Prevention and Treatment of Type 2 Diabetes

John Palmer DO

Monument Endocrinology

Times are changing quickly

- In the past few years the landscape of diabetes and the focus of treatment goals have changed considerably

- The focus of management goals are now broader, more intricate and more important than ever

- We have never had more agents to manage the disease and are tools are as sharp as they have ever been

The Past

- Focus of care for diabetes and related conditions was very glycemic centric

- We oftentimes were myopic on metrics such as the A1c, SMBG and less attentive to associated endpoints such as weight gain, hypoglycemia and cardiovascular considerations

The Present

- Our understanding of diabetes and its interplay with cardiovascular morbidity and mortality has grown widely
- More importantly, we now have agents that directly impact the burden of disease
- It is now not simply enough to be gluco-centric. We must stylistically tailor therapy to our patients to not only manage the ups and down of blood glucose levels, but more importantly, reduce risk
- Our therapeutic decisions we make today for disease management have the ability to save lives and reduce morbidity

Philosophy of Care

- What are we doing?
- What is our aim?
- Our we treating symptoms or the core root problems?

Philosophy of Care

- Important considerations
  - Impact on disease state.
  - Impact on weight
  - Risk of hypoglycemia
  - Cardiovascular considerations
  - Individual goals
  - Comorbid considerations

Philosophy of Care

- What we cannot do
  - Continue to miss opportunity to screen, diagnose and intervene
  - Continue to fall victim of clinical inertia
  - Miss opportunity to reduce CV risk by using appropriately tailored therapeutics

Prevention of Type 2 diabetes

- At its core, prevention is the best medicine

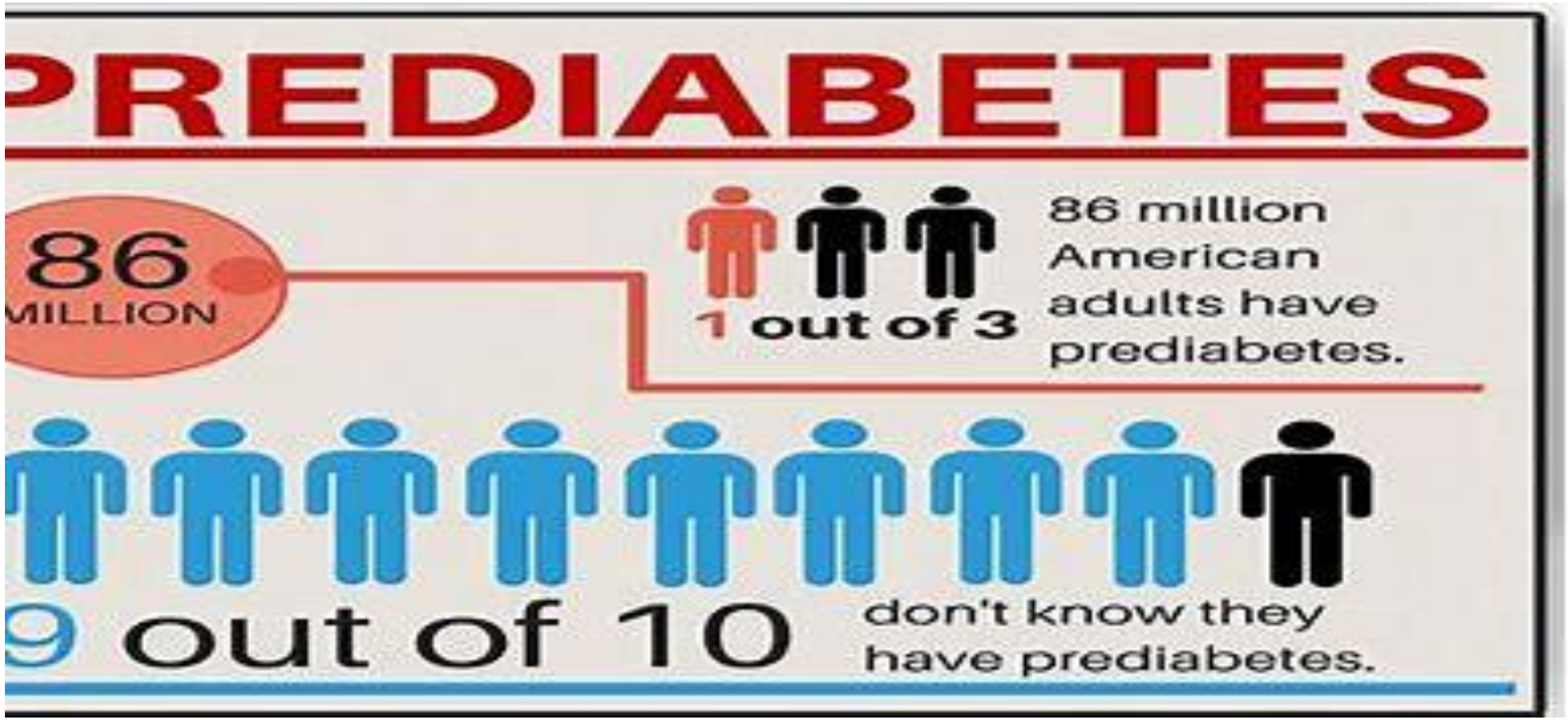
- **The word prevention embodies the goals of medicine: to promote health, to preserve health, to restore health when it is impaired, and to minimize suffering and distress.**
  - **Last M, 1995: Dictionary of epidemiology**

Preventive strategies

- **A population-based strategy, involving altering the lifestyle and environmental determinants of Type 2 diabetes.**

Why should we prevent diabetes?

- **To reduce human suffering.**
- **To alleviate the economic burden.**
- **To prevent morbidity and mortality from diabetes-related CVD.**


PREDIABETES
86
MILLION
1 out of 3
86 million
American
adults have
prediabetes.
9 out of 10
don't know they
have prediabetes.

Levels of prevention in Type 2 diabetes

- **Primary: Includes activities aimed at preventing diabetes from occurring in susceptible populations or individuals.**
- **Secondary: Early diagnosis and effective control of diabetes in order to avoid or at least delay the progress of the disease.**
- **Tertiary: Includes measures taken to prevent complications and disabilities due to diabetes.**

Secondary prevention

- **The purpose of secondary prevention activities such as screening is to identify asymptomatic people with diabetes.**

- **Is there an effective intervention that may retard the progression of disease or the severity of its complications?**

Screening approaches

- **Population screening**
- **Selective screening**
- **Opportunistic screening**

Rationale for Prediabetes Screening

- Epidemiologic evidence suggests the complications of diabetes begin early in the progression from normal glucose tolerance to frank type 2 diabetes

- Prediabetes and diabetes are conditions in which early detection is appropriate, because: – Duration of hyperglycemia is a predictor of adverse outcomes – There are effective interventions to prevent disease progression and to reduce complications

Risk Factors

- Age ≥45 years
- Family history of T2D or cardiovascular disease
- Overweight or obese
- Sedentary lifestyle
- Non-Caucasian ancestry
- Previously identified IGT, IFG, and/or metabolic syndrome
- Delivery of baby weighing >4 kg (>9 lb)
- Antipsychotic therapy for schizophrenia or severe bipolar disease
- Chronic glucocorticoid exposure
- Sleep disorders – Obstructive sleep apnea – Chronic sleep deprivation – Night shift
- PCOS, acanthosis nigricans, or NAFLD
- Hypertension (BP >140/90 mmHg)
- Dyslipidemia (HDL-C 250 mg/dL)
- History of gestational diabetes

Tertiary prevention

- **Includes actions taken to prevent and delay the development of acute or chronic complications.**
- **Acute complications: such as hypoglycemia, severe hyperglycemia and infections.**
- **Chronic complications: such as atherosclerosis, retinopathy, nephropathy, neuropathy and foot problems.**

Obstacles and barriers for prevention

- **Economic problems: unavailability of needed resources.**
- **Socio-cultural problems.**
- **Lack of data, knowledge and skills.**

Examples of socio-cultural barriers:

- **Obesity is not considered negatively.**
- **No value given to physical exercise.**
- **Changing diet is very difficult.**
- **No time is granted to do physical exercise at work.**
- **Fatalism.**

Major components of effective prevention programs

- **Standardized data collection on disease magnitude, risk factors and mortality statistics.**
- **Clear action plan with specific targets, and well defined evaluation.**
- **Initiating community-based interventions for primary prevention.**
- **Advocacy for influencing policies.**

Major components of effective prevention programs- Cont

- **Advocacy for the rights of people with diabetes for quality care at all levels.**
- **Establishing acceptable standards for health care for people with diabetes.**
- **Establishing an effective referral system and defining the role of each level of health care.**

Major components of effective prevention programs- Cont

- **Educating the population about this important global epidemic.**
- **Provision of appropriate training for health care providers.**
- **Coordination of prevention efforts.**

