well as
safety,
tolerability,
cost.

The early introduction of basal insulin

when HbA1c levels are very high (11)

in particular

when symptoms of hyperglycemia are present, or there is evidence of ongoing catabolism (e.g.weight loss).

This constellation of symptoms can occur in type 2 diabetes with insulin deficiency and raise the possibility of autoimmune (type 1) or pancreatogenic diabetes .

SGLT2 inhibitors

and GLP-1 receptor agonists

have demonstrated efficacy in patients with HbA1c exceeding 9%,

with the additional benefits of

weight reduction

and

reduced risk of hypoglycemia.

SGLT2 Inhibitors

SGLT2 inhibitors are oral medications that reduce plasma glucose by enhancing urinary excretion of glucose .

The glucose-lowering efficacy of these medications is dependent on renal function.

Not approved for use by at an GFR below 45

All SGLT2 inhibitors are associated with a

reduction

in weight and blood pressure.

Alone or with metformin, they do not increase the risk for hypoglycemia.

Empagliflozin and canagliflozin have
cardiac and renal benefits
in patients with
established or at high risk of CVD.

The class is associated with increased risk for mycotic genital infections (mostly vaginitis in women, balanitis in men).

Case reports of diabetic ketoacidosis with SGLT2 inhibitors in type 2 diabetes ?

Therefore, the SGLT2 inhibitors should be used with caution for those with insulin deficiency.

SGLT2 inhibitors have been associated with an

increased risk of

acute kidney injury, dehydration, and orthostatic hypotension;

caution

should be taken when SGLT2 inhibitors are used in combination with diuretics and/or ACE inhibitors and angiotensin receptor blockers.

GLP-1 Receptor Agonists

GLP-1 receptor agonists are currently delivered by subcutaneous injection.

These medications stimulate insulin secretion and reduce glucagon secretion in a

glucose-dependent manner,

improve satiety, and promote weight loss.

Dulaglutide, exenatide extended-release, and semaglutide are administered

once weekly.

Liraglutide and lixisenatide are administered once daily,

and exenatide

twice-daily

All GLP-1 receptor agonists reduce weight ;

the reduction ranges from about 1.5 kg to 6.0 kg over about 30 weeks of therapy .

Liraglutide and semaglutide have been shown to improve cardiovascular outcomes .

The most common side effects of GLP-1 receptor agonists are nausea, vomiting, and diarrhea, though these tend to diminish over time.

GLP-1 receptor agonists have minimal risk for hypoglycemia, but may increase the hypoglycemic potential of insulin and sulfonylureas when combined with those medications .

Contrary to early signals, GLP-1 receptor agonists do not seem to substantially increase risk for pancreatitis, pancreatic cancer, or bone disease .

They are associated with increased risk of gallbladder events .

DPP-4 Inhibitors

DPP-4 inhibitors are oral medications that increase insulin secretion and reduce glucagon secretion in a glucose-dependent manner.

They have moderate glucose lowering efficacy .

DPP-4 inhibitors are well tolerated, have a neutral effect on weight, and have minimal risk of hypoglycemia when used as monotherapy.

When added to sulfonylurea therapy, however, the risk for hypoglycemia is increased 50% compared with sulfonylurea therapy alone .

The recommended dose for each DPP-4 inhibitor is determined and needs to be adjusted based on renal function; linagliptin is the exception as it has minimal renal excretion.

Rare but increased rates of pancreatitis and musculoskeletal side effects have been reported .

The cardiovascular safety but no cardiovascular benefit of three DPP-4 inhibitors (saxagliptin, alogliptin, and sitagliptin) .

Thiazolidinediones

Thiazolidinediones (TZDs) (pioglitazone and rosiglitazone) are oral medications that increase insulin sensitivity and are of high glucose-lowering efficacy .

TZDs increase HDL-cholesterol, and pioglitazone has been shown to reduce cardiovascular end points and hepatic steatohepatitis ,but without conclusive evidence for benefit.

TZDs are associated with the best evidence among glucose lowering medications for glycemic durability.

However, these notable benefits must be balanced with safety concerns regarding fluid retention and congestive heart failure weight gain , bone fracture , and, possibly, bladder cancer .

Lower-dose therapy (e.g., pioglitazone 15–30 mg) mitigates weight gain and edema, but the broader benefits and harms of low-dose TZD therapy have not been evaluated.

Sulfonylureas

Sulfonylureas are oral medications that lower glucose by stimulating insulin secretion from pancreatic b-cells. They are inexpensive, widely available, and have high glucose-lowering efficacy .

