Type 2 Diabetes Update:
Incorporating the Latest Strategies Into Your Practice

Silvio E. Inzucchi, MD
Professor of Medicine, Endocrinology
Clinical Director, Section of Endocrinology
Director, Yale Diabetes Center
Director, Endocrinology & Metabolism Fellowship
Director, Yale Affiliated Hospitals
Yale School of Medicine
New Haven, CT

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Disclosure

Consultant: Astra Zeneca; Bayer; Boehringer Ingelheim; Lilly; Merck; Novo Nordisk; Pfizer

Lectures: Astra Zeneca; Boehringer Ingelheim

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OBJECTIVES

1) Describe the current landscape of non-insulin therapies for T2D management, with a specific focus on which glucose lowering medications have confirmed cardiac and kidney benefits.

2) Discuss how to individualize care, including risks/benefits of these therapies

3) Offer a framework to move through a T2D office visit effectively & efficiently

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T2D Update: Incorporating the Latest Strategies

1. **Pathogenesis of T2D**
2. **Major T2D Medication Categories**
3. **Calibrating A1c Targets**
4. **Previous T2D Guidelines (as context)**
5. **CV / Renal Impact of T2D Therapies**
6. **Updated T2D Guidelines**
7. **Diabetes Office Visit Checklist**

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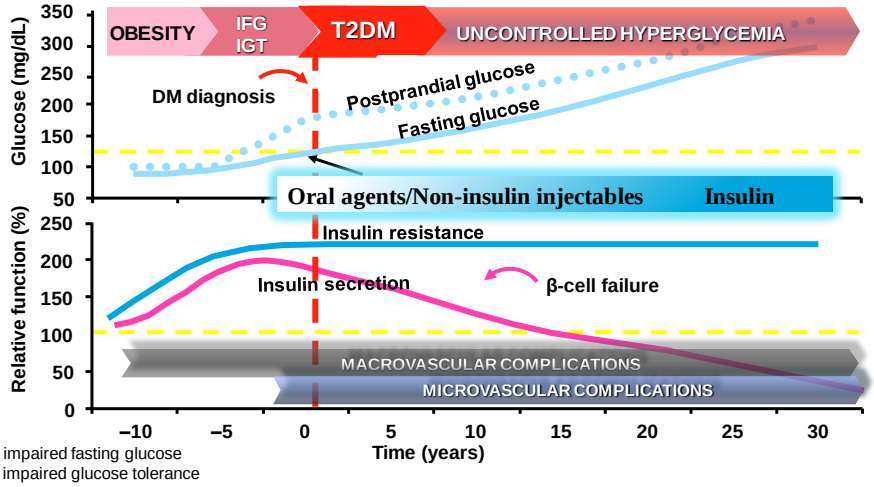
Pathophysiologic Progression of T2DM & Its Vascular Complications

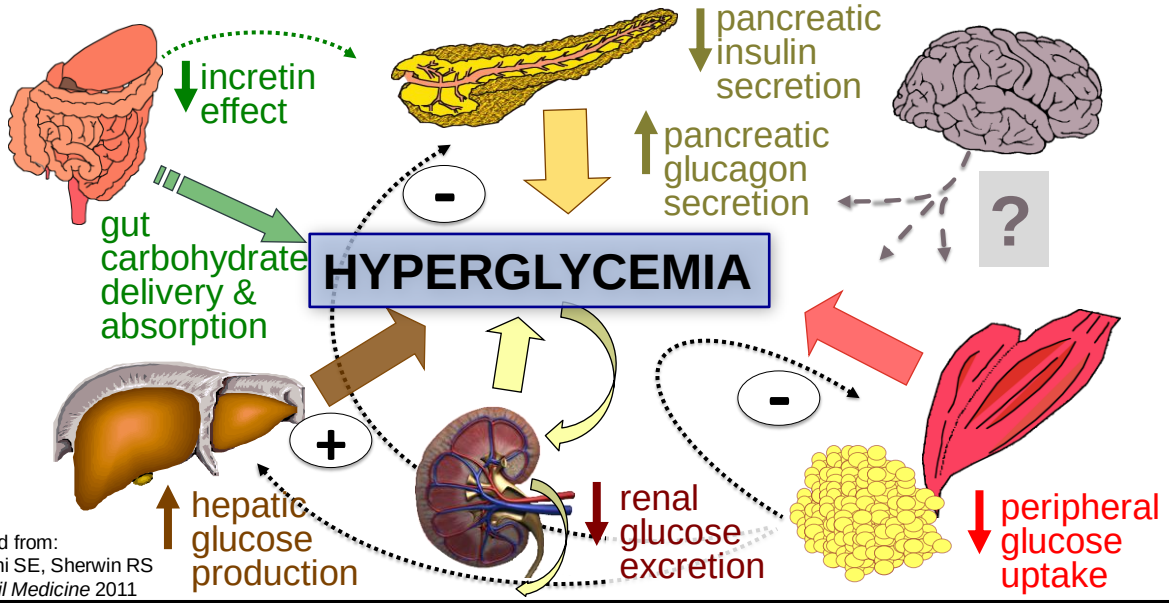


IFG = impaired fasting glucose
IGT = impaired glucose tolerance
T2DM = type 2 diabetes mellitus

Defronzo RA. *Diabetes*. 2009;58:773-795. Fehse F et al. *J Clin Endocrinol Metab.* 2005;90:5991-5997.
Figure adapted from Kendall DM et al. *Am J Med.* 2009;122(6 suppl):S37-S50.

5

Multiple Complex Pathophysiological Abnormalities in T2DM



Adapted from:
Inzucchi SE, Sherwin RS
in: *Cecil Medicine* 2011

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T2D Update: Incorporating the Latest Strategies

1. Diagnosis & Pathogenesis of T2D
2. **Major T2D Medication Categories**
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7. Proposed Diabetes Office Visit Checklist

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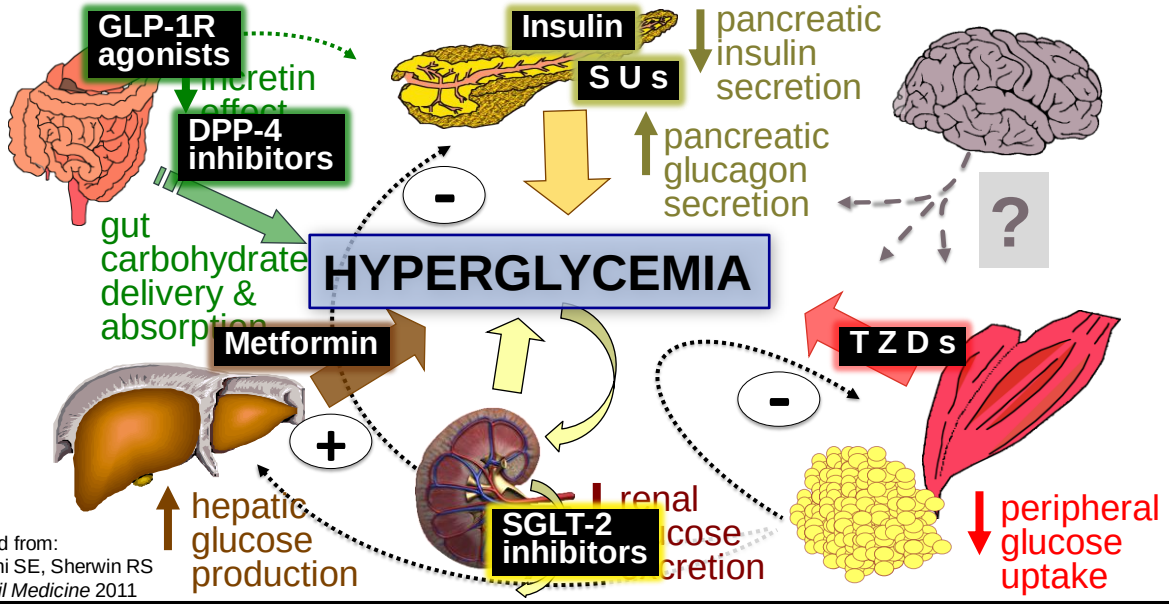
The 7 Major Glucose-Lowering Drug Classes in Use in Patients with T2DM



Adapted from:
Inzucchi SE, Sherwin RS
in: *Cecil Medicine* 2011

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Agent Class	Mechanism(s) of Action	Advantages	Disadvantages	Cost
Biguanides *Metformin*	• Activates AMP-kinase • ↓ Hepatic glucose production	• Extensive experience • **No hypoglycemia** • Weight neutral • **? ↓ CVD events**	• **Diarrhea, abdominal pain** • **Lactic acidosis** • B-12 deficiency • Contraindications	Low
Sulfonylureas *Glyburide* *Glipizide* *Glimepiride*	• Closes KATP channels • ↑ Insulin secretion	• Extensive experience • **↓ Microvascular risk**	• **Hypoglycemia** • Weight gain • **Low durability** • ? ↓ Ischemic preconditioning	Low
TZDs *Pioglitazone* ~~*Rosiglitazone*~~	• Activates PPAR-γ • ↑ Insulin sensitivity	• **No hypoglycemia** • **Durability** • ↓ TGs, ↑ HDL-C • **↓ CVD events (pio)**	• **Weight gain** • **Edema / HF** • **Bone fractures** • ? ↑ MI (rosi) • ? Bladder ca (pio)	Low

Properties of glucose-lowering meds for T2DM

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Agent Class	Mechanism(s) of Action	Advantages	Disadvantages	Cost
DPP-4 Inhibitors *Sitagliptin* *Saxagliptin* *Linagliptin* *Alogliptin*	• Inhibits DPP-4 • Increases GLP-1, GIP	• **No hypoglycemia** • **Well tolerated**	• Modest ↓ A1c • ? Pancreatitis • Urticaria	High
SGLT-2 Inhibitors ***Canagliflozin*** ***Dapagliflozin*** ***Empagliflozin*** *Ertugliflozin* *Bexagliflozin** * lower cost option	• Inhibits renal SGLT-2 • Increases glucosuria	• **No hypoglycemia** • Weight loss • ↓ BP • **↓ CVD events** • **↓ HF hospitalizations** • **↓ CKD progression**	• Modest ↓ A1c • Polyuria/Dehydration • **Genital mycotic infections** • ? UTIs • ? Fournier's gangrene • ? Amputations (cana) • Fractures (cana) • **Euglycemic DKA**	High

Note: **Bold** denotes FDA indications for organ protection (CV, renal)

