DIY Diabetes

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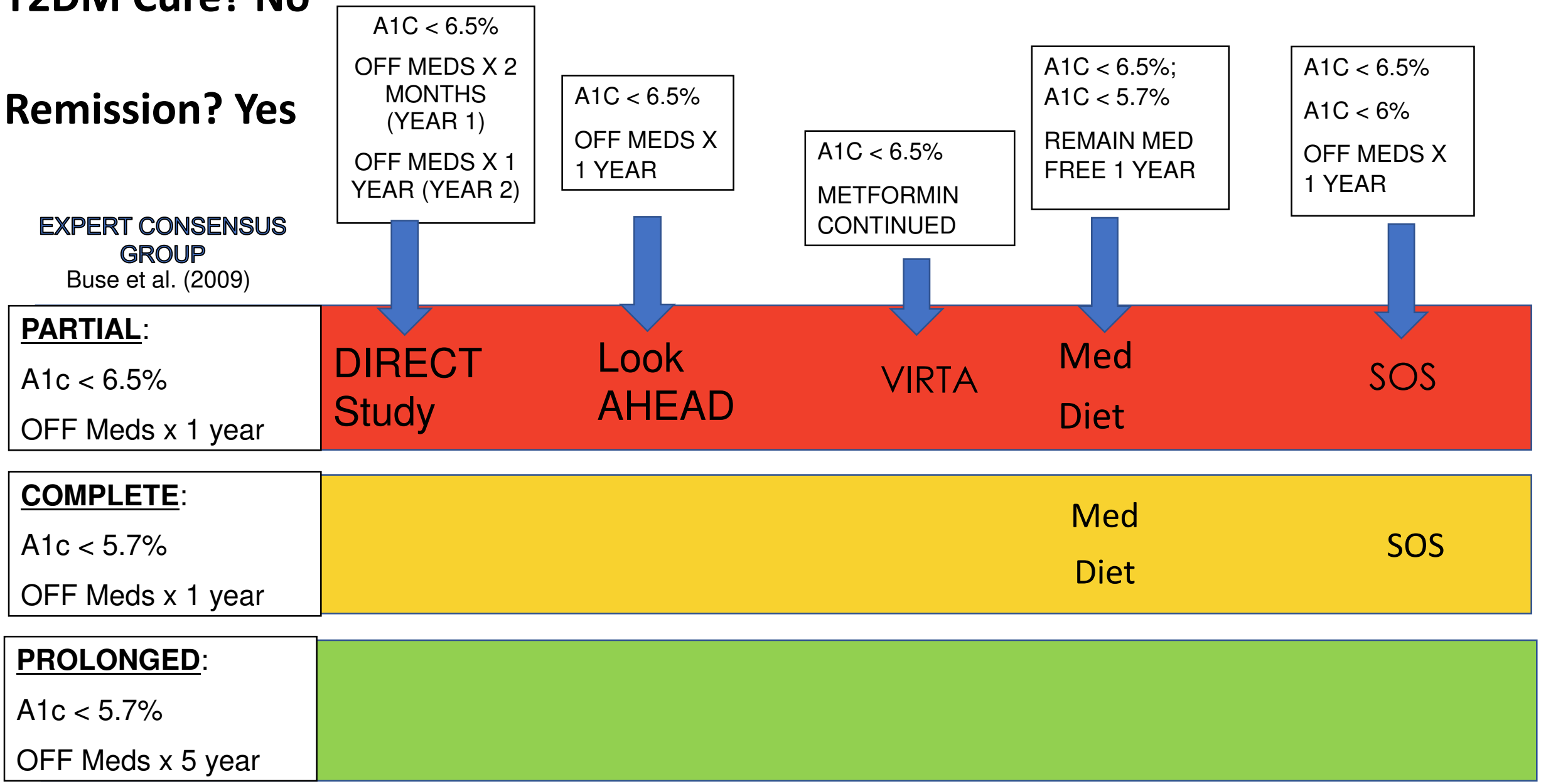
Disclosures

COMPANY	**RELATIONSHIP**
Novo Nordisk	Advisory Board/Speaker
Lilly/BI	Advisory Board/Speaker
Sanofi	Advisory Board
Various Med Ed Co	Speaker
ADA, AANP, ADCES	Speaker

T2DM Cure? No

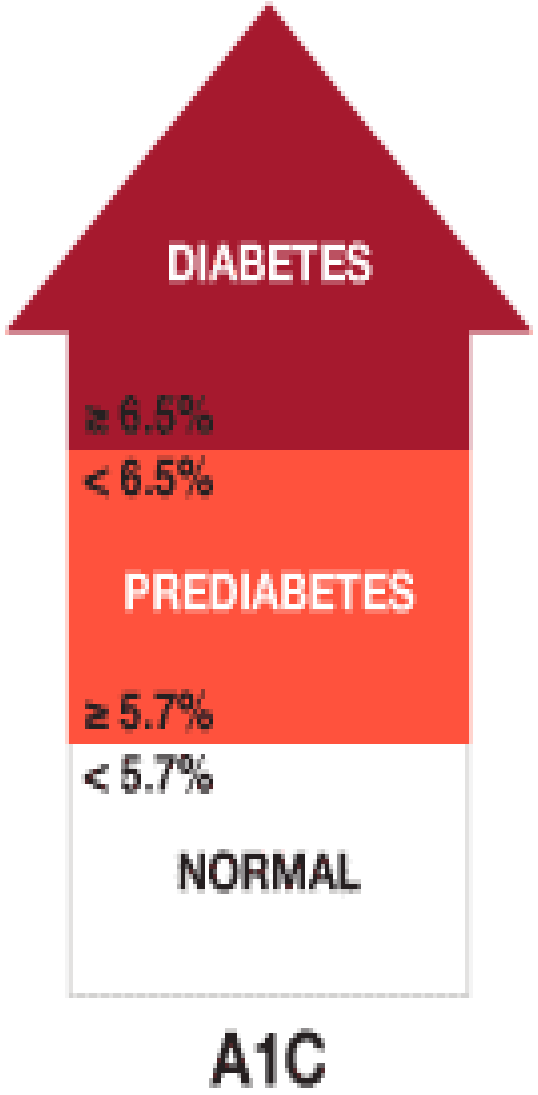
Remission? Yes

EXPERT CONSENSUS GROUP
Buse et al. (2009)



Diabetes Remission Clinical Trial. Published Results. Esposito et al, (2014), Gregg et al, (2012), Athinarayanan et al (2019), Sjöström et al. (2014)

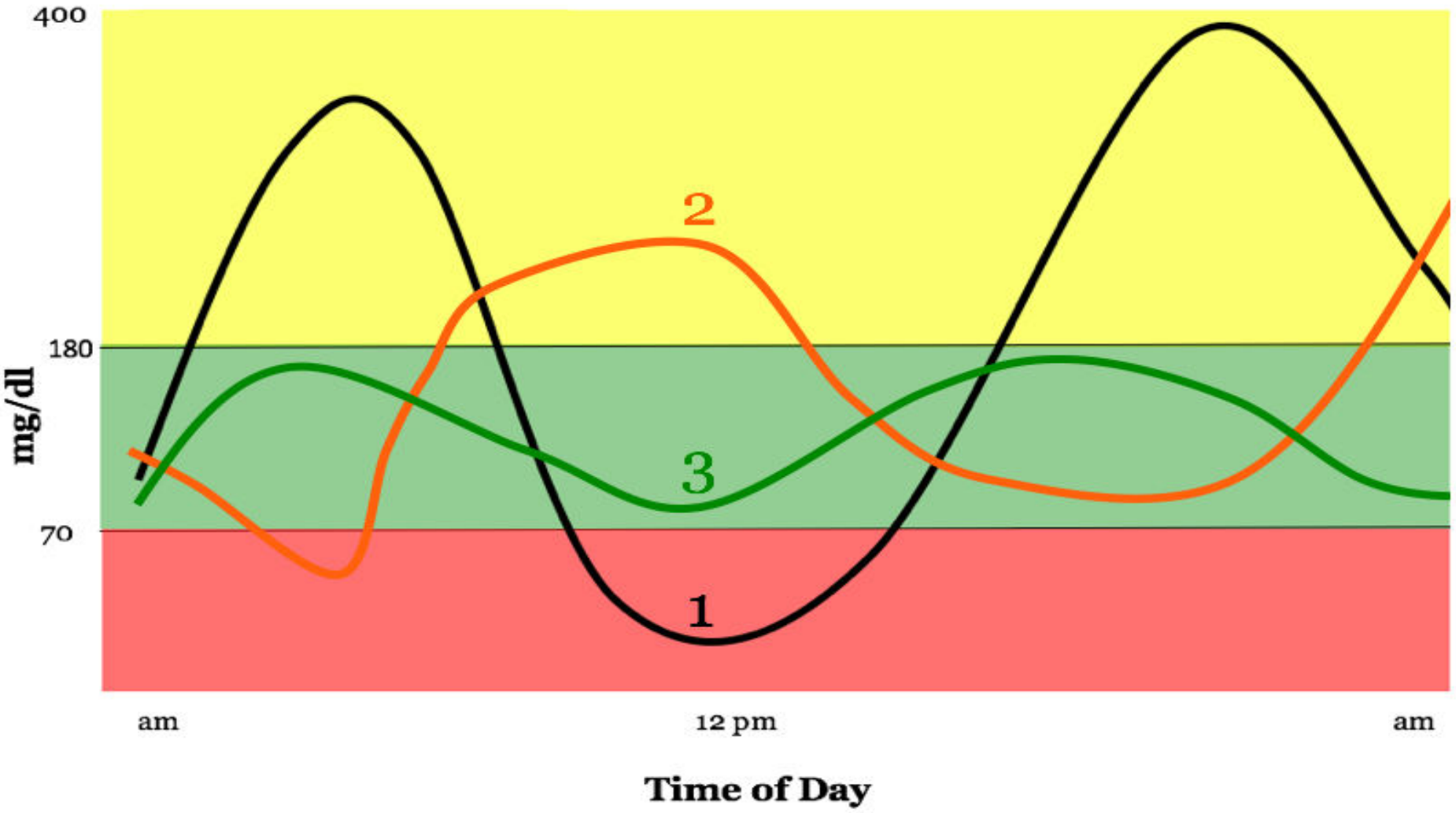
Hemoglobin A1c vs Glucose



A1C%	eAG mg/dl
5	97
5.5	111
6	126
6.5	140
7	154
7.5	169
8	183
8.5	197
9	212
9.5	226
10	240
10.5	255
11	269
11.5	283
12	298

A1c vs. Time In Range

Same A1C….very different glucose variability…



Diabetes Glucose Goals

Glycemic Goals for T2DM

	ADA	IDF	AACE/ACE
HbA_{1c} (%)	<7.0	<6.5	<6.5
FPG (mg/dl)	<130	<110	<110
2 Hr PG (mg/dl)	<180	<140	<140

ADA = American Diabetes Association
IDF = International Diabetes Federation
AACE= American Assoc of Clinical Endocrinologists

