DIABETES UPDATE 2022: A CASE BASED APPROACH

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METABOLISM, ENDOCRINOLOGY & NUTRITION

Disclosures

- Advisory boards for Abbott Diabetes Care

Objectives

1. To understand the use of newer therapies for weight management in individuals with diabetes without cardiorenal disease
2. To learn how to use newer diabetes therapies for cardiorenal disease in individuals with and without diabetes
3. To recognize the expanding role of CGM in primary care diabetes

Diabetes management in 2022

1. Weight management in individuals with diabetes without cardiorenal disease
2. Newer diabetes therapies for cardiorenal disease in individuals with and without diabetes
3. Expanding role of CGM in primary care diabetes

You are probably thinking…

1. I don’t know which one to pick…
2. My patient can’t afford any of the new expensive drugs or technology, why are you telling me to use these?

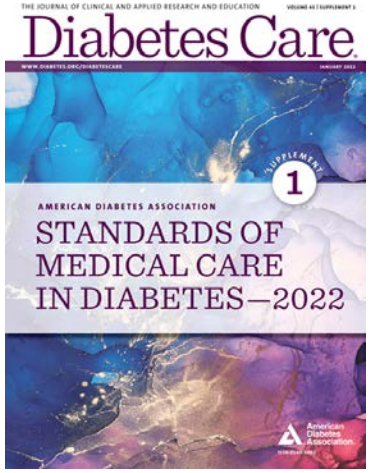
Diabetes management in 2022

1. Weight management in individuals with diabetes without cardiorenal disease
2. Newer diabetes therapies for cardiorenal disease in individuals with and without diabetes
3. Expanding role of CGM in primary care diabetes

Case 1

- 55 year old woman with 5 years of type 2 diabetes, no complications
- On metformin ER 2000mg daily, empagliflozin 25mg
- Has gained 15 lbs early during pandemic working from home
- Commercially insured
- A1C 8.6-9% over 15 months (7.6 → 8.6 → 9.2%)
- Had seen ads for two different weekly GLP-1 receptor agonists, a friend had lost significant weight on a weekly preparation
- You agree that GLP1RA therapy will be helpful for weight loss

Algorithm for Type 2 Diabetes Treatment – 2022



Incorporate agents that provide adequate EFFICACY to achieve and maintain glycemic goals

Higher glycemic efficacy therapy: GLP-1 RA; insulin; combination approaches (Table 9.2)

- **Consider additional comorbidities, patient-centered treatment factors, and management needs in choice of therapy, as below:**

MINIMIZE HYPOGLYCEMIA

No/low inherent risk of hypoglycemia: DPP-4i, GLP-1 RA, SGLT2i, TZD

For SU or basal insulin, consider agents with lower risk of hypoglycemia[3,4]

IF A1C ABOVE TARGET

Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs

MINIMIZE WEIGHT GAIN/ PROMOTE WEIGHT LOSS

PREFERABLY

GLP-1 RA with good efficacy for weight loss

OR

SGLT2i

IF A1C ABOVE TARGET

For patients on a GLP-1 RA, consider incorporating SGLT2i and vice versa

- If GLP-1 RA not tolerated or indicated, consider DPP-4i (weight neutral)

Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs

CONSIDER COST AND ACCESS

Available in generic form at lower cost:

- Certain insulins: consider insulin available at the lowest acquisition cost
- SU
- TZD

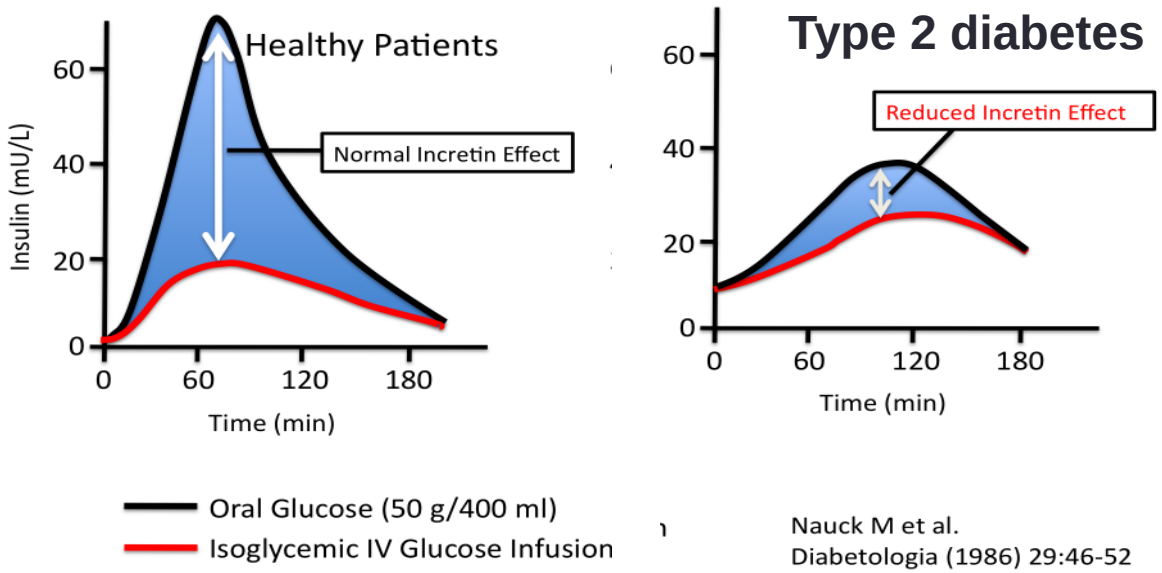
IF A1C ABOVE TARGET

Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2022*. *Diabetes Care 45: S125-143*

The Incretins

- Glucagon like peptide 1 (GLP-1) and Glucose-dependent insulinotropic polypeptide (GIP)
- Incretin effect - term describing greater insulin secretory responses after oral glucose loads than after intravenous glucose infusions that lead to identical glycemic excursions



Nauck M et al.
Diabetologia (1986) 29:46-52

GLP-1 receptor agonists: the “tides”

SHORT ACTING GLP1RA

Exenatide
Byetta®
5–10 mcg
twice daily
SC

Lixisenatide
Lyxumia®
10–20 mcg
twice daily
SC

Exenatide LAR
Bydureon®
2 mg
per week
SC

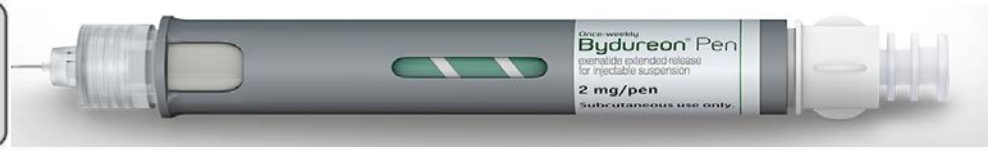
LONG ACTING GLP1RA

Dulaglutide
Trulicity®
0.75–1.5 mg
per week
SC

Semaglutide
Ozempic®
0.25–0.5–1 mg
per week
SC

Liraglutide
Victoza® Saxenda®
0.6–1.2–1.8 mg
once a day
SC

Semaglutide
Rybelsus®
3–7–14 mg
once a day
OS



DRUG	A1c %	Wt. change kg
Exenatide (Byetta)	-1	-2.3
Lixisenatide (Adlyxin)	-1	-2.9
Exenatide LAR (Bydureon)	-1.5-2	-2.8
Dulaglutide (Trulicity)	-1.4	-2.9
Semaglutide (Ozempic)	-1.5	-4.5-6
Liraglutide (Victoza)	-1.5	-2.2