Properties of glucose-lowering meds for T2DM

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Agent Class	Mechanism(s) of Action	Advantages	Disadvantages	Cost
GLP-1 receptor agonists (RA) *Exenatide* ***Liraglutide*** *Lixisenatide* ***Dulaglutide*** ***Semaglutide*** *Tirzepatide** *combined GLP-1/GIP RA	• Activates GLP-1 receptor • ↑ Insulin, ↓ glucagon • ↓ gastric emptying • ↑ satiety	• **Weight loss** • **No hypoglycemia** • ? ↑ Beta cell mass • **↓ CVD events** • **↓ CKD progression**	• **Nausea/vomiting/diarrhea** • ? Pancreatitis • ↑ Gallbladder events • Medullary ca (rodents) • **Injectable** (most)	High
Insulin *Glargine, Degludec* *NPH* *Regular* *Lispro†, Aspart†, Glulisine* *Inhaled* *Pre-Mixed* † also available in ultra-rapid forms	• Activates insulin receptor • ↑ Glucose disposal • ↓ Hepatic glucose production	• Universally effective • Unlimited efficacy • **↓ Microvascular risk**	• **Hypoglycemia** • **Weight gain** • ? Mitogenicity • **Injectable** (most) • Training requirements • 'Stigma'	V A R I A B L E

Properties of glucose-lowering meds for T2DM

Note: **Bold** denotes FDA indications for organ protection (CV, renal)

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ADA: 2024 Standards of Medical Care

Glycemic Goals

6.5a. **An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate**. **A**

6.5b. **If using ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal for many nonpregnant adults is a time in range (TIR) of >70% with time below range (TBR) <4% and time <54 mg/dl <1%. For those with frailty or at high risk of hypoglycemia, a goal of >50% TIR with <1% time below range is recommended**. **B**

6.6. On the basis of health care professional judgment and the preference of the person with diabetes, achievement of **lower A1C levels than the goal of 7%** (53 mmol/mol) may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. **B**

6.7. **Less stringent glycemic goals** may be appropriate for individuals with limited life expectancy or where the harms of treatment are greater than the benefits. **B**

6.8a. **De-intensify** hypoglycemia-causing medications (insulin, sulfonylureas, or meglitinides), or switch to a medication class with lower hypoglycemia risk, for individuals who are at high risk for hypoglycemia, within individualized glycemic goals. **B**

6.8b. **De-intensify** diabetes medications for individuals for whom the harms and/or burdens of treatment may be greater than the benefits, within individualized glycemic goals. **B**

Diabetes Care 2024; 47(Suppl 1)

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CGM: A Useful Adjunctive Tool in the Management of Any Patient with Diabetes, Especially on Insulin Therapy and Particularly on Advanced Regimens

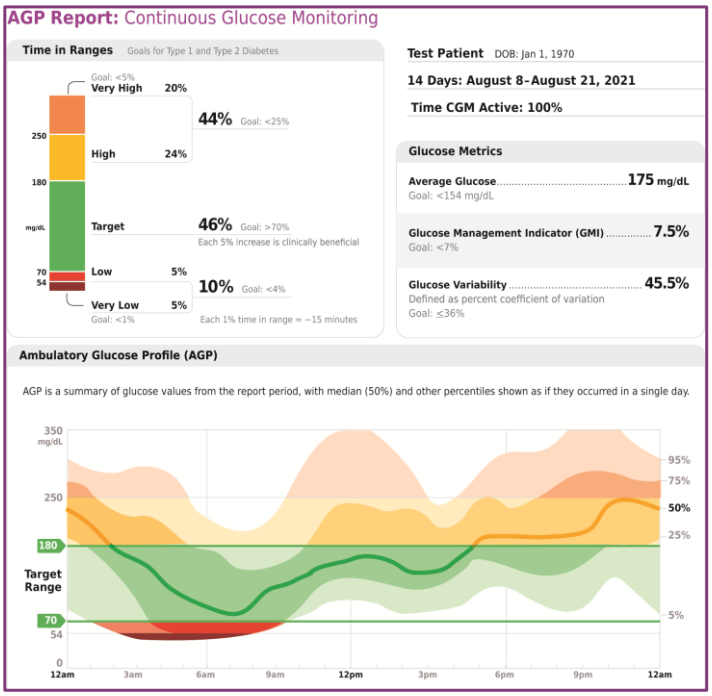
Standardized CGM Metrics for Clinical Care

1. Number of days CGM device is worn (recommend 14 days)	
2. Percentage of time CGM device is active (recommend 70% of data from 14 days)	
3. Mean glucose	
4. GMI	
5. Glycemic variability (%CV) target ≤36%*	
6. TAR: % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2 hyperglycemia
7. TAR: % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1 hyperglycemia
8. TIR: % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1 hypoglycemia
10. TBR: % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2 hypoglycemia

TARGETS[1]

- **CGM active: ≥70%**
- **TIR 70-180 mg/dL: >70%**
- **TBR <70 mg/dL: < 4%**
- **TBR <54 mg/dL: < 1%**
- **TAR >180 mg/dL: <25%**
- **TAR >250 mg/dL: < 5%**

[1]Battelino T *et al. Diabetes Care* 2019;42:1593-1603



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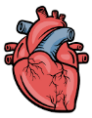
A Quarter Century of Outcome Trials in Diabetes

1. More intensive glucose control ↓'s micro-vascular complication risk in both T1D (DCCT, 40-75%) and T2D (UKPDS, -25%), mainly for retinal & kidney disease.



2. Impact of intensive glucose control itself on macro-vascular complications in T2DM is small to non-existent (RRR ~15%), and solely on non-fatal MI. No stroke, HF, or mortality benefit. (Impact may be larger in T1D, but data are not robust.)




3. Some data (i.e., the ACCORD trial) has suggested an actual ↑ in CV mortality when overly stringent strategies are employed in high-risk patients.

4. Re: older drugs, SUs & insulin are neutral from a CV perspective. Metformin may have CV benefits, but studies to date are small & old. Pioglitazone has clear anti-atherosclerotic properties - but counter-balanced by side effects.

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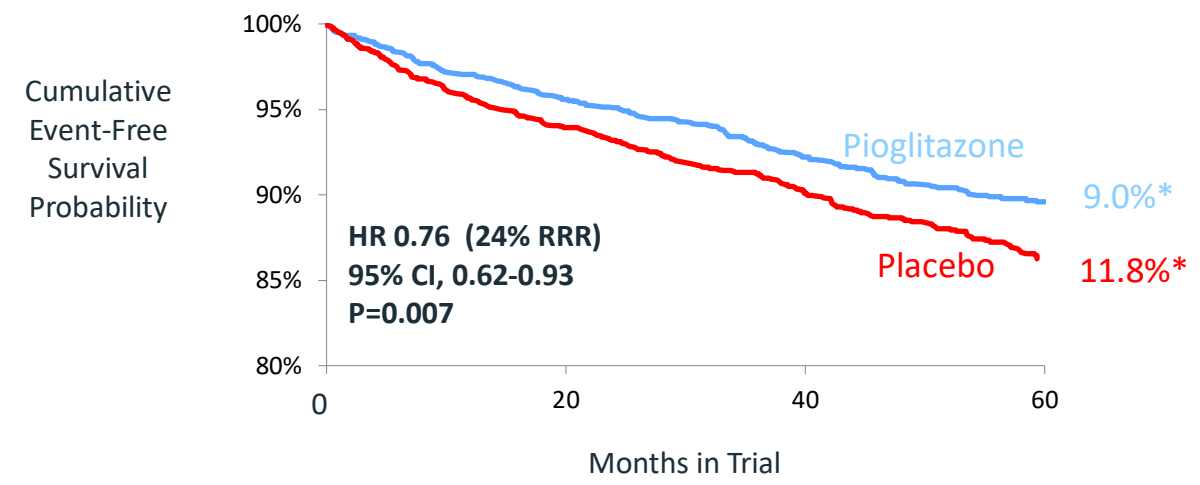
1° Outcome in the IRIS Trial: Fatal/Nonfatal MI or Stroke in Non-Diabetic Insulin-Resistant Patients with Stroke



Kernan WN *et al. N Engl J Med* 2016;374:1321-31

*cumulative event rates

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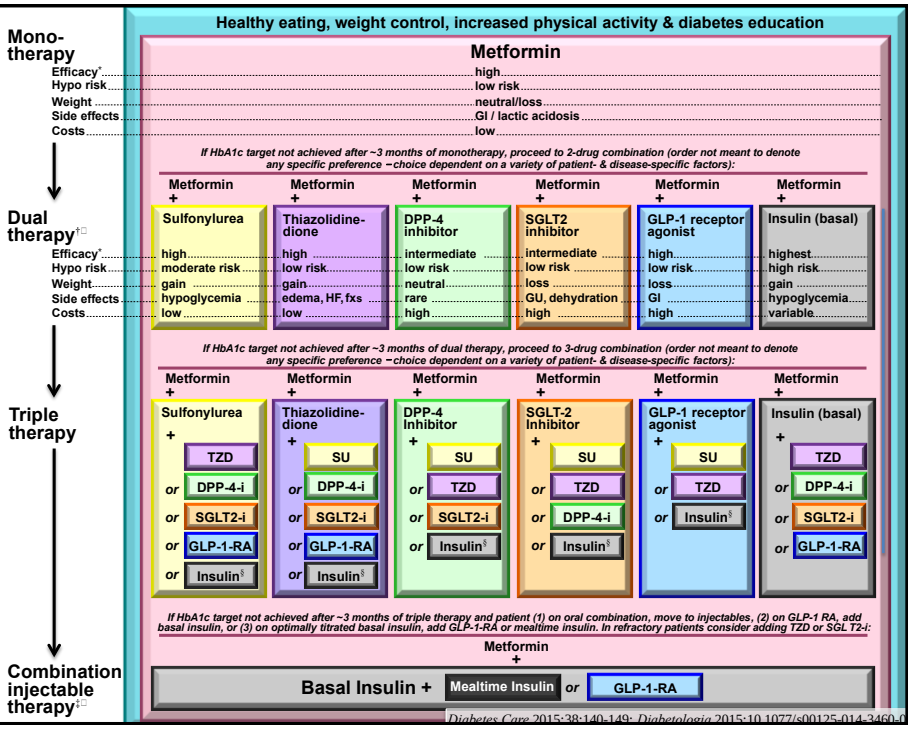
American Diabetes Association. EASD European Association for the Study of Diabetes

Position Statement on the Management of Hyperglycemia in Patients with Type 2 Diabetes: A Patient-Centered Approach