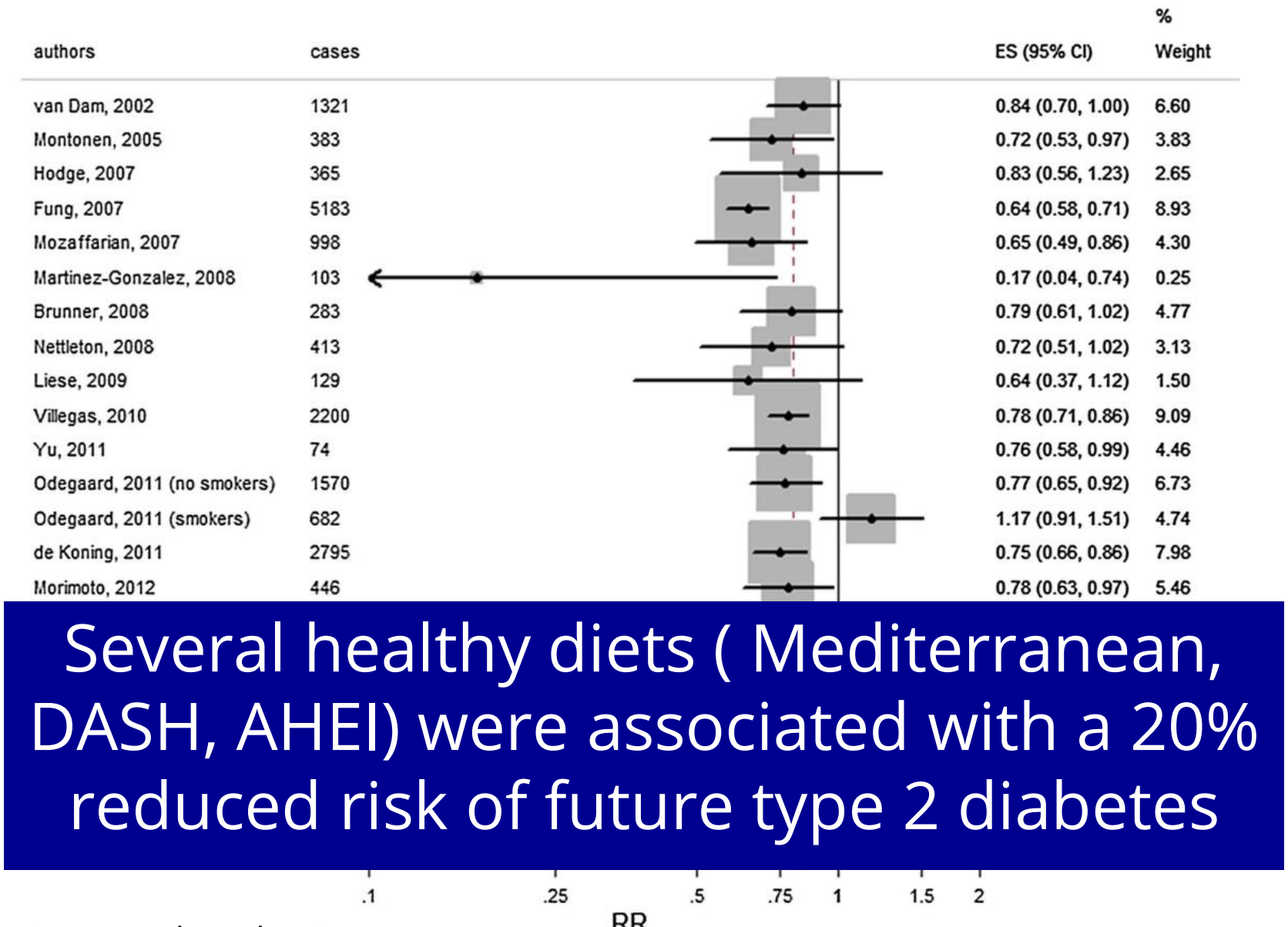
Types of interventions

- **Behavioral interventions: including changing diet and increasing physical activity.**

  And/or

- **Pharmacological interventions: utilizing pharmaceutical agents to improve glucose tolerance and insulin sensitivity.**

Meta-analysis of healthy dietary patterns and reduced risk of type 2 diabetes

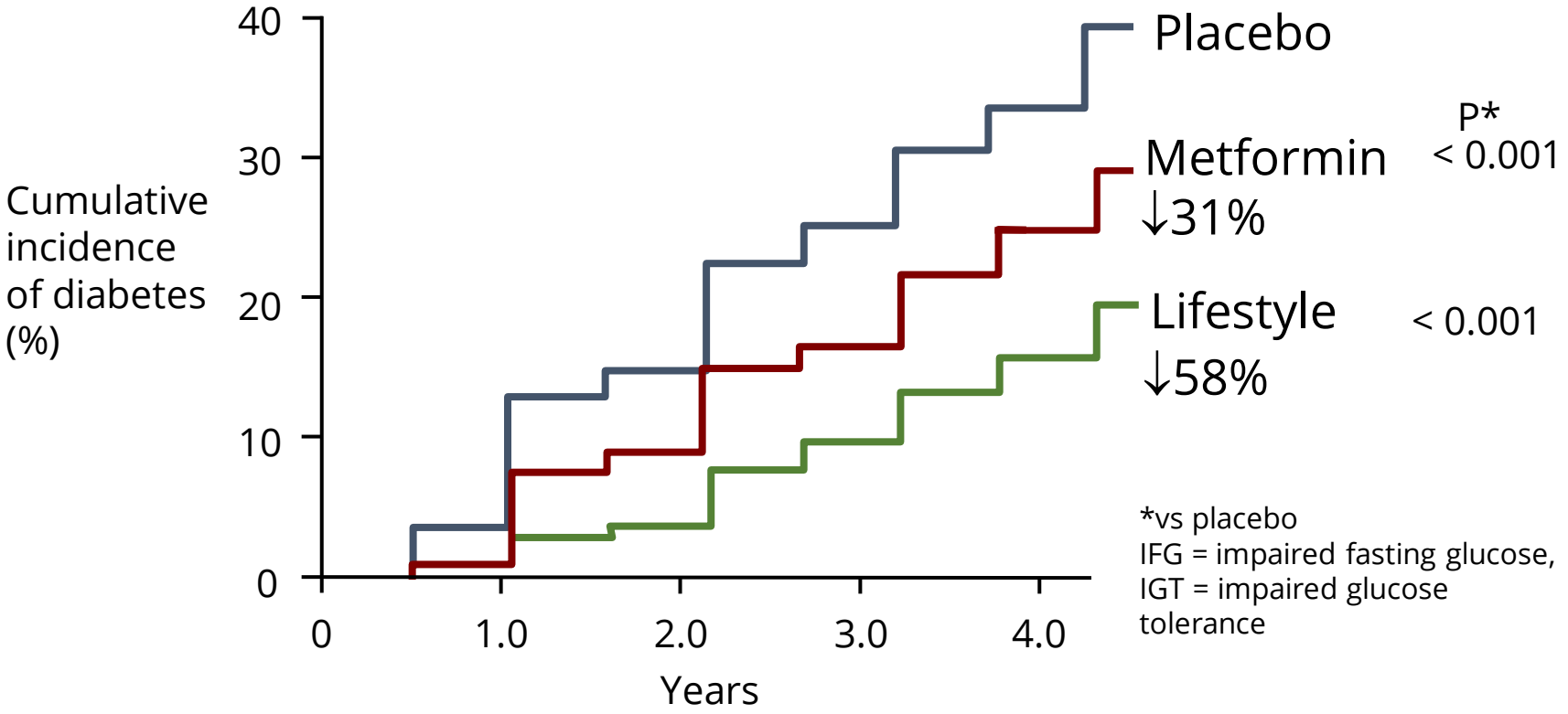


Several healthy diets (Mediterranean, DASH, AHEI) were associated with a 20% reduced risk of future type 2 diabetes

Esposito K et al. Endocrine 2014;47:107-116.

Diabetes Prevention Program (DPP)

- Benefit of diet and exercise or metformin on diabetes prevention in at-risk patients
- N = 3234 with IFG and IGT, without diabetes

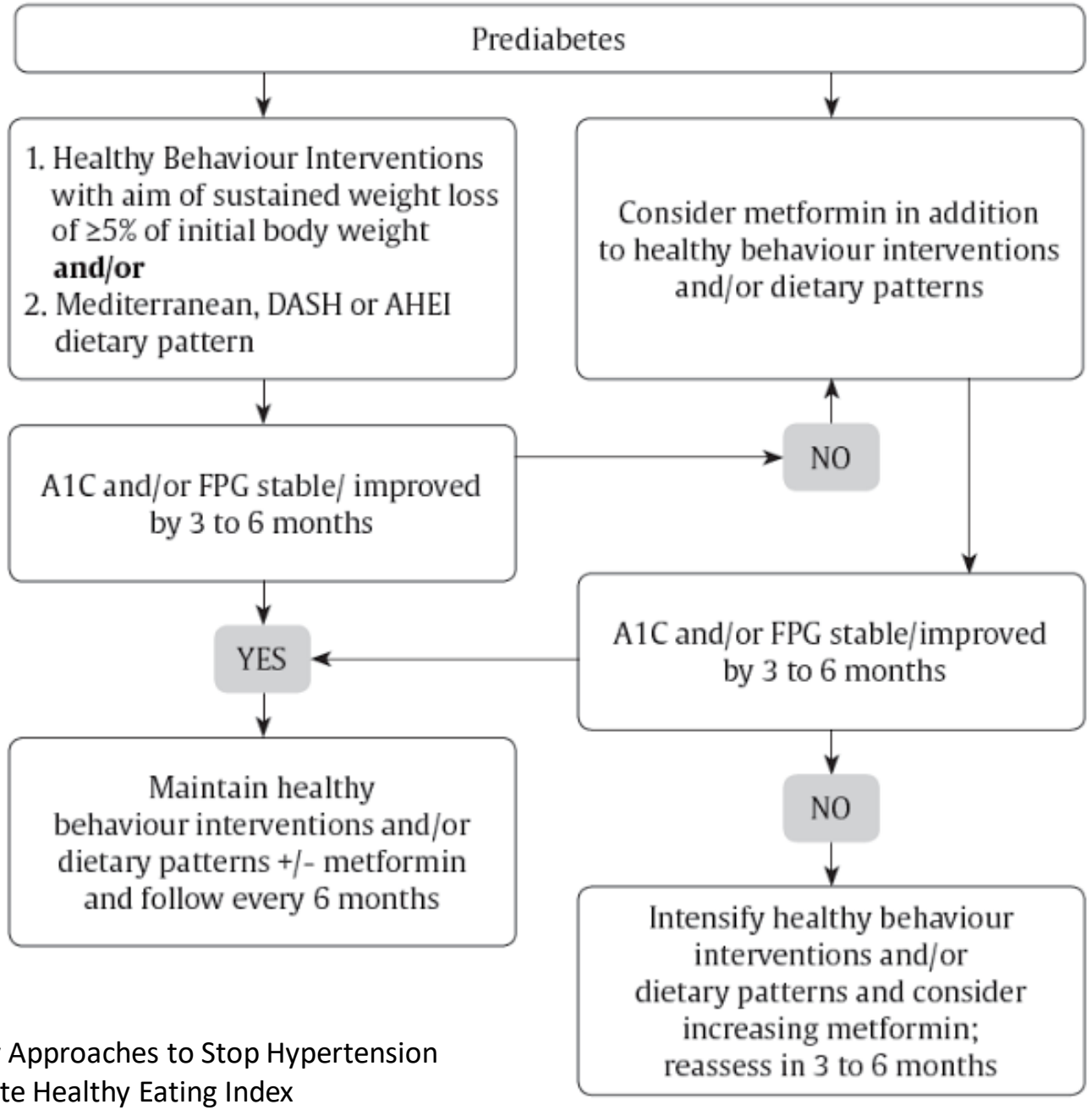


Diabetes Prevention Program (DPP) Research Group. *N Engl J Med* 2002;346:393-403.