Sulfonylureas are associated with weight gain and risk for hypoglycemia and down titration of dose to reduce the risk of hypoglycemia results in higher HbA1c.

Sulfonylureas are known to be associated with a lack of durable effect on glucose lowering .

Important differences among sulfonylureas affect both safety and efficacy.

Glibenclamide (known as glyburide in the U.S. and Canada) has a higher risk of hypoglycemia compared with other sulfonylureas . Glipizide, glimepiride, and gliclazide may have a lower risk for hypoglycemia compared with other sulfonylureas.

Greatest caution in this regard is warranted for people at high risk of hypoglycemia, such as older patients and those with CKD.

Insulin

NUMEROUS FORMULATIONS OF INSULIN ARE AVAILABLE WITH DIFFERING DURATIONS OF ACTION.

Basal Insulin

Basal insulin refers to longer-acting insulin that is meant to cover the body's basal metabolic insulin requirement (regulating hepatic glucose production), in contrast to bolus or prandial insulin, which is meant to reduce glycemic excursions after meals.

Basal insulin is the preferred initial insulin formulation in patients with type 2 diabetes. Options include once- or twicedaily administration of intermediate acting NPH or detemir insulin and the once-daily administration of glargine (U100 or U300) or degludec (U100 or U200).

Long-acting insulin analogs (degludec [U100 or U200], glargine [U100 and U300], detemir) have a modestly lower absolute risk for hypoglycemia compared with NPH insulin, but cost more.

However, in real-world settings where patients are treated to conventional treatment targets, initiation of NPH compared with determir or glargine U100 did not increase hypoglycemia related emergency department visits or hospital admissions.

When comparing human and analog insulins, cost differences can be large while differences in hypoglycemia risk are modest and differences in glycemic efficacy minimal.

Short- and rapid-acting insulin

Short- and rapid-acting insulin formulations administered at mealtime are generally used to intensify basal insulin therapy in patients not meeting glycemic targets. Rapid-acting insulin analogs have a modestly lower risk for hypoglycemia compared with human regular insulin but at a higher cost.

Other Glucose-Lowering Medications

Other oral glucose-lowering medications (i.e., meglitinides, a-glucosidase inhibitors, quick-release bromocriptine, pramlintide) are not used commonly in theU.S. and some are not licensed at all in Europe. No major new scientific information on these medications has emerged in recent years.