Time in Range Goals: Continuous Glucose Monitoring- CGM

- Target: 70-180mg/dl: >70%
- High: <25%
  - 180-250mg/dl
  - Very High: >250mg/dl <20%
- Low: <70mg/dl <5%
  - 54-50mg/dl <4%
  - Very low: <54mg/dl: <1%

ADA Standards of Medical Care in Diabetes. Diabetes Care. January 2022. S86
Living Standards Updates Available at:
http://care.diabetesjournals.org/living-standards

GLYCEMIC TARGETS

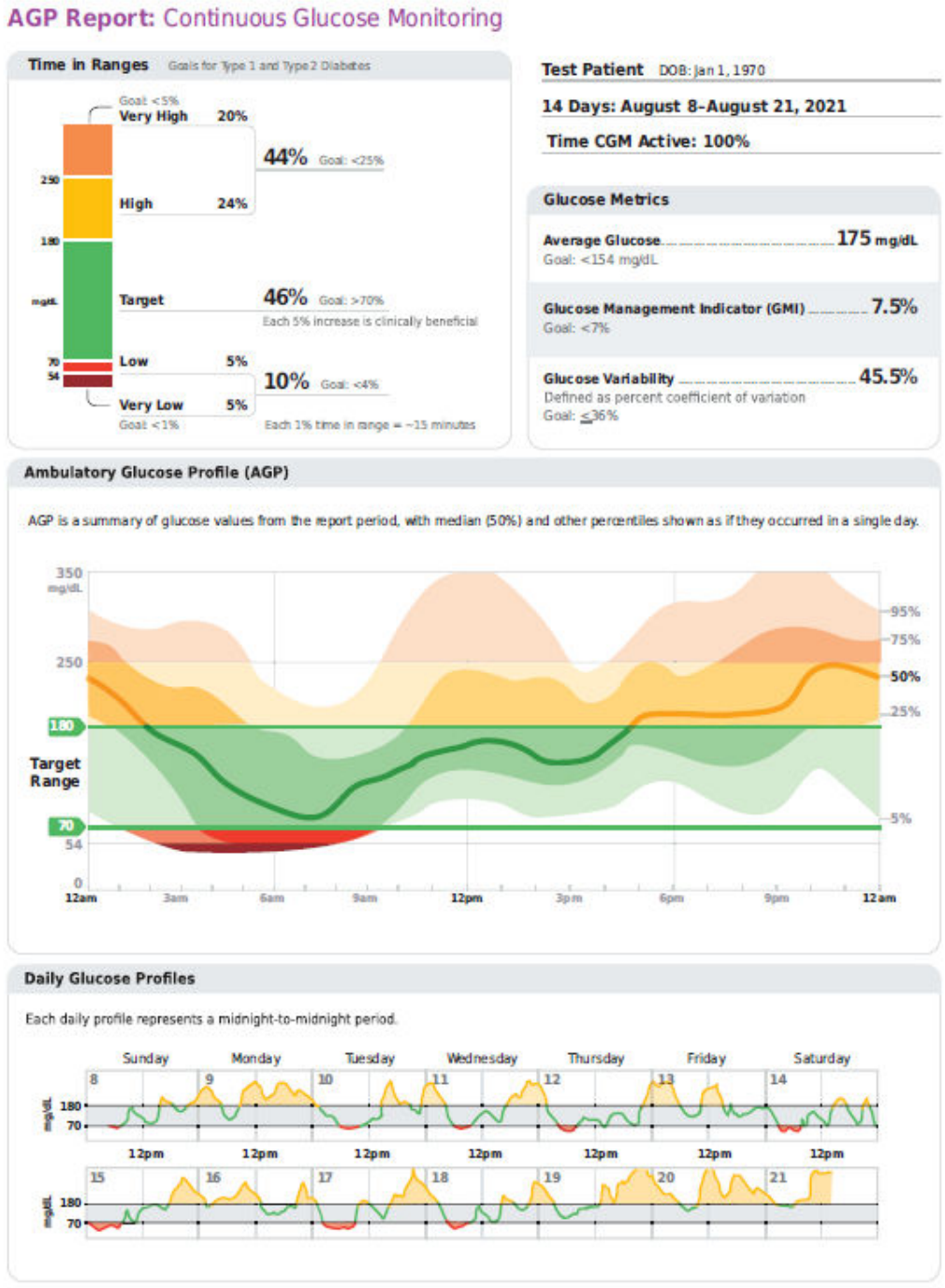


Figure 6.1—Key points included in standard ambulatory glucose profile (AGP) report. Reprinted from Holt et al. (33).

Glycemic Targets:
Standards of Medical Care in Diabetes - 2022. *Diabetes Care* 2022;45(Suppl. 1)

DCCT vs UKPDS endpoints:

Both large studies that compared intensive control vs conventional control

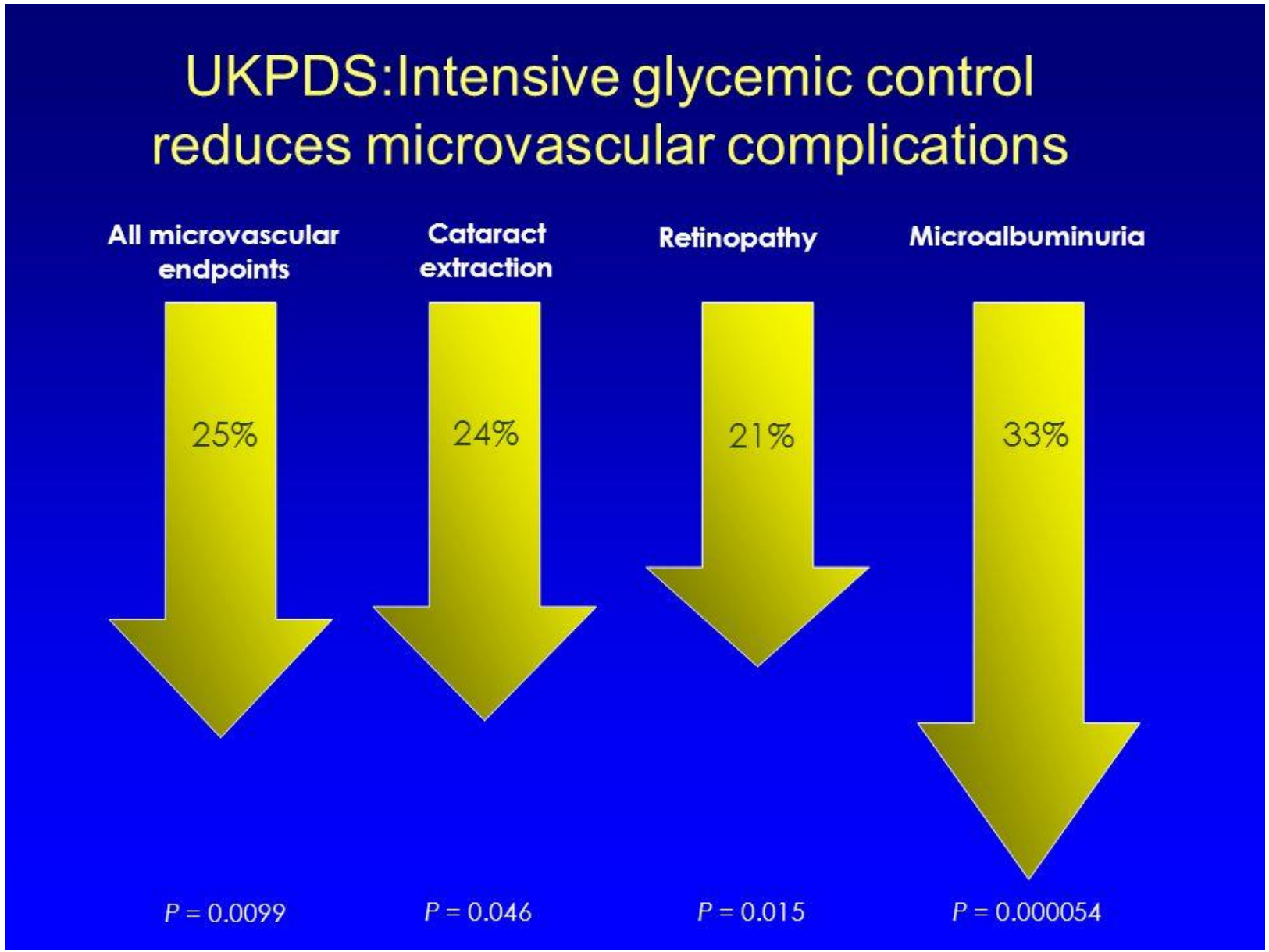
Lower A1C Reduces Incidence of Complications

A1C	DCCT 9 → 7%	Kumamoto 9 → 7%	UKPDS 8 → 7%
Retinopathy	63%	69%	17-21%
Nephropathy	54%	70%	24-33%
Neuropathy	60%	–	–
Macrovascular disease	41%*	–	16%*

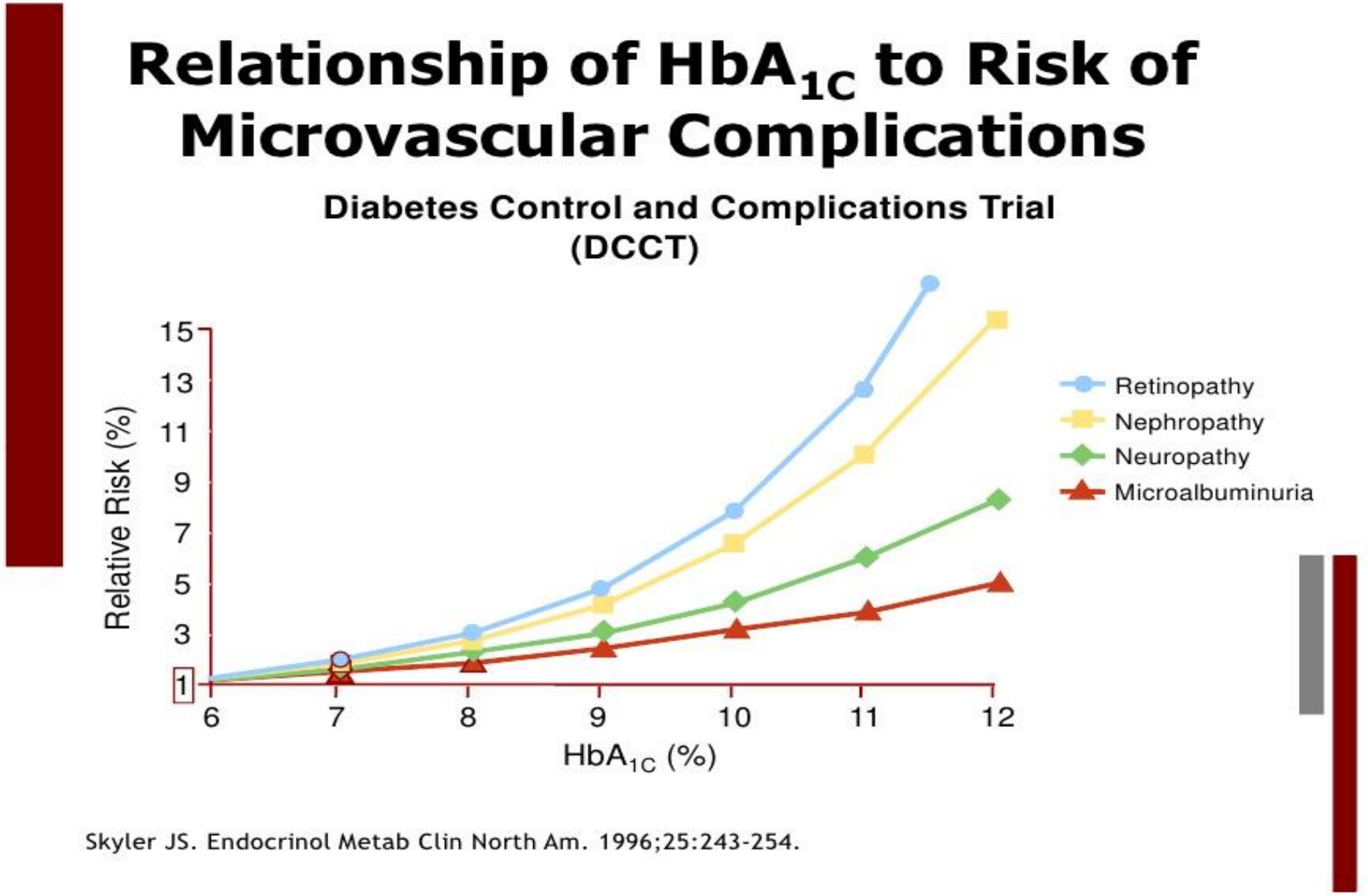
* Not statistically significant.