Pharmacology to Reduce Progression to type 2 diabetes

- Metformin has been shown to reduce the incidence of type 2 diabetes by approximately 30% in the Diabetes Prevention Program (DPP)
- Acarbose has been shown to reduce the risk of progression to diabetes by approximately 30% in the Study to Prevent Non-Insulin Dependent Diabetes (STOP-NIDDM) study

Diabetes Prevention Program (DPP) Research Group. *N Engl J Med* 2002;346:393
STOP-NIDDM. Lancet 2002;359:2072



DASH=Dietary Approaches to Stop Hypertension
AHEI= Alternate Healthy Eating Index

The Future

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., ulio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D ean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc and Robert F. Kushner, M.D., for the STEP 1 Study Group*

JAMA Network™

QUESTION In adults with overweight or obesity without diabetes, what effect does once-weekly subcutaneous semaglutide, 2.4 mg, have on body weight when added to intensive behavioral therapy with an initial low-calorie diet?

CONCLUSION When used as an adjunct to intensive behavioral therapy and initial low-calorie diet, once-weekly subcutaneous semaglutide produced significantly greater weight loss than placebo during 68 weeks in adults with overweight or obesity.

POPULATION

495 Women
116 Men

Adults with overweight (BMI ≥27) plus 1 comorbidity or obesity (BMI ≥30) without diabetes

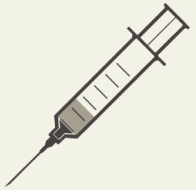
Mean age: **46** years

LOCATIONS

41
Sites in the US

INTERVENTION

611 Patients randomized



407

Semaglutide

Semaglutide, 2.4 mg, once weekly subcutaneously, plus low-calorie diet (for initial 8 weeks) and intensive behavioral therapy for 68 weeks

204

Placebo

Placebo once weekly subcutaneously, plus low-calorie diet (for initial 8 weeks) and intensive behavioral therapy for 68 weeks

CO-PRIMARY OUTCOMES

Percentage change in body weight and loss of ≥5% of baseline weight at week 68

FINDINGS

Weight change by week 68

Semaglutide

Weight change: **−16.0%**

86.6% lost ≥5% of baseline weight

Placebo

Weight change: **−5.7%**

47.6% lost ≥5% of baseline weight

Between-group difference was significant for weight change:

−10.3 percentage points

(95% CI, −12.0 to −8.6); $P < .001$
and for losing ≥5% of baseline weight: $P < .001$

Wadden TA, Bailey TS, Billings LK, et al; STEP 3 Investigators. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight

JAMA Network™

QUESTION What effect does continued treatment with subcutaneous semaglutide, 2.4 mg once weekly, have on the maintenance of body weight loss in adults with overweight or obesity without diabetes?

CONCLUSION Among adults with overweight or obesity who completed a 20-week run-in of semaglutide treatment, maintaining treatment with semaglutide vs switching to placebo resulted in continued weight loss over the following 48 weeks.

POPULATION

634 Women
169 Men

Adults with body mass index of at least 30 (or ≥27 with ≥1 weight-related comorbidity) and without diabetes

Mean age: **46** years

LOCATIONS

73 Sites
in 10 countries

INTERVENTION

Continued semaglutide
Continued to receive semaglutide, 2.4 mg once weekly, for 48 weeks (after 20-week run-in period with semiglutide)

Placebo
Switched to once-weekly placebo for 48 weeks (after 20-week run-in period with semaglutide)

PRIMARY OUTCOME

Percent change in body weight from week 20 to week 68

FINDINGS

Mean body weight change from week 20 to week 68

Continued semaglutide	Weight change: **−7.9%**
Placebo	Weight change: **+6.9%**

Between-group difference in percent change in body weight was statistically significant:

−14.8 percentage points

(95% CI, −16.0 to −13.5); $P < .001$

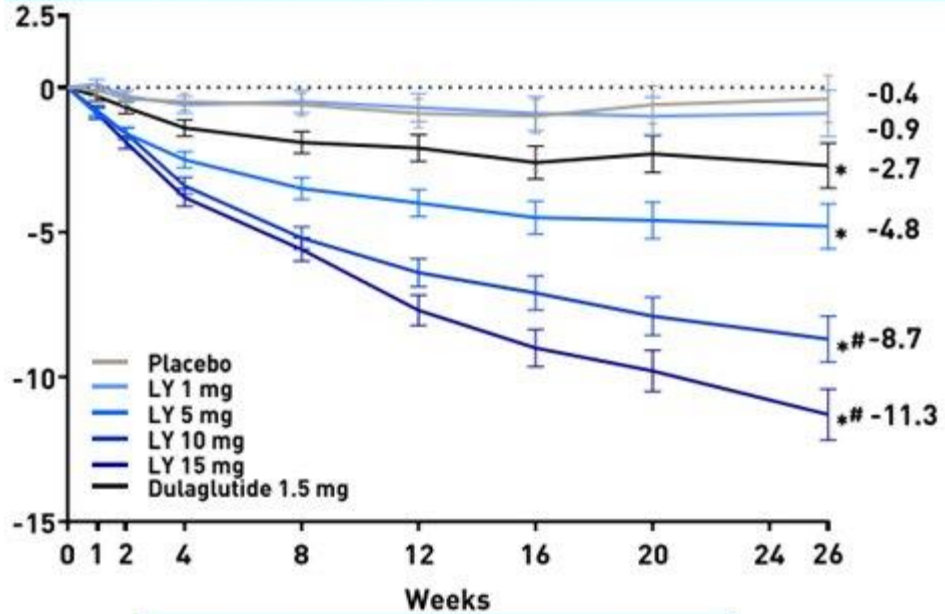
Rubino D, Abrahamsson N, Davies M, et al; STEP 4 Investigators. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA*. Published online March 23, 2021. doi:10.1001/jama.2021.3224

TIRZEPATIDE PHASE 2

ACHIEVED POSITIVE RESULTS IN WEIGHT LOSS (ON TREATMENT ANALYSIS)

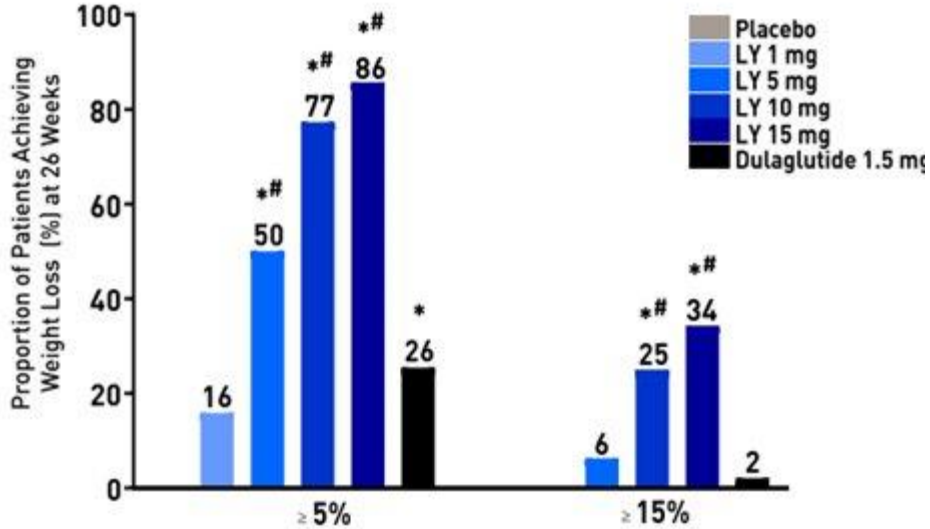
Lilly

WEIGHT LOSS (KG)



Observed significant and dose-related decreases in body weight (kg)

WEIGHT LOSS (%) TARGET



34% of 15 mg dose patients achieve ≥15% body weight reduction

Data presented are LS mean ± SE. MMRM on treatment analysis.
Trial Description: 26 week randomized trial; 1mg, 5mg, 10mg: 2 week titration, 15mg: 6 week titration, dulaglutide 1.5mg
Baseline Characteristics: Mean age 57, weight 91.5 kg, BMI 32.6, A1c 8.1%, 90% on metformin

HbA1c (%) target data are logistic regression, on treatment analysis
*, #p<.05 vs placebo and vs. dulaglutide 1.5 mg, respectively

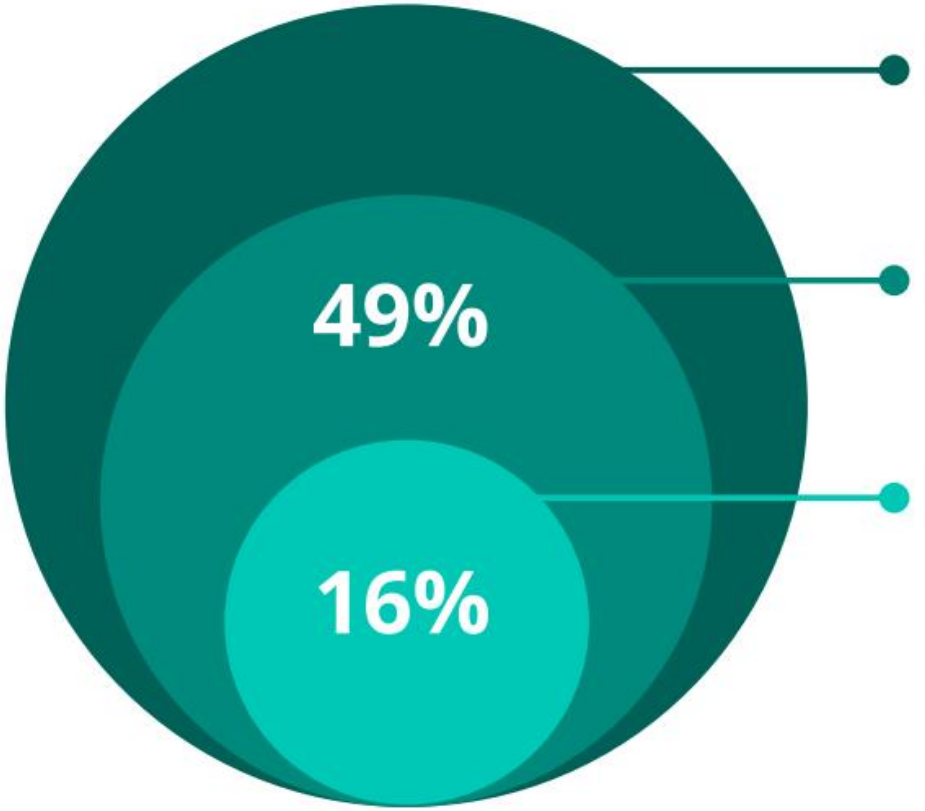
https://investor.lilly.com/static-files/ff772c9a-05f7-4d6a-a01d-340e2c4d9198