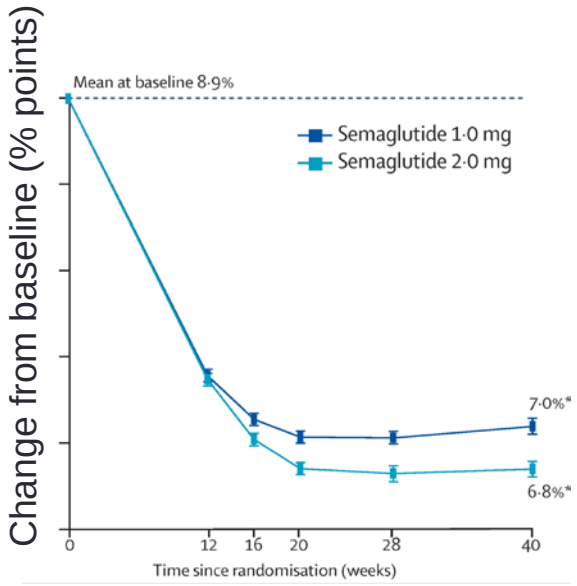
Patient #1 55 y/o with weight gain and no cardiorenal disease on metformin and SGLT2i

- Started on dulaglutide - 0.75mg weekly and increased to 1.5mg weekly
- Lost 10 lbs over 3 months and is very happy but weight has plateaued
- A1C is 7.2%
- Can you increase the dose further with benefit?

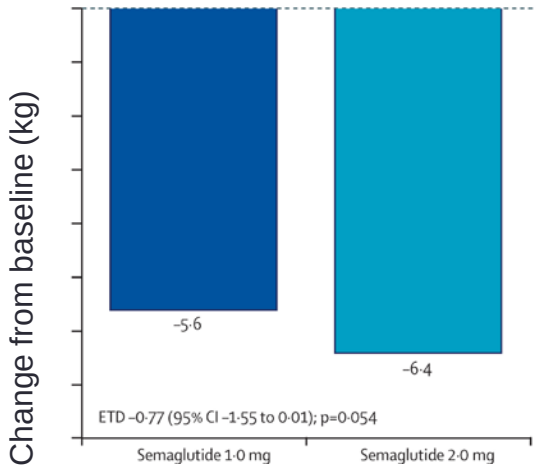
How high to go with GLP1RA dosing?

SUSTAIN FORTE trial
Semaglutide

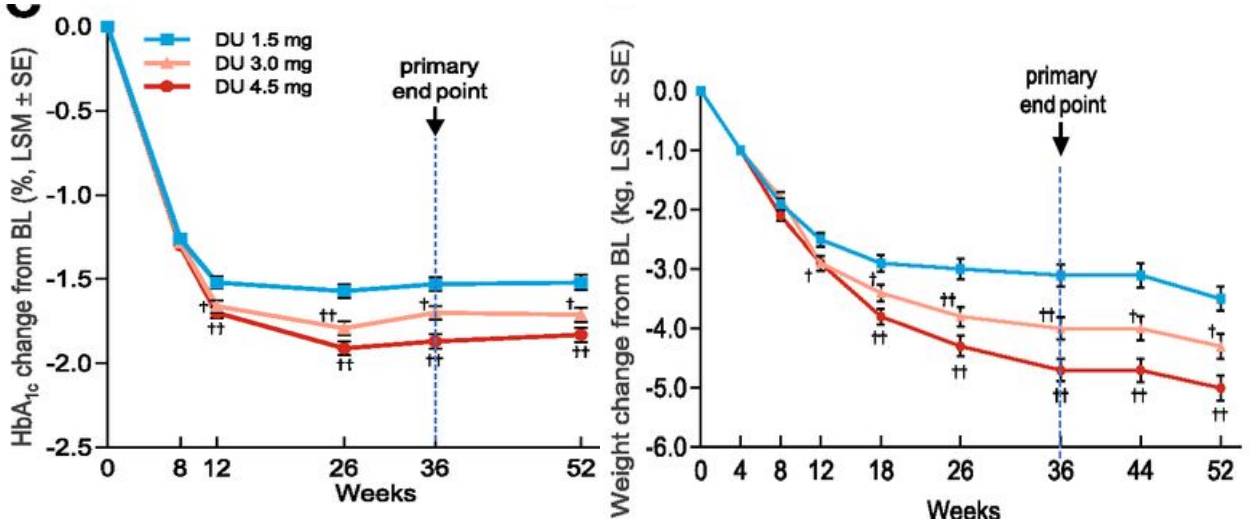
A1c reduction



Weight loss



AWARD-11 trial
Dulaglutide



Incremental benefits for glucose and weight at higher doses

Frias JP et al AWARD-11, Diab Care 2021; Frias JP et al SUSTAIN FORTE 2021 Lancet Diab Endocrinol

Patient 1

- Dulaglutide dose increase to 3mg
- Weight loss ~ about 5 more lbs
- Able to get up to 4.5mg weekly dose

- Read an article online on a new drug called Mounjaro

FDA NEWS RELEASE

FDA Approves Novel, Dual-Targeted Treatment for Type 2 Diabetes

In Clinical Trials, Treatment Proved More Effective Than Other Therapies Evaluated

Share Tweet Linkedin Email Print

For Immediate Release: May 13, 2022

Dual agonism of GLP-1 and GIP

Glucagon-like Peptide-1 Receptor Agonism

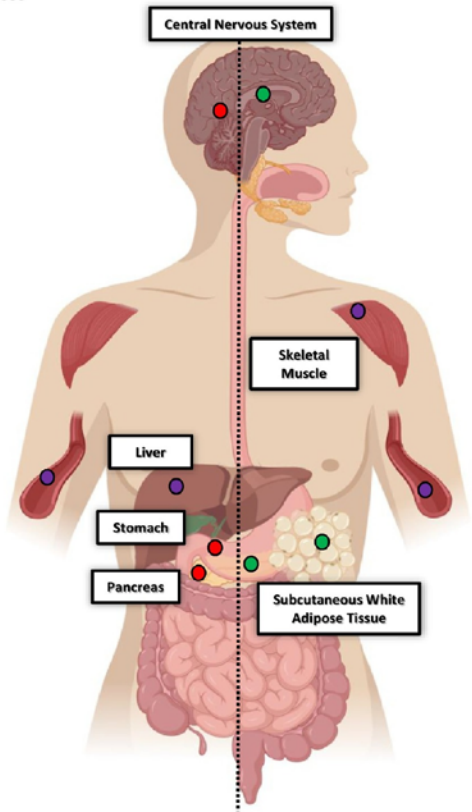
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation



Glucose-dependent Insulinotropic Polypeptide Receptor Agonism
Glucagon-like Peptide 1 Receptor Agonism
Indirect Action

Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

Central Nervous System
- ↓ Food Intake
- ↓ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

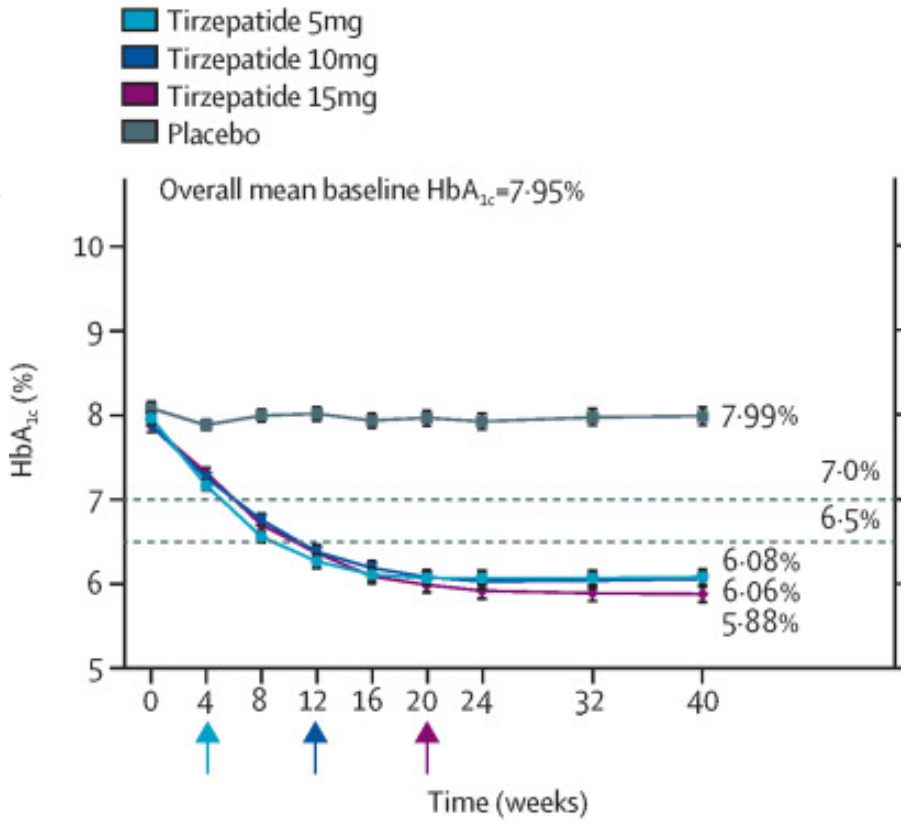
Skeletal Muscle
- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation

Trends in Endocrinology & Metabolism

Tirzepatide

- GLP-1 and GIP dual receptor agonist (“Twincretin”)
- SURPASS program - Superior glycemic efficacy to placebo, semaglutide 1mg weekly, insulin degludec and insulin glargine
- A1C reduction 1.7-2.6%
- Weight reduction of **7-9.5kg**

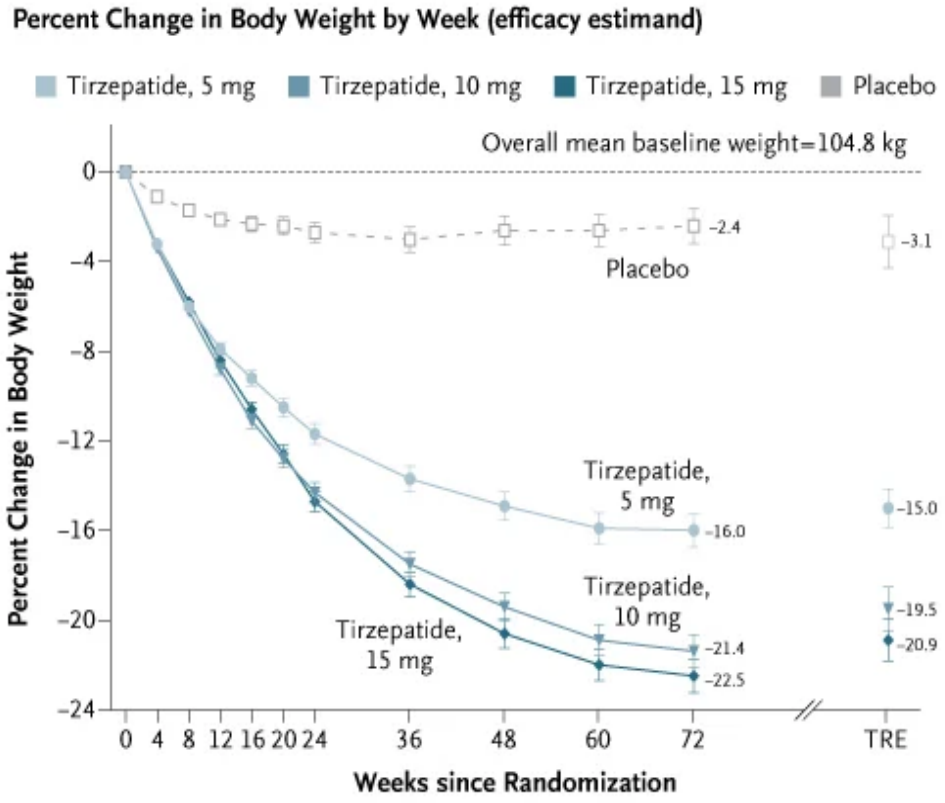
- No increase in MACE (SURPASS-CVOT trial ongoing)



Rosenstock J et al, SURPASS-1, Lancet 2021

Tirzepatide in obesity – SURMOUNT 1

- Tirzepatide 5, 10 or 15 mg weekly for 72 wks
- BMI ≥ 30kg/m^2
- More weight loss with higher dosing mean wt loss ~20%
- **34% had >25% wt loss**
- All groups lost weight of at least 5%



Jastreboff AM et al SURMOUNT-1 NEJM 2022

Using tirzepatide

- Approved for use to improve glucose control in adults with Type 2 diabetes
- Three doses 5, 10, 15 mg sc weekly

- Adverse effects – GI side effects (esp with higher doses)
- Coverage for type 2 diabetes - copay card available; “failed on current therapies” (rising A1C /weight)

- Not yet approved for weight management

Diabetes management in 2022

1. Weight management in individuals with diabetes without cardiorenal disease
2. Newer diabetes therapies for cardiorenal disease in individuals with and without diabetes
3. Expanding role of CGM in primary care diabetes

Case 2

- 71 year old male
- 17 years of type 2 diabetes; has retinopathy and nephropathy
- On metformin, glipizide, sitagliptin and glargine
- Other meds- losartan, amlodipine, HCTZ, spironolactone, atorvastatin
- BP 132/78 mmHg, BMI 34
- A1C 9%
- U ACR 2210mg/g; eGFR 31 ml/min/1.73m^2

What do you do next?