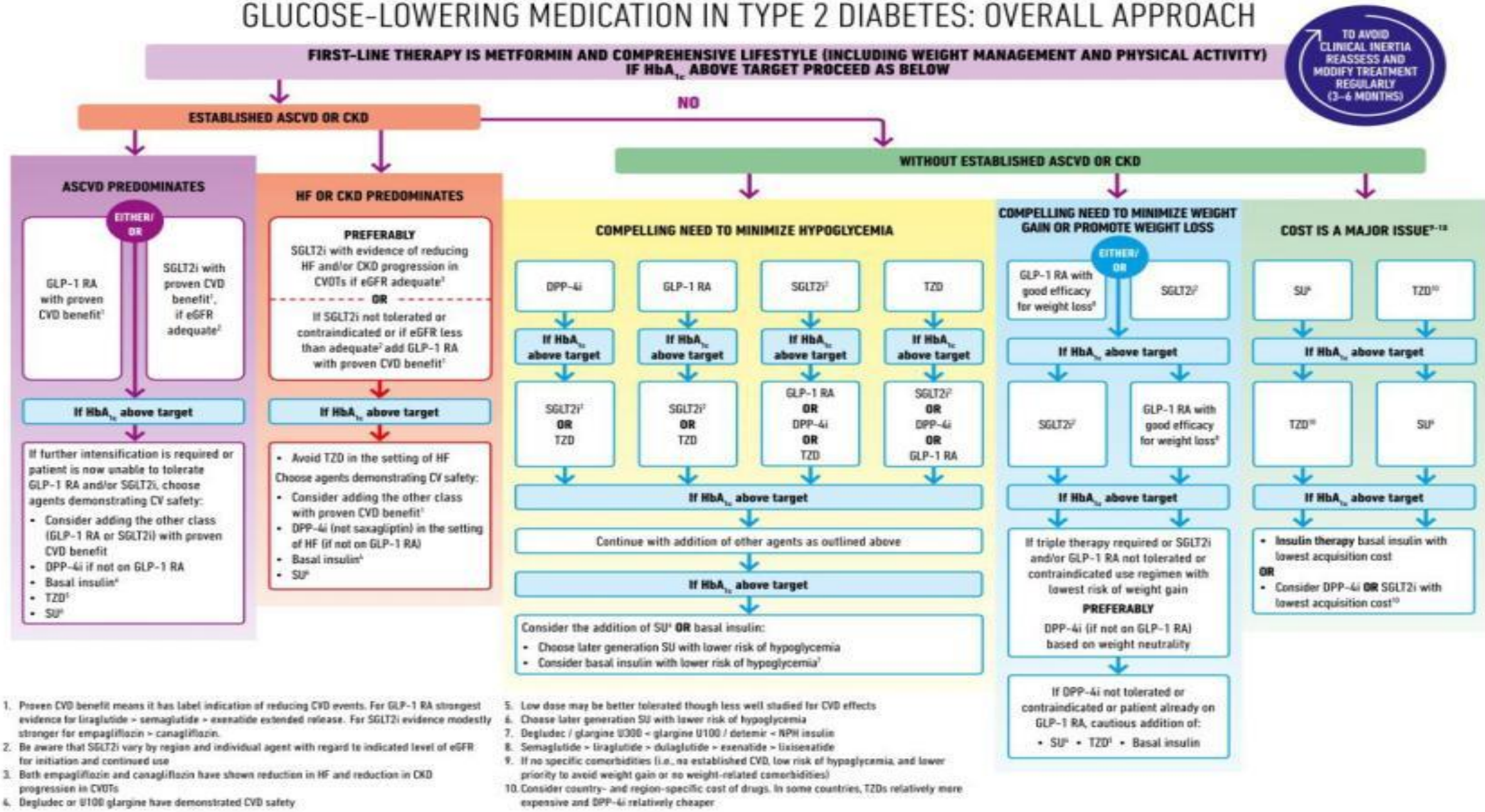
Metabolic Surgery

Metabolic surgery is highly effective in improving glucose control and often produces disease remission . The effects can be sustained for at least 5 years . Benefits include a reduction in the number of glucose-lowering medications needed to achieve glycemic targets.

Metabolic surgery is a recommended treatment option for adults with type 2 diabetes and 1) a BMI $40.0 kg/m2 (BMI $37.5 kg/m2 in people of Asian ancestry) or 2) a BMI of 35.0–39.9 kg/m2 (32.5– 37.4 kg/m2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities with reasonable nonsurgical methods.

Adverse effects of bariatric surgery,which vary by procedure, include surgical complications (e.g., anastomotic or staple line leaks, gastrointestinal bleeding, intestinal obstruction, the need for reoperation), late metabolic complications (e.g., protein malnutrition, mineral deficiency, vitamin deficiency, anemia, hypoglycemia), and gastroesophageal reflux

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

Figure 2—Glucose-lowering medication in type 2 diabetes: overall approach. CV, cardiovascular; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.

Pharmacologic Therapy For T2DM: Recommendations

Metformin, if not contraindicated and
if tolerated, is the preferred initial pharmacologic agent for the treatment of T2DM. A

Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B

SAIR.(

INTENSIFYING TO INJECTABLE THERAPIES

Use principles in Figure 1

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Consider insulin as first injectable if

- HbA_{1c} very high >97 mmol/mol (11%)
- Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia, which suggest insulin deficiency
- If type 1 diabetes is a possibility

Consider initial injectable combination (i.e., GLP–1 RA + basal insulin or prandial/basal insulin) if HbA_{1c} >86 mmol/mol (10%) and/or >23 mmol/mol (2%) above target

$_{1c}$ above target despite dual/triple therapy

Consider initial injectable combination (i.e., GLP–1 RA + basal insulin or prandial/basal insulin) if HbA_{1c} >86 mmol/mol (10%) and/or >23 mmol/mol (2%) above target

sider GLP–1 RA in most prior to insulin[1]
Consider: • INITIATION • TITRATION

Consider insulin as first injectable if
- HbA_{1c} very high >97 mmol/mol (11%)
- Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia, which suggest insulin deficiency
- If type 1 diabetes is a possibility

If already on GLP–1 RA or if GLP–1 RA not appropriate OR insulin preferred

If above HbA_{1c} target

Add basal insulin
Consider: • INITIATION • TITRATION

For patient on GLP–1 RA and basal insulin
Consider FRC of GLP–1 RA and insulin (iDegLira or iGlarLixi)
But note max dose of insulin in the FRCs

INITIATION
- If on GLP–1 RA use 10–16 dose steps (iDegLira) or 10–15 units (iGlarLixi)

TITRATION
- Titrate to FPG target and tolerability

- 4 IU a day or 10% of basal dose
- If HbA_{1c} <64 mmol/mol (8%) consider lowering the total dose by 4 IU a day or