Type 2 diabetes management

- A new era

- Details matter
  - Age
  - Comorbid conditions
  - Goal of therapy
  - Capabilities
  - Economics

A1C Levels in Patients With Diabetes



Total US Population With Diabetes

A1C >7%

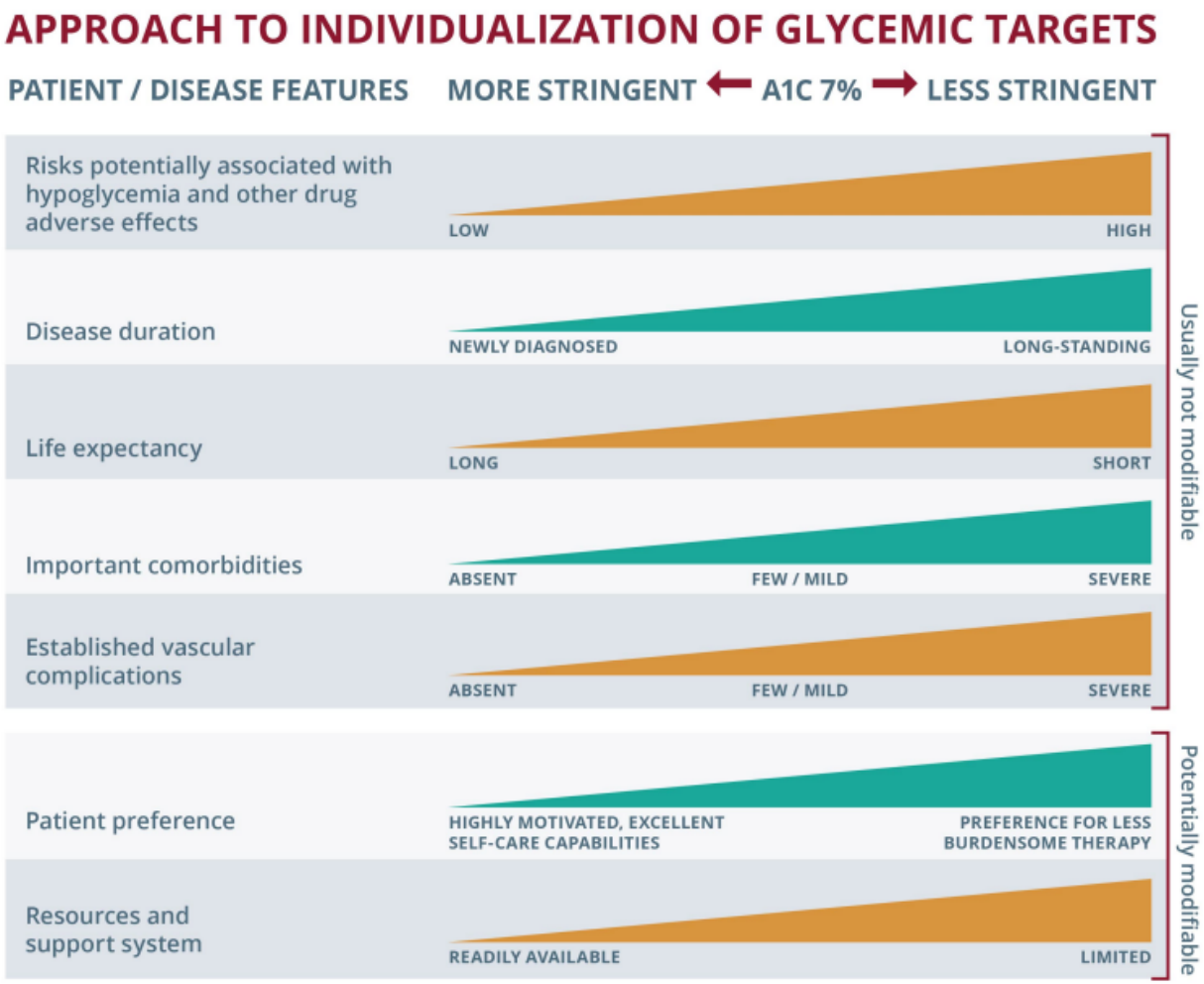
A1C >9%

Many patients with diabetes remain above target levels

A1C, glycated hemoglobin; ADA, American Diabetes Association.
Carls G, et al. *Diabetes Ther*. 2017;8:863-873.

Glycemic Target Individualization: American Diabetes Association

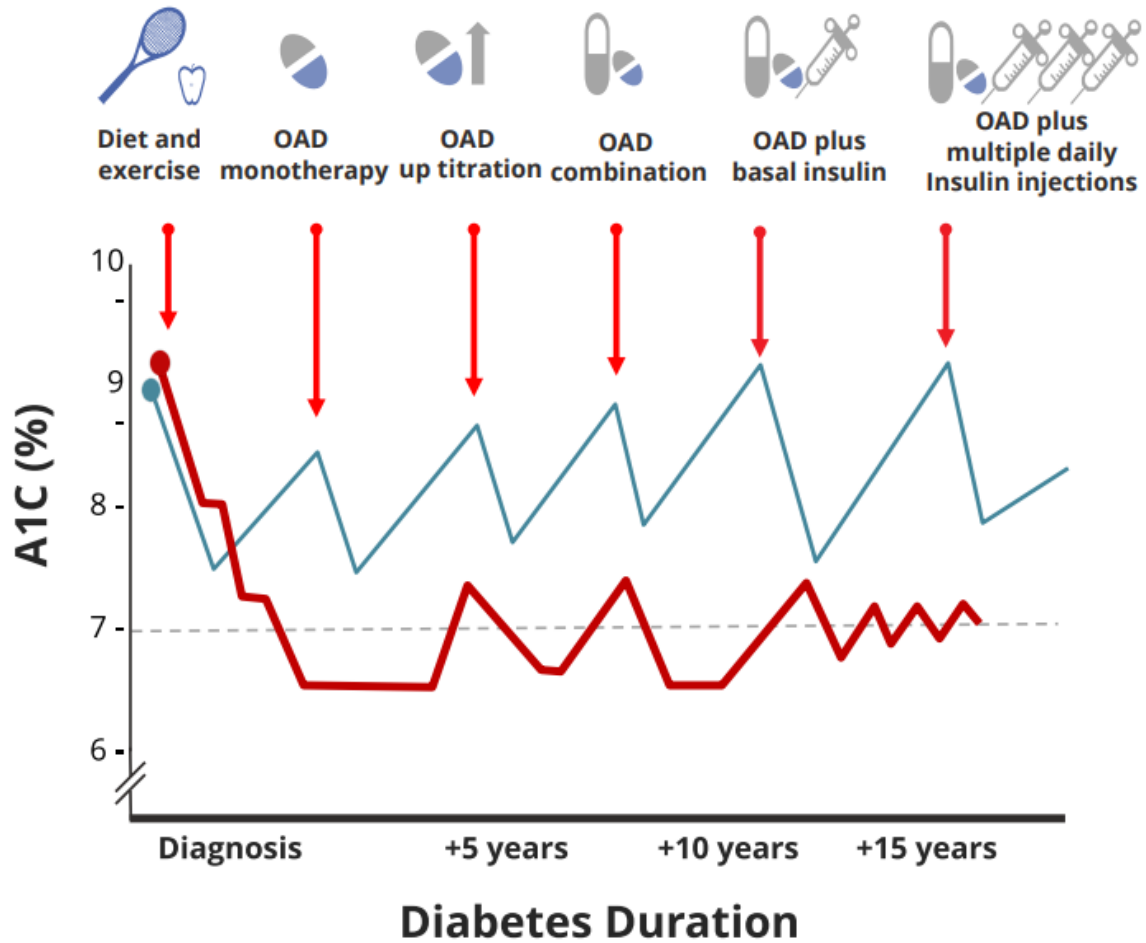
- Patient and disease factors used to determine optimal A1C targets
- Characteristics toward the left justify more stringent efforts to lower A1C
- Characteristics toward the right suggest less stringent efforts
- A1C 7% = 53 mmol/L



A1C, glycated hemoglobin.
American Diabetes Association. *Diabetes Care*. 2019;42:S61-S70.

Sequential Management of Hyperglycemia: "Treatment to Failure"

- A stepwise treatment approach has traditionally been used to manage patients with T2D. New treatments are added only when acute symptoms become apparent.
- Earlier intensification with combination therapy is recommended to achieve and maintain target goals among patients with high A1C levels at baseline.



A1C, glycated hemoglobin; OAD, oral antidiabetic drug; T2D, type 2 diabetes.