Diabetes Control and Complications Trial (DCCT) Research Group. *N Engl J Med.* 1993;329:977-86.
Ohkubo Y et al. *Diabetes Res Clin Pract.* 1995;28:103-17.
UK Prospective Diabetes Study Group (UKPDS) 33. *Lancet.* 1998;352:837-53.

UKPDS: 1% A1C drop decreases eye and kidney complications



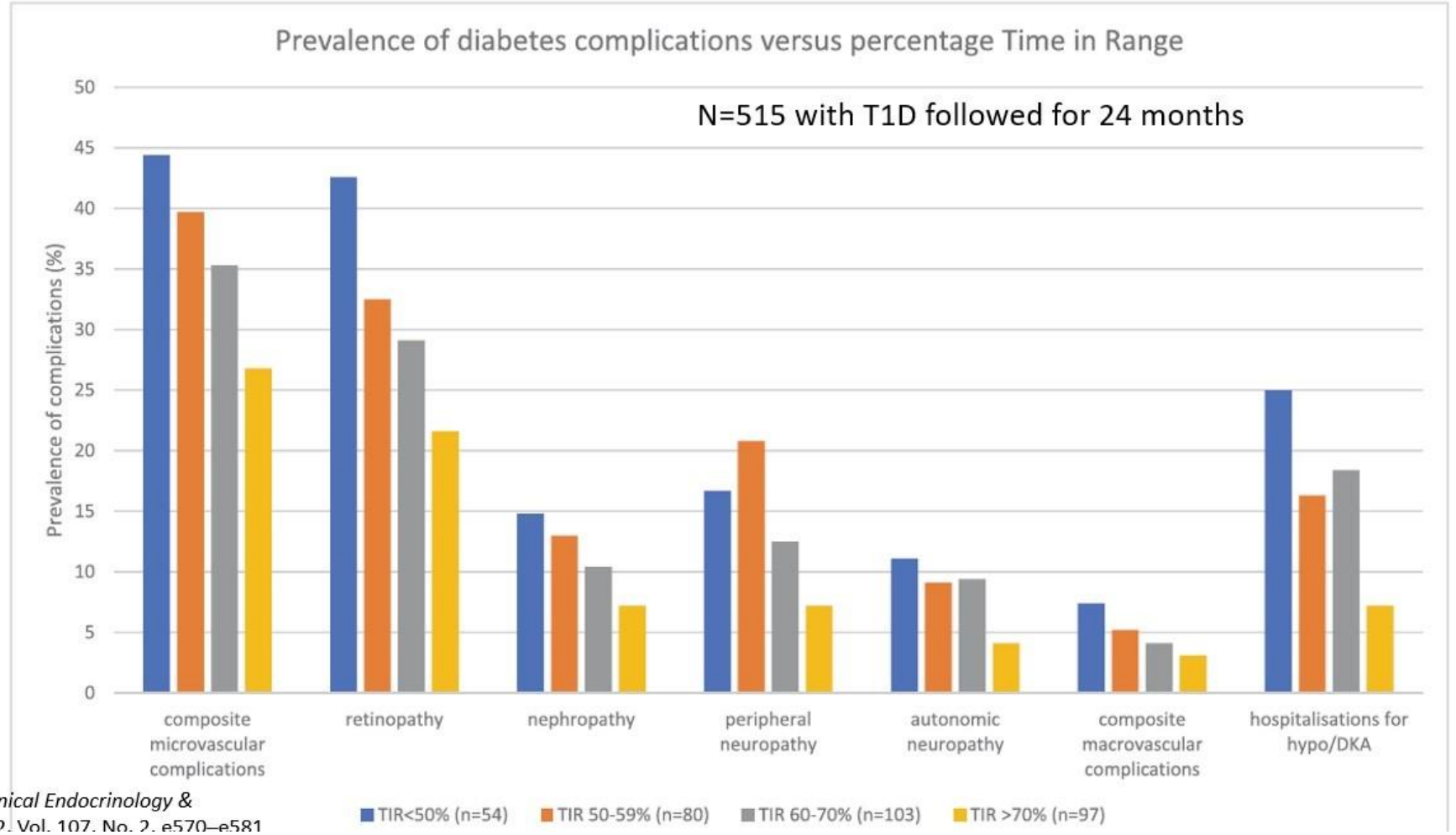
DCCT trial and relationship of small vessel disease (Eyes & Kidneys) to A1C



Skyler JS. Endocrinol Metab Clin North Am. 1996;25:243-254.

A1C is the old standard.
TIR is the Gold Standard:

Data Continues to Accumulate That TIR Is Associated with Complications and Acute Glycemic Emergencies



he Journal of Clinical Endocrinology & Metabolism, 2022, Vol. 107, No. 2, e570–e581

In a Nut Shell…..

Life Style Recommendations The PWD Job:	-**Healthy Eating**: 5 Minute Nutrition Consult : -After your assessment, be sure you have worked these tips into the discussion: -Don't drink sugar. *Juice is sugar.* Sweeteners are ok. Try Stevia. Coke and Pepsi have it. - Be consistent and modest with Carb intake. 100% of carbohydrate turns into sugar. – Generally the RD's recommend 2-3 carb servings/meal - Have solid protein with all meals. It improves satiety. -It's ok to have a piece of B-Day cake. On *YOUR* birthday -**Activity**: 30-60 minutes activity/day. *Starting is the hardest part.* -**Weight loss** goal: 5-10% body weight, *But every pound counts*
Treatment: Your Job:	- Start: +/-Metformin XR 500mg. 1 tab/in pm, increase 1x/week til 1000mg bid - Add GLP1-RA or SGLT2. Then the other one ASAP - Continue Mod/high intensity statin, HTN mgt - Self Monitoring of Blood Glucose (SMBG);finger stick or CGM - Foot Exam - Annual: Standards of Care: Eye/Retinal Exam, UACR, eGFR, immunizations
Referral: Your Job:	- Diabetes Self Management Training/Support!! *As important as eRX* - *1. At Dx, 2.Annually, 3.When changes, ie, complications, insulin start, 4. Life changes* -

In a Nut Shell…..

Life Style Recommendations The PWD Job:	-**Healthy Eating**: 5 Minute Nutrition Consult : -After your assessment, be sure you have worked these tips into the discussion: -Don't drink sugar. *Juice is sugar.* Sweeteners are ok. Try Stevia. Coke and Pepsi have it. - Be consistent and modest with Carb intake. 100% of carbohydrate turns into sugar. – Generally the RD's recommend 2-3 carb servings/meal - Have solid protein with all meals. It improves satiety. -It's ok to have a piece of B-Day cake. On *YOUR* birthday -**Activity**: 30-60 minutes activity/day. *Starting is the hardest part.* -**Weight loss** goal: 5-10% body weight, *But every pound counts*
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The 5 Minute Nutrition Consult
for the non-RD

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Advanced Practice Nurse and Certified Diabetes Care and Education Specialist

University of Colorado Health

Colorado Springs, CO

Do you even hear:

What can I eat?

Just give me a list.

Standards of Medical Care in Diabetes—2022

Goals of Nutrition Therapy for Adults With Diabetes

1. To promote and *support healthful eating patterns*, emphasizing a variety of nutrient-dense foods in appropriate portion sizes, to improve overall health and:
    - achieve and maintain body weight goals
    - attain individualized glycemic, blood pressure, and lipid goals
    - delay or prevent the complications of diabetes
2. To address *individual nutrition* needs based on personal and cultural preferences, health literacy and numeracy, access to healthful foods, *willingness and ability to make behavioral changes*, and existing barriers to change

Goals of Nutrition Therapy for Adults With Diabetes (continued)

3. To maintain the pleasure of eating by *providing nonjudgmental messages* about food choices while limiting food choices only when indicated by scientific evidence

4. To provide an individual with diabetes the *practical tools* for developing healthy eating patterns rather than focusing on individual macronutrients, micronutrients, or single foods

Eating Patterns Reviewed

- For type 2 diabetes, prediabetes, type 1 diabetes
  - Low-fat ≤30% of total kcal
  - Mediterranean olive oil, nuts/seeds, fruits, vegetables, beans, fish, seafood, less red meat
  - DASH (Dietary Approaches to Stop Hypertension) rich in fruits, vegetables, whole grains, low-fat dairy products, and low in fat, refined grains, and sweets; max sodium of 2,400 mg per day
  - Paleo lean meat, fish, fruits, vegetables, root vegetables, eggs, and nuts; avoids grains, dairy, salt, refined fats, sugars
  - Very Low Fat (Ornish or Pritikin) very low-fat (10% of kcal), exercise, stress management
  - Vegetarian or vegan
  - Low-carbohydrate 26 to 40% of calories from CHO
  - Very low-carbohydrate 20 to 50 g CHO/day or <26% calories from CHO

Low-Carbohydrate and VLC and Type 2 DM: 3 Meta-analyses

- Carbohydrate-restricted diets (<45% , especially <25% energy) produced greater reductions in A1c at 3 and 6 months, but no difference at 12 and 24 months[1]
- Compared to low-fat diets (<30% energy), LC diet (<40% energy) improved A1c more (up to 6 months), improved triglycerides, increased HDL-C, lowered blood pressure and reduced need for diabetes medications (varying time lengths)[2]
- The greater the carbohydrate restriction, the greater the reduction in A1c up to 1 year (-0.34%); reduction in A1c was similar at 1 year and after [3]

[1]Sainsbury E te al. Diab Res Clin Pract 2018;139:239-252
[2]vanZuren EJ et al. Am J Clin Nutr 2018;108:300-331
[3] Snorgaard O et al. BMJ Open Diabetes Res Care 2017;5:e000354

Now let’s talk food with your neighbor….