Case 2

- 71 year old male
- 17 years of type 2 diabetes; has retinopathy and nephropathy
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- Other meds - losartan, amlodipine, HCTZ, spironolactone, atorvastatin
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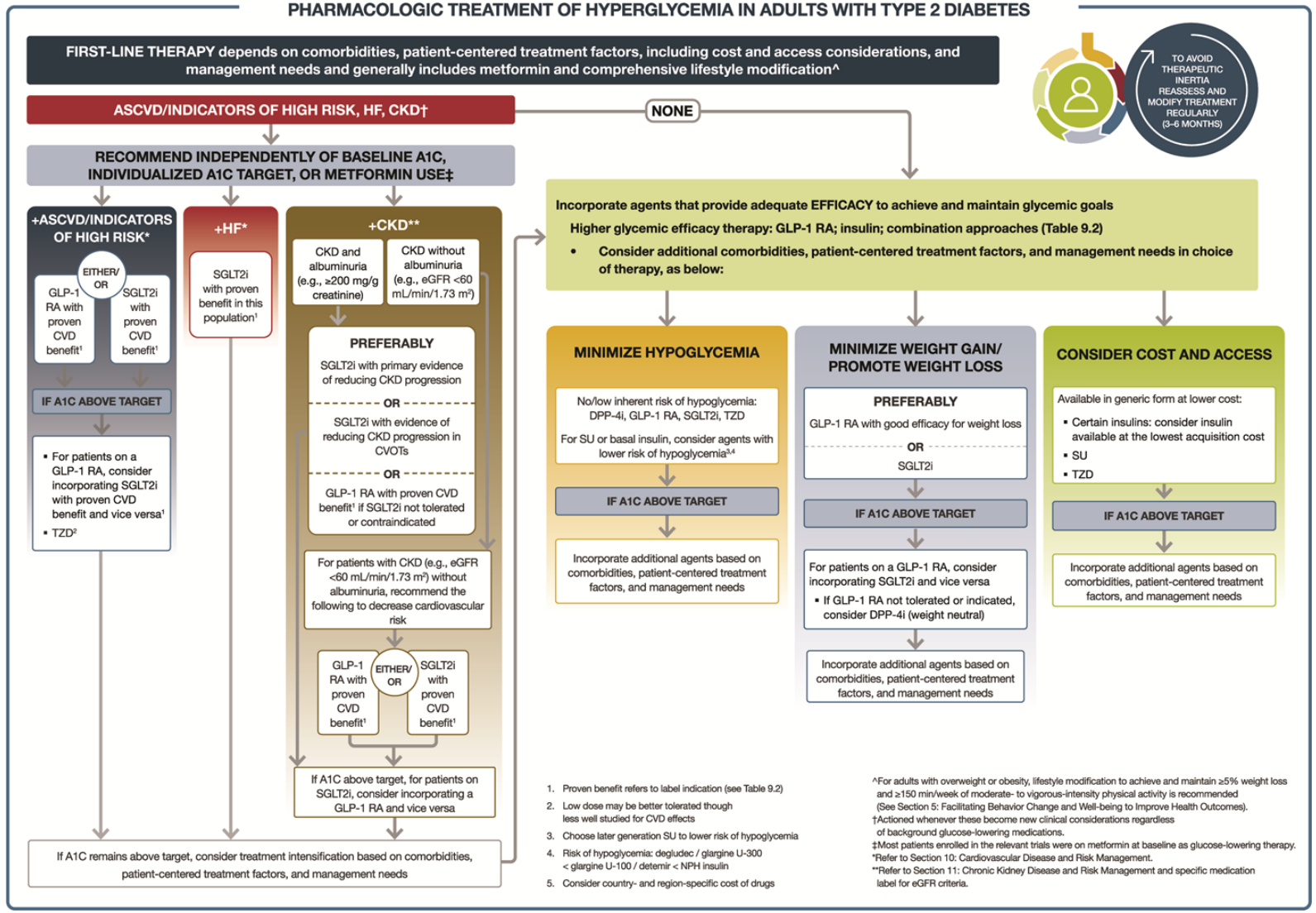
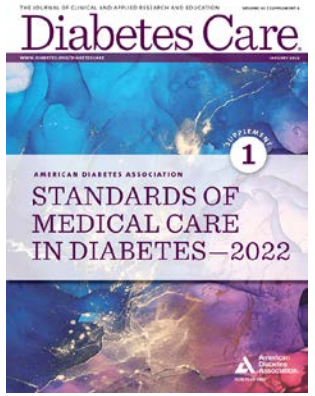
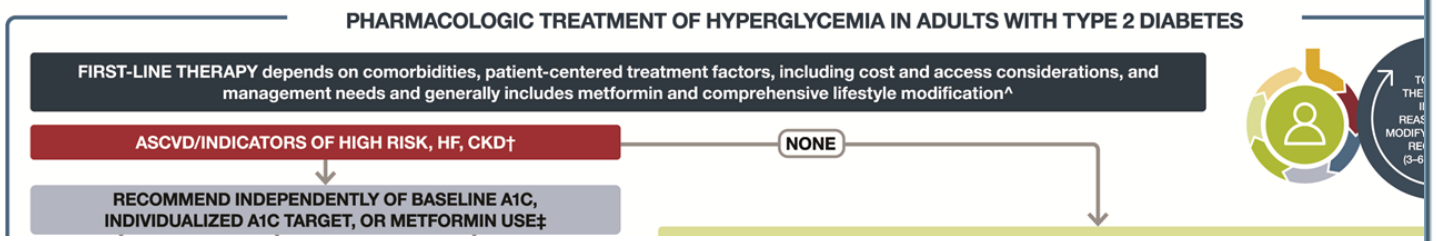
Algorithm for Type 2 Diabetes Treatment – v2022