1. Campbell IW. Br J Cardiol. 2000;7:625-631. 2. Del Prato S, et al. Int J Clin Pract. 2005;59:1345-1355.
3. https://www.aace.com/disease-state-resources/diabetes/clinical-practice-guidelines-treatment-algorithms/comprehensive

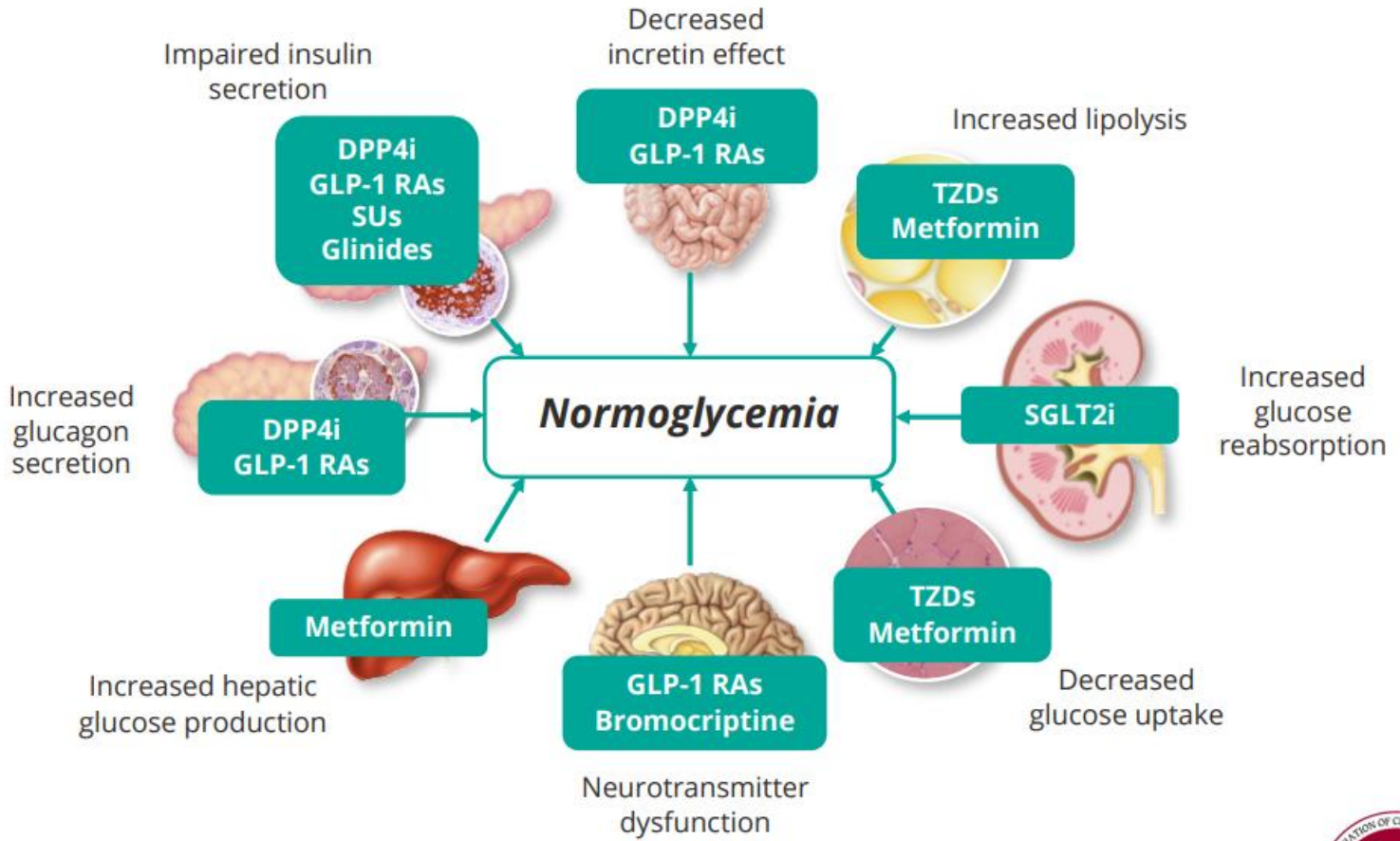
Considerations

- Weight
- Efficacy
- Is the agent disease modifying
- Risk of hypoglycemia
- CV Data

The "Ominous Octet" Multifactorial Pathophysiology of T2D

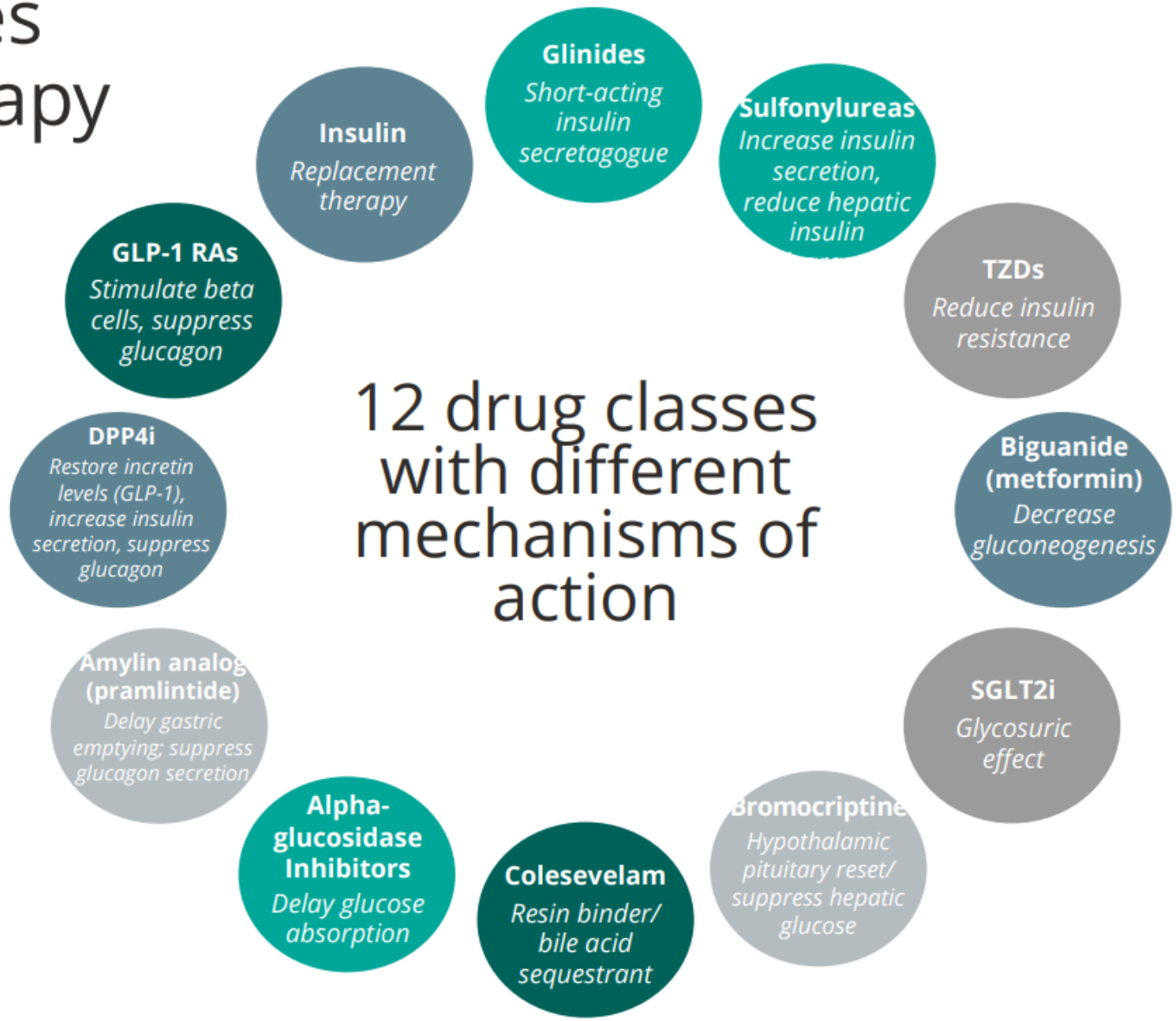
To optimally manage T2D:

1. Therapy should be individualized based on known pathophysiologic defects
2. Multiple agents are necessary to target different aspects of this disorder



DPP4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SLGT2i, sodium-glucose cotransporter 2 inhibitors; SU, sulfonylureas; T2D, type 2 diabetes; TZD, thiazolidinediones.
Adapted from DeFronzo RA. *Diabetes* 2009;58:773-795.

Type 2 Diabetes Pharmacotherapy



DPP4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SLGT2i, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones.

1. Garber AJ, et al. *Endocr Pract*. 2019;25:69-90. 2. Inzucchi et al Diabetes Care. 2015 Jan,38(1):140-9.

AACE: Profiles of Antidiabetic Medications

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP1-RA	SGLT2i	DPP4i	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 if eGFR <30 mL/min/ 1.73 m^2	Exenatide Not Indicated CrCl <30 Possible Benefit of Liraglutide	Not Indicated for eGFR <45 mL/ min/1.73 m^2 Genital Mycotic Infections Possible CKD Benefit	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	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	See #1	See #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC ASCVD						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

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

AACE, American Association of Clinical Endocrinologists; ASCVD, atherosclerotic cardiovascular disease; AGi, alpha-glucosidase inhibitors; BCR-QR, bromocriptine quick release; CHF, congestive heart failure; COLSVL, colesevelam; CrCl, creatinine clearance; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide receptor agonist; GI Sx, gastrointestinal symptoms; GU, genito-urinary; MET, metformin; SLGT2i, sodium-glucose cotransporter 2 inhibitors; SU, sulfonylureas; TZD, thiazolidinediones.

Garber AJ, et al. *Endocr Pract*. 2019;25:69-90.

Cobra Kai


STRIKE FIRST, STRIKE HARD
NO MERCY
HTTP://WWW.COBRAKAIDOJO.COM

Act early. Treat Decisively

- Do not wait for things to get bad (worse)
- Play from ahead
- Use the agents in combination to compliment each other

Act early. Treat Decisively

- In 2022, in my humble opinion we need triple therapy where we can use it

- Metformin, SGLT2 and GLP used in combination
  - Potent
  - Weight loss
  - Limited hypoglyemia
  - Slow disease progression
  - Treat the problems, not just the symptoms

Combination Therapy: Patients With High CV Risk

- Substantial historical evidence indicates that intensive, ongoing glucose control in newly diagnosed T2D patients may decrease long-term CVD rates[1]
- In 2008, FDA guidance mandated CV safety assessment of all new antihyperglycemic agents[2]
  - RCT studies required to demonstrate that study drug was not associated with more major adverse CV events than placebo (noninferiority)
    - Some studies tested for superiority if noninferiority criteria were met
  - **Primary outcome:** Composite of CV death, nonfatal MI, and nonfatal stroke
    - Some studies included additional endpoints
- Several studies of SGLT-2 inhibitors and GLP-1 RA have shown superiority compared with placebo.

cardiovascular; CVD, cardiovascular disease; FDA, US Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MI, myocardial infarction; RCT, randomized controlled trial; SGLT-2, sodium-ose cotransporter 2; T2D, type 2 diabetes.

merican Diabetes Association. *Diabetes Care*. 2019;42:S61-S70.