- The person with the most jewelry is the patient
- Remember this is 5 minutes to help them ***get started***
- Please complete the assessment
  - In NO MORE than 2-3 minutes
- Use ~ 2-3 minutes for discussion

Your Role

1. Keep that poker face on. Don't interrupt
2. People know what foods cause problems. You want them to identify it and "own" it

3. Offer support when the patient identifies *any* changes, even if they are not what you think is best.

4. Help figure out how to work in "the one food". Even in small amounts. Less than what they are doing is better than "cold turkey" that will make them feel deprived and likely give up.

5. To close the deal: Ask "on a scale of 1-10, how likely are you to be able to do this?" Why is it a "5" and not a "7"? or a 3 not a 5.
   a. Then problem solve some of those barriers……
   b. Don't let the patient "bite off too many changes"

5 Minute Food Discussion...

1. ***When*** **do you eat/drink first? _____am/pm**
   a. ***What*** **do you eat/drink? How much?**

2. ***When*** **do you eat/drink after that? _____ am/pm**

3. ***What*** **do you eat/drink after that? How much?**

4. **Do you have snacks? What/When/How much?**
5. **Does your schedule change on weekends/days off? How?**
6. **Of what you are eating, what do you think makes your blood sugars high?**

7. **What changes do you think would help?**

8. **What is the one food/drink that you absolutely don't want to give up?**

9. **What changes are you able/willing to try?**

Pt Educ Resources and Handouts: DM Nutrition

1. https://diabetes.org/healthy-living/recipes-nutrition
2. https://www.niddk.nih.gov/health-information/diet-nutrition
3. https://www.eatright.org/food
4. https://www.novomedlink.com/diabetes/patient-support/disease-education/library.html
5. https://education.lillymedical.com/en-en/educational-materials/patient-education-nutrition-in-the-fast-lane-fast-facts-about-fast-food-90093
6. https://www.cdc.gov/diabetes/managing/eat-well/meal-plan-method.html#:~:text=The%20plate%20method%20is%20a,impact%20on%20your%20blood%20sugar

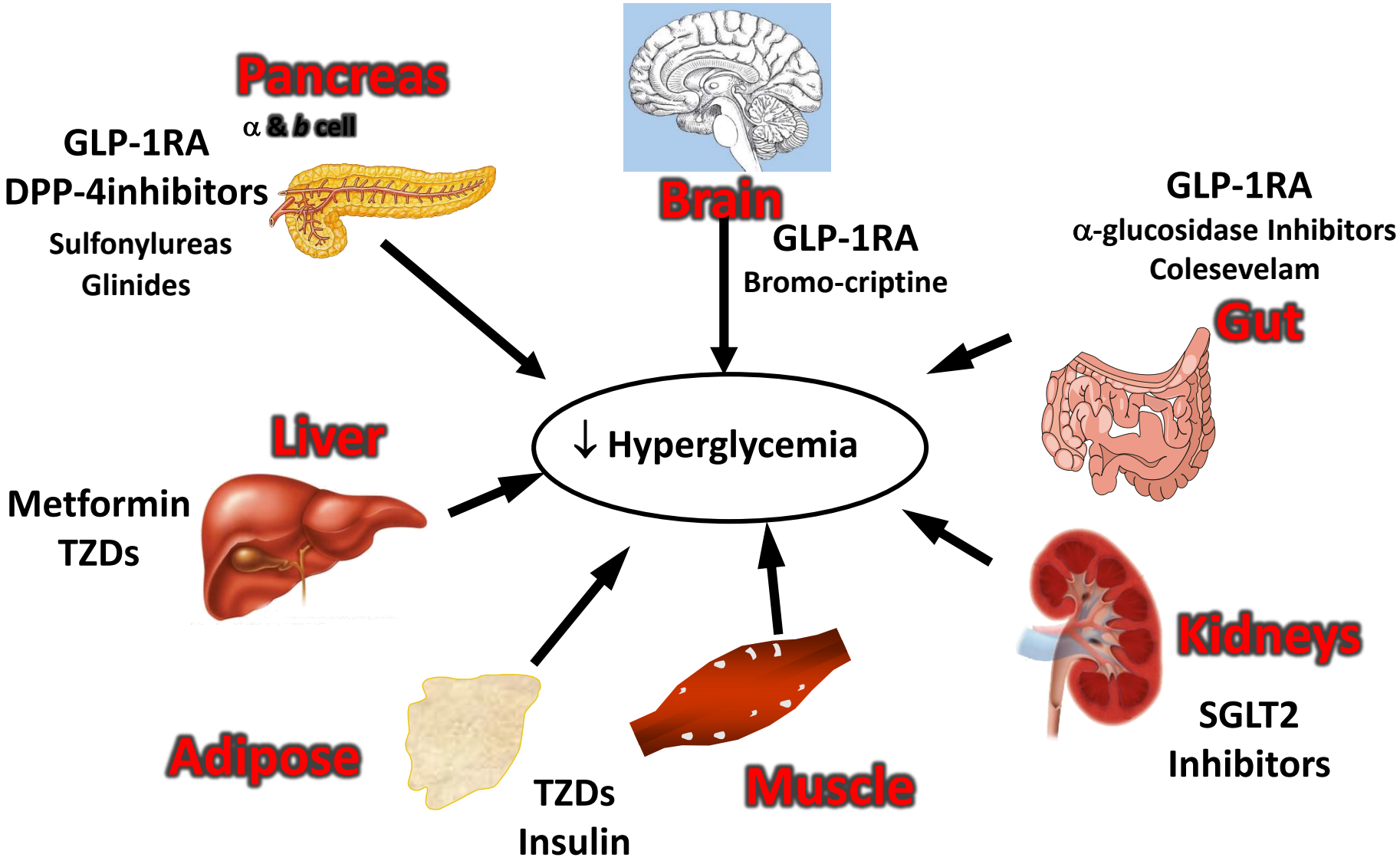
Apps

1. MyFitnessPal is an excellent way to keep track of what you're eating throughout the day. It offers both free and premium memberships and has millions of different foods registered in the database. MyFitnessPal allows you to scan barcodes to enter food in your daily diary and gives you the breakdown of fats, proteins, carbohydrates, and sugars in each item. To take full advantage of the features on this app you can use the exercise tracker and set daily hydration goals
2. Fooducate is similar to MyFitnessPal in that it allows you to track your food intake, but it has a few different features. Fooducate assigns a grade to each food that you track so you know what the overall nutrition quality is at a glance. For those foods that are poorly rated, Fooducate offers healthy alternatives for you to try. It is free for both iPhone and Android use.
3. Glucose Buddy is an iPhone specific app for tracking your blood glucose levels. Its features allow for insulin, medication, A1C, and carbohydrate tracking. It can be synced with certain blood glucose monitors and offers areas to track your physical exercise and food intake. You can set up notifications in the app to remind you to check your blood sugar, get some exercise, and more. There are both free and paid options.
4. MySugr allows you to log all of your diabetes data in one place. It's easy to use and gives you a convenient overview of your blood glucose levels on the home screen. MySugr also allows you to input medications, meals, and carbohydrates. It can by synced with Apple health to create a more comprehensive overview and has integration capabilities with certain continuous glucose monitors. There are both free and paid options for use.
5. Diabetes Connect allows you to record everything—blood sugar levels, insulin dosage, medications, and more. It provides you with more of a big-picture overview and allows you to turn off any features that you don't need or use. It's a great option for those looking for something simple.
6. One Drop is a free app that gives you a truly comprehensive experience. It has everything you need to log all of your diabetes data and includes a food tracking section that mimics popular apps listed above. You can connect compatible devices via Bluetooth for even easier use. One Drop also includes a built in "coaching" aspect that can help you boost morale and keep up with your management efforts.
7. ***CaloreKing*:** As the name implies, CalorieKing was designed to be a weight loss focused app and website that helps people count calories. (For the record, I do not support counting calories.) However, they offer the most robust database of nutrition info in app form that I have found. This information is necessary for accurately counting carbohydrates and dosing medication when you have diabetes. I also really like their recipe builder. It allows you to create your own recipes and foods, and calculate your own nutrition information.

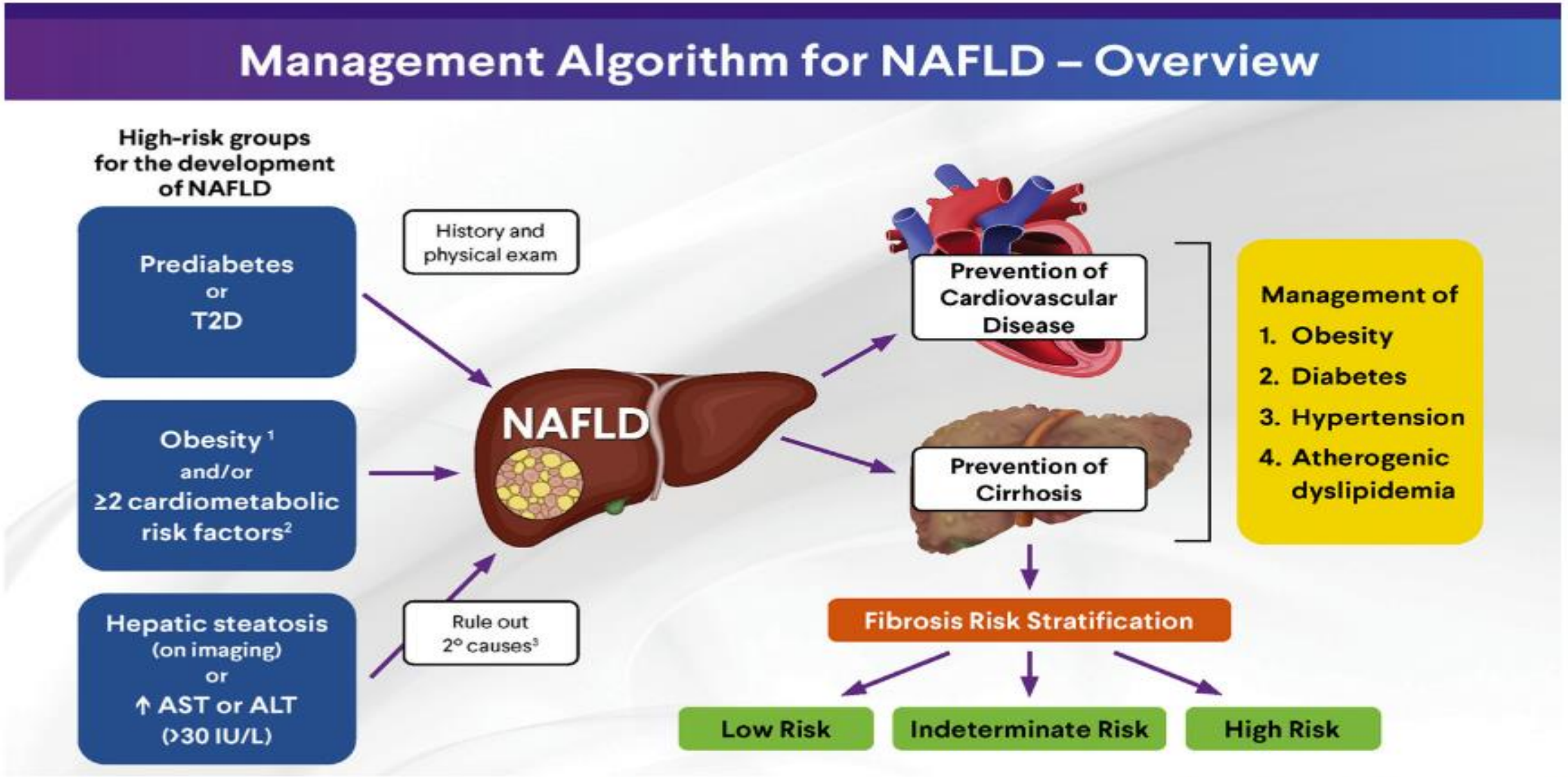
Healthy Eating Summary

- Have the conversation…..
  - “Don’t eat anything white”, or “if it tastes good, spit it out” *Doesn’t Count*
- Remember, you’re not the expert on the patient. They are.
  - You’re the expert on diabetes, prescriptions, lab work….
- Help your patients “Get Started” with some tools and goals *they choose*
- Make the referral to the RD
- Follow up with progress and problems

Diabetes Medications→ *Metabolic defects*



Holst JJ, Ørskov C. *Diabetes.* 2004;53:S197-S204.
Lebovitz HE. *Diabetes Rev.* 1999;7:139-153.