Inzucchi SE *et al. Diabetes Care* 2015;38:140-9; *Diabetologia* 2015;58:429-42

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

18

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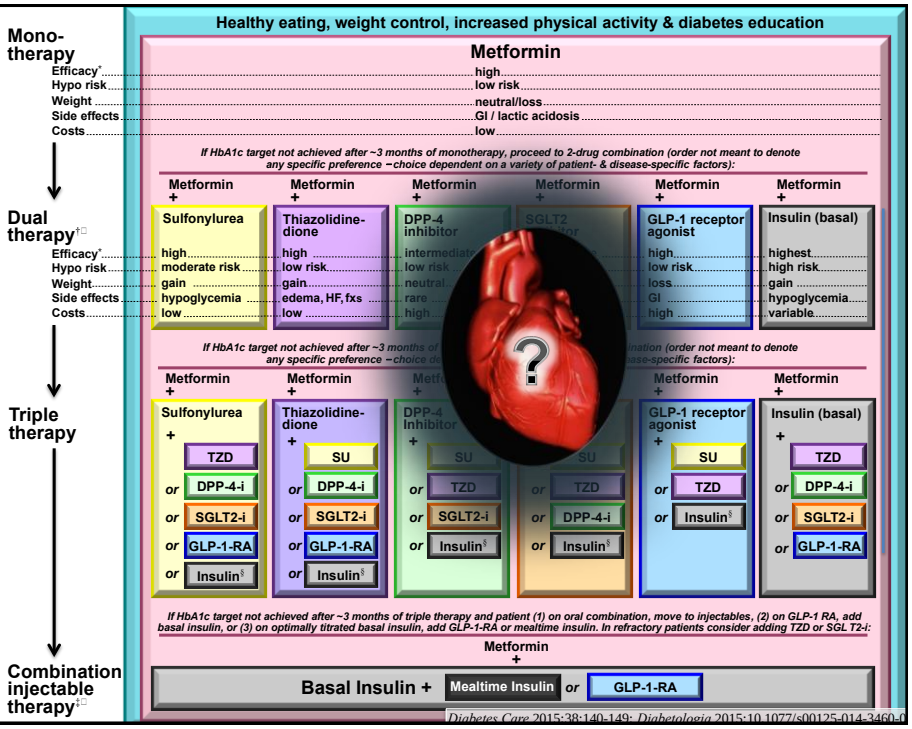

Inzucchi SE *et al. Diabetes Care* 2015;38:140-9; *Diabetologia* 2015;58:429-42

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Overview of Major Glucose-Lowering Classes for T2D

Classes	Generic Names	↓A1c	Mechanism(s)	Positive(s)	Negative(s)	Cost
Insulin	Degludec, Glargine, Detemir, NPH, Regular, Lispro, Aspart, Glulisine	No limit	Replaces deficient insulin supply	No ceiling; most titratable agent	Hypo, weight gain	highly variable
SU	Glyburide, Glipizide, Glimepiride	1-1.5%	↑ endogenous insulin production	Extensive experience	Hypo, weight gain	$
Metformin	Metformin	1-1.5%	↓ hepatic glucose production (? others)	±Wt loss, no hypo, ↓ CV events (?)	GI, lactic acidosis, B-12 deficiency	$
TZD	Rosiglitazone, Pioglitazone*	1-1.5%	Enhances peripheral insulin sensitivity	Durability, no hypo, ↓ CV events*, ↓ NASH	Weight gain, edema, HF, bone fxs, ?bladder ca*	$ - $$$
DPP-4 i	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin	0.5-1%	↓ DPP-4 activity and ↑ incretins (GLP1, GIP)	Well-tolerated; no hypo	Urticaria, ? pancreatitis, ? HF*	$$$$
GLP-1[a] RA [a](+GIP)	Exenatide, Liraglutide*, Dulaglutide*, Albiglutide*, Lixisenatide, Semaglutide*; Tirzepatide[a]	1-1.5%	↑insulin, ↓ glucagon, ↓ gastromotility, ↓ hunger	Wt loss, no hypo, ↓ BP, ↓ MACE*	GI, ? Pancreatic/ biliary disease, ? medullary thyroid ca	$$$$
SGLT2-i	Canagliflozin*†#‡, Dapagliflozin†# Empagliflozin*†#, Ertugliflozin	0.5-1%	↑ urinary glucose excretion	Wt loss, no hypo, ↓ BP, ↓ MACE*, HF†, ↓ CKD#	Polyuria, GU, DKA, bone fxs‡, amputations‡	$$$$

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CV Impact of Major Glucose-Lowering Classes for T2D

Classes	Generic Names	↓A1c	Mechanism(s)	Positive(s)	Negative(s)	Cost
Insulin	Degludec, Glargine, Detemir, NPH, Regular, Lispro, Aspart, Glulisine	NEUTRAL	Replaces deficient insulin supply	No ceiling; most titratable agent	Hypo, weight gain	highly variable
SU	Glyburide, Glipizide, Glimepiride	NEUTRAL	↑ endogenous insulin production	Extensive experience	Hypo, weight gain	$
Metformin	Metformin	1-1.5%	↓ hepatic glucose production (? ot	±Wt loss, no hypo, ↓ CV events (?)	GI, lactic acidosis, B-12 deficiency	$
TZD	Rosiglitazone, Pioglitazone*	1-1.5%	Enhances peripheral insulin sensitivi	Durability, no hypo, ↓ CV events*, ↓ NASH	Weight gain, edema, HF, bone fxs, ?bladder ca*	$ - $$$
DPP-4 i	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin	0.5-1%	↓ DPP-4 activity and	Well-tolerated; no hypo	Urticaria,	$$$$
GLP-1[a] RA [a](+GIP)	Exenatide, Liraglutide*, Dulaglutide*, Albiglutide*, Lixisenatide, Semaglutide*; Tirzepatide[a]					
SGLT2-i	Canagliflozin*†#‡, Dapagliflozin†# Empagliflozin*†#, Ertugliflozin			t loss, no hypo, BP, ↓ MACE*, HF†, ↓ CKD#	Polyuria, GU, DKA, bone fxs‡, amputations‡	$$$$

? +/-

FDA 2008 GUIDANCE TO INDUSTRY FOR **CV SAFETY TRIALS**

Extensive **data on CV impact of these 3 classes!**

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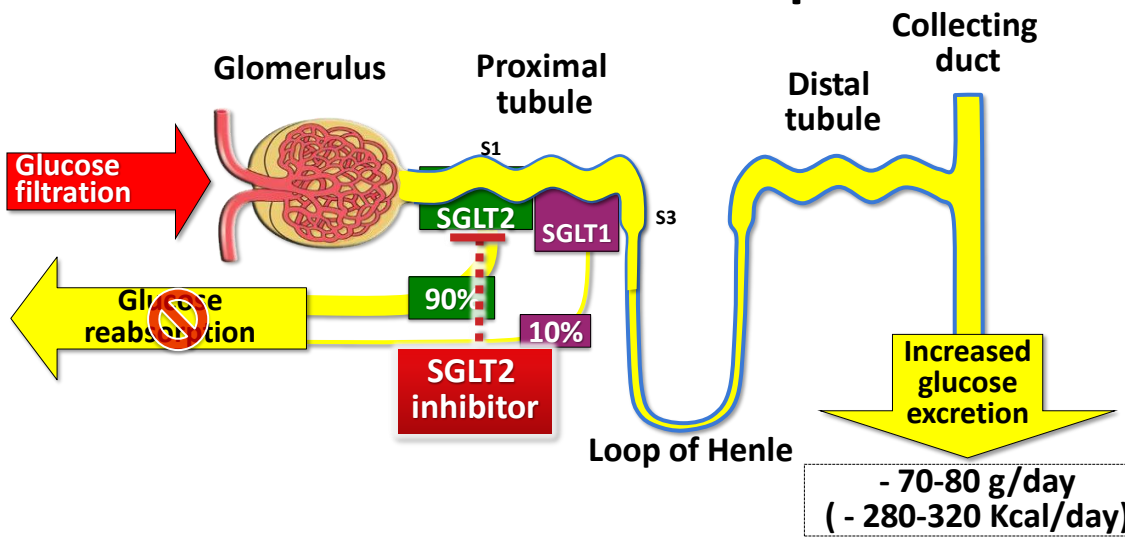
SGLT2 Inhibition Reduces Renal Glucose Reabsorption



Wright EM. *Am J Physiol Renal Physiol.* 2001;280:F10-F18; Lee YJ *et al. Kidney Int Suppl.* 2007;106:S27-S35; Han S. *Diabetes.* 2008;57:1723-1729.

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Empagliflozin Demonstrated Superiority versus Placebo for 3P-MACE*

- **3P-MACE* was the primary outcome for EMPA-REG OUTCOME®**
- **Empagliflozin on top of standard of care† demonstrated a 14% relative risk reduction in 3P-MACE* versus placebo**

3P-MACE*

↓14% RRR

HR 0.86 (95.02% CI 0.74, 0.99)
p=0.04 for superiority

RRR for 3P-MACE: 14%; ARR for 3P-MACE: 1.6%. Absolute rates 10.5% (empagliflozin) vs 12.1% (placebo). Cumulative incidence function
*A composite of CV death, non-fatal MI or non-fatal stroke; †Standard of care included CV medications and glucose-lowering agents given at the discretion of physicians
3P-MACE, 3-point major adverse cardiovascular events; ARR, absolute risk reduction; CV, cardiovascular; RRR, relative risk reduction
Zinman B *et al. N Engl J Med* 2015;373:2117; Zinman B. *EASD* 2015; oral presentation

EMPA-REG OUTCOME®

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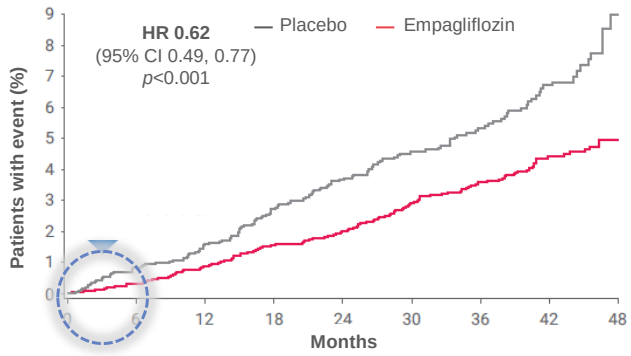
Empagliflozin Significantly Reduced the Relative Risk of CV Death by 38% on Top of Standard of Care*†

CV death

↓38% RRR



Cumulative incidence function. RRR for CV death: 38%; ARR for CV death: 2.2%; rates of CV death: 3.7% (empagliflozin) vs 5.9% (placebo)
*Exploratory endpoint; †Standard of care included CV medications and glucose-lowering agents given at the discretion of physicians
ARR, absolute risk reduction; RRR, relative risk reduction
Zinman B *et al. N Engl J Med* 2015;373:2117