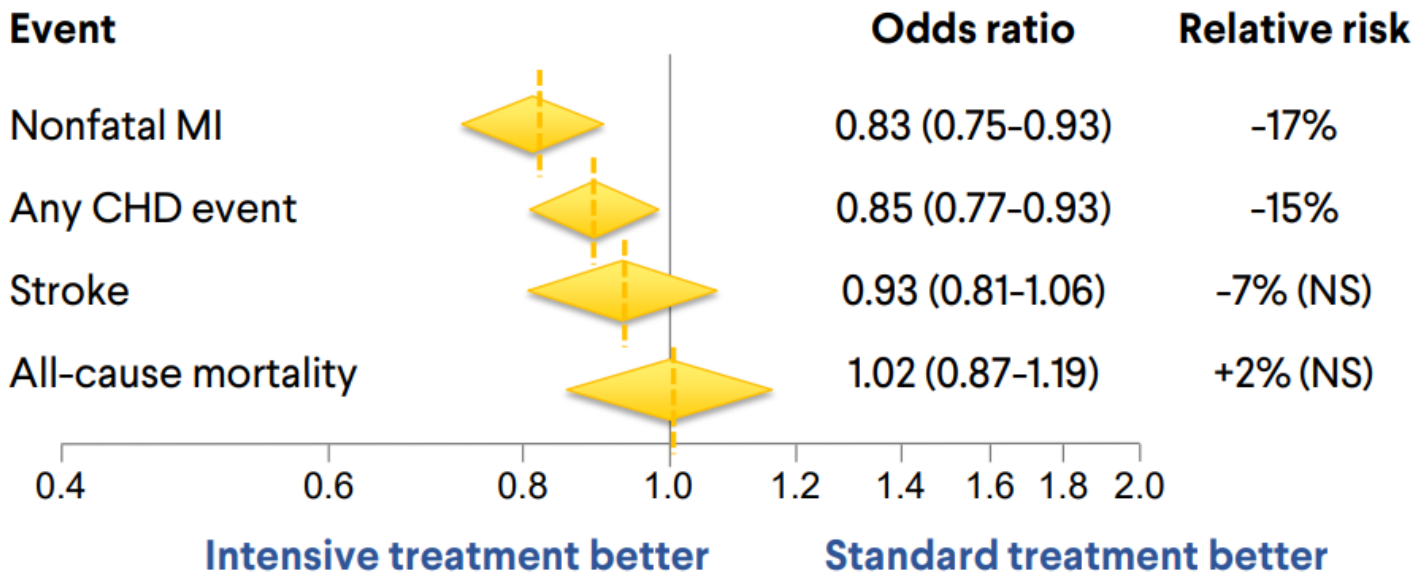
DA. Guidance for industry: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. https://www.fda.gov/media/71297/download.

Cardiovascular Risk and Diabetes Type 2 Diabetes

- Type 2 Diabetes is a significant risk factor for cardiovascular disease (CVD)
- Cardiovascular complications are main cause of mortality in T2D patients
- The Emerging Risk Factors Collaboration: Diabetes and CVD N=698,782; 102 prospective studies; 52,765 events
  - Cardiovascular heart disease death HR = 2.31
  - Non-fatal myocardial infarction HR = 1.82
  - Ischemic cerebral vascular accident HR = 2.27
  - Hemorrhagic cerebral vascular accident HR = 1.84
  - Duration of diabetes is associated with higher risk of cardiovascular disease
  - Diabetes + CV disease (MI or CVA) reduces life expectancy

Prior Landmark Clinical Trials: Intensive Glucose Control and Macrovascular Risk in T2D

Meta-analysis of Five Prospective RCTs Assessing Effect of Intensive Glucose Lowering on CV Outcomes (ACCORD, ADVANCE, PROactive, UKPDS, VADT)



Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009 May 23;373(9677):1765-7.

Cardiovascular Risk and Diabetes

- Intensive vs. conventional glucose control in older studies did not reduce short term all-cause, CV or non-CV mortality
  - Lowering HbA1c below conventional targets did not confer CV benefit
  - Intensive control confirmed reduction in microvascular disease
- Newer diabetes drugs (SGLT-2 inhibitor and GLP-1 receptor analogs) have consistently shown cardiovascular and renal protection in large cardiovascular outcome trials
- Individualized diabetes management approach is important for:
  - HbA1c lowering
  - Microvascular risk reduction (nephropathy, retinopathy, neuropathy)
  - Macrovascular risk reduction (ASCVD, Heart failure, diabetic kidney disease)

Pharmacologic Treatment for T2D

- Two classes of newer DM2 therapy with added cardiovascular benefits.
  - Sodium-Glucose CoTransporter 2 (SGLT2) Inhibitors
  - Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists
  - Each will be reviewed for:
  - Mechanism
  - Summary of CV outcome trials (CVOT)
  - Benefits
  - Adverse effects

Pharmacologic Treatment for T2D With Existent Cardiovascular Disease

SGL T2 inhibitors:

- Canagliflozin
- Empagliflozin
- Dapagliflozin
- Ertugliflozin

Human analog GLP-1 RA:

- Liraglutide
- Dulaglutide*
- Semaglutide
- Albiglutide (off the market)

*Only drug with primary prevention indication

- •Improved Glycemia •
- Rare hypoglycemia •
- Weight loss •Average weight loss of 1-3 kg •
- Blood pressure •
- ↓ Triglycerides •Oral route •
- Cardiac and renal protection

SGLT2 Inhibitors

Mechanisms for Cardioprotection

- Reduce preload and afterload segment
- Improved profile of anti-inflammatory vs. pro-inflammatory cytokine
- Reduced cardiac fibrosis
- Increased hematocrit and erythropoietin production
- Increased cardiac metabolic efficiency

Mechanisms for Renoprotection

- Glycosuria
- Natriuresis
- Decreased glomerular pressure
- Reduced albuminuria

Physiological Effects of SGLT2 Inhibitors

Selectively blocks the transporter responsible for > 90% of glucose reabsorption in the nephron (SGLT2).

- This results in reduced absorption of glucose and sodium, leading to glycosuria and natriuresis.
- Greatest rate of glycosuria occurs during periods of hyperglycemia.
- Risk for hypoglycemia is not significant

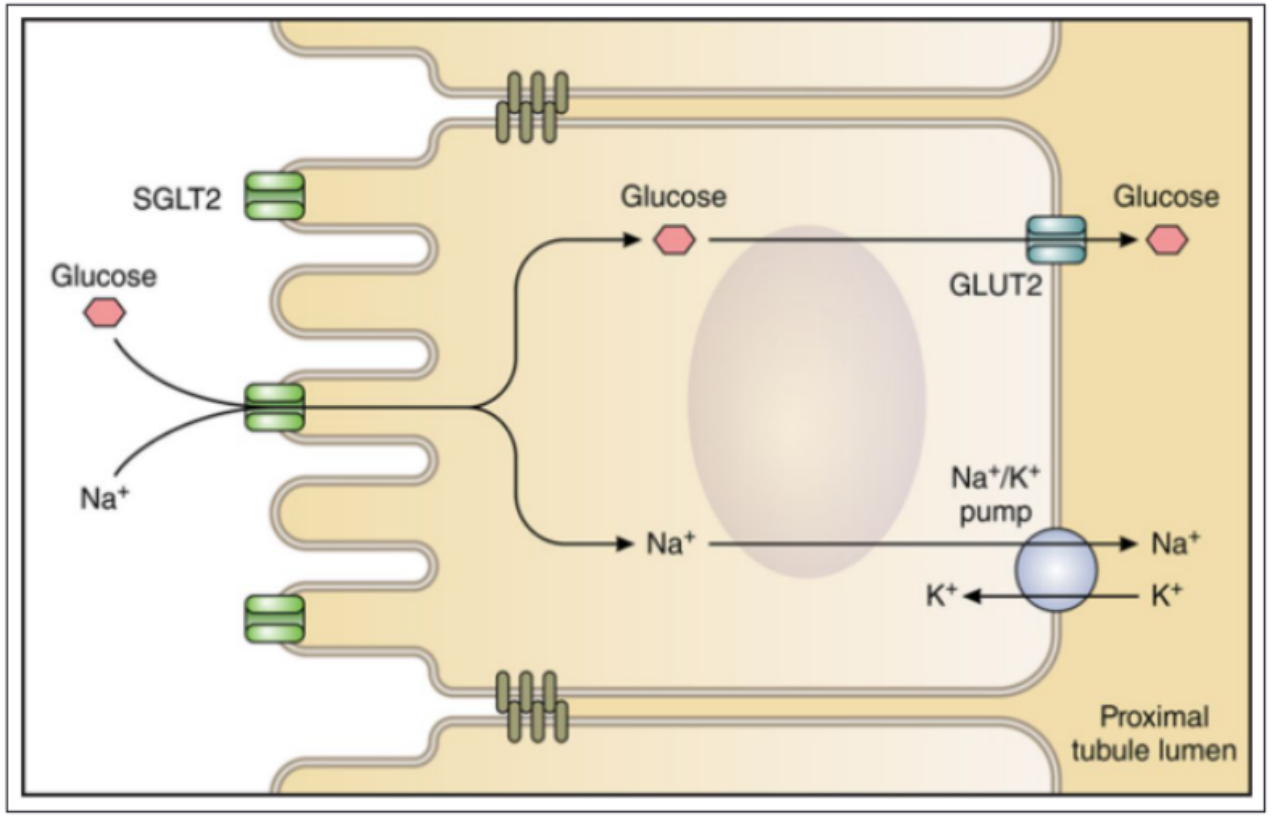


Figure 1. The sodium-glucose cotransporter-2 (SGLT2) mechanism in the proximal tubule. Modified from Bakris et al[4] with permission of the publisher. Copyright © 2009, Elsevier.