- **A major barrier to NAFLD diagnosis is the lack of non-invasive testing options, as liver biopsy still remains the "Gold Standard" diagnostic technique**. However, using metrics such as the FIB-4 index, which estimates the risk of hepatic cirrhosis using age, plasma aminotransferases (AST and ALT), and platelet count, simpler screening options are starting to exist. Dr. Cusi heavily emphasized that while the FIB-4 is not the most sensitive test, it is an inexpensive way to identify the most at-risk patients. The guidelines recommend that all patients with diabetes be screened using the FIB-4 index.

Cusi et al. AACE NAFLD Diagnosis and Treatment Guidelines. May 2022 Endocrine Practice

Weight Management in NAFLD

Fibrosis Risk Stratification

	 **Low Risk** FIB-4: <1.3 LSM <8 kPa ELF <7.7	 **Indeterminate Risk** FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	 **High Risk** FIB-4: >2.67 LSM >12 kPa ELF >9.8
General lifestyle changes	Decrease sedentary time and increase daily movement. Stress reduction through exercise and other methods.		
Dietary recommendations	Creating an energy deficit is the priority with reduction of saturated fat, starch, & added sugars. Persons with cirrhosis need an individualized nutritional assessment and treatment plan.		
Exercise	To improve cardiometabolic health, support weight loss and mitigate sarcopenia. Aerobic exercise for 30-60 min (3-5 days/week) + resistance training 20-30 min (2-3 times/week).		
Alcohol intake	Minimize	Minimize	Avoid if F3 or cirrhosis (F4)[1]
Weight loss goal to treat NAFLD (if overweight or obesity)[2]	Greater weight loss associated with greater liver and cardiometabolic benefit.		
Weight loss tools	Behavioral modification counseling. In person or remote programs.	Greater intensity of weight loss to reverse steatohepatitis and fibrosis.	Specialized obesity management, with a structured program, anti-obesity medications, bariatric surgery.
Medical therapy to treat obesity	Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liragluitde 3 mg/d, semaglutide 2.4 mg/wk	GLP-1 RA preferred for NASH.[3,4]	GLP-1 RA preferred for NASH.[3,4]
Bariatric surgery	Consider to treat obesity and comorbidities.	Strong consideration to treat steatohepatitis and fibrosis.	Stronger consideration to treat steatohepatitis and fibrosis. Avoid in decompensated cirrhosis.

Cusi K,et al AACE Task Force. Clinical Practice Guidelines-NAFLD (nonalcoholic fatty liver disease) Endocrine Practice.May 12, 2022

Diabetes Medications *non-generics*

- **SGLT2 inhibitors: S**odium **Gl**ucose **T**ransporters
  - Invokana, Farxiga, Jardiance, Steglatro
- **GLPs: G**lucagon **R**eceptor **A**gonists: Non-Insulin Injections
  - Victoza 1x/day
  - Trulicity, Bydureon, Ozempic 1x/week, Rybelus –oral/d
- **Ultra Long Basal Insulins**:
  - Toujeo (32 hours), Tresiba (42 hours)
- **Ultra fast meal time insulins**:
  - FiAsp (Aspart)
  - Lyumjev(Lispro)
- **Insulin/GLP combinations**: 1x/day
  - Soliqua,
  - Xultophy

The bottom line on Diabetes Meds……

To reduce risk of hypoglycemia, provide CV and Renal protection and HF treatment

- +/-Metformin XR 500mg, titrate 1/wk, 2 bid if GFR>50; 1 bid if GFR<50; Stop if GFR <30, ***Then***
- GLP1-RA
  - ~ 0.9-**3.2**% A1C drop
  - Once weekly analog injections can be used to GFR 15, no changes needed for hepatic
  - Weight loss is usually proportional to level of obesity: 8-13 lbs
  - AE:~ GI: Coach→ snack first 2-3 days, stop eating when full, power through if queasy…Please!
- SGLT2i - use first if HF, (bilateral edema, ↑NPproBNP, diastolic dysfunction…)
  - ~ 0.8-1.5% A1C drop: low dose to eGFR 30 for DM and CV; eGFR 20- HF
  - Weight loss 8-10 lbs
  - Use in HF regardless of DM dx or LVrEV or LVpEF
  - AE: UTI – GMI: Coach→ Good hygiene- clean and dry, 1 extra glass water/day
- ***add*** Basal insulin when/if needed
  - Formulary preference: NOT NPH. Glargine U100 or U300, detemir, Degludec.
  - Modest dose, with slow titrate weekly. Start: Wt in lbs x 10% *or* 10u/d
- Meal time insulin may not be needed in T2DM. If already on meal time consider:
  - if > 10u, reduce by 50% and add non-insulin regimen
  - If <10u, discontinue and add non-insulin regimen

DM and Seniors:

- Life Style
  - Avoid simple sugars, don’t drink sugar; regular soda, juice
  - Try to have consistent carbohydrate at meals
    - “Older people shouldn't eat health food, they need all the preservatives they can get.” —
  - Safe exercise
- Diabetes Education
  - Large print
  - Small groups or individual
  - Interactive discussion, with hands-on skills training and teach back
  - Modest, small changes with care partner support and frequent repeat
- Diabetes Medication
  - Reduce risk of Hypoglycemia; Simplify regimen
  - SGLT2 (adjust for volume depletion),
  - Weekly GLP1 or
    - DPP4: Linagliptin (Tradjenta) 5mg
    - ~0.5% A1C reduction
    - Excreted unchanged from the bile and feces. Side effects negligible. No dose adjustments needed for renal or hepatic

Glucose-Lowering Agents: T2DM

		Metformin	DPP-4 inhibitors	GLP-1 receptor agonists	SGLT2 inhibitors	SUs (second generation)	TZDs	Insulin
Glucose-lowering efficacy		High	Intermediate	High	Intermediate	High	High	Highest
Hypoglycemia						Yes		Yes
Weight		Neutral (potential for modest weight loss)	Neutral	Loss	Loss	Gain	Gain	Gain
CV effect	ASCVD	Potential benefit	Neutral	Benefit/neutral[a]	Benefit[a]	Neutral	Potential benefit[a]	Neutral
	HF	Neutral	Potential risk[a]	Neutral	Benefit[a]	Neutral	Increased risk	Neutral
Adverse events		GI effects, potential B12 deficiency	Joint pain, potential acute pancreatitis	GI effects, potential acute pancreatitis, thyroid C-cell tumors	Genitourinary infection, volume depletion,	GI effects, increased risk of CV mortality	Congestive HF, fluid retention, fractures	Injection site reactions

[a] Depending upon specific agent; always check the product label.
ASCVD, atherosclerotic cardiovascular disease; DKA, diabetic ketoacidosis; HF, heart failure.

ADA. *Diabetes Care*. 2021;44(Suppl 1):S1–S232.

Antihyperglycemic Therapy

DCRM Multispecialty Practice Recommendations for the Management of Diabetes, Cardiorenal, and Metabolic Diseases

Prevent CVD/CKD Events Regardless of Glycemic Status

Manage Glycemia to Individualized, Established Goals

Lifestyle Therapy

Reduce ASCVD and Kidney Risks Based on Comorbidities

CAD	HFrEF HFpEF	CKD	Stroke/TIA
LA GLP1-RA	SGLT2i	SGLT2i	LA GLP1-RA
SGLT2i		LA GLP1-RA	Pio
Pio			

Recommended Hierarchy

Preferred

- GLP1-RA
- SGLT2i
- Metformin
- TZD
- DPP4i
- Insulin
- SU

Less used

- Glinide
- Colesevelam
- AGI
- Bromocriptine QR
- Pramlintide

Manage Hyperglycemia to Individualized Goal

Younger, healthier, at lower CV risk

A1C: 6.0% 6.5% 7.0% 7.5%

Most patients

Older, complex, more frail, at higher CV risk

- Use initial combination therapy for patients with A1C >1-2% above goal
- Assess glucose control with A1C (3 months), CGM or SMBG (daily, weekly, or monthly), glycated albumin or fructosamine (3 weeks)
- Add agents with complementary MOA to maintain glucose control at goal[a]
- Choose agents according to recommended hierarchy, based on patient's individualized risks and benefits, preferences, and access to therapies
- Insulin is necessary for patients with diabetes symptoms