EMPA-REG OUTCOME®

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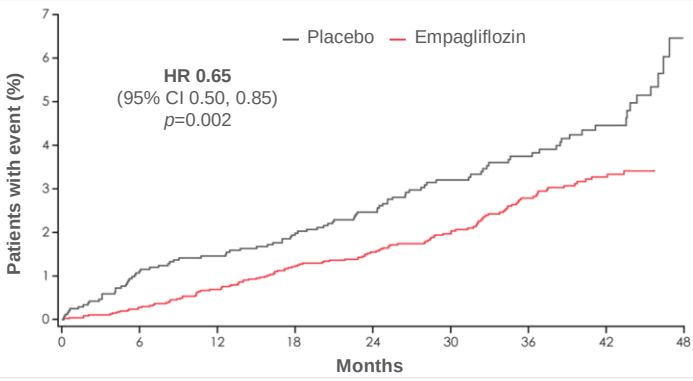
Empagliflozin Significantly Reduced the Relative Risk of HHF by 35% on Top of Standard of Care*†[1–3]

HHF

↓35% RRR



Empagliflozin is not indicated for the treatment of heart failure
RRR for HHF is 35%; rates of HHF: 2.7% (empagliflozin) vs 4.1% (placebo); ARR for HHF is 1.4%
*Exploratory endpoint; †Standard of care included CV medications and glucose-lowering agents given at the discretion of physicians
Cumulative incidence function
ARR, absolute risk reduction; HF, heart failure; HHF, hospitalisation for heart failure; RRR, relative risk reduction
1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Boehringer Ingelheim Pharmaceuticals, Inc. Jardiance® (empagliflozin) Prescribing Information. 2017; 3. Fitchett D *et al. ESC-HF* 2017; poster 301

EMPA-REG OUTCOME®

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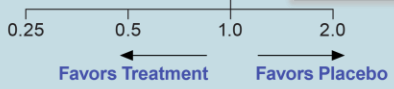
SGLT2i Meta-analysis: Time to First MACE

MACE

	Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	37.4	43.9	0.86 (0.74-0.99)
CANVAS Program	26.9	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	22.6	24.2	0.93 (0.84-1.03)
CREDENCE	38.7	48.7	0.80 (0.67-0.95)
VERTIS CV*	40.0	40.3	0.99 (0.88-1.12)
Pooled estimate (Q statistic $P = 0.27$; $I^2 = 23.4\%$)			**HR 0.90** (0.85–0.95)



*Intention-to-treat population was used for consistency with other trials.
MACE, major adverse cardiovascular events; CI, confidence interval; HR, hazard ratio

McGuire DK *et al. JAMA Cardiol* 2020;6:148-158

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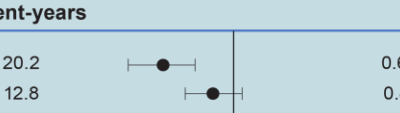
SGLT2i Meta-analysis: Time to CV Death

CV DEATH

	Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	12.4	20.2	0.62 (0.49-0.77)
CANVAS Program	11.6	12.8	0.87 (0.72-1.06)
DECLARE-TIMI 58	7.0	7.1	0.98 (0.82-1.17)
CREDENCE	19.0	24.4	0.78 (0.61-1.00)
VERTIS CV	17.6	19.0	0.92 (0.77-1.10)
Pooled estimate (Q statistic $P = 0.02$; $I^2 = 64.3\%$)			**HR 0.85** (0.78–0.93)



*Intention-to-treat population was used for consistency with other trials.
CI, confidence interval; HR, hazard ratio

McGuire DK *et al. JAMA Cardiol* 2020;6:148-158

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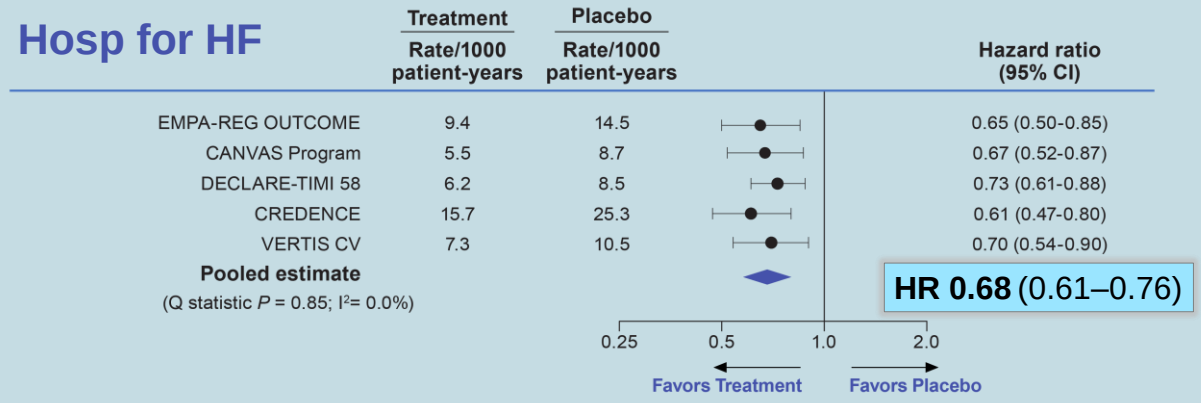
SGLT2i Meta-analysis: Time to First Hospitalization for HF



*Intention-to-treat population was used for consistency with other trials.
Hosp, hospitalization; HF, heart failure; CI, confidence interval; HR, hazard ratio

McGuire DK *et al. JAMA Cardiol* 2020;6:148-158

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Effects of SGLT2i on HF Hosp'n, CV Death in HF Trials

Trial (SGLT2i)	Pop.	1 Outcome	RRR (p)	Comments
DAPA-HF (dapa)	HFrEF	HHF*, CV mortality	**26%** (p<0.001)	*Effective in both T2D, non-DM*
EMPEROR-Reduced (empa)	HFrEF	HHF, CV mortality	**25%** (p<0.0001)	*Effective in both T2D, non-DM*
EMPEROR-Preserved (empa)	HFpEF	HHF*, CV mortality	**21%** (p<0.001)	*Effective in both T2D, non-DM*
DELIVER (dapa)	HFpEF	HHF*, CV mortality	**18%** (p<0.001)	*Effective in both T2D, non-DM*
SCORED† (sota)	DKD	HHF*, CV mortality	**26%** (p<0.001)	*T2D only*
SOLOIST† (sota)	Acute HF	HHF*, CV mortality	**33%** (p<0.001)	*T2D only*
DAPA-ACT (dapa)	Acute HF	HHF*, CV mortality	*underway*	*Both T2D and non-DM*
HF meta-analysis[1]	**All HF**	**HHF,CV mortality**	**23% (p<0.001)**	*Effective, both T2D, non-DM*

*including urgent HF visits

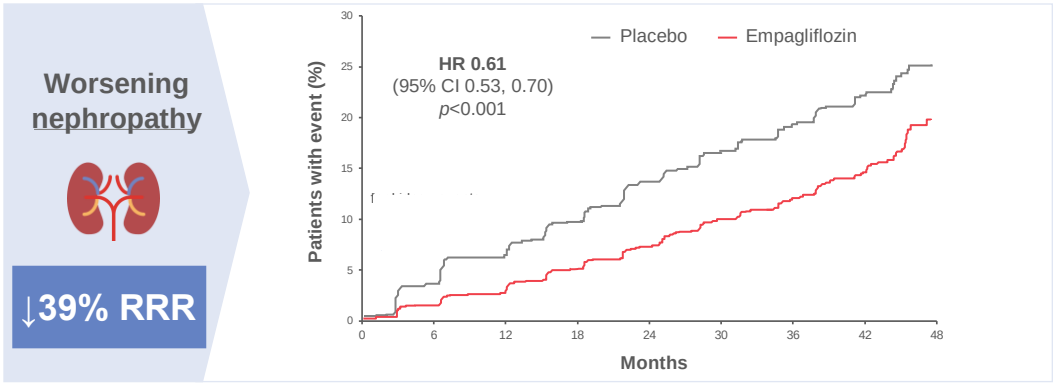
† SGLT-1 / 2 inhibitor

HFrEF=heart failure w/ reduced ejection fraction; HFpEF= heart failure w/ preserved ejection fraction; HHF= hospitalization for HF; DKD=diabetic kidney disease; CKD=chronic kidney disease; T2D=type 2 diabetes, CV=cardiovascular. dapa=dapagliflozin; empa=empagliflozin; sota=sotagliflozin; cana=canagliflozin

[1]Vaduganathan M, Docherty KF *et al. Lancet* 2022

30

Empagliflozin Significantly Reduced the Relative Risk of Incident or Worsening Nephropathy*† by 39% on Top of Standard of Care‡



Empagliflozin is not indicated for the treatment of chronic kidney disease

*Exploratory endpoint; †Defined as progression to macroalbuminuria, doubling of serum creatinine (accompanied by eGFR [MDRD] ≤45 ml/min/1.73 m^2), initiation of renal replacement therapy or death from kidney disease; ‡Standard of care included CV medications and glucose-lowering agents given at the discretion of physicians; Kaplan–Meier estimate

eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease

Wanner C *et al. N Engl J Med* 2016;375:323

EMPA-REG OUTCOME®

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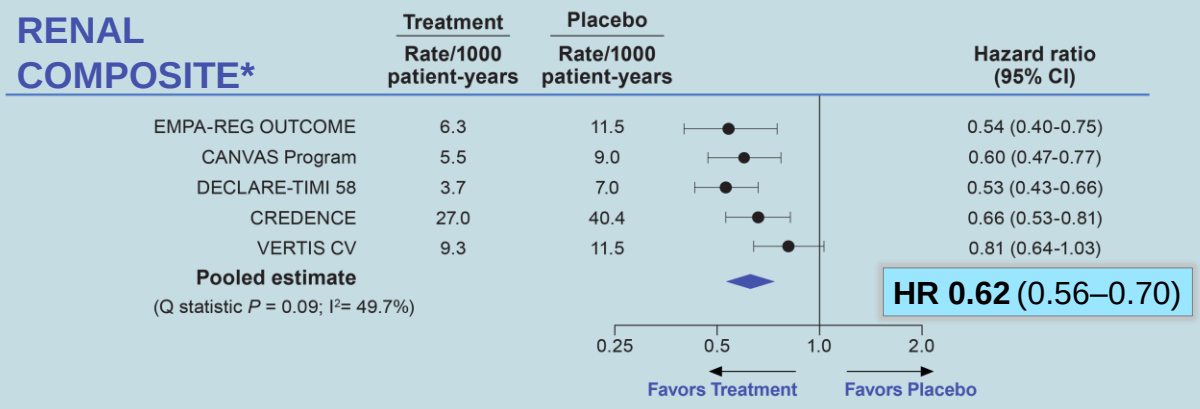
Time to First Renal Composite Outcome



*Renal composite outcome definitions varied across trials.
CI, confidence interval.

