Jorge De Jesús MD

Mastering the outpatient Type 2 Management

Objectives:

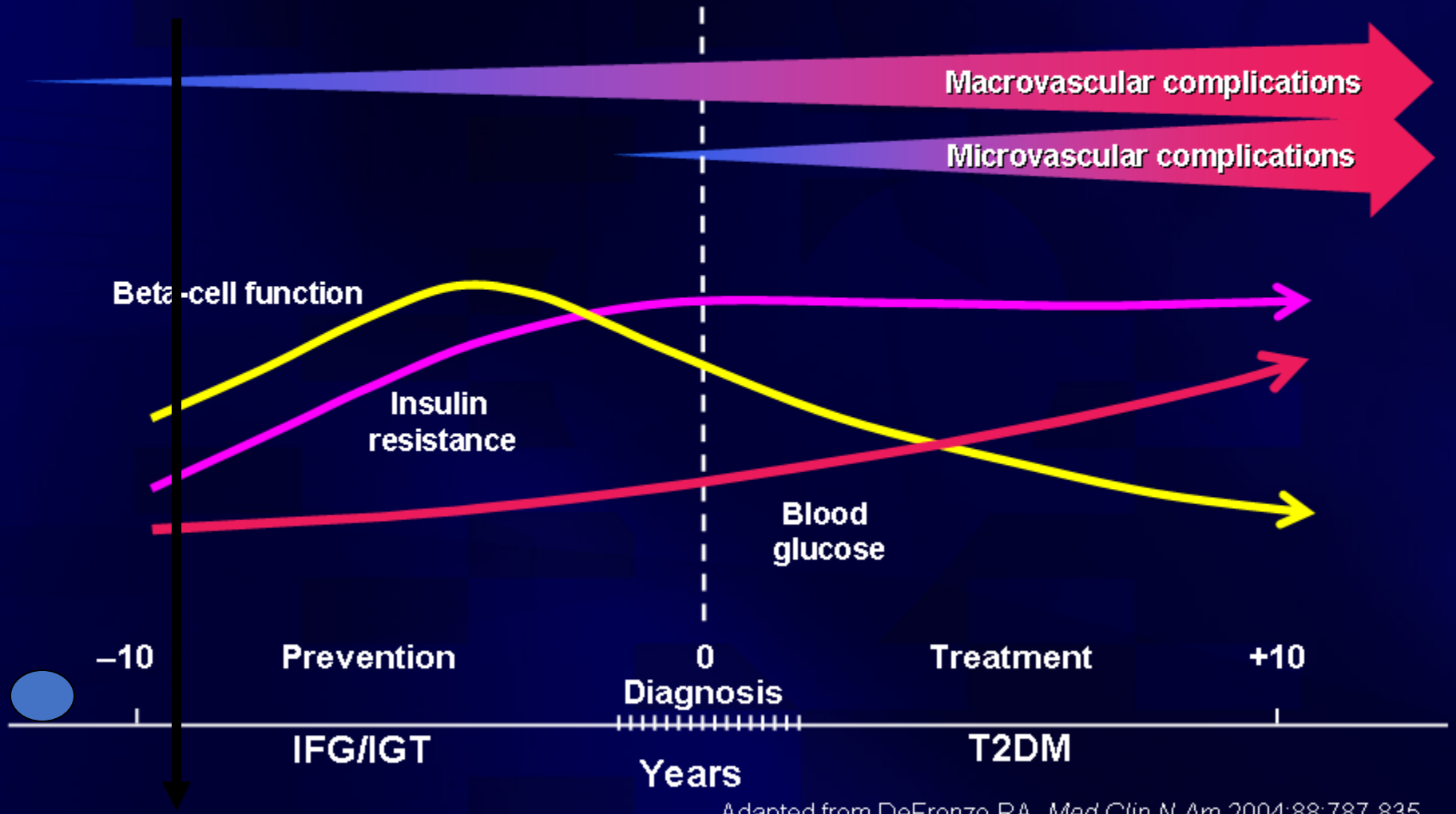
After this presentation you will be able to recognize:

.Diabetes Mellitus is a progressive disease

.Prevention is possible for selected high risk individuals

- Outline the clinical considerations in the selection of pharmacotherapy for type 2 diabetes, including degree of A1C lowering achieved, patient-specific concerns, adverse drug reactions, and contraindications
- Discuss the role and timing of combination therapy in achieving A1C goals
- Explain the implications of recent, large randomized clinical trials on clinical decision-making
- Modifications in 2019 ADA guidelines based on recent RCT trials

T2DM is a progressive disease: Do microvascular and macrovascular complications begin at different times?



Adapted from DeFronzo RA. *Med Clin N Am* 2004;88:787-835.

LIFESTYLE THERAPY

RISK STRATIFICATION FOR DIABETES COMPLICATIONS

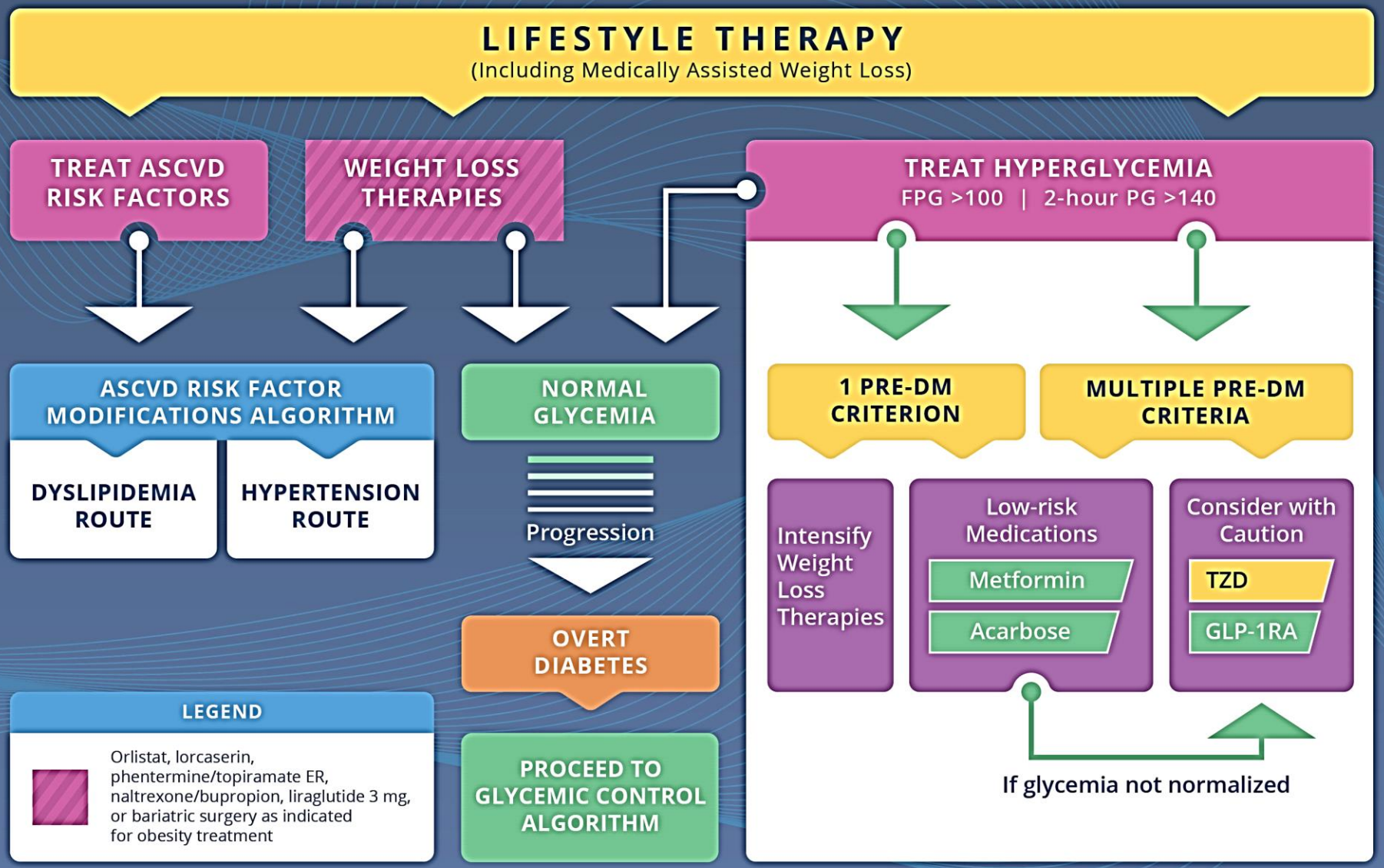
INTENSITY STRATIFIED BY BURDEN OF OBESITY AND RELATED COMPLICATIONS

Nutrition	• Maintain optimal weight • Calorie restriction (if BMI is increased) • Plant-based diet; high polyunsaturated and monounsaturated fatty acids	• Avoid *trans* fatty acids; limit saturated fatty acids	• Structured counseling • Meal replacement
Physical Activity	• 150 min/week moderate exertion (e.g., walking, stair climbing) • Strength training • Increase as tolerated	• Structured program • Wearable technologies	• Medical evaluation/ clearance • Medical supervision
Sleep	• About 7 hours per night • Basic sleep hygiene	• Screen OSA • Home sleep study	• Referral to sleep lab
Behavioral Support	• Community engagement • Alcohol moderation	• Discuss mood with HCP	• Formal behavioral therapy
Smoking Cessation	• No tobacco products	• Nicotine replacement therapy	• Referral to structured program

 DOI 10.4158/CS-2018-0535

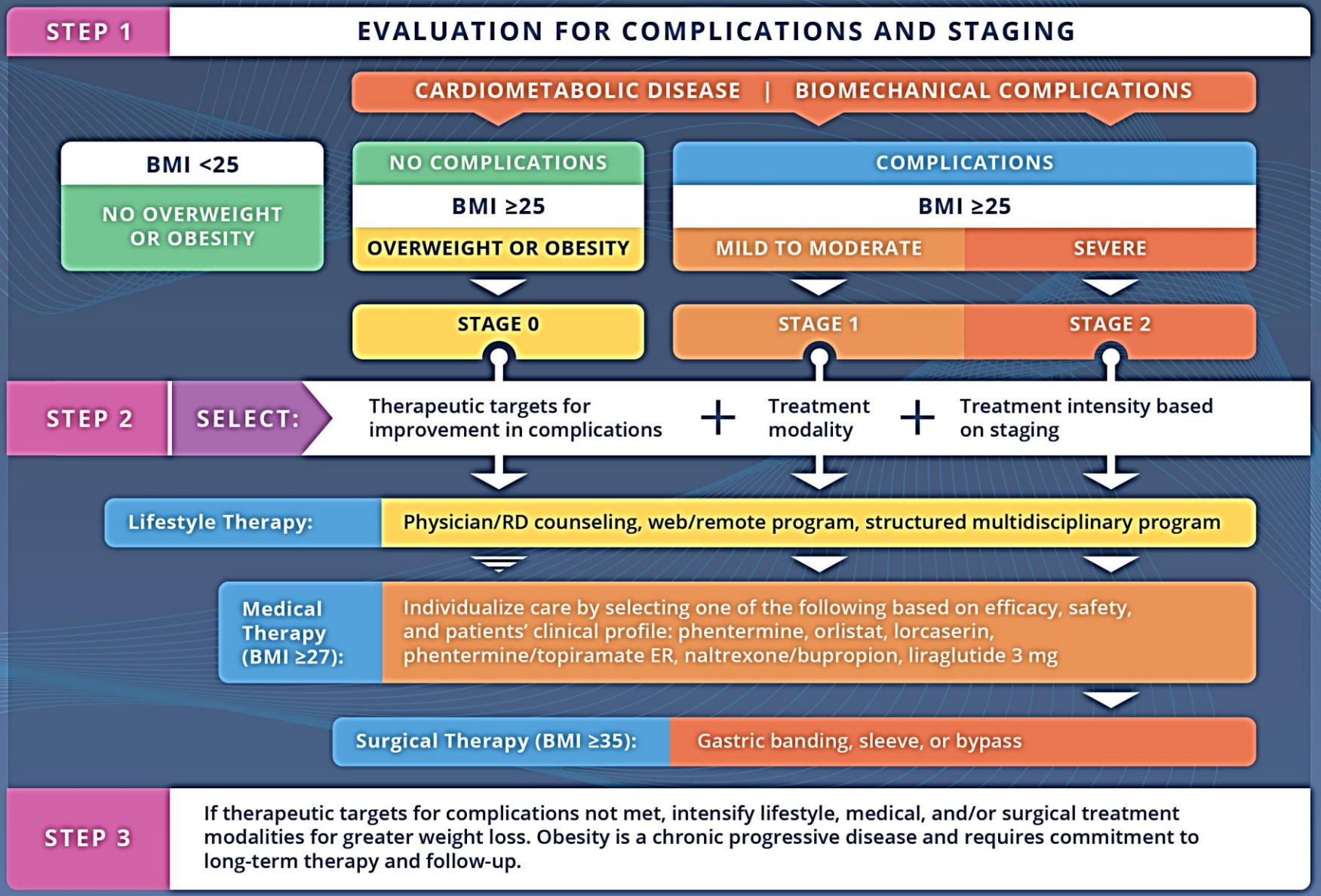
PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)



 DOI 10.4158/CS-2018-0535

COMPLICATIONS-CENTRIC MODEL FOR CARE OF THE PATIENT WITH OVERWEIGHT/OBESITY



 DOI 10.4158/CS-2018-0535

CMS Finalizes Expanded Diabetes Prevention Program

In its just-released final rule for the 2018 physician fee schedule (PFS), the Centers for Medicare & Medicaid Services (CMS) issued detailed regulations for the expanded model of the Medicare Diabetes Prevention Program (MDPP). Under this expanded model, which builds on an earlier test of MDPP and was announced in 2016, CMS will add MDPP as a covered benefit for Medicare beneficiaries who meet certain criteria, starting on April 1, 2018.

MDPP is designed to supply coaching services to prediabetic patients to help them lose weight and avoid developing type 2 diabetes. Community health workers and health professionals will supply these services in community and healthcare settings.

"The sessions provide practical training in long-term dietary change, increased physical activity, and problem-solving strategies for overcoming challenges to maintaining weight loss and a healthy lifestyle," the final rule said.

The set of MDPP services includes core sessions (first 6 months), core maintenance sessions (second 6 months), and ongoing maintenance sessions (second year). Sixteen weekly sessions must be completed within the first 6 months, when the likelihood of losing weight is greatest.

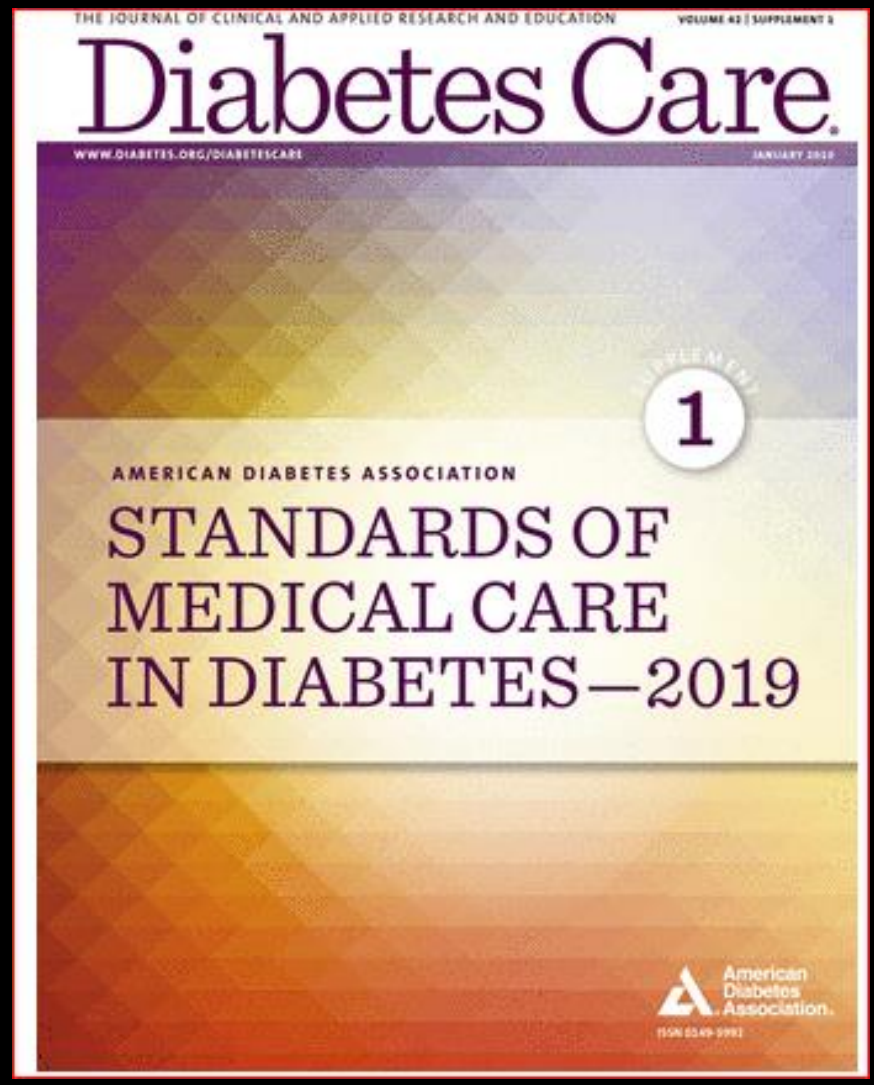
Individualize

Choose A1c goal

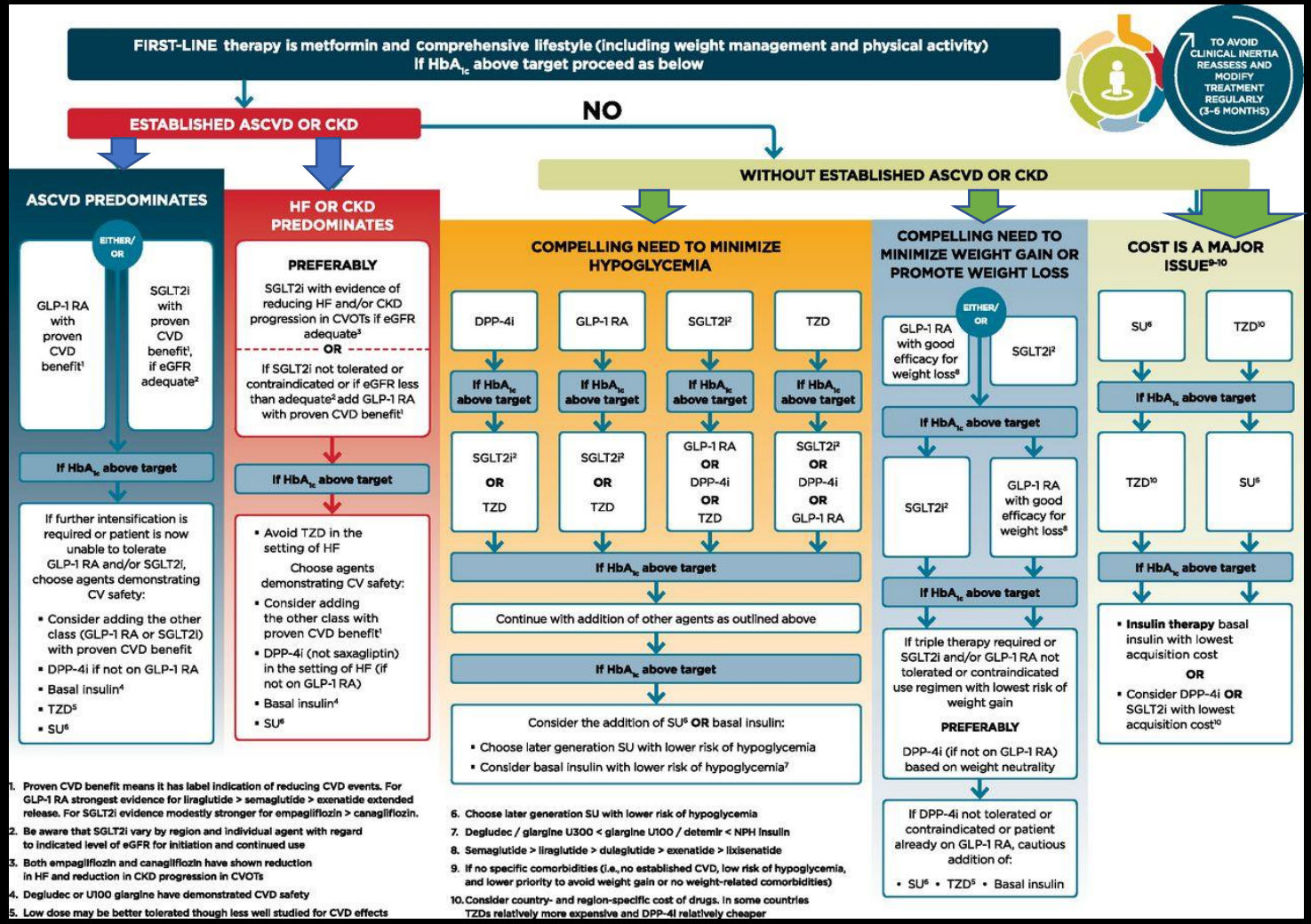
7% for most patients

< 7% younger with few comorbidities

Older group with multiple
Comorbidities could be around 8%



Glucose-lowering medication in type 2 diabetes: overall approach.



American Diabetes Association Dia Care 2019;42:S90-S102

10: COST !!!

American Diabetes Association

Case 1: Carmen

55 year-old female with **newly** diagnosed type 2 diabetes

Active: she takes care of her grandchildren while their mother works

Too busy to exercise. Eats the same food as her grandchildren

No alcohol

Has hypertension and sleep apnea

No history of pancreatitis, no abnormal liver function, or CHF

On physical examination , she is alert oriented cooperative no acute distress

Height: 64” Weight 188# BMI=33
BP=160/100
Foot Exam : normal pulses ; normal sensory

Fundoscopy , no retinopathy
A1c=7.4%;
creatinine .9 mg /dL;
no microalbuminuria;
LDL=146 mg /dL
Current Medications:
Valsartan 80 mg ; Atenolol 50mg ;
HCT 25 po daily

Dr Jose Garcia Mateo

Dr Banch

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

DYSLIPIDEMIA

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

LIPID PANEL: Assess ASCVD Risk

STATIN THERAPY
If TG >500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

Intensify therapies to attain goals according to risk levels

RISK LEVELS	HIGH	VERY HIGH	EXTREME
	DESIRABLE LEVELS	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70	<55
Non-HDL-C (mg/dL)	<130	<100	<80
TG (mg/dL)	<150	<150	<150
Apo B (mg/dL)	<90	<80	<70

RISK LEVELS:
- **HIGH:** DM but no other major risk and/or age <40
- **VERY HIGH:** DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4)*
- **EXTREME:** DM plus established clinical CVD

If not at desirable levels: Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

To lower LDL-C: Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin
To lower Non-HDL-C, TG: Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
To lower Apo B, LDL-P: Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin
To lower LDL-C in FH:** Statin + PCSK9i

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED ** FAMILIAL HYPERCHOLESTEROLEMIA

HYPERTENSION

GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg

ACEi or ARB

For initial blood pressure >150/100 mm Hg:
DUAL THERAPY

ACEi or ARB + Calcium Channel Blocker ✓ / ß-blocker ✓ / Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, ß-blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical

 DOI 10.4158/CS-2018-0535

Medscape Nephrology > Viewpoints

COMMENTARY

Is Metformin Safe for Patients With Chronic Kidney Disease?

Lynda Szczech, MD, MSE

Biguanides

Metformin

Endocrine Practice

Metformin: Nonglycemic Effects and Potential Novel Indications

Mechanism	↕ Insulin sensitivity Hepatic glucose production ↓↓ FPG more than PPG
Efficacy	↓ A1C 1%-2%
Advantages	No weight gain or hypoglycemia, potential weight loss
Disadvantages	GI side effects Lactic acidosis *(rare)*
Contraindications	Renal disease; CHF

Combinations available with SU, TZD, repaglinide, and DPP-4 inhibitors

A1C = glycated hemoglobin; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GI = gastrointestinal; PPG = post-prandial glucose; SU = sulfonylurea; TZD = thiazolidinedione

Metformin [package insert]. Princeton NJ; Bristol Myers Squibb; 2009.

Metformin Background Treatment

- Low risk of Hypoglycemia
- Does NOT promote weight gain
- Good antihyperglycemic efficacy
- Durable effects
- Robust cardiovascular safety
- Vitamin B12 malabsorption and deficiency in 16% of users

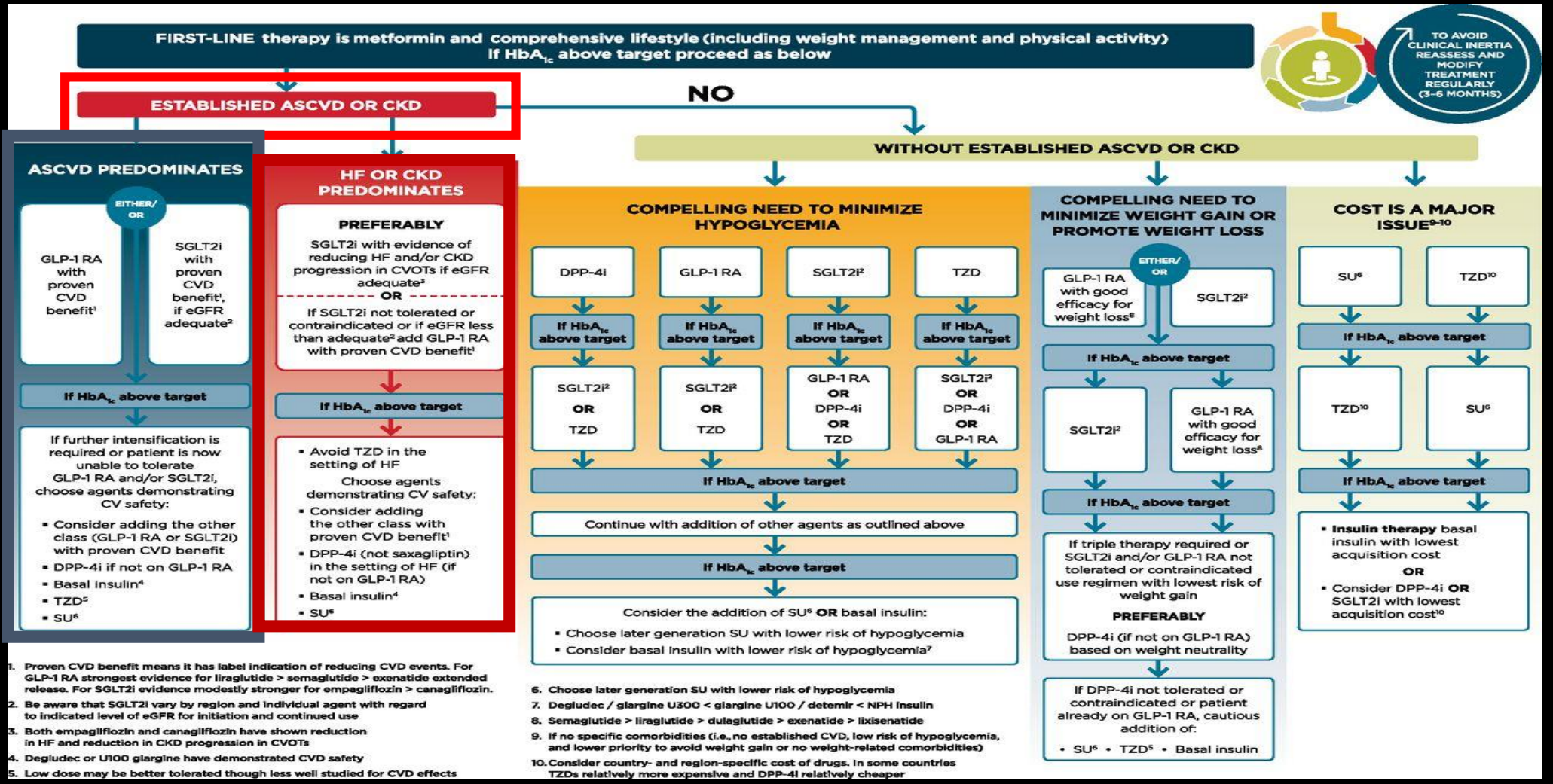
- Dosing is adjusted in eGFR
  - Under 30 ml/min:
    - Do NOT use
  - 30-45 ml/min:
    - Do NOT start metformin
    - Adjust to Max dose ~1000mg/day
  - 45-60 ml/min:
    - Can use full dose but monitor renal function every 3-6 months

Garber AJ ***Endocrine Practice*** 2018; 24:91.
Lipska, KJ ***Diabetes Care*** 2011;34:1431.

After Metformin what do we use??

What we all struggle with is what to choose as our second medicine, and this is where the new guidelines provide some very clear advice. We start by asking: Does the patient have established cardiovascular (CV) disease, congestive heart failure (CHF), or renal disease? If they do (and that encompasses about 20% of our patients), then we start with either a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a glucagon-like peptide-1 receptor agonist (GLP-1RA) with proven CV benefit. The GLP-1s are preferred if someone's main issue is atherosclerotic heart disease. Evidence of benefit is strongest for liraglutide, favorable for semaglutide, and less certain for exenatide. With the release of the topline results from the REWIND trial, which were issued after the guidelines were published, we now know that dulaglutide has CV benefit in a broad population and is also on the map.

Glucose-lowering medication in type 2 diabetes: overall approach.



American Diabetes Association Dia Care 2019;42:S90-S102

GLP1-RA Increase Active Incretin Levels

Exenatide (Byetta-Bydureon)

Liraglutide (Vyctoza)

Dulaglutide (Trulicity)

Lixisenatide

Semaglutide (Ozempic)

Normal Physiology

Active GLP-1

DPP-4

Inactive GLP-1

GLP-1 RA

DPP-4 inhibitor

Resistance

Increased circulating GLP-1 levels

- ***Increased insulin secretion***
- ***Decreased glucagon release***

Glucose control improved

GLP-1 = glucagon-like peptide-1; GLP1-RA = glucagon-like peptide-1 receptor agonist; DPP-4 = dipeptidyl peptidase 4

Umpierrez et al. Endocrine Practice 2014

Reduction in CV Death, Nonfatal MI, and Nonfatal Stroke With Some GLP-1 Receptor Agonists

Exenatide (less certain)

Dulaglutide (benefit)

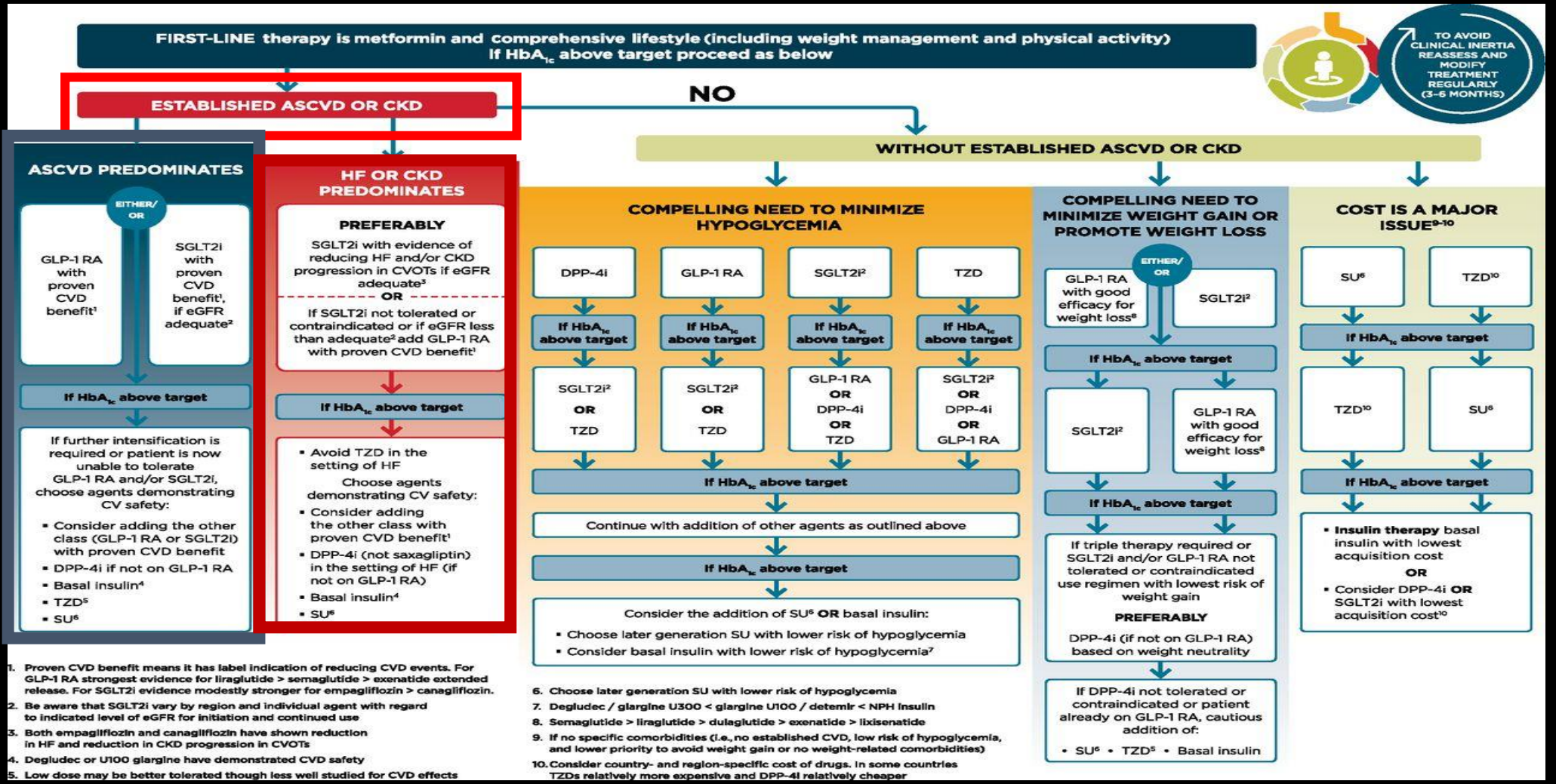
	LEADER (liraglutide) N = 9340[a]	SUSTAIN-6 (semaglutide) N = 3297[b]
Primary composite endpoint	CV death, MI, or stroke HR = 0.87 (0.78, 0.97) *P* < .001 for noninferiority *P* = .01 for superiority	CV death, MI, or stroke HR = 0.74 (0.58, 0.95) *P* < .001 for noninferiority *P* = .02 for superiority
CV death	0.78 (0.66, 0.93) *P* = .007	0.98 (0.65, 1.48) *P* = .92
Nonfatal MI	0.86 (0.73, 1.00) *P* = .046	0.74 (0.51, 1.08) *P* = .12
Nonfatal stroke	0.86 (0.71, 1.06) *P* = .16	0.61 (0.38, 0.99) *P* = .04
Hospitalization for HF	0.87 (0.73, 1.05) *P* = .14	1.11 (0.77, 1.61) *P* = .57

a. Marso SP, et al. *N Engl J Med*. 2016;375:311-322; b. Marso SP et al. *N Engl J Med*. 2016;375:1834-1844.

GLP-1 RA limitations and special considerations

- Nausea
- … pancreatitis
- …MTC and associated multiple endocrine neoplasia
- …renal for exenatide
- … parenterals

Glucose-lowering medication in type 2 diabetes: overall approach.

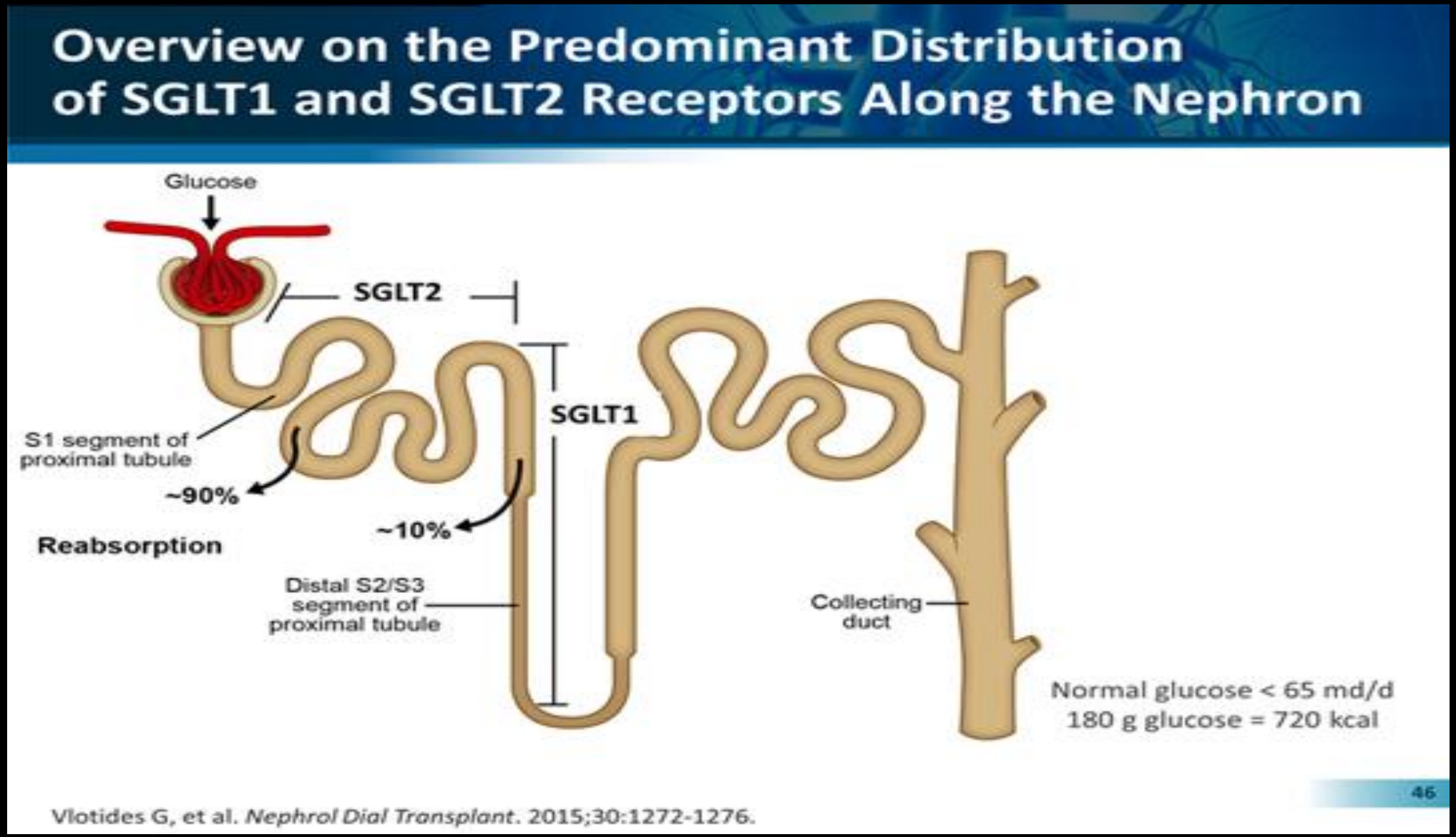


1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent 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

American Diabetes Association Dia Care 2019;42:S90-S102

American Diabetes Association.

Sodium/Glucose cotransporter



SGLT2 Inhibitors

- Mechanism of action:
  - Decrease re-absorption of glucose in the proximal convoluted tubule
  - Decrease renal threshold so urinary glucose excretion occurs at lower plasma glucose concentration
- FDA-approved
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin
  - Ertuglifozin

FDA = U.S. Food and Drug Administration; SGLT-2 = sodium-dependent glucose cotransporters-2.

Bays, H. Diabetes Therapy, 2013.

SGLT2

Among SGLT2s, we have excellent outcome data on empagliflozin and canagliflozin, both of which are mentioned in the guidelines. But things are happening quickly. After the guidelines came out, the DECLARE trial[3] results, looking at dapagliflozin, were published. That trial did not show a lower rate of MACE (major adverse cardiovascular events) with dapagliflozin, but treatment with the drug did result in a lower rate of CV death or hospitalization for heart failure. So the SGLT2s are also on the map.

Empaglifozin—Jardiance
Canaglifozin---Invokana
Dapaglifozin---Farxiga

EMPA-REG OUTCOME and CANVAS CVOTs

CVOT	Patient Population
EMPA-REG OUTCOME[a] N = 7020	99% of patients had prior CV event (obstructive coronary lesions or revascularization, nonfatal MI, nonfatal stroke, evidence of occlusive peripheral vascular disease)
CANVAS, CANVAS-R[b] N = 10142	33% of patients at risk for CV events 66% of patients had established CV events

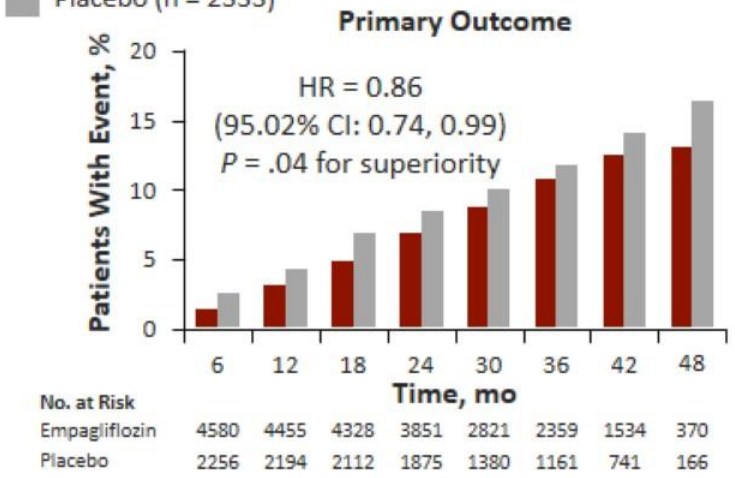
3-point MACE: nonfatal MI, nonfatal stroke, and CV death[a,b]

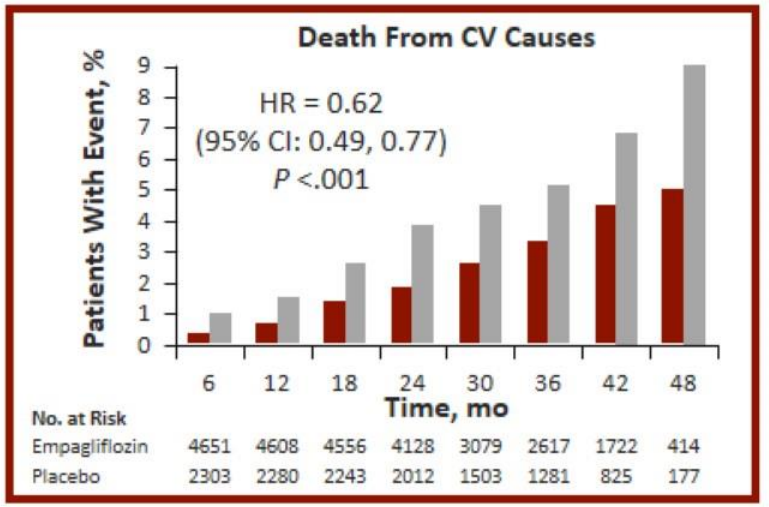
a. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128; b. Neal B, et al. *N Engl J Med*. 2017;377:644-657.

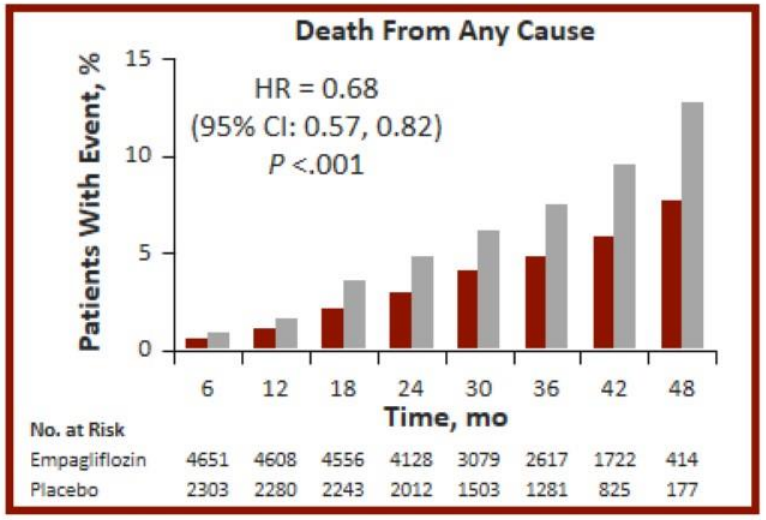
EMPA-REG OUTCOME CV Outcome Trial: Empagliflozin Reduced CV Mortality

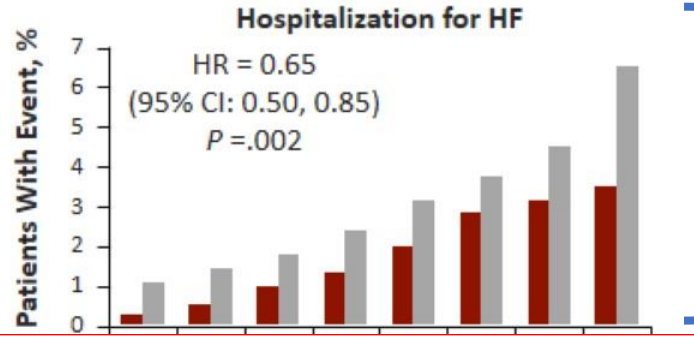
Empagliflozin (n = 4687)

Placebo (n = 2333)









?

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

FDA News Release

FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes

Study links Jardiance to improved survival in patients with type 2 diabetes with cardiovascular disease

Canagliflozin Reduced MACE Similarly to Empagliflozin in the CANVAS CV Outcome Trial

	CANVAS[a] (canagliflozin) N = 10,142	EMPA-REG OUTCOME[b] (empagliflozin) N = 7034
Primary composite endpoint	**CV death, nonfatal MI, or nonfatal stroke HR = 0.86 (0.75, 0.97) *P* < .001 for noninferiority *P* = .02 for superiority**	**CV death, MI, or stroke HR = 0.86 (0.74, 0.99) *P* < .001 for noninferiority *P* = .04 for superiority**
CV death	0.87 (0.72, 1.06)	0.62 (0.49, 0.77) *P* < .001
Nonfatal MI	0.85 (0.69, 1.05)	0.87 (0.70, 1.09) *P* = .23
Nonfatal stroke	0.90 (0.71, 1.15)	1.24 (0.92, 1.67) *P* = .16
Hospitalization for UA	--	0.99 (0.74, 1.34) *P* = .97
Hospitalization for heart failure	0.67 (0.52, 0.87)	0.65 (0.50, 0.85) *P* = .002

a. Neal B, et al. *N Engl J Med*. 2017;377:644-657; b. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

Canaglifozin New Approved Indications *

Indicated as adjunct to diet and exercise to improve glycemic events in adults with Type 2 Diabetes Mellitus

Indicated to reduce major adverse cardiovascular events

Cardiovascular Death, Non fatal Myocardial Infarction, non fatal stroke In adults with Type 2 Diabetes Mellitus and established cardiovascular disease

Canaglifozin (Invokana) Package Insert.

DECLARE-TIMI58 and VERTIS-CV
Demographics

DECLARE-TIMI58 (dapagliflozin)[a,b]

	Total (N = 17,160)	CVD (n = 6971)	Multiple Risk Factors (n = 10,189)
Men, *n* (%)	10738 (62.6)	5023 (72.1)	5715 (56.1)
Mean age, y (± SD)	63.8 (6.8)	62.5 (8.1)	64.7 (5.6)
Mean HbA_{1c} (%)	9.7	9.7	9.7
Cardiac history, n (%) HF	1698 (9.9)	1133 (16.3)	565 (5.5)

VERTIS-CV (ertugliflozin)[c]

	Total (N = 8237)
Men, *n* (%)	5763 (70.0)
Mean age, y	64.4
Mean HbA_{1c} (%)	8.3

a. ClinicalTrials.gov. NCT01730534; b. Raz I, et al. *Diabetes Obes Metab*. 2018;20:1102-1110; c. Cannon CP, et al. ACC 2018. Poster 1212-406.

Higher Risk for Amputations in Patients Taking Canagliflozin

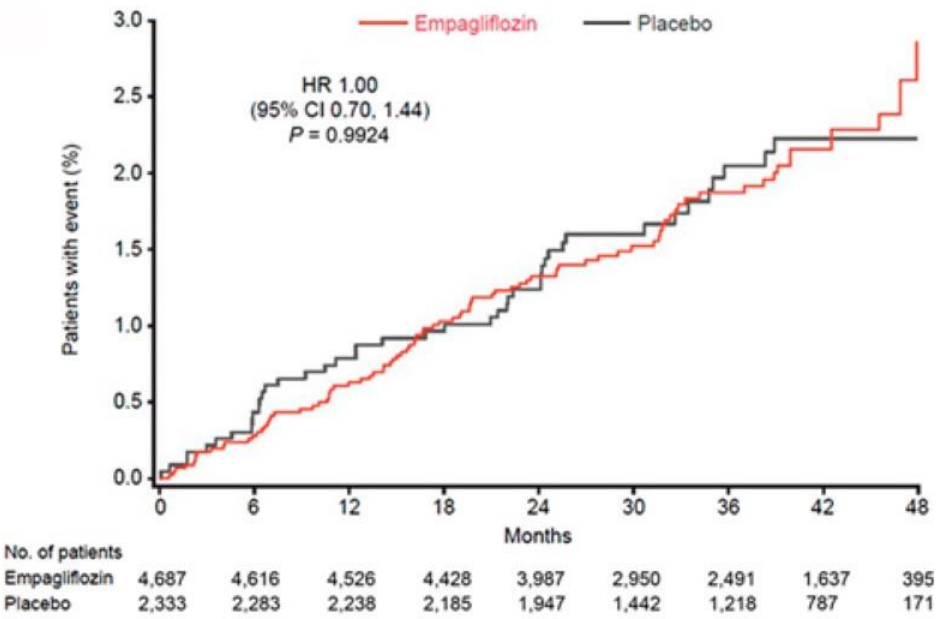
- 2-fold excess risk for amputations in patients who take canagliflozin compared with placebo
- ~ 180 amputations, 71% of those amputations were toes and metatarsal bones
- 3 independent risk factors for amputation identified across CANVAS program, whether the participant received canagliflozin or placebo

Exert caution in people who have 1) a prior amputation, 2) neuropathy, or 3) PVD; canagliflozin may not be the best antihyperglycemic agent in these situations

Neal B, et al. *N Engl J Med*. 2017. [Epub ahead of print]

EMPA-REG OUTCOME and CANVAS
Lower Limb Amputations

EMPA-REG OUTCOME[a]



- CANVAS, CANVAS-R[b]
- 92% of the patients who eventually had an amputation, a premorbid event of either an infection or an ulcer was identified

Perform foot exams and discuss foot care

a. Inzucchi SE, et al. *Diabetes Care*. 2018;41:e4-e5; b. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

ORIGINAL ARTICLE FREE PREVIEW

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

Stephen D. Wiviott, M.D., Itamar Raz, M.D., Marc P. Bonaca, M.D., M.P.H., Ofri Mosenzon, M.D., Eri T. Kato, M.D., M.P.H., Ph.D., Avivit Cahn, M.D., Michael G. Silverman, M.D., M.P.H., Thomas A. Zelniker, M.D., Julia F. Kuder, M.A., Sabina A. Murphy, M.P.H., Deepak L. Bhatt, M.D., M.P.H., Lawrence A. Leiter, M.D., et al., for the DECLARE–TIMI 58 Investigators*

January 24, 2019
N Engl J Med 2019; 380:347-357
DOI: 10.1056/NEJMoa1812389

Abstract

BACKGROUND The cardiovascular safety profile of dapagliflozin, a selective inhibitor of sodium–glucose cotransporter 2 that promotes glucosuria in patients with type 2 diabetes, is undefined.

METHODS We randomly assigned patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease to receive either dapagliflozin or placebo. The primary safety outcome was a composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. Secondary efficacy outcomes were a renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.

CONCLUSIONS In patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure, a finding that reflects a lower rate of hospitalization for heart failure. (Funded by AstraZeneca; DECLARE–TIMI 58 ClinicalTrials.gov number, NCT01730534.)

Diabetes and HF

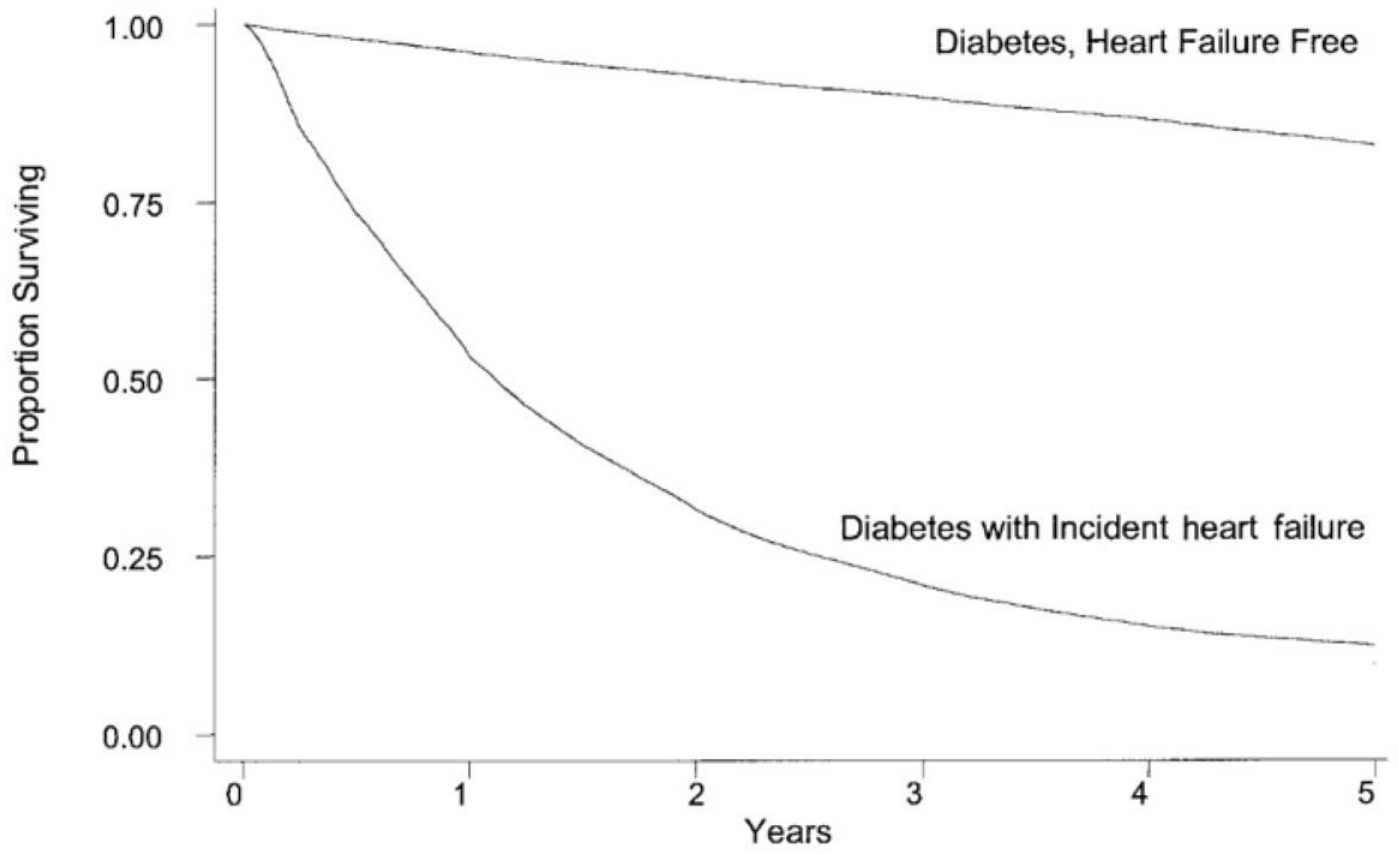
- Diabetes is a major risk factor for incident HF
- Diabetes is very common in prevalent HF
- HF is the most disabling and deadly complication of diabetes – patients with both conditions do especially badly
- Therapies for HF are effective in patients with diabetes

Diabetes and Incident HF in the United States

- Framingham study: the risk of development of HF in increased by:[a]
  - 2 × in diabetic males
  - 5 × in diabetic females
  - 4 × in diabetic males ≤ 65 years
  - 8 × in young diabetic females
- US HMO prevalence study[b]
  - With diabetes, incident HF developed at a rate of 3.3% per year

a. Kannel WB, et al. *JAMA*. 1979;241:2035-2038; b. Nichols GA. *Diabetologia*. 2000;43(suppl A2):7.

5-Year Kaplan–Meier Survival Estimates for 115,803 Adults Aged 65 Years With Diabetes by Incident HF



Bertoni AG, et al. *Diabetes Care*. 2004;27:699-703.

Importance of Real-World Data

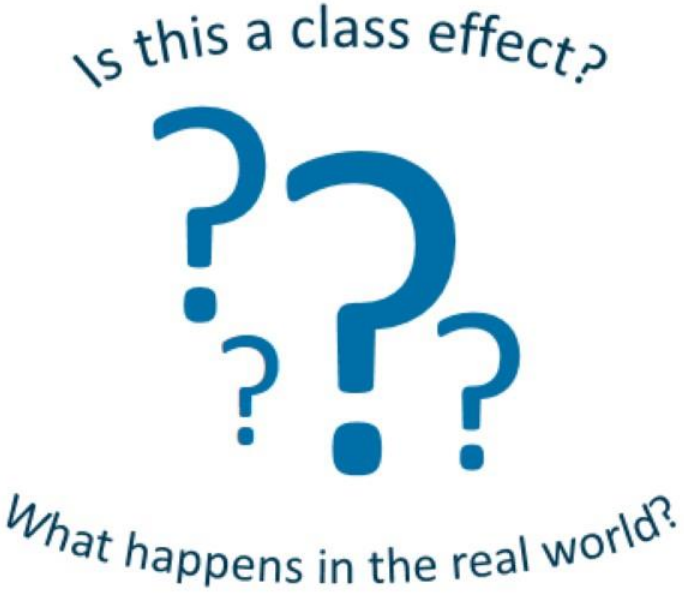
- Complement clinical trial data[a]
- Real-world data provide evidence of the effect of a health care intervention in clinical practice[a]
- Clinicians need to understand how to interpret clinical trial and real-world data

"Real-world evidence can inform therapeutic development, outcomes research, patient care, research on healthcare systems, quality improvement, safety surveillance, and well-controlled effectiveness studies."[b]

a. Berger ML, et al. *Pharmacoepidemiol Drug Saf*. 2017;26:1033-1039.
b. Sherman RE, et al. *N Engl J Med*. 2016;375:2293-2297.

CVD-REAL Study: Real-World Data Evaluating SGLT2 Inhibitors

- Assessed data from 309,056 patients with T2D in 6 countries
- Treatment with SGLT2 inhibitors (dapagliflozin, canagliflozin, and empagliflozin) associated with a 39% reduction in the rate of hospitalization for heart failure
- Directionally similar decreases in all-cause death



Kosiborod M, et al. *Circulation*. 2017;136:249-259.

Practice Essentials

Diabetic nephropathy is a clinical syndrome characterized by the following[1]:

- Persistent albuminuria (>300 mg/d or >200 µg/min) that is confirmed on at least 2 occasions 3-6 months apart
- Progressive decline in the glomerular filtration rate (GFR)
- Elevated arterial blood pressure

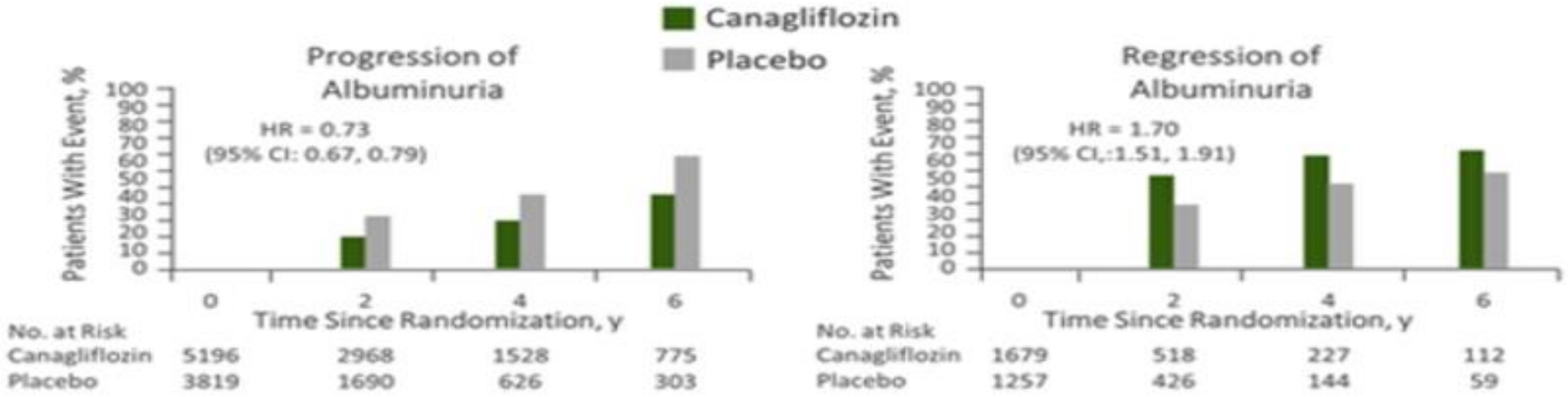
Cardiorenal Benefit With SGLT2 Inhibitors

	CANVAS[a] (canagliflozin) N = 10,142
Progression of albuminuria	0.73 (0.67, 0.79)
Composite of 40% reduction in eGFR, ESRD, or renal death	0.60 (0.47, 0.77)
Regression of albuminuria	1.70 (1.51, 1.91)

	EMPA-REG OUTCOME[b] (empagliflozin) N = 7034
Incident or worsening nephropathy or CV death	0.61 (0.55, 0.69)
Doubling of serum creatinine level accompanied by eGFR of ≤ 45 mL/min/1.73 m^2	0.56 (0.39, 0.79)
Initiation of renal replacement therapy	0.45 (0.21, 0.97)

a. Neal B, et al. *N Engl J Med*. 2017;377:644-657; b. Wanner C, et al. *N Engl J Med*. 2016;375:323-334.

Exploring the Potential Renal Benefits of Canagliflozin



~70% of the patients in CANVAS had normal renal function and not micro- or macro-albuminuria

Neal B, et al. *N Engl J Med*. 2017. [Epub ahead of print]

Special considerations for SGLT-2

- Hypotension
- Volume depletion
- Genital mycotic infections
- Hyperkalemia
- Fractures (upper extremities first 12 weeks canaglifozin)
- “euglycemic DKA”(case selection important)
- Fournier gangrene (rare)
- Amputations lower limb (canaglifozin)

Raúl: Taxi Driver ; age 54
T2DM x 7 years

Glimepiride 2 mg po once daily
Metformin 1000 mg po bid

Lack of adherence due to hypoglycemic episodes; refuses injections; concerned frequent urination due to his type of work

Table 2. Raul's Clinical Presentation and Blood Test Results

Height	175 cm
Weight	85.7 kg
BMI	28 kg/m^2
Heart rate	80 beats/min
Blood pressure (left arm)	130/80 mm Hg
Skin	Normal
Neurologic	Persistent, mild numbness and tingling in legs
Eye	Dilated fundus exam indicates early retinopathy
HbA1c	7.6%
Mean fasting plasma glucose	126 mg/dL (range: 115-140)
Mean postprandial plasma glucose	160 mg/dL (range: 140-200)
LDL cholesterol	90 mg/dL
HDL cholesterol	44 mg/dL
Triglycerides	240 mg/dL
eGFR	>90 mL/min/1.73 m^2
Serum creatinine	0.7 mg/dL

BMI = body mass index; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; eGFR = estimated glomerular filtration rate.

GLYCEMIC CONTROL ALGORITHM

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

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C <7.5%

MONOTHERAPY[1]

- ✓ Metformin
- ✓ GLP1-RA [2,3]
- ✓ SGLT2i [2,3]
- ✓ DPP4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥7.5%

DUAL THERAPY[1]

MET or other 1st-line agent +

- ✓ GLP1-RA [2,3]
- ✓ SGLT2i [2,3]
- ✓ DPP4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY[1]

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP1-RA [2,3]
- ✓ SGLT2i [2,3]
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ DPP4i
- ✓ 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

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

2 Certain GLP1-RAs and SGLT2is have shown CVD and CKD benefits—preferred in patients with those complications

3 Include one of these medications if CHD present

PROGRESSION OF DISEASE

 DOI 10.4158/CS-2018-0535

Rationale for using Incretin-Based Therapies in the Treatment of T2 DM in this case

- A-Incretins play an important role in glucose homeostasis
- B-Incretin Effects are Diminished in T2DM
- C-Incretin based therapies (GLP-1RA and DPP4 inhibitors)
- D-Target multiple defects in DM type 2, not addressed by traditional medications
- E-Not associated with hypoglycemia
- F-Either weight neutral or can cause weight loss(GLP-1 RA)

DPP-4 Inhibitors

Generic	Trade Name	FDA Approval	CV Safety Study	GoodRx	Medical Letter	Cost per Day
Alopgliptin	Nesina™	Jan 2013	Oct 2013[a]	$95	$312	
Linagliptin	Tradjenta™	May 2011	**May 2019**	$356	$331	
Saxagliptin	Onglyza™	Jul 2009	Oct 2013[b]	$394	$325	$ 13/day
Sitagliptin	Januvia™	Oct 2006	Jul 2015[c]	$427	$331	

- Omarigliptin is an oral once weekly DPP-4 inhibitor NOT FDA approved but used in Japan.
  - Completed CVOT with results similar to above and without HF noise

GoodRx accessed on Jan 20, 2018
[c]NEJM 2015;373:232
[d]Cardiovasc Diabetol. 2017 Sep 11;16(1):112

The Medical Letter 2015;57:65
[a]NEJM 2017;369:1327
[b]NEJM 2013;369:1317

Some DPP-4 Inhibitors Increase Risk of Hospitalization for Heart Failure

	SAVOR-TIMI 53[a] (saxagliptin) N = 16,492	EXAMINE[b] (alogliptin) N = 5380	TECOS[c] (sitagliptin) N = 14,671
Primary composite endpoint	CV death, MI, or stroke HR = 1.00 (0.89, 1.12) *P* = .99 for superiority *P* < .001 for noninferiority	CV death, MI, or stroke HR = 0.96 (≤ 1.16) *P* = .32 for superiority *P* < .001 for noninferiority	CV death, MI, stroke, or hospitalization for UA HR = 0.98 (0.89, 1.08) *P* = .65
Hospitalization for heart failure	1.27 (1.07, 1.51) *P* = .007	1.07 (0.79, 1.46) *P* = .657[d]	1.00 (0.83, 1.20) *P* = .98

- FDA has updated labels for products containing saxagliptin and alogliptin to include warning about heart failure
- CAROLINA (linagliptin) study is ongoing

a. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326; b. White WB, et al. *N Engl J Med*. 2013;369:1327-1335; c. Green JB, et al. *N Engl J Med*. 2015;373:232-242; d. Zannad F, et al. *Lancet*. 2015;385:2067-2076.

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 Benefit of Empagliflozin	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	Mild Fracture Risk	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

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.
4. Only empagliflozin and canagliflozin show CVD and CKD benefits.
5. Liraglutide only shows CVD and CKD benefits.

DOI 10.4158/CS-2018-0535

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 GLP1-RA

Or SGLT2i
Or DPP4i

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

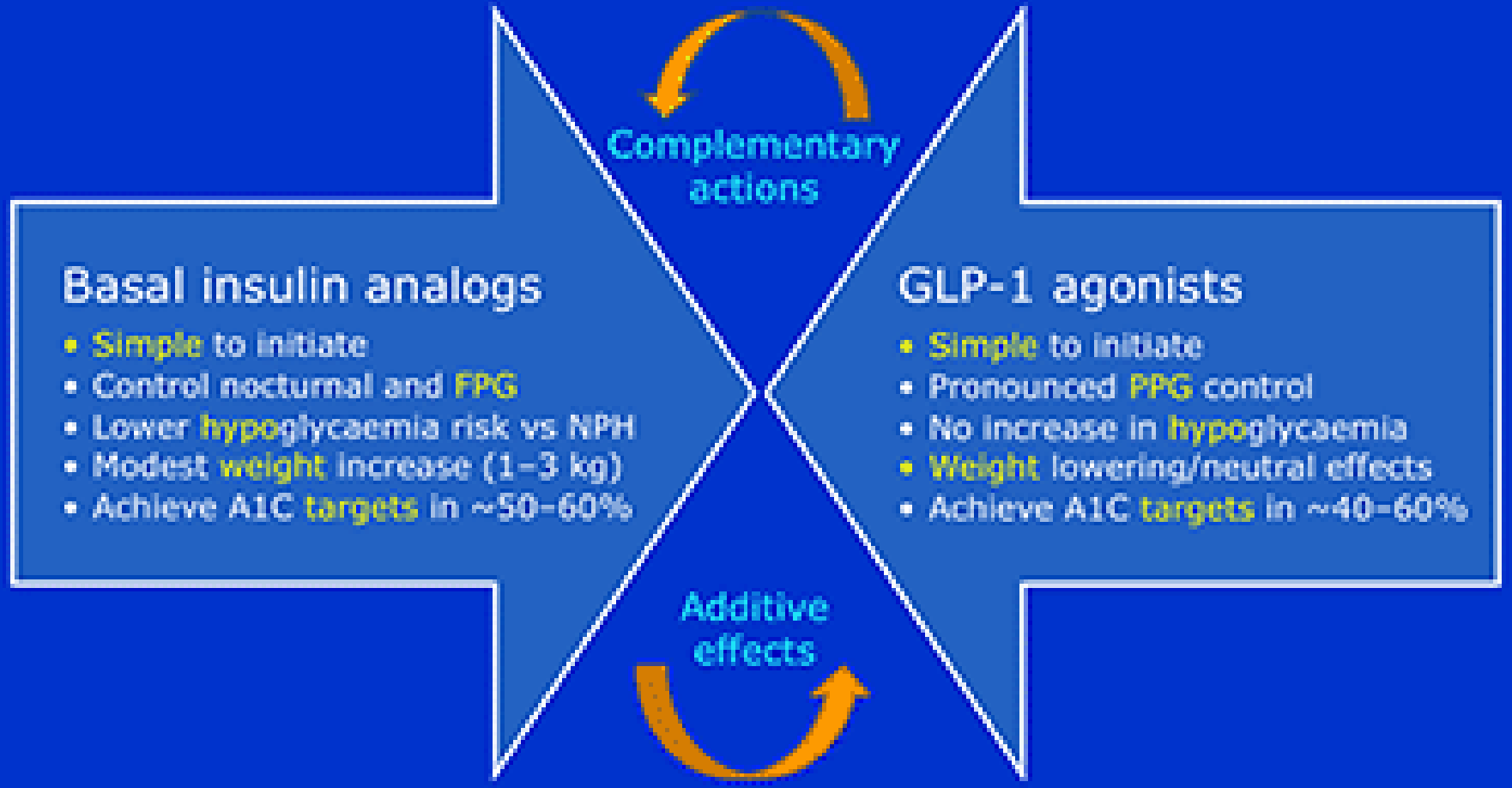
- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
- **Start: 50% of TDD in three doses before meals**

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/CS-2018-0535

Combination of Basal Insulin with a GLP-1 Agonist Has a Scientific Logic

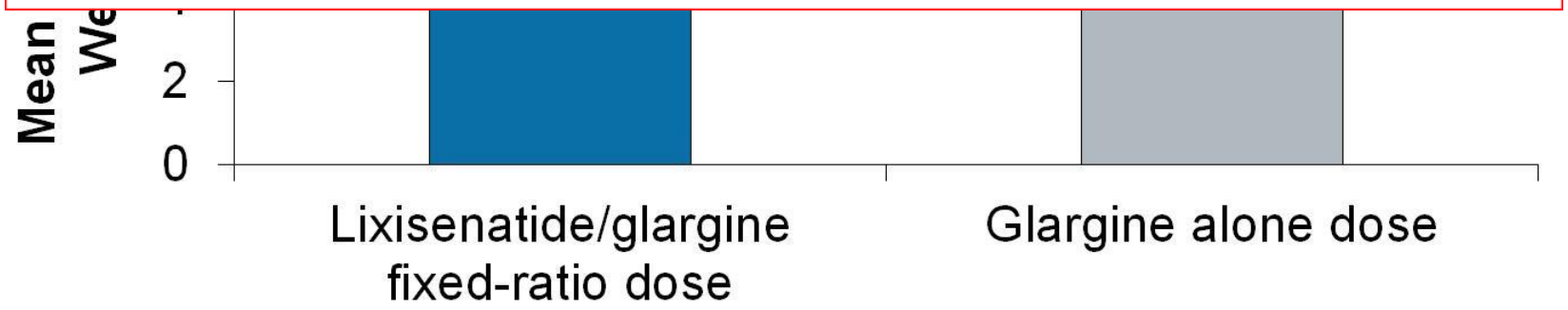


Fixed Formulation

LixiLan* – fixed-ratio formulation glargine with lixisenatide in a single-pen device

February 28, 2019

Soliqua 100/33 Indication Expanded to Include T2D Patients Uncontrolled on Oral Antidiabetic Agents



Soliqua*

Rosenstock J, et al. ADA 2014. Abstract 332-OR.[13]

IDegLira* vs Glargine

Comparison of Efficacy and Safety in DUAL V

Degludec and liraglutide

	IDegLira* (N = 278)	Glargine (N = 279)	*P* Value
Mean HbA_{1c} at randomization, %	8.4	8.2	-
Mean HbA_{1c} at wk 26, %	6.6	7.1	< .001
HbA_{1c} change at wk 26, %	-1.8	-1.1	< .001
HbA_{1c} < 7% at wk 26, %	71.6	47.0	< .001
Body weight at baseline, kg	88.3	87.3	-
Body weight at wk 26, kg	86.9	89.1	< .001
Body weight change at wk 26, kg	-1.4	+1.8	< .001
Hypoglycemia rate, events/patient year of exposure			
Confirmed	2.23	5.05	< .001
Nocturnal	0.22	1.23	< .001

Xultophy

Buse JB, et al. ADA 2015. Abstract 166-OR.[11]