SGLT2 inhibitors: Summary of CV Outcome Trials

	MACE HR (95%CI)	CV Death HR (95%CI)	HHF HR (95%CI)
EMPA-REG (empagliflozin)	0.86 (0.74-0.99)	0.62 (0.49-0.77)	0.65 (0.50-0.85)
CANVAS (canagliflozin)	0.86 (0.75-0.97)	0.87 (0.72-1.06)	0.67 (0.52-0.87)
DECLARE-TIMI (dapagliflozin)	0.93 (0.84-1.03)	0.98 (0.82-1.17)	0.73 (0.61-0.88)
VERTIS-CV (ertugliflozin)	0.97 (0.85-1.11)	0.92 (0.77-1.11)	0.70 (0.54-0.90)

MACE = composite of death from CV cause, nonfatal MI and nonfatal stroke; CV death = cardiovascular death; HHF = hospitalization for heart failure

SGLT-2 inhibitors in patients with heart failure and reduced ejection fraction (with and without diabetes)

	Dapagliflozin (DAPA-HF)	**Empagliflozin (EMPEROR HF)**
Proportion without diabetes	58%	50%
Duration	1.5 years	1.3 years
Primary Outcome Composite Components	CV death, urgent visit or Hospitalization for HF	CV death or Hospitalization for HF
Primary Outcome [HR (95% CI)]	**0.74 (0.65 to 0.85)**	**0.75 (0.65 to 0.86)**
CV Death or Hospitalization HF	**0.75 (0.65 to 0.85)**	**0.75 (0.65 to 0.86**)
CV death	**0.82 (0.69 to 0.98)**	0.92 (0.75 to 1.12)
Hospitalizations HF	**0.70 (0.59 to 0.83)**	**0.69 (0.59 to 0.81)**
All-cause mortality	0.83 (0.71 to 0.97)	0.92 (0.77 to 1.10)

Guerron AD, Davis GM, Pasquel FJ. Advances in Pharmaco-Therapeutics, Metabolic Surgery, and Technology for Diabetes. Endocrinol Metab Clin North Am. In press.

SGLT2 Inhibitors: Summary of CV Outcome Trials

For T2D patients with or *without established CVD*

- Reduced hospitalization for heart failure
- Renoprotection

For T2D patients *with established CVD*

- Reduced MACE (EMPA-REG, CANVAS, CREDENCE)
- Reduced hospitalization for heart failure
- Renoprotection
- Some cases of reduced mortality (EMPA-REG, CREDENCE)

Cardiorenal benefit also shown in patients without diabetes (DAPA-CKD, DAPA-HF, EMPEROR HF) [1]

SGLT2 Inhibitors: Adverse Effects

- Genital mycotic infections (women › men)
- Urinary tract infections
- Polyuria
- Volume depletion/hypotension/dizziness
- ↑ LDL-C
- ↑ Creatinine (transient)
- DKA/ euglycemic DKA
- Increased rate of lower extremity amputations (seen in CANVAS, not CREDENCE)
  - CANVAS: numerically low numbers but statistically significant; 6.3 vs. 3.4%, HR 1.97 (95%CI 1.41-2.75)
- Side effect of Fournier's gangrene
- Increased risk of bone fractures

Glucagon-Like Peptide 1 Receptor Agonists (GLP-1RA)

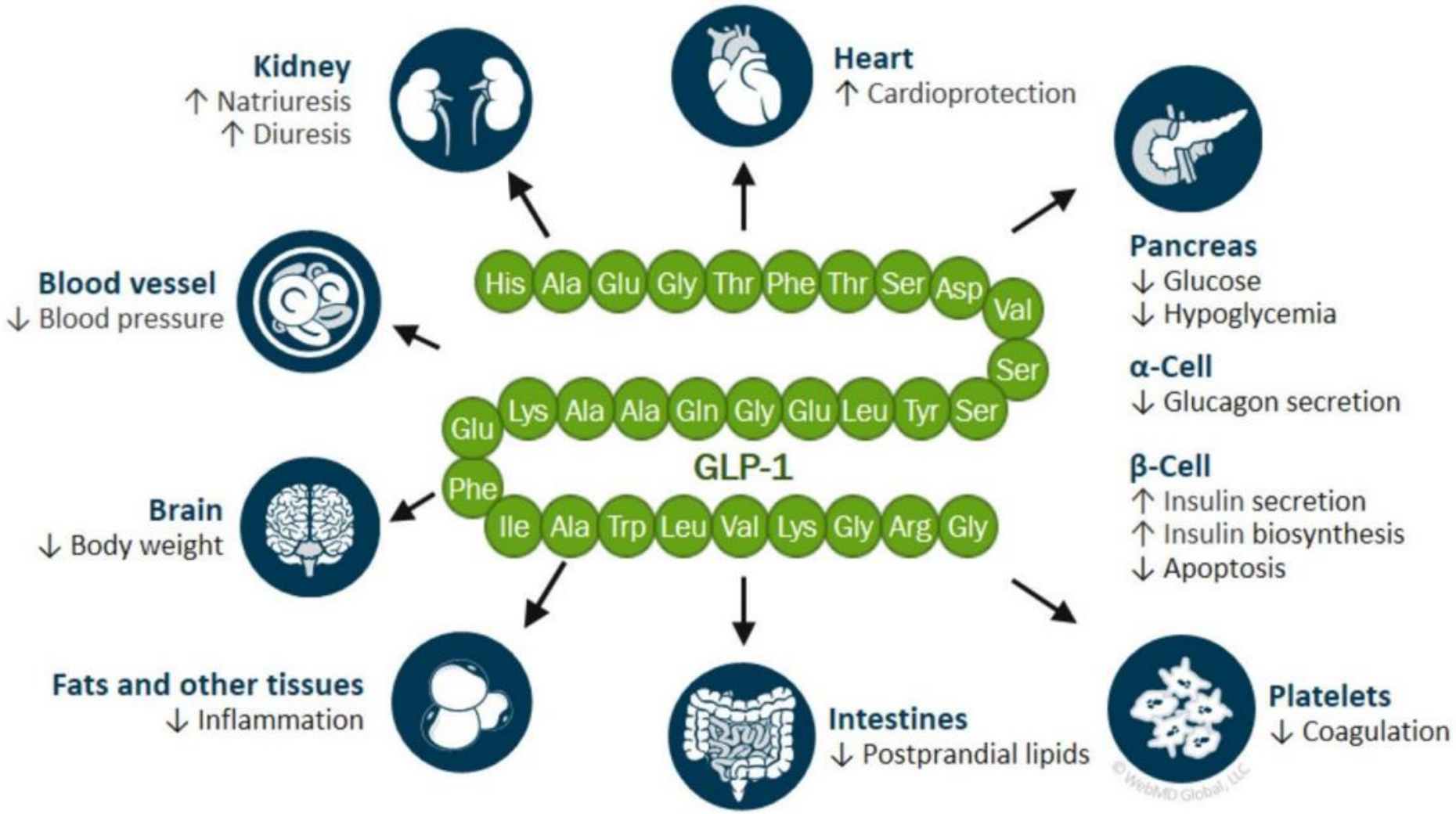
Currently available drugs:

- Exenatide (Byetta, Bydureon)
- Liraglutide (Victoza)
- Lixisenatide (Adlyxin, component of Soliqua) (Available in US as a fixed ratio combination drug)
- Semaglutide (Ozempic, Rybelsus)
- Dulaglutide (Trulicity)

Mechanisms for Cardioprotection:

- GLP-1 receptor is expressed in cardiomyocytes and coronary endothelial cells
- Improved left ventricular and endothelial function

GLP-1 RAs: Mechanism of Action



Drucker DJ. *Cell Metab.* 2016;24:15-30.

GLP-1 RA: Summary of CV Outcome Trials

	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide
MACE, HR (95% CI)	1.02 (0.89-1.17)	**0.87 (0.78-0.97)**	**0.74 (0.58-0.95)**	0.91 (0.83-1.00)	**0.78 (0.68-0.90)**	**0·88 (0.79-0.99)**
CV death, HR (95% CI)	0.98 (0.78-1.22)	**0.78 (0.66-0.93)**	0.98 (0.65-1.48)	0.88 (0.76-1.02)	0.93 (0.73-1.19)	0·91 (0.78-1.06)
Fatal or nonfatal MI, HR (95% CI)	1.03 (0.87-1.22)	0.86 (0.73-1.00)	0.74 (0.51-1.08)	0.97 (0.85-1.10)	**0.75 (0.61-0.90)**	0·96 (0.79-1.15)
Fatal or nonfatal stroke, HR (95% CI)	1.12 (0.79-1.58)	0.86 (0.71-1.06)	**0.61 (0.38-0.99)**	0.85 (0.70-1.03)	0.86 (0.66-1.14)	**0·76 (0.62-0.94)**
All-cause mortality, HR (95% CI)	0.94 (0.78-1.13)	**0.85 (0.74-0.97)**	1.05 (0.74-1.50)	**0.86 (0.77-0.97)**	0.95 (0.79-1.16)	0.90 (0.80-1.01)
HF hospitalization, HR (95% CI)	0.96 (0.75-1.23)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.94 (0.78-1.13)		0·93 (0.77-1.12)

GLP1 Receptor Agonists Summary of CV Outcome Trials

- All trials met non-inferiority
- Superiority for MACE
  - Semaglutide, liraglutide, albiglutide, dulaglutide
- Reduced ischemic events (stroke or MI)
- Renoprotection in meta-analysis (mediated by reduction in albuminuria)
- Potential benefit for heart failure hospitalization (small effect in meta-analysis)
- Mortality benefit seen only in LEADER

GLP1 Receptor Agonists Benefits

- ↓ Postprandial glucose excursions
- Weight loss
  - Average weight loss of 2-4 kg
- Increased satiety
- ↓ LDL-C and ↓triglycerides
- Low rate of hypoglycemia
- Cardiac and renal protection