McGuire DK *et al. JAMA Cardiol* 2020:e204511. doi:10.1001/jamacardio.2020.4511

32

Effects of SGLT2i on CKD Progression in CKD Trials

Trial (SGLT2i)	Population	1° Outcome	RRR	Comments
CREDENCE (cana)	DKD	CKD progression[a]	**30%** (p<0.001)	T2D only
DAPA-CKD (dapa)	CKD	CKD progression[b]	**39%** (p<0.0001)	*Effective in both T2D, non-DM*
EMPA-Kidney (empa)	CKD	CKD progression[c]	**28%** (p<0.001)	*Effective in both T2D, non-DM*
Meta-analysis[1]* (4 trials, N=25,898)	CKD,DKD	CKD progression[d]	**38%** (95% CI: 31%, 44%)	*Effective in both T2D, non-DM*

*includes SCORED

a: doubling SCr, ESKD, renal/CV death

b: ↓eGFR ≥50%, ESKD, renal/CV death

c: ↓eGFR ≥40%, ESKD, renal/CV death

d: varied (but exclusive of CV death)

DKD=diabetic kidney disease; CKD=chronic kidney disease; T2D=type 2 diabetes, CV=cardiovascular, dapa=dapagliflozin; empa=empagliflozin; cana=canagliflozin

a

[1]Baignet C *et al. Lancet* 2022;400:1788-1801

33

SGLT2 Inhibitor Use in Type 2 Diabetes

WHEN TO FAVOR

- T2D + HF
- T2D + CKD
- T2D + CVD*
- T2D + obesity †

* All other things being equal, GLP-1 RA may be preferred (especially in those with h/o stroke)

† All other things being equal, GLP-1 RA is preferred, due to larger effect on body weight/BMI

WHEN TO AVOID

- Recurrent GUIs (instrumentation)
- T1D, LADA & 'T1D-ish' (DKA-prone)
- Orthostatic hypotension
- Frail elderly (?)
- Advanced PAD with amputations (?)
- h/o Fournier's (?) (severe obesity, bed-bound, poor perineal hygiene)

GUIs = genitourinary infections

LADA = latent autoimmune diabetes of adults

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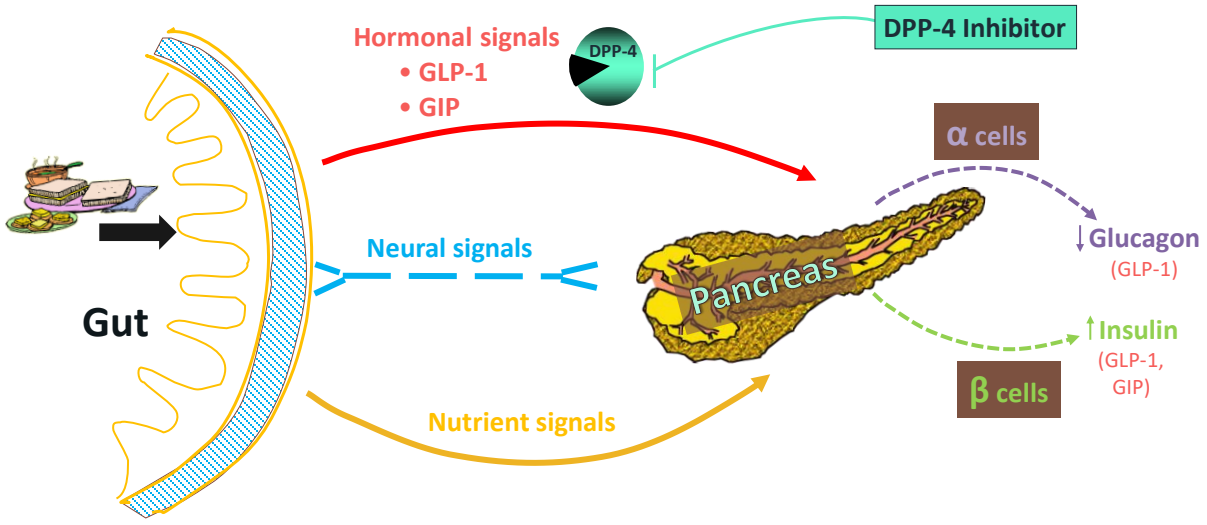
SGLT2 Inhibitor Use in Type 2 Diabetes

- Adjust other diuretics based on volume status
- Tolerate small initial decreases in eGFR
- Duration of action is >24 hrs
- Hold 3 days prior to surgery
- Hold during moderate-severe illness
- Discuss genital yeast infections & treatment
- Dapa- / empagliflozin dose = 10 mg
- To save $, Rx empa 25mg and take half (or use less costly ertu- or bexagliflozin)

35

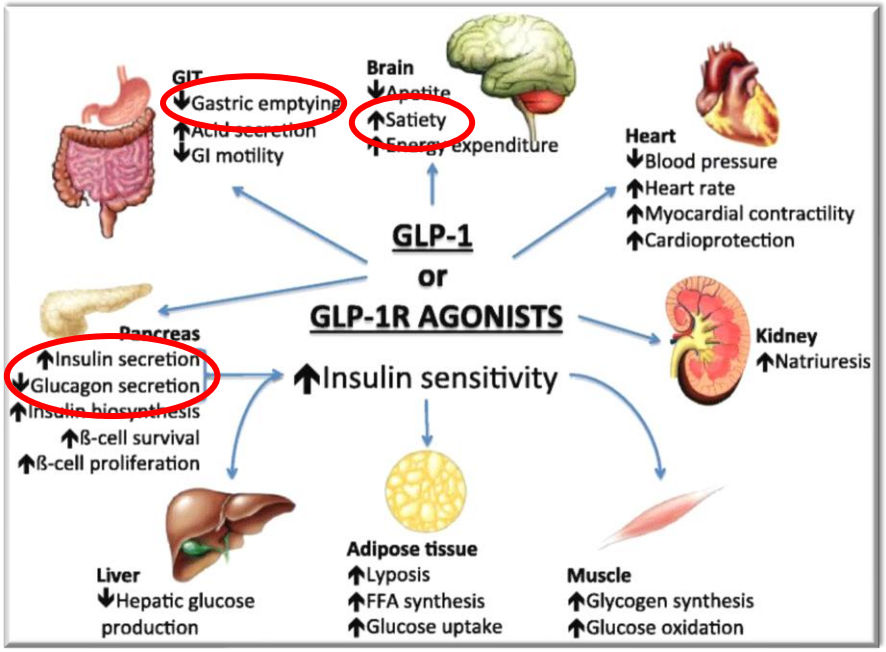
The 'Enteroinsular Axis'



Adapted with permission from Creutzfeldt W. *Diabetologia*. 1979;16:75-85. Copyright © 1979 Springer-Verlag. Drucker DJ. *Diabetes Care*. 2003;26:2929-2940. Kieffer TJ, Habener JF. *Endocr Rev*. 1999;20:876-913. Nauck MA et al. *Diabetologia*. 1993;36:741-744.

36

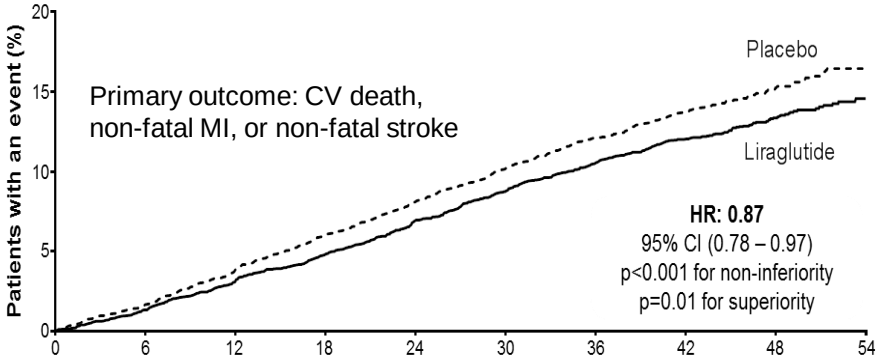
Protean Effects of Glucagon-like Peptide (GLP)-1 and GLP-1 Receptor Agonists



Saraiva FK. *Cardiovasc Diabetol* 2014;13:142

37

LEADER: Liraglutide and CV Outcomes in Patients with T2DM at High CV Risk



Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

LEADER® Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

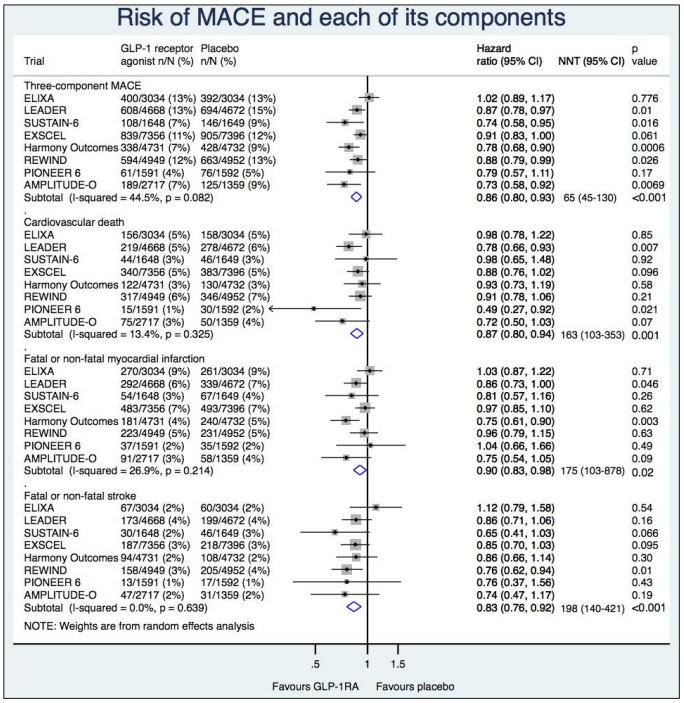
The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Marso SP *et al. N Engl J Med* 2016; 375:311

38

THE LANCET

Cardiovascular, Mortality, and Kidney Outcomes with GLP-1 Receptor Agonists in Patients with T2DM: A Systematic Review and Meta-analysis of Randomized Trials

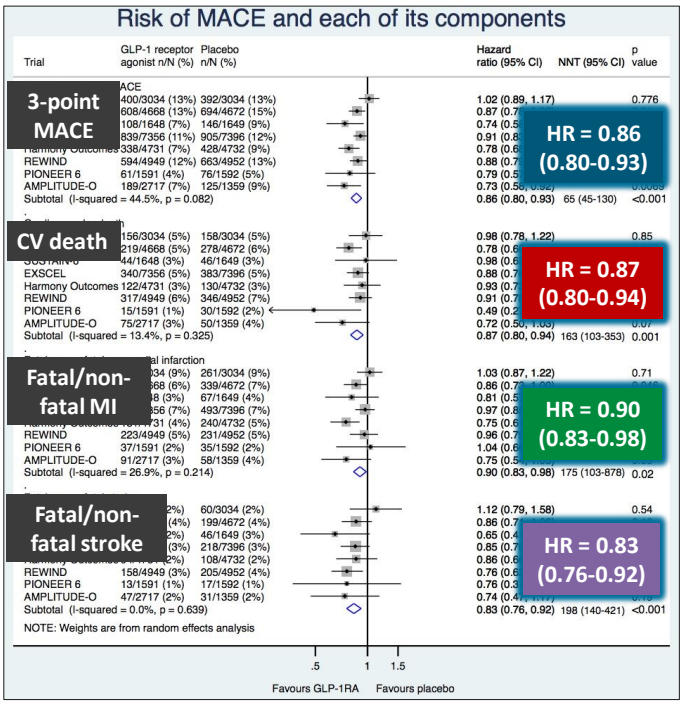


Sattar N *et al. Lancet Diabetes Endocrinol* 2021;9:653-662

39

THE LANCET

Cardiovascular, Mortality, and Kidney Outcomes with GLP-1 Receptor Agonists in Patients with T2DM: A Systematic Review and Meta-analysis of Randomized Trials

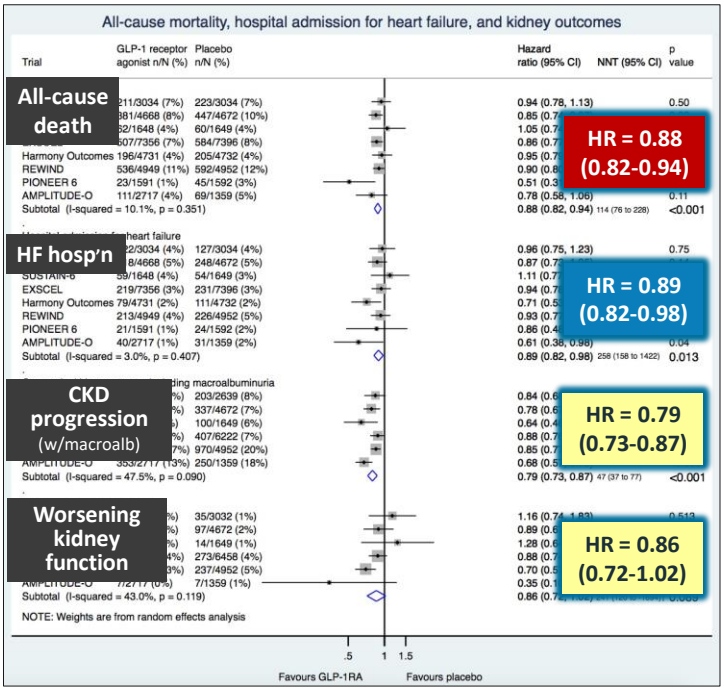


Sattar N *et al. Lancet Diabetes Endocrinol* 2021;9:653-662

40

THE LANCET

Cardiovascular, Mortality, and Kidney Outcomes with GLP-1 Receptor Agonists in Patients with T2DM: A Systematic Review and Meta-analysis of Randomized Trials



Sattar N *et al. Lancet Diabetes Endocrinol* 2021;9:653-662

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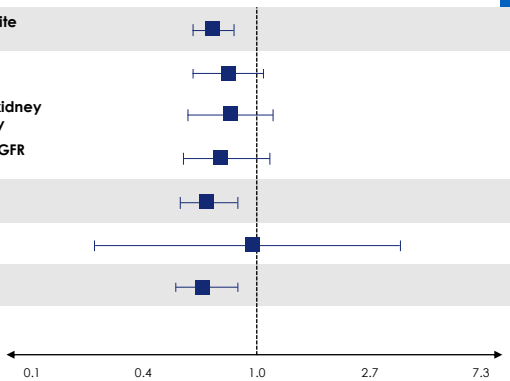
Primary Composite Kidney Outcome

FLOW semaglutide | renal outcomes trial

N=3533 adults with T2D + CKD



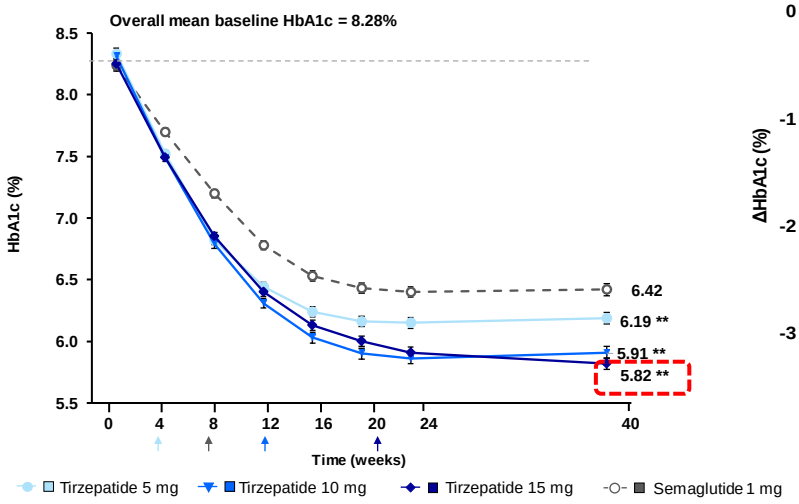
	HR (95% CI)	Semaglutide (n/N)	Placebo (n/N)
Primary outcome: Composite kidney outcome	**0.76** (0.66, 0.88)	331/1767	410/1766
Kidney failure†	**0.83** (0.66, 1.03)	142/1767	165/1766
Initiation of chronic kidney replacement therapy	**0.84** (0.63, 1.12)	87/1767	100/1766
Onset of persistent eGFR <15 mL/min/1.73 m²	**0.80** (0.61, 1.06)	92/1767	110/1766
Onset of persistent ≥50% reduction in eGFR	**0.73** (0.59, 0.89)	165/1767	213/1766
Kidney death	**0.97** (0.27, 3.49)	5/1767	5/1766
CV death	**0.71** (0.56, 0.89)	123/1767	169/1766

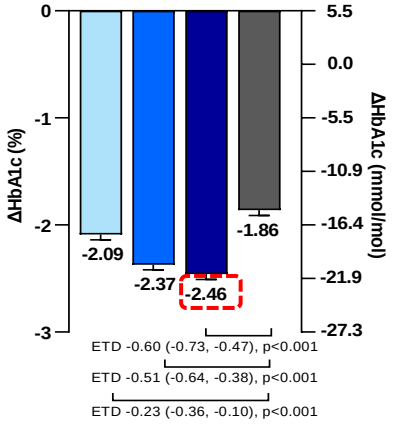
Full analysis set. Data from the in-trial period. CV death includes undetermined cause of death.
†Data on file. Kidney failure was a three-component composite outcome consisting of:
(1) initiation of chronic replacement therapy (dialysis or kidney transplantation), (2) onset of persistent eGFR <15 mL/min/1.73 m² or (3) kidney death.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

Courtesy, R. Prately MD

42

SURPASS 2: Change from Baseline HbA1c at 40 Weeks with Tirzepatide (GLP-1/GIP Receptor Co-agonist) vs. Semaglutide





Data are LSM (SE). Estimated treatment differences at 40 weeks are LSM (95%CI); mITT (efficacy estimand) ANOVA analysis (week 0) and MMRM analysis (week 40).
Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg and 15 mg and semaglutide 1 mg are achieved. **p<0.001 vs. semaglutide 1 mg

Frias JP *et al. N Engl J Med* 2021;385:503-515

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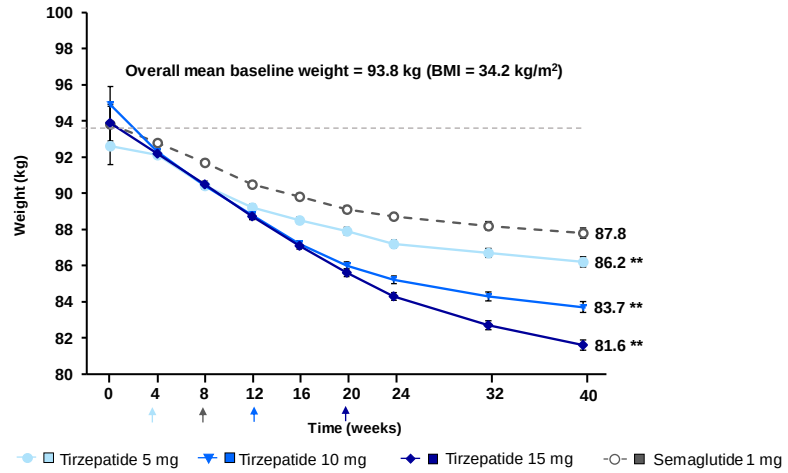
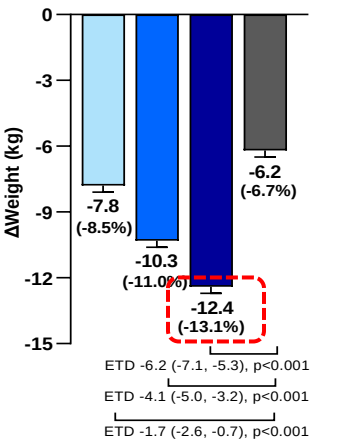
SURPASS 2: Change from Baseline Weight at 40 Weeks with Tirzepatide (GLP-1/GIP Receptor Co-agonist) vs. Semaglutide





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Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg and 15 mg and semaglutide 1 mg are achieved. **p<0.001 vs. semaglutide 1 mg

Frias JP *et al. N Engl J Med* 2021;385:503-515

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GLP-1 (/ GIP) RA Use in Type 2 Diabetes

WHEN TO FAVOR

- T2D + CVD
- T2D + obesity
- T2D + CKD*
- T2D + HFpEF †

* All other things being equal, SGLT2i is preferred due to larger effect size based on hazard ratios from RCTs

† All other things being equal, SGLT2i is preferred due to benefits on harder clinical outcomes in RCTs

WHEN TO AVOID

- Normal weight (?)
- Gastroparesis
- Intestinal obstruction
- Chronic GI symptoms
- Medullary thyroid ca (or MEN-2)
- Pancreatitis (?)

RCT = randomized clinical trials

MEN = multiple endocrine neoplasia

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GLP-1 (/ GIP) RA Use in Type 2 Diabetes

- **Adjust insulin (or SU) doses if tightly controlled**
- **Counsel about GI side effects* & increased risk of gall bladder events**
- **Eat slowly, stop when full; avoid fatty/greasy foods**
- **Start with lowest dose and increase gradually**
- **Duration of action of weekly meds is >1 week**
- **If weekly dose missed → resume same dose w/i 1-2 wks; if 2-3 wks → titrate from half latest dose; if >3 wks, → retitrate from start**
- **Hold at least 1 week prior to surgery**
- **"Counting clicks" on some pens (intermediate doses)**
- **If weight loss substantial, adjust weight-based meds**

***nausea/vomiting, abdominal discomfort, constipation, diarrhea**

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Major Glucose Lowering Drugs Classes for T2DM

Classes	Generic Names	↓A1c	Mechanism(s)	Positive(s)	Negative(s)	Cost
Insulin	Degludec, Glargine, Detemir, NPH, Regular, Lispro, Aspart, Glulisine	No limit	Replaces deficient insulin supply	No ceiling; most titratable agent	Hypo, weight gain	highly variable
SU's	Glyburide, Glipizide, Glimepiride	1-1.5%	↑ endogenous insulin production	Extensive experience	Hypo, weight gain	$
Metformin	Metformin	1-1.5%	↓ hepatic glucose production (? others)	±Wt loss, no hypo, ↓ CV events (?)	GI, lactic acidosis, B-12 deficiency	$
TZD's	Rosiglitazone, Pioglitazone*	1-1.5%	Enhances peripheral insulin sensitivity	Durability, no hypo, ↓ CV events*, ↓ NASH	Weight gain, edema, HF, bone fxs, ? bladder ca*	$ - $$$
DPP-4 i's	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin	0.5-1%	↓ DPP-4 activity and ↑ incretins (GLP1, GIP)	Well-tolerated; no hypo	Urticaria, ? pancreatitis, ? HF*	$$$$
GLP-1 RA's	Exenatide, Liraglutide*, Dulaglutide*, Albiglutide*, Lixisenatide, Semaglutide*	1-1.5%	↑ insulin, ↓ glucagon, ↓ gastromotility, hunger	Wt loss, no hypo, ↓ BP, ↓ MACE*	GI, ? Pancreatic/ biliary disease, ? medullary thyroid ca	$$$$
SGLT2-i's	Canagliflozin*†#‡, Dapagliflozin†# Empagliflozin*†#, Ertugliflozin	0.5-1%	↑ urinary glucose excretion	Wt loss, no hypo, ↓ BP, ↓ MACE*, HF†, ↓ CKD#	Polyuria, GU, DKA, bone fxs‡, amputations‡	$$$$

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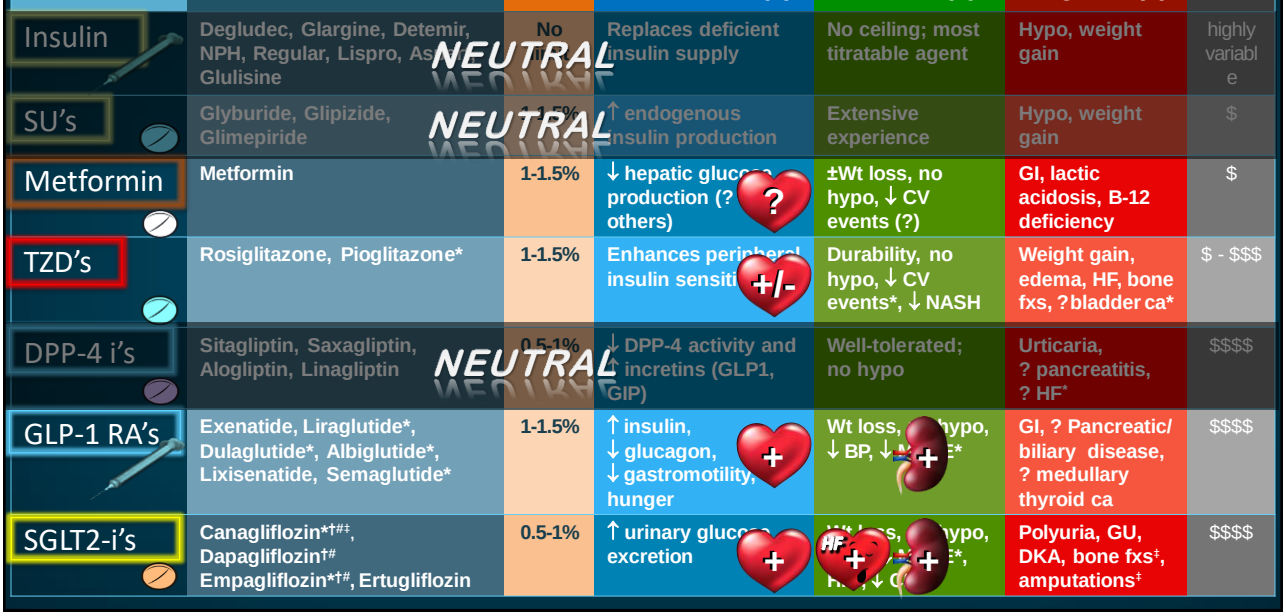
Major Glucose Lowering Drugs Classes for T2DM

Classes	Generic Names	↓A1c	Mechanism(s)	Positive(s)	Negative(s)	Cost
Insulin	Degludec, Glargine, Detemir, NPH, Regular, Lispro, Aspart, Glulisine	NEUTRAL	Replaces deficient insulin supply	No ceiling; most titratable agent	Hypo, weight gain	highly variable
SU's	Glyburide, Glipizide, Glimepiride	NEUTRAL	↑ endogenous insulin production	Extensive experience	Hypo, weight gain	$
Metformin	Metformin	1-1.5%	↓ hepatic glucose production (? others)	±Wt loss, no hypo, ↓ CV events (?)	GI, lactic acidosis, B-12 deficiency	$
TZD's	Rosiglitazone, Pioglitazone*	1-1.5%	Enhances peripheral insulin sensitivity	Durability, no hypo, ↓ CV events*, ↓ NASH	Weight gain, edema, HF, bone fxs, ? bladder ca*	$ - $$$
DPP-4 i's	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin	NEUTRAL	↓ DPP-4 activity and ↑ incretins (GLP1, GIP)	Well-tolerated; no hypo	Urticaria, ? pancreatitis, ? HF*	$$$$
GLP-1 RA's	Exenatide, Liraglutide*, Dulaglutide*, Albiglutide*, Lixisenatide, Semaglutide*	1-1.5%	↑ insulin, ↓ glucagon, ↓ gastromotility, hunger	Wt loss, ↓ BP, ↓ MACE*	GI, ? Pancreatic/ biliary disease, ? medullary thyroid ca	$$$$
SGLT2-i's	Canagliflozin*†#‡, Dapagliflozin†# Empagliflozin*†#, Ertugliflozin	0.5-1%	↑ urinary glucose excretion	Wt loss, no hypo, ↓ BP, ↓ MACE*, HF†, ↓ CKD#	Polyuria, GU, DKA, bone fxs‡, amputations‡	$$$$



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T2D Update: Incorporating the Latest Strategies

1. =Pathogenesis of T2D
2. Major T2D Medication Categories
3. Calibrating A1c Targets
4. Older T2D Guidelines (as context)
5. CV / Renal Impact of T2D Therapies
6. **Updated T2D Guidelines**
7. Diabetes Office Visit Checklist

Yale NewHaven Health

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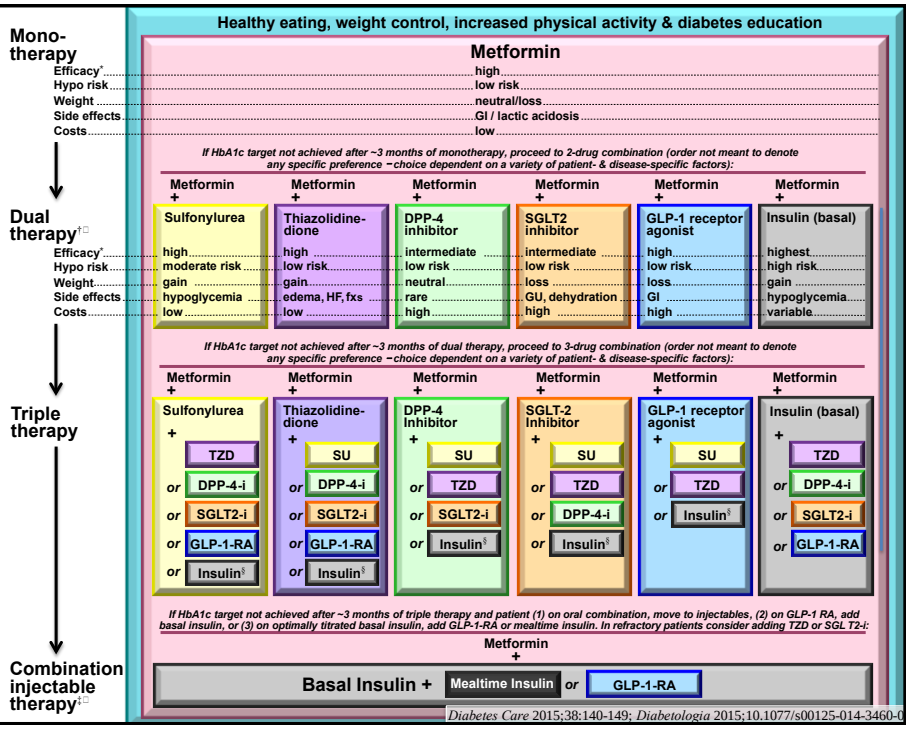
American Diabetes Association. EASD European Association for the Study of Diabetes

Position Statement on the Management of Hyperglycemia in Patients with Type 2 Diabetes: A Patient-Centered Approach

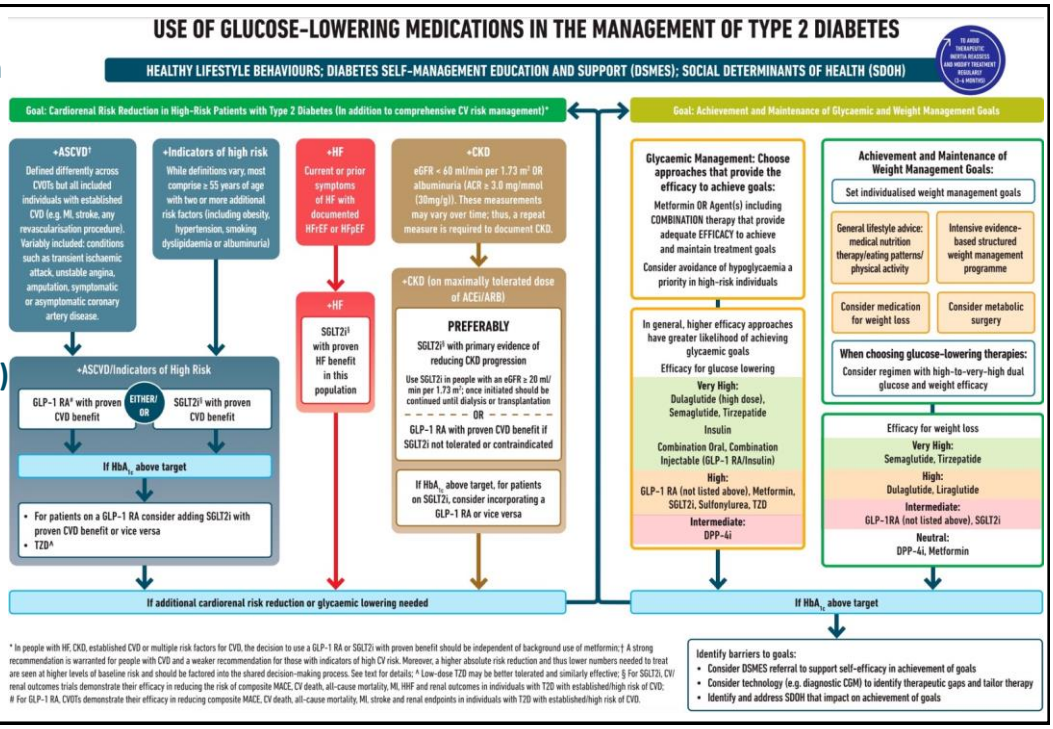


Inzucchi SE *et al. Diabetes Care* 2015;38:140-9; *Diabetologia* 2015;58:429-42

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

50

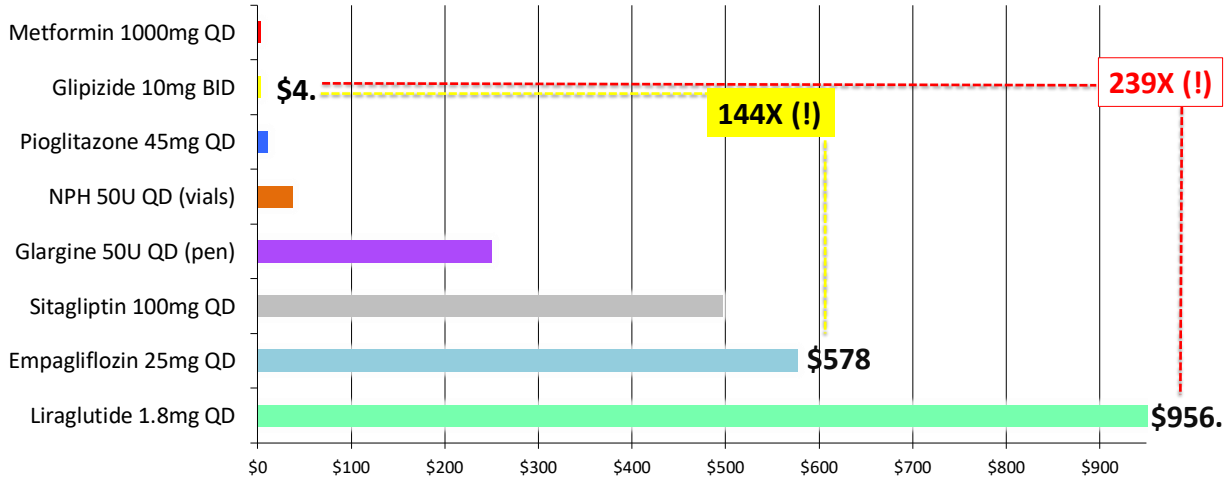
Management of Hyperglycemia in Type 2 Diabetes. 2022 Consensus Report by the ADA & EASD (Included in the ADA 2024 *"Standards of Care in Diabetes"*)



Davies M, *et al. Diabetes Care* 2022
ADA. Diabetes Care 2024

51

Costs of 30 Days of Diabetes Medications in U.S.



www.GoodRx.com/, accessed April 25, 2024,
(lowest price for New Haven, CT 06510)

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T2D Update: Incorporating the Latest Strategies

1. Pathogenesis of T2D
2. Major T2D Medication Categories
3. Calibrating A1c Targets
4. Older T2D Guidelines (as context)
5. CV / Renal Impact of T2D Therapies
6. Updated T2D Guidelines
7. **Diabetes Office Visit Checklist**

Yale NewHaven Health

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Diabetes Office Visit Checklist

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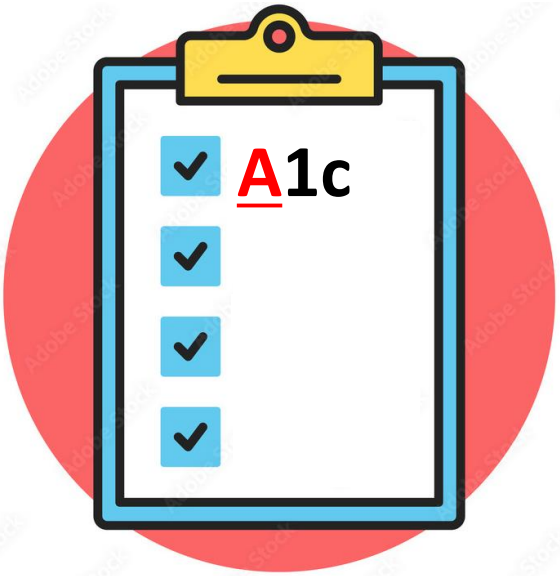
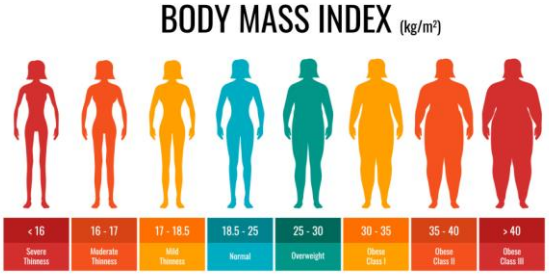
Diabetes Office Visit Checklist



- Optimize target (? <6.5%, <7%, <8%)
- Choose DM meds based on comorbidities & other factors
- Assess for side effects
- Ensure compliance
- Inquire about cost$

55

Diabetes Office Visit Checklist



- Any BMI reduction is good
- Lifestyle changes
- Stress DM meds that reduce WT (GLP-1(/GIP) RA, SGLT2i, metformin)
- Avoid obesogenic medications

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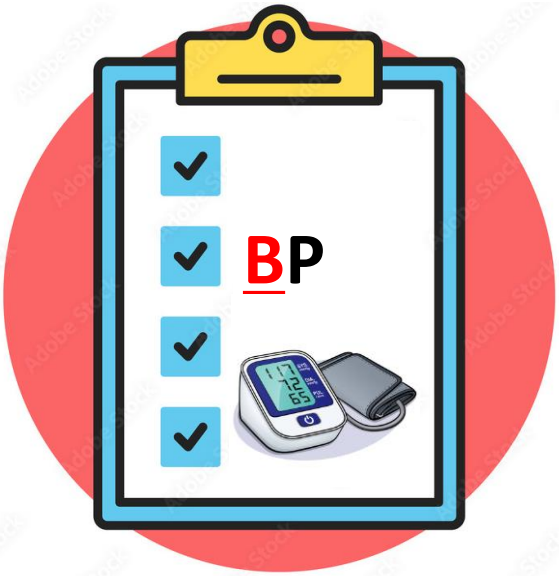
Diabetes Office Visit Checklist



- Optimize target (? <130/80, <140/90)
- Make sure on RAS blocker
- Add-on meds: HCTZ→CCB→MRA
- R/O 2ndary HTN if uncontrolled
- Check K^+, Na^+, eGFR
- Assess for side effects
- Ensure compliance

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Diabetes Office Visit Checklist

- Optimize LDL target (? <70, <55)
- Make sure on adequate dose of high-potency statin (rosuva, atorva)
- ? Combination tx (eze, BPA)
- Consider injectable PCSK9i
- Assess TGs (? target <150)
  - ➢ Get BG down first!
  - ➢ Treat if persistently >300-400

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Diabetes Office Visit Checklist

- Heart-healthy, controlled carb diet
- Mediterranean diet?
- Avoid sugared beverages
- Limit concentrated sweets
- Referral to Nutritionist/CDE
- Regular physical activity
  - 5000 steps/day to maintain WT
  - 10000 steps/day to lose WT

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Diabetes Office Visit Checklist

- Retinal exams (or photos) by ophthalmologist or optometrist every 1-2 years

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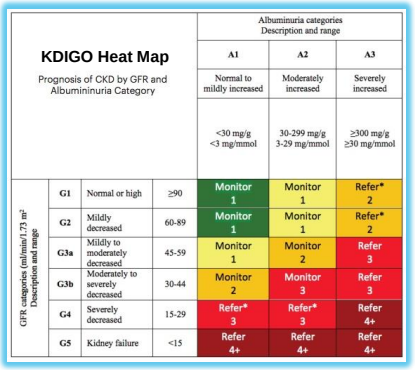
Diabetes Office Visit Checklist

- Regular podiatry visits if:
  - Neuropathy
  - PAD
  - Bone deformities
  - Nail care is difficult

61

Diabetes Office Visit Checklist



KDIGO Heat Map

Prognosis of CKD by GFR and Albuminuria Category

GFR categories (ml/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	Monitor 1	Monitor 1	Refer* 2
	G2	Mildly decreased	60-89	Monitor 1	Monitor 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Monitor 1	Monitor 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Monitor 2	Monitor 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

- Annual eGFR & UACR
- RASi + SGLT2i (?GLP1RA) if CKD
- Nephrologist if eGFR <30-45 or macroalbuminuria (?)
- Avoid nephrotoxins (dehydration, NSAIDs, certain contrast dyes)

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T2D Update: Incorporating the Latest Strategies

Take-Home Points

1. **There are a growing number of glucose-lowering agents for patients with T2D.**
2. **First, determine the optimal A1c target for each patient.**
3. **Then, select meds with a focus on their potential additional benefits on underlying comorbidities, including obesity. Metformin is no longer required as foundation therapy (but still often used in that manner.)**
4. **Data from SGLT2i and GLP-1RA trials have led to their positioning as favored in certain circumstances: ASCVD, HF, CKD.**
5. **Sequentially, add additional glucose-lowering meds until the HbA1c target is achieved, typically to a total of 3 (?4); then consider insulin.**
6. **Don’t forget about other ways to reduce CV risk (BP, lipids, anti-platelet therapy).**

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