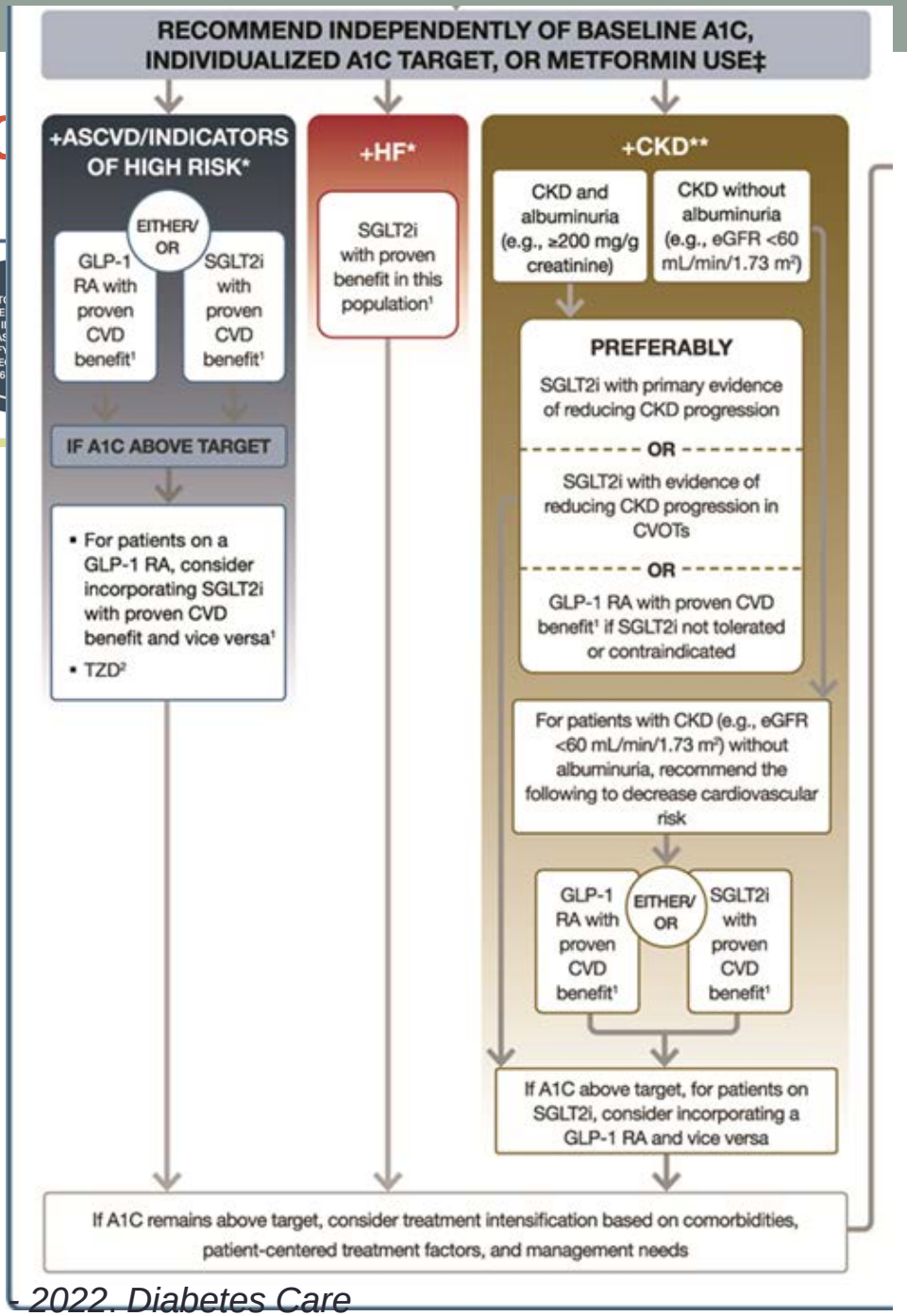
Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2022*. *Diabetes Care*

Medication selection sequence in type 2 d



INDICATORS OF HIGH RISK OR ESTABLISHED ASCVD, CKD OR HF

CONSIDER INDEPENDENT OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET



Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2022. Diabetes Care*

Choosing Based on Cardiac and/or Renal status: Key Concepts

If patients have :

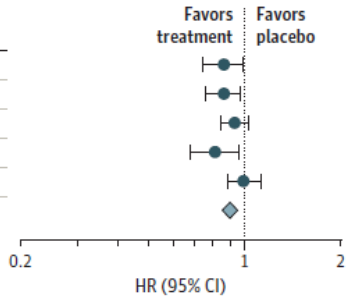
- **ASCVD** (established ASCVD or indicators of high risk)
  - Add GLP-1 RA with proven benefit
  - Add SGLT2i with proven benefit
- **Heart failure**:
  - Add SGLT2i with evidence of reducing HF progression
- **CKD**:
  - With albuminuria - add SGLT2i with evidence of reducing CKD progression
  - Without albuminuria (eg eGFR <60) – add SGLT2i or GLP-1 RA

Standards of Medical Care in Diabetes - 2022. Diabetes Care

SGLT2i improve CV & kidney outcomes in T2D

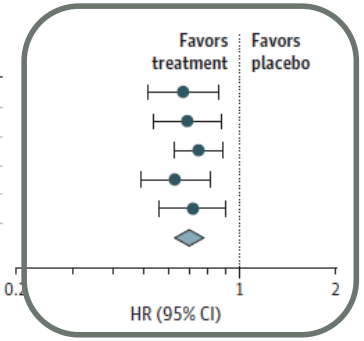
3 point MACE ↓ 10%

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (Q = 5.22; *df* = 4; *P* = .27; I^2 = 23.4%)					0.90 (0.85-0.95)



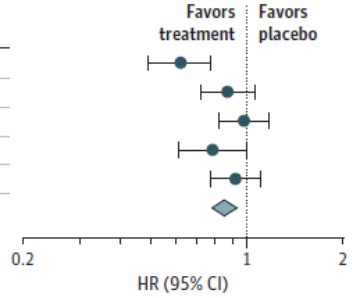
Hosp. heart failure ↓ 32%

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model (Q = 1.39; *df* = 4; *P* = .85; I^2 = 0.0%)					0.68 (0.61-0.76)



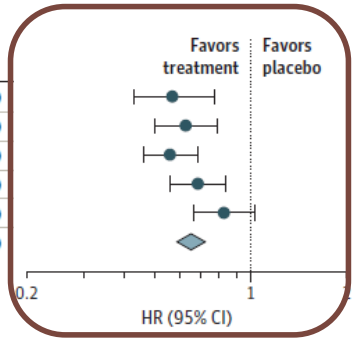
Cardiovascular death ↓ 15%

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)
CANVAS program	NA/5795	11.6	NA/4347	12.8	0.87 (0.72-1.06)
DECLARE-TIMI 58	245/8582	7.0	249/8578	7.1	0.98 (0.82-1.17)
CREDENCE	110/2202	19.0	140/2199	24.4	0.78 (0.61-1.00)
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)
Fixed-effects model (Q = 11.22; *df* = 4; *P* = .02; I^2 = 64.3%)					0.85 (0.78-0.93)



CKD progression ↓ 38%

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 7.96; *df* = 4; *P* = .09; I^2 = 49.7%)					0.62 (0.56-0.70)