Proven benefits in CVOTs

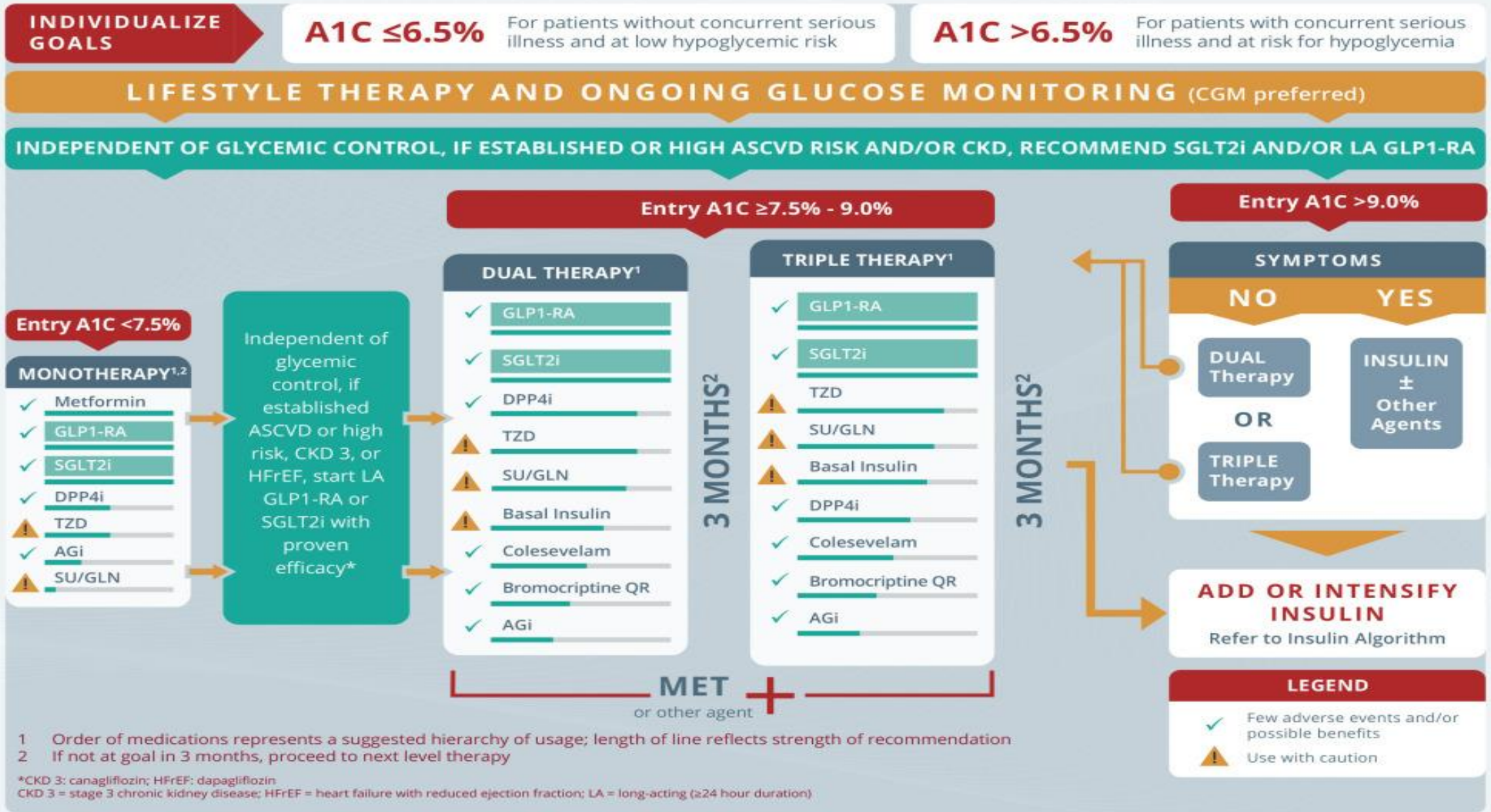
Hypoglycemia and/or HF risk

Y Handelsman, J Anderson, et al DCRM Multispecialty Practice Recommendations for the management of diabetes, cardiorenal, and metabolic diseases, Journal of Diabetes and its Complications. Volume 36, Issue 2, 2022,

LA GLP1-RA = dulaglutide, liraglutide, or semaglutide.

[a] Do not combine GLP1-RA and DPP4i. Use caution when combining insulin + SU or insulin + TZD.

GLYCEMIC CONTROL ALGORITHM



Diabetes Management Algorithm, *Endocr Pract.* 2020;26(No. 1) 137

How Do GLP-1 RAs and SGLT2 Inhibitors Stack Up Against SUs and DPP-4 Inhibitors?

		DPP-4 inhibitors	GLP-1 RAs	SGLT2 inhibitors	SUs (second generation)
Glucose-lowering efficacy[1]		Intermediate	High	Intermediate	High
Hypoglycemia[1]		No	No	No	Yes
Weight[1]		Neutral	Loss	Loss	Gain
CV effect[1]	ASCVD	Neutral	Benefit/neutral[a]	Benefit[a]	Neutral
	HF	Potential risk[a]	Neutral	Benefit[a]	Neutral
Cost[b]		++	+++	++	+

Increased risk of hypoglycemia with SUs[1]

No weight benefit with DPP-4is or SUs[1]

No CV benefit with DPP-4is or SUs[1]

SUs cost less; DPP-4i and SGLT2i costs comparable[1]

- Real-world analysis (N=128,293):[2] SGLT2is associated with reduced risk of all-cause mortality versus SUs, *regardless of existing CVD or albuminuria status*
- Review of GLP-1 RAs versus SUs:[3] preference for GLP-1 RAs, especially for patients at high CV risk; difference in annual cost per person associated with GLP-1 RAs versus SUs is likely less than anticipated
- GRADE (N=5407):[4] Liraglutide and insulin glargine more effective for maintaining A1C <7% than glimepiride or sitagliptin

[a] Agent-specific; [b] National average drug acquisition cost of maximum approved daily dose.

1. ADA. *Diabetes Care.* 2021;44(suppl 1):S1-S232; 2. Xie Y, et al. *JAMA Internal Med.* 2021 Jun 28. [Epub ahead of print]; 3. Frederici MO, et al. *Diabetes Metab Res Rev.* 2021;1-18; 4. Gerstein H, et al. Symposium at: ADA 81st Scientific Sessions; June, 2021. Virtual.

Characteristics of GLP-1 RAs: Administration, Dosing Frequency, Time To Effect[1-3]

Name	Approved doses	Route	Dosing frequency	Exendin-4 or hGLP-1?	Half-life	Time to effect (steady state)	Metabolism
Short-acting, injectable							
EXN BID	5, 10 mcg	Injectable	Twice daily (before breakfast and dinner)	Exendin-4	2.4 hours	NA	Renal excretion; proteolysis
LIXI	10, 20 mcg	Injectable	Once daily (before largest meal)	Exendin-4	3 hours	NA	Renal excretion; proteolysis
Long-acting, injectable							
DULA	0.75, 1.5, 3.0, 4.5 mg	Injectable	Once weekly	hGLP-1	4.5-4.7 days	2-4 weeks	Proteolysis
EXN ER	2 mg	Injectable	Once weekly	Exendin-4	Sustained-release formulation	6-7 weeks	Renal excretion; proteolysis
LIRA	0.6, 1.2, 1.8 mg	Injectable	Once daily (same time each day)	hGLP-1	13 hours	3 days	Proteolysis
SEMA	0.5, 1.0 mg	Injectable	Once weekly	hGLP-1	≈ 1 week	4-5 weeks	Proteolysis
Oral							
SEMA	3, 7, 14 mg	Oral	Once daily (30 min before breakfast)	hGLP-1	≈ 1 week	4-5 weeks	Proteolysis

[a] Range across all PIONEER trials on a background of various glucose-lowering agents. +, demonstrated benefit; ±, neutral; (+), potential increased benefit.
hGLP-1, human glucagon-like peptide-1; NA, not applicable

1. Drugs@FDA. Accessed June 4, 2021. https://www.accessdata.fda.gov/scripts/cder/daf/; 2. Nauck MA, Meier JJ. *Eur J Endocrinol*. 2019;181:R211-R234; 3. Htike ZZ, et al. *Diabetes Obes Metab*. 2017;19:524-536; 4. Rodbard HW, et al. *Am J Manag Care*. 2020;26:S335-S343.

Available FDA-Approved GLP-1 RAs: Dosage and Administration Characteristics

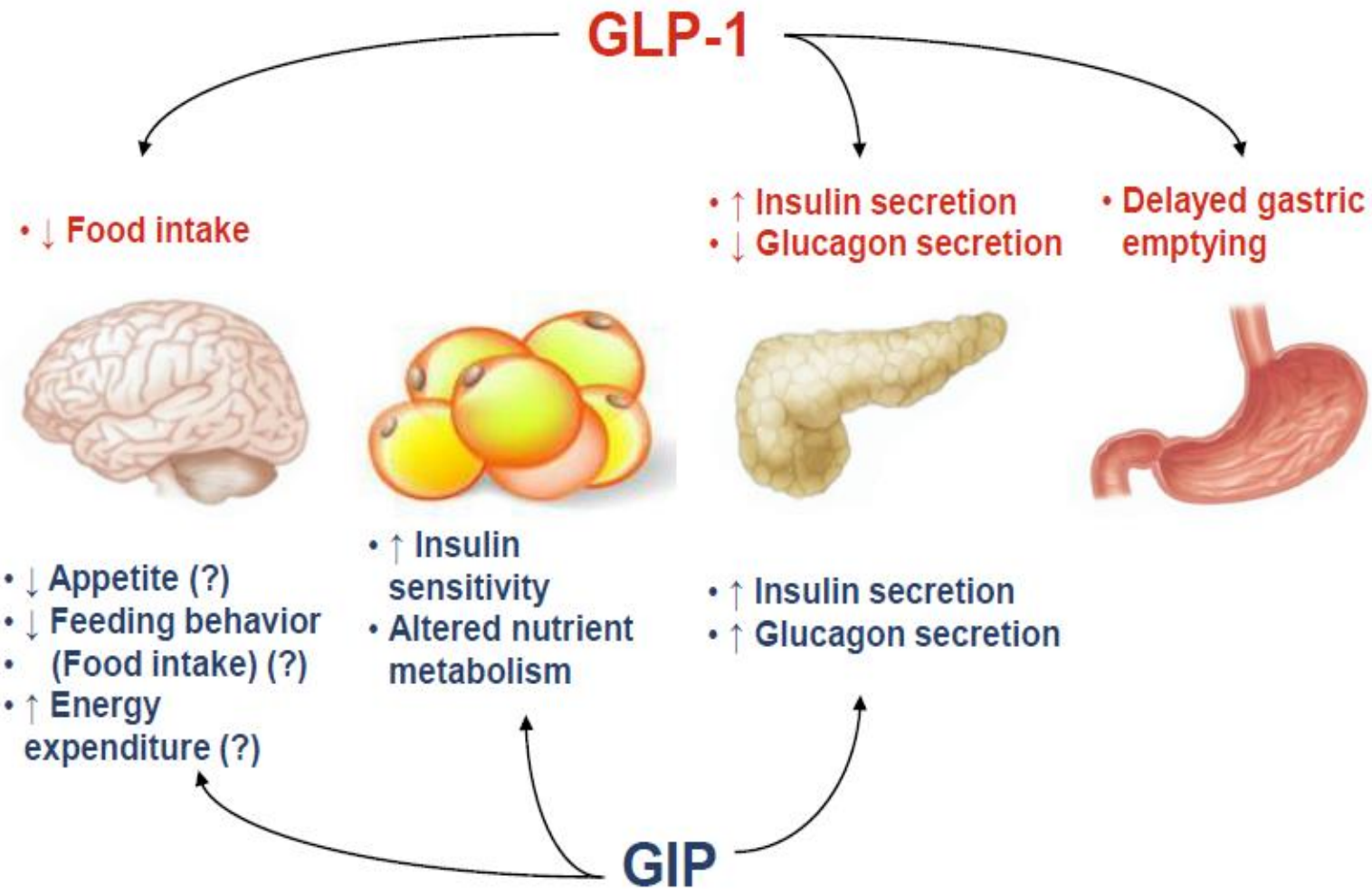
Agent[1-5]	Route	Dosage and Timing			Needle		Reconstitute	Titrate to Avoid GI AEs
					Gauge	Provided?		
EXN	SC	BID	10 µg	1 h before main meals, ≥ 6 h apart	HCP advise			X
LIXI	SC	QD	20 µg	1 h before first meal	HCP advise			X
LIRA	SC	QD	1.2, 1.8 mg	Any time	32			X
SEMA	Oral	QD	7, 14 mg	≥ 30 min before first food, beverage, oral medications, with 4 oz plain water only	NA	NA		X
DULA	SC	QW	0.75, 1.5 mg	Any time	29	X		
EXN ER[a]	SC	QW	2.0 mg	Any time	23	X	X[a]	
SEMA	SC	QW	0.5, 1.0 mg	Any time	32	X		X

NA, not applicable; ND, not disclosed.
[a] Available as autoinjector, pen, or vial and syringe; reconstitution required for vial and syringe.

1. Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/; 2. AstraZeneca. http://www.azpicentral.com/byetta/ifu_byetta.pdf; 3. Novo Nordisk. https://www.victoza.com/get-started-using-victoza-/your-first-injection.html; 4. Wysham CH, et al. *Diabetes Obes Metab*. 2018;20:165-172; 5. Matfin G, et al. *J Diabetes Sci Technol*. 2015;9:1071-1079.

Next-Generation Incretin: A Novel GIP and GLP-1 Receptor Dual Agonist

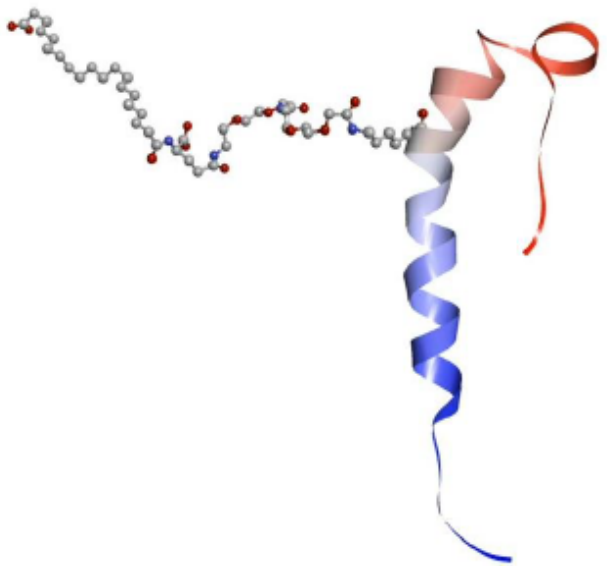
- GLP-1 has suggested direct actions in CNS, islets, and stomach[1,2]
- GIP has shown potential actions in current research in CNS, adipose, and islets[2,3,4]
- A single molecule GIP/GLP-1 receptor dual agonist may enable improved physiology over the sum of its individual agonist components[5,6]



1. Müller TD, et al. *Mol Metab*. 2019;30:72-130. 2. Seino Y, et al. *J Diabetes Investig*. 2010;1)1-2):8-23. 3. Fukuda M. *Diabetes*. 2021;70(8):dbi210001. 4. Nauck MA, et al. *Diabetes Obes Metab*. 2021 (Ahead of Print). DOI: 10.1111/dom.14496. 5. Samms RJ, et al. *Trends Endocrinol. Metab*. 2020;31(6):410-421. 6. Bastin M, et al. *Diabetes Metab Syndr Obes*. 2019;12:1973-1985.
CNS = central nervous system; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1.

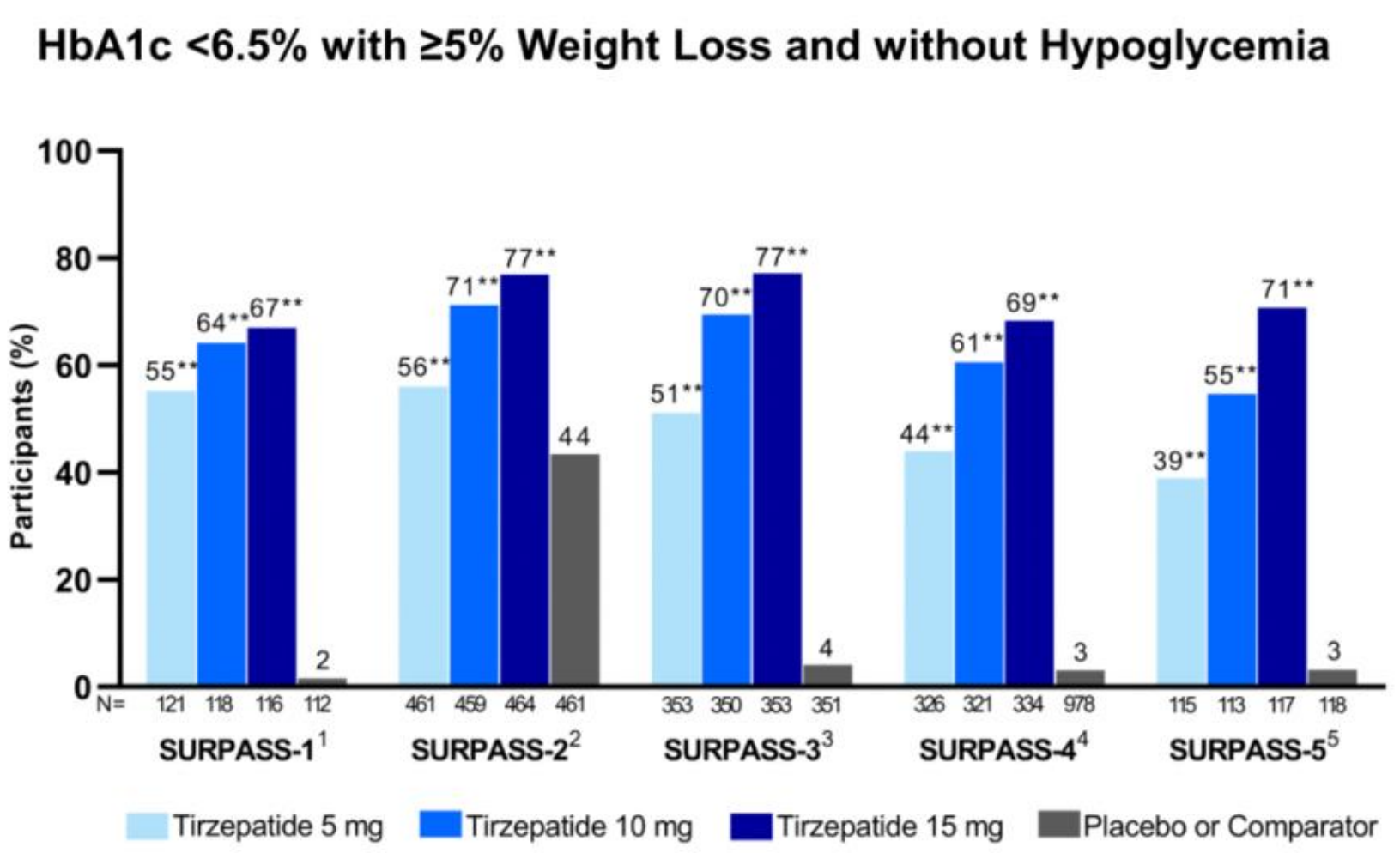
Tirzepatide

- Structure: 39 amino acid linear and multi-functional peptide based on the native GIP peptide sequence[1]
  - modified to bind to both GIP and GLP-1 receptors[1]
  - Includes a C20 fatty diacid moiety[1]
- Mean half-life: approximately 5 days, enabling once-weekly dosing[1]
- Plasma concentrations in people with renal and hepatic impairment do not differ from healthy people[2]



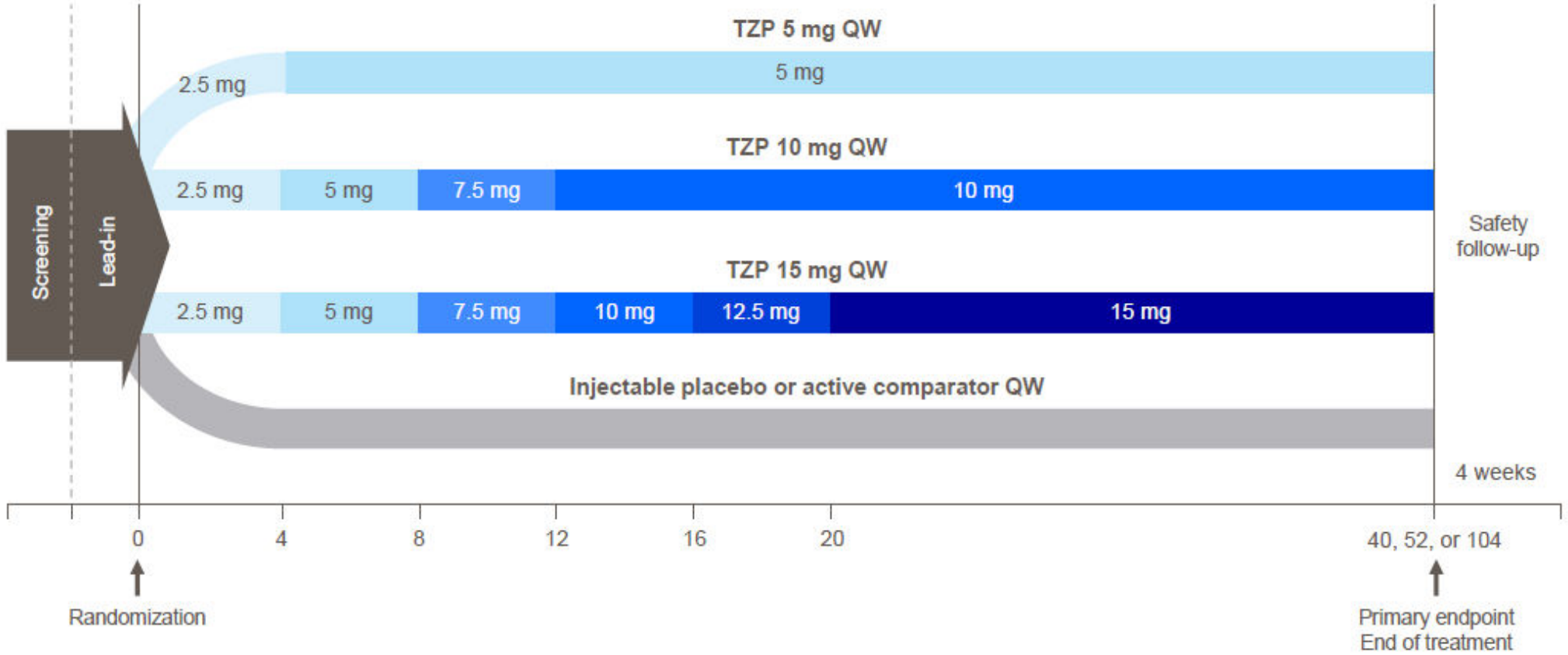
Note: This 3-dimensional rendering of tirzepatide is not an exact reproduction of the molecule and should be used for representative purposes only.
GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1.
1. Coskun T, et al. *Mol Metab*. 2018;18:3-14. 2. Urva S, et al. *Diabetes*. 2020;69(suppl 1):Abstract 971-P.