If above HbA_{1c} target
Despite adequately titrated basal insulin **OR** once basal dose > 0.7–1.0 IU/kg **OR** FPG at target

If above HbA_{1c} target
Additional basal insulin or additional prandial insulin

r twice or three
s daily premix
ulin regimen

on higher risk
ypoglycemia
and/or weight gain
Consider:
• INITIATION
• TITRATION

INITIATION
- In insulin-naive patients 10–12 IU or 0.3 IU/kg
- If on existing insulin regimen usually unit to unit at the same total insulin dose but may require adjustment to individual needs

TITRATION
- Individual dose adjustment depends on type of biphasic insulin
- More complex if on three times daily regimen

every 3 months if HbA_{1c} > target is associated with lower risk of hypoglycemia and increases patient satisfaction compared with immediate introduction of full basal–bolus regimen

TITRATION FOR PRANDIAL

Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)
Consider: • INITIATION • TITRATION

If above HbA_{1c} target

INITIATION FOR PRANDIAL

TITRATION FOR PRANDIAL

Proceed to FULL basal–bolus regimen, i.e., basal insulin and prandial insulin with each meal
Consider:
• INITIATION • TITRATION

IF HbA_{1c} DOES NOT IMPROVE REVIEW ONGOING NEED FOR BASAL–BOLUS REGIMEN. CONSIDER ADDITIONAL DSMES

1. Consider choice of GLP–1 RA considering: patient preference, HbA_{1c} lowering, weight–lowering effect, or frequency of injection. If CVD, consider GLP–1 RA with proven CVD benefit

Table 8.4—Median cost of insulin products in the U.S. calculated as AWP (39) and NADAC (40) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC (min, max)*
Rapid-acting analogs	• Lispro	U-100 vial;	$330	$264
		U-100 3 mL cartridges;	$408	$326
		U-100 prefilled pen; U-200 prefilled pen	$424	$339
	• Aspart	U-100 vial;	$331	$265
		U-100 3 mL cartridges;	$410	$330
		U-100 prefilled pen	$426	$341
	• Glulisine	U-100 vial;	$306	$245
		U-100 prefilled pen	$394	$315
	• Inhaled insulin	Inhalation cartridges	$725 ($544, $911)	N/A†
Short-acting analogs	• Human Regular	U-100 vial	$165 ($165, $178)	$135 ($135, $145)
Intermediate-acting analogs	• Human NPH	U-100 vial;	$165 ($165, $178)	$135 ($135, $145)
		U-100 prefilled pen	$377	$305
Concentrated Human Regular insulin	• U-500 Human Regular insulin	U-500 vial;	$178	$143
		U-500 prefilled pen	$230	$184
Basal analogs	• Glargine	U-100 vial; U-100 prefilled pen; U-300 prefilled pen	$298	$239 ($239, $241)
	• Glargine biosimilar	U-100 prefilled pen	$253	$203
	• Detemir	U-100 vial; U-100 prefilled pen	$323	$259
	• Degludec	U-100 prefilled pen; U-200 prefilled pen	$355	$285
Premixed insulin products	• NPH/Regular 70/30	U-100 vial;	$165 ($165, $178)	$134 ($134, $146)
		U-100 prefilled pen	$377	$305
	• Lispro 50/50	U-100 vial;	$342	$278
		U-100 prefilled pen	$424	$339
	• Lispro 75/25	U-100 vial;	$342	$273
		U-100 prefilled pen	$424	$340
	• Aspart 70/30	U-100 vial;	$343	$275
		U-100 prefilled pen	$426	$341
Premixed insulin/GLP-1 receptor agonist products	• Degludec/Liraglutide	100/3.6 prefilled pen	$763	N/A†
	• Glargine/Lixisenatide	100/33 prefilled pen	$508	$404

*AWP or NADAC calculated as in **Table 8.3**; median listed alone when only one product and/or price. †Not applicable; data not available.

Guidelines for Comprehensive Medical Care for Patients with Diabetes

Optimal and individualized glycemic control.

SMBG (individualized frequency).

HbA1c testing (2–4 times/year).

Patient education in diabetes management (annual).

Medical nutrition therapy and education (annual).

Eye examination (annual or biannual).

Foot examination (1–2 times/year by physician; daily by patient).

Screening for diabetic nephropathy (annual).

Blood pressure measurement (quarterly).

Lipid profile and serum creatinine (estimate GFR) (annual).

Influenza/pneumococcal/hepatitis B immunizations.

Consider antiplatelet therapy.

Thank You!