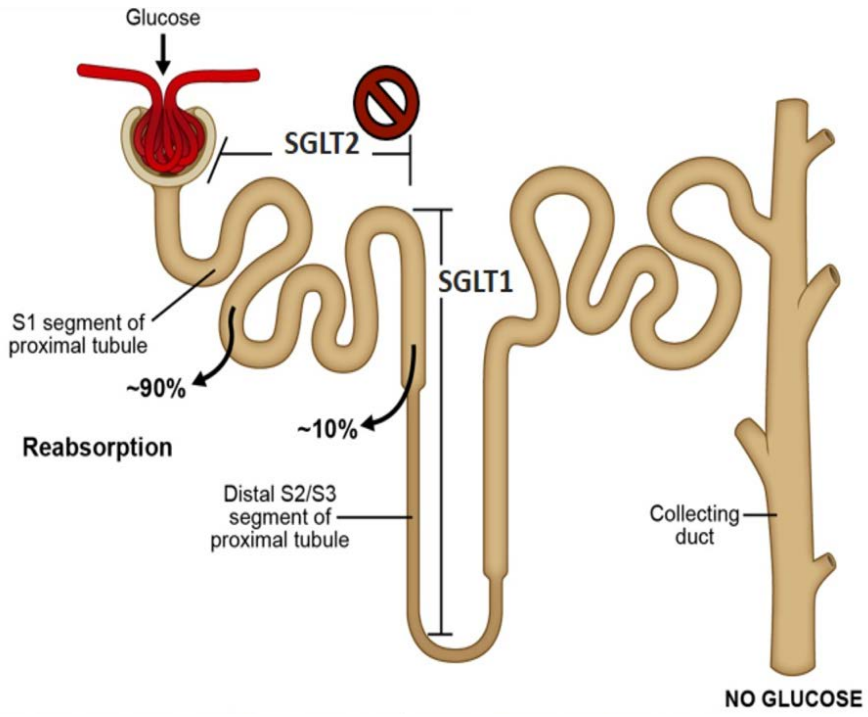


McGuire DK *et al*, *JAMA Cardiology* 2020

SGLT2 inhibitors – expanding scope

- Reduced plasma glucose by enhancing urinary glucose excretion

- Mechanism independent of insulin or incretin pathways
- Intermediate to high glycemic efficacy – A1C ↓ 0.6%
  - Lower efficacy at lower eGFR
- Despite this CV benefits are preserved even in patients with renal impairment
- Mechanisms are likely different from glycemic control

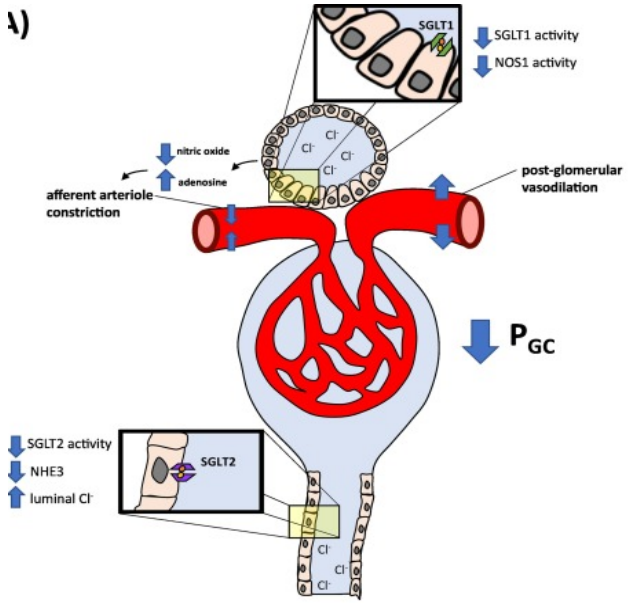


Can you use at lower eGFRs?

- Effects on eGFR
  - Initiation results in acute decline in eGFR, should be expected
  - Reversible (partly hemodynamic)
  - Less than 30% drop is not associated with adverse events

- eGFR threshold is 20 ml/min/1.73m^2 (ADA, KDIGO)
- Early initiation of SGLT2i is beneficial

- *Soon can be used in patients without diabetes with CKD*



Case 2

- 71 year old male with Type 2 diabetes; retinopathy, nephropathy
- On metformin, glipizide, glargine
- A1C 9%
- U ACR 2210mg/g;
- eGFR 31 ml/min/1.73m^2

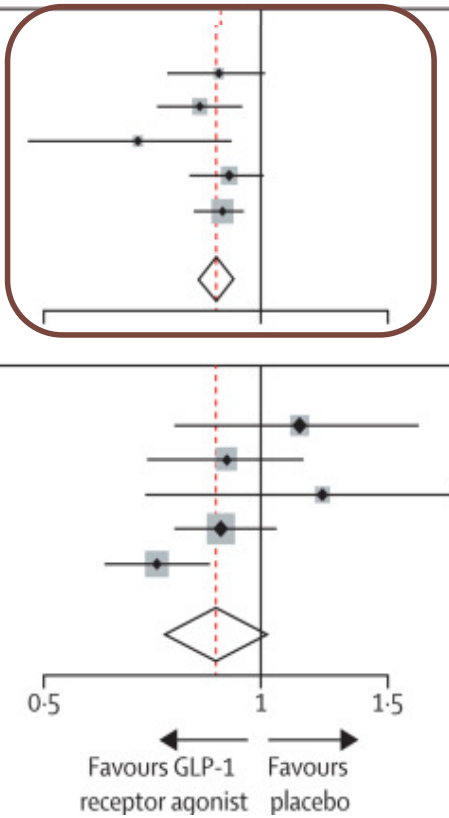
- Patient started on empagliflozin 10mg
- eGFR dropped to 27 ml/min/1.73m^2 and hovered
- Metformin and HCTZ were discontinued

- Lost 5 lbs; some hypoglycemia
- Sulfonylurea discontinued
- Continue on empagliflozin and glargine

Could you use a GLP-1RA or GIP/GLP-1RA?

- No completed studies on CKD outcomes

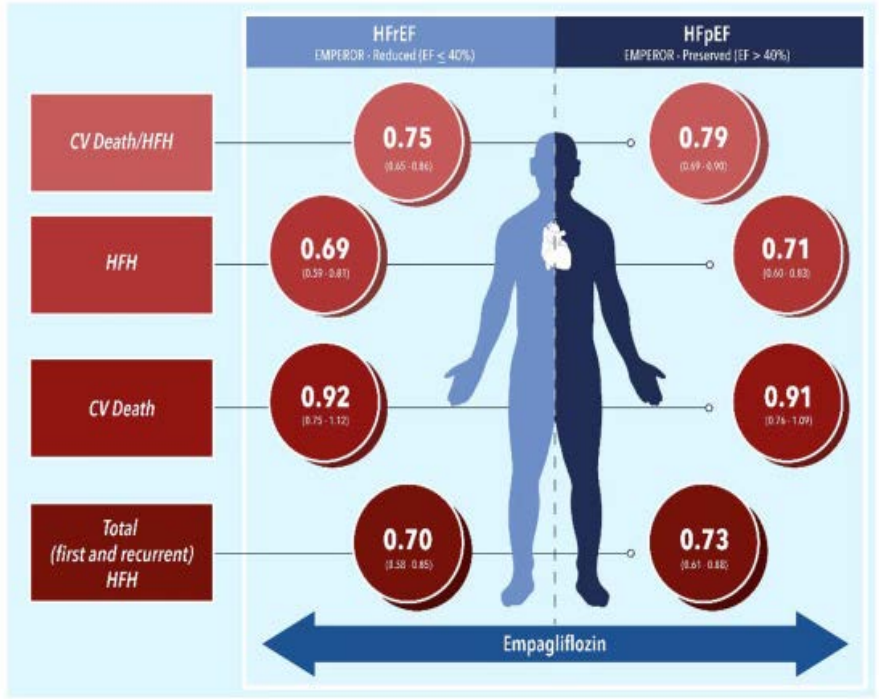
	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2647 (6%)	203/2639 (8%)	0·84 (0·68–1·02)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·67–0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46–0·88)		0·006
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76–1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77–0·93)		<0·001
Overall (I^2=0·0%, p=0·413)	**1716/20168 (9%)**	**2017/20134 (10%)**	**0·83 (0·78–0·89)**	**62 (48 to 96)**	**<0·001**
Worsening of kidney function					
ELIXA	41/3031 (1%)	35/3032 (1%)	1·16 (0·74–1·83)		0·513
LEADER	87/4668 (2%)	97/4672 (2%)	0·89 (0·67–1·19)		0·43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1·28 (0·64–2·58)		0·48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0·88 (0·74–1·05)		0·164
REWIND	169/4949 (3%)	237/4952 (5%)	0·70 (0·57–0·85)		<0·001
Overall (I^2=42·7%, p=0·137)	**561/20752 (3%)**	**656/20763 (3%)**	**0·87 (0·73–1·03)**	**247 (119 to –1072†)**	**0·098**

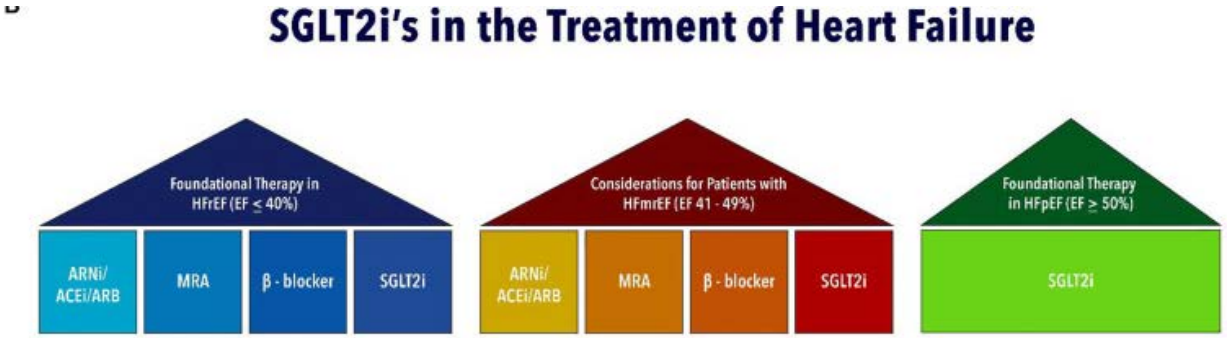


Kristensen SL et al Lancet Diabetes Endocrinol 2019

SGLT2i use in heart failure

- Relative risk reduction in heart failure hospitalizations ~35%
- Bedrock of therapy for heart failure regardless of ejection fraction or care setting
- A class effect
- Improvement in self reported health status with the SGLT2i compared with placebo





Bhatt DL Cell Metabolism 2021

Cost of newer agents on WA Medicaid and Medicare plans

- At least 1 SGLT2 inhibitor is Tier 1 on all state Medicaid plans
- Liraglutide is available on all Medicaid plans
- Weekly GLP-1RAs can be obtained if you document “failure” on other agents including daily GLP-1RA

- Medicare coverage and monthly pricing highly variable
  - depends upon deductible, post-deductible, donut-hole and post-donut hole
- Pricing for SGLT2i and GLP-1RA is comparable to insulins

Luo J et al JAMA Netw Open. 2020;3(10)

Diabetes management in 2022

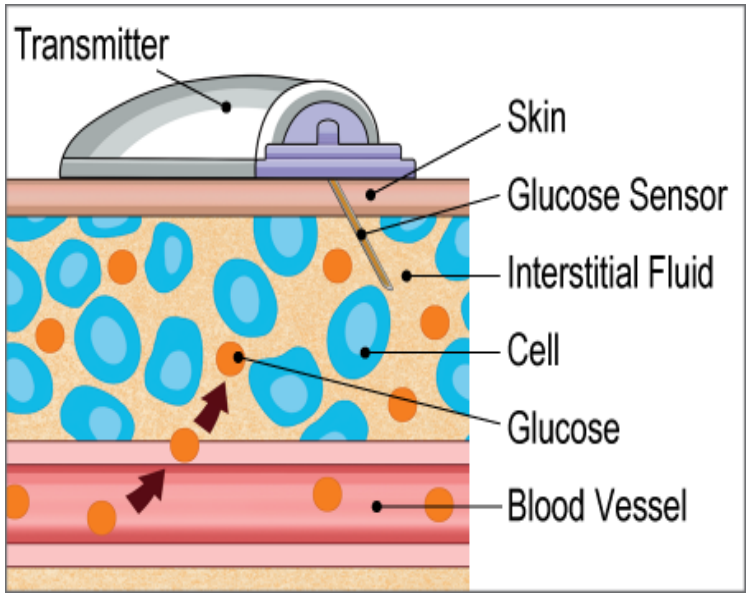
1. Weight management in individuals with diabetes without cardiorenal disease
2. Newer diabetes therapies for cardiorenal disease in individuals with and without diabetes
3. Expanding role of CGM in primary care diabetes

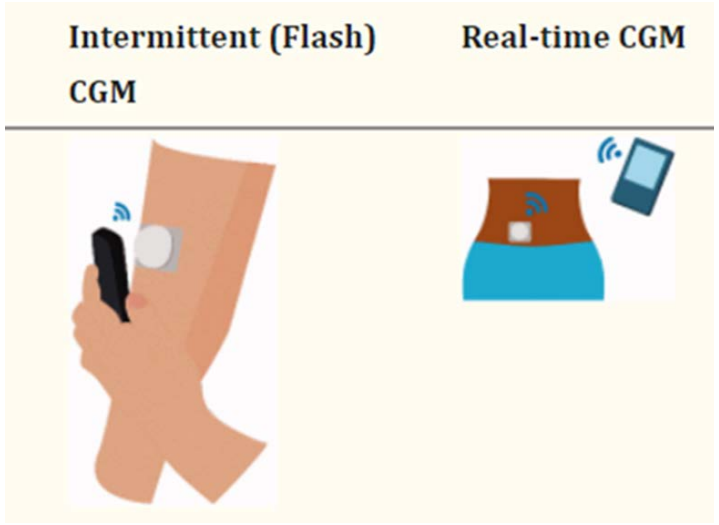
Patient 3. I want a “patch”

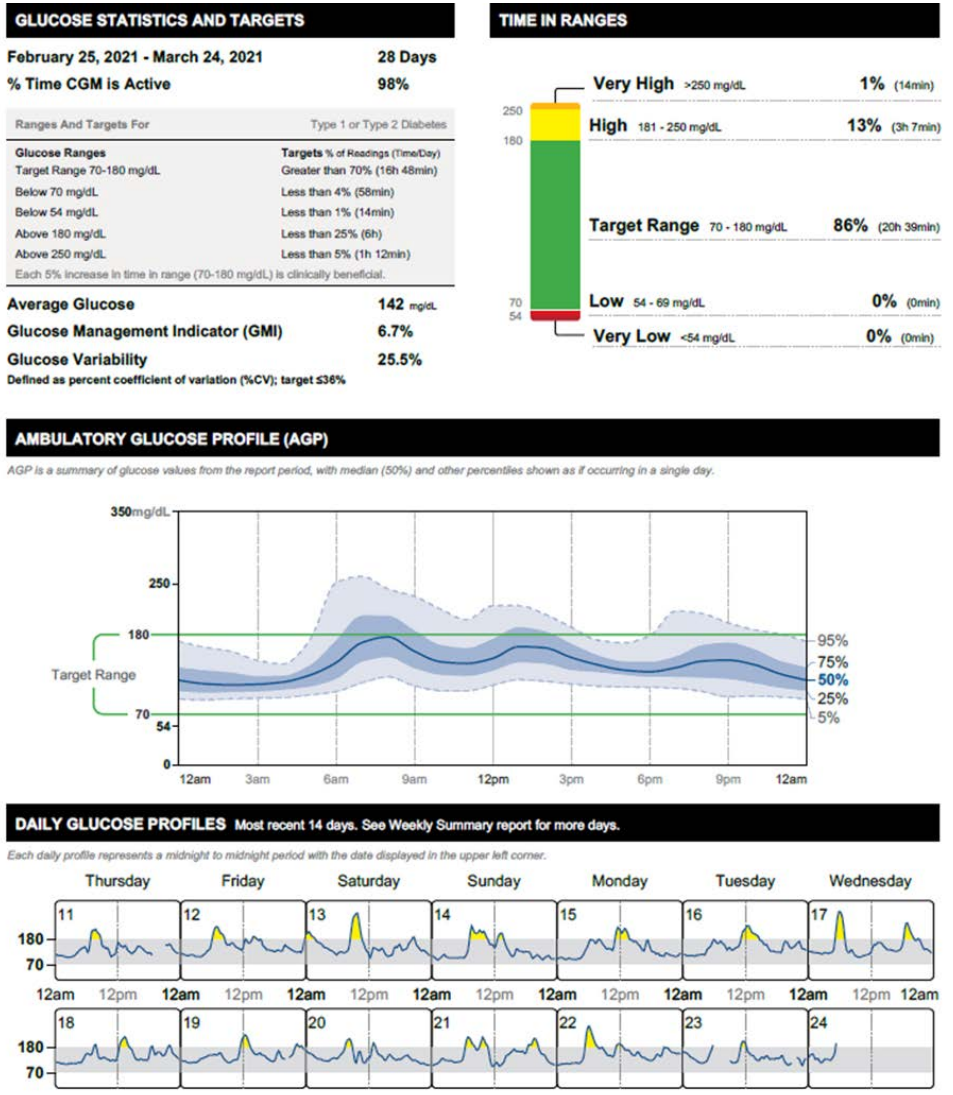
- 62 y/o man with diabetes
- Current regimen: metformin, empagliflozin and glargine 35 units daily
- Has a friend who wears an arm glucose patch and is interested in one

- What do you do?

Continuous glucose monitoring (CGM) – personal devices







Who can use CGM?

- Real-time CGM has been shown to improve diabetes control, reduce hypoglycemia, and be cost-effective for patients with type 1 diabetes
- Medicare and Medicaid cover CGM for patients with diabetes on intensive insulin therapy -> 3 injections/d

- Use in patients with less intensive insulin regimens
- Feasibility of implementation in primary care settings where most of T2D care occurs

The MOBILE study

QUESTION For adults with poorly controlled type 2 diabetes treated with basal insulin without prandial insulin in primary care practices, does continuous glucose monitoring (CGM) improve hemoglobin A_{1c} (HbA_{1c}) levels compared with blood glucose meter (BGM) monitoring?

POPULATION

88 Women
87 Men

Adults with type 2 diabetes treated with basal insulin without prandial insulin

Mean age: 57 years

LOCATIONS

15
Primary care practices in the US

INTERVENTION

175 Patients randomized

116
Continuous glucose monitoring
CGM with BGM testing performed as needed

59
Blood glucose meter monitoring
BGM testing performed when fasting and postprandial 1 to 3 times daily

PRIMARY OUTCOME

HbA_{1c} level at 8 months adjusted for the baseline value

FINDINGS

Mean HbA_{1c} level at 8 months

Continuous glucose monitoring		Blood glucose meter monitoring	
HbA_{1c}		HbA_{1c}	
Baseline	8 Months	Baseline	8 Months
9.1%	▶ 8.0%	9.0%	▶ 8.4%

Risk-adjusted difference was significant,
−0.4% (95% CI, −0.8% to −0.1%)

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CONCLUSION This randomized clinical trial found there was a significantly greater decrease in HbA_{1c} level over 8 months with CGM than with BGM monitoring.

Martens T et al. MOBILE study group. JAMA June 2021

Will this work for my practice?

- In 2022, the American Diabetes Association expanded its guideline recommendation on CGM to include adults on once-daily or long-acting insulin
- Other organizations have included individuals on basal insulin since 2018 (The Endocrine Society) and 2021 (AACE)

'important policy changes in Medicare eligibility to CGM for type 2 diabetes and institutional changes that promote its use in primary care will go a long way to improving diabetes control and reducing complications, particularly among populations most in need. The time has come to broaden access to CGM for patients with type 2 diabetes'

Peek & Thomas JAMA 2021

Summary of Diabetes Update for 2022

1. Higher doses of GLP1RAs have improved glycemic lowering and weight loss capability
2. GIP/GLP-1RA have markedly improved ability for glucose control and weight management
3. SGLT2 inhibitors are now indicated for use in people with or without diabetes and CKD and heart failure
4. CGM in primary care is expanding

Thank you!

UNIVERSITY of WASHINGTON
METABOLISM, ENDOCRINOLOGY & NUTRITION