Mounjaro (Tirzepatide – GLP/GIP agonist)



** P<0.001 tirzepatide versus placebo or comparator p-value for logistic regression model. Hypoglycemia included blood glucose level <54 mg/dL with symptoms of hypoglycemia or severe hypoglycemia.

SURPASS General Study Design[1-5]

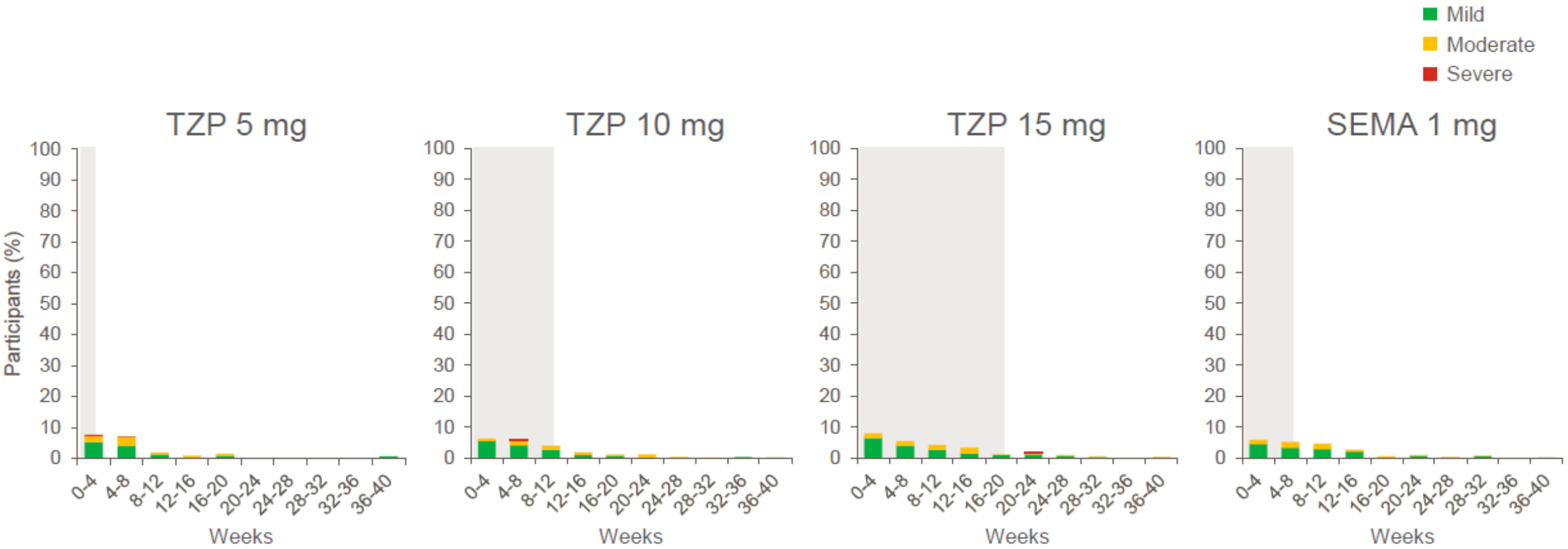


Primary Objective: Superiority and/or noninferiority of TZP 5 mg and/or 10 mg and/or 15 mg vs. placebo or active comparator in mean change in HbA1c from baseline at 40 or 52 weeks.

HbA1c = glycated hemoglobin; QW = once weekly; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. Poster presented at: *ADA* 2021. Poster LB-20.

Incidence of Nausea Over Time Through 40 Weeks (SURPASS-2)



Most cases of nausea were mild to moderate, transient, and occurred during the dose-escalation period in all groups

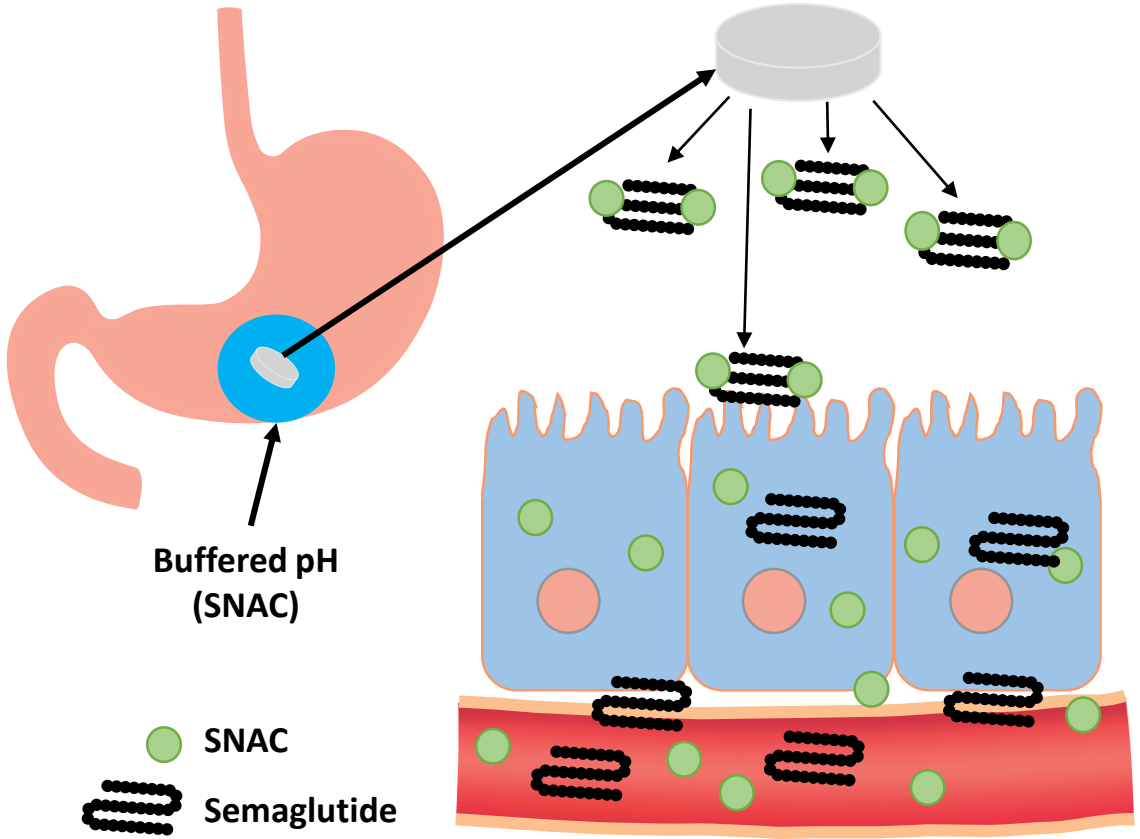
Data are percentage of participants who reported a new event relative to participants at risk during a time interval; mITT population (safety analysis set). Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments. Incidence refers to the proportion of participants who have a new event during a time interval.
mITT = modified intent to treat; SEMA = semaglutide; TZP = tirzepatide.
Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515.

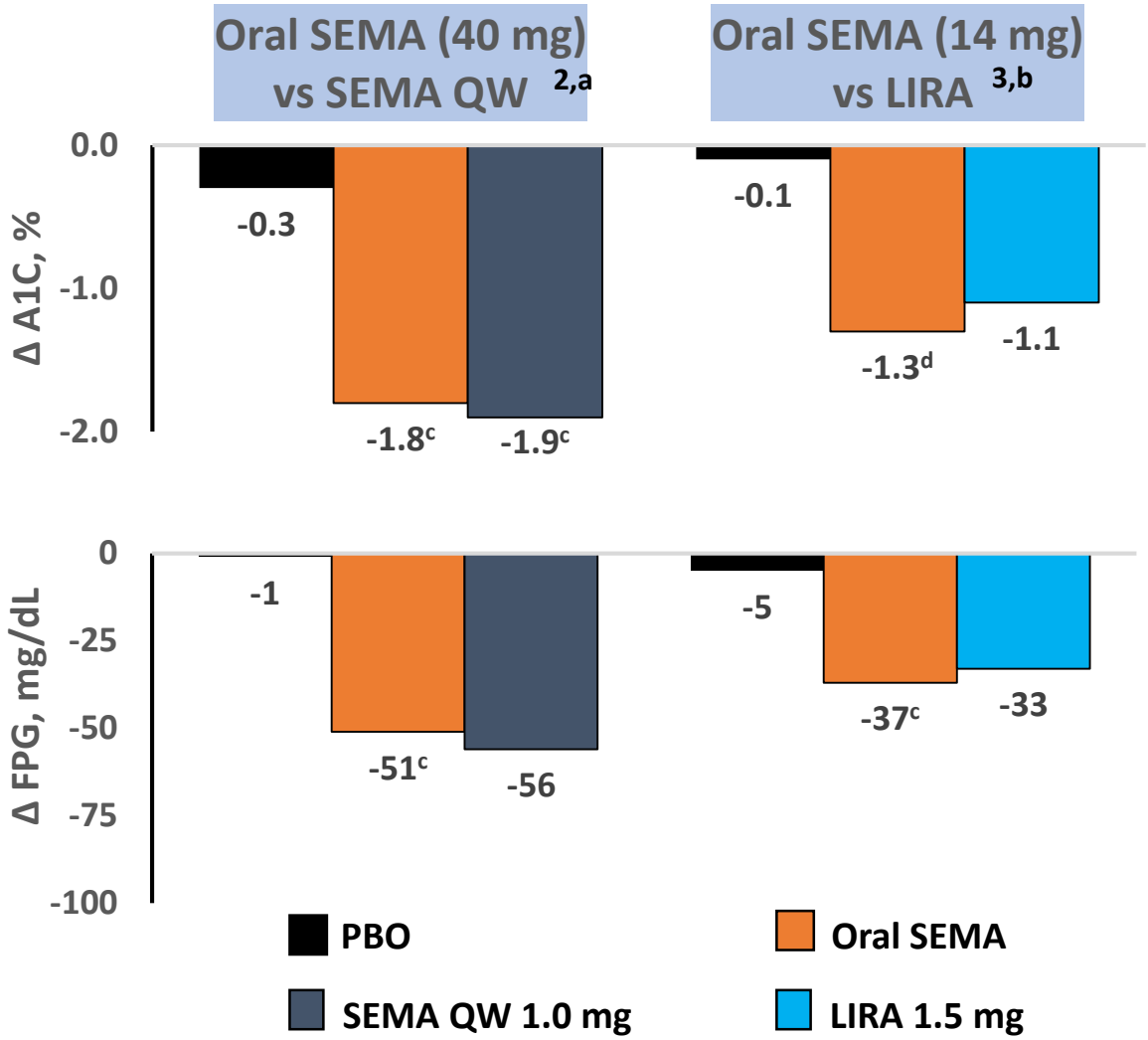
Let's help your patient get started…..

- Download **Coverage Search** if you don't have it already on your phone
- Your