GLP-1 RA: Adverse Effects

- Gastrointestinal side effects
  - Nausea, vomiting most common
  - Diarrhea
  - Association with acute gallstone disease
- ↑ Heart rate
- Acute pancreatitis
  - Risk not confirmed in CVOT

GLP1 Receptor Agonists: Adverse Effects

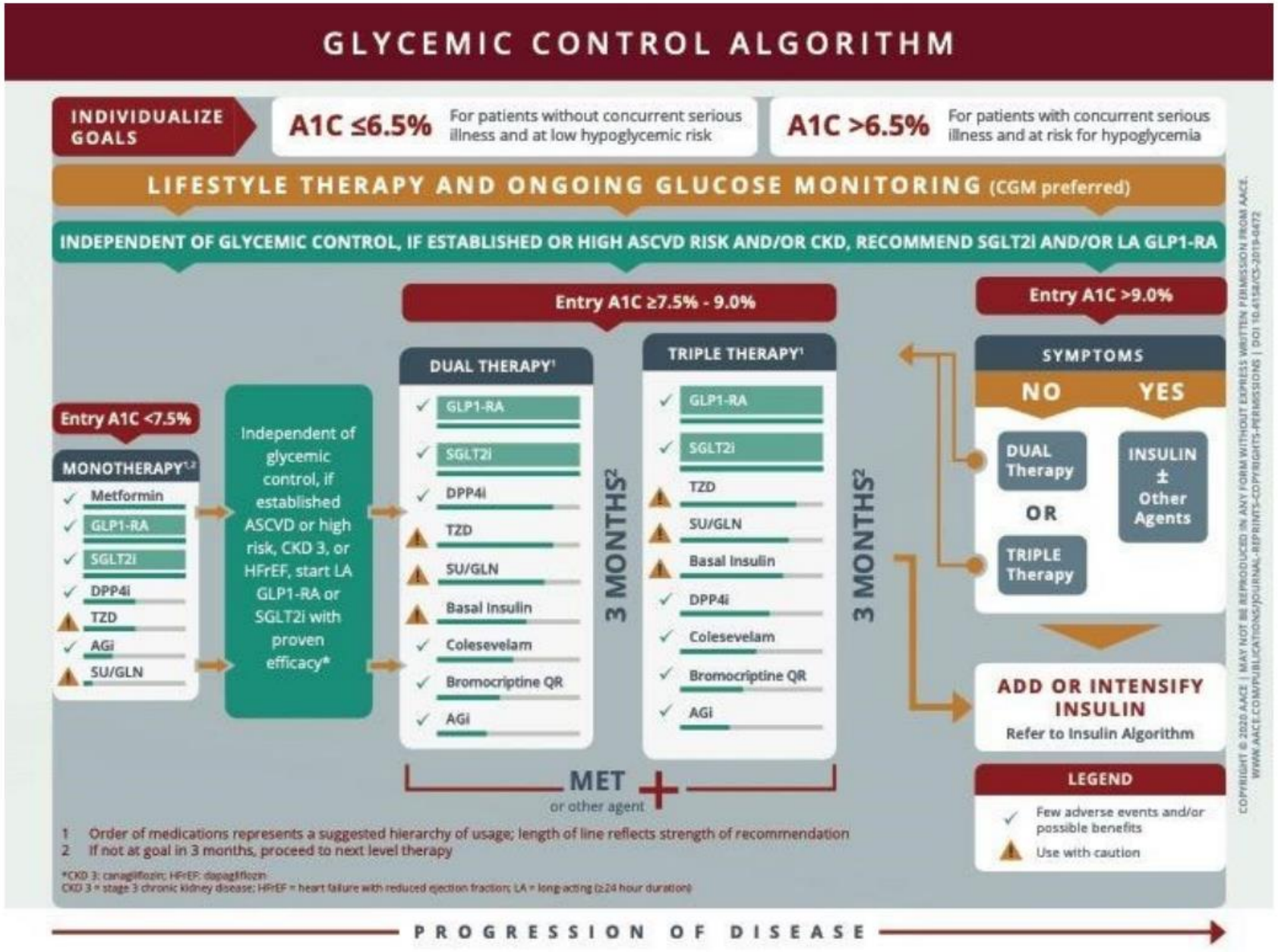
- C-cell hyperplasia/medullary thyroid tumors in animals . Do not prescribe if personal or family history of multiple endocrine neoplasia syndrome type 2.
- Increased risk of worsening retinopathy with semaglutide
  - SUSTAIN-6 trial: semaglutide vs. placebo, 3.0 vs. 1.8%, HR 1.76, 95% CI 1.11-2.78.

Drug selection: SGLT2-i vs. GLP1-RA

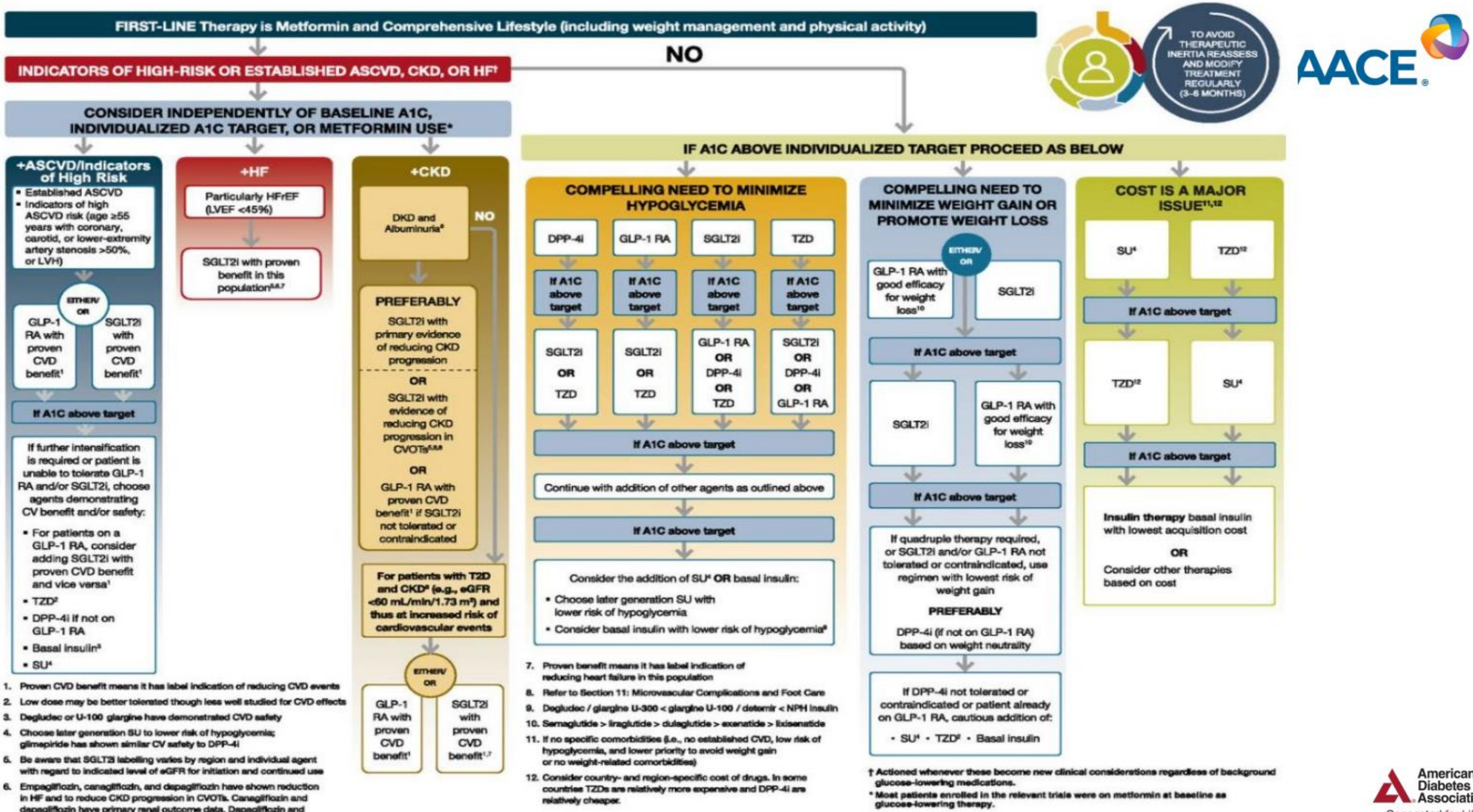
AACE/ADA/EASD/ACC

- Can begin with metformin monotherapy for T2D but consider adding GLP-1 RA or SGLT2-i independent of HbA1c target.
- Can consider beginning therapy with GLP-1 RA or SGLT2-i prior to metformin in patients with higher risk.

- **If atherosclerotic CVD or stroke predominates:**
  Choose GLP-1 RA with proven benefit
- **If heart failure or CKD predominates:**
  Choose SGLT2-I with proven benefit



ACE/ACE Comprehensive Type 2 Diabetes Algorithm App. American Association of Clinical
docrinologists (AACE) 25th Annual Scientific & Clinical Congress, May 25-29, 2016. Orlando, FL.



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. 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)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

American Diabetes Association.
Connected for Life

Medication Access/Medication Cost

- Despite promising data described above, many patients are unable to utilize these classes of medications due to high cost involved and economic hardship.
- Uninsured patients, and even some insured patients, with high copays or deductibles may be limited in their ability to obtain diabetes medications with the best profiles for organ protection.
- Often a particular insurance company will only cover one agent within a particular class so ability to select a specific drug may be limited.
- Be aware of limitations when prescribing and consider options for cost-reduction or alternative medications if cost remains prohibitive.

Conclusions

Diabetes is a multifactorial disease

Many people with T2DM have ASCVD, kidney disease, and/or HF

Role for PCPs, cardiologists, nephrologists, and diabetologists in risk management for T2DM and CVD, or CKD, or risk factors

We can prevent progression of diabetes complications

Latest guidelines recommend SGLT2 inhibitors and GLP-1 RAs for organ protection in individualized diabetes care

Novel glucose-lowering drugs have a role beyond T2DM: in HF, ASCVD, and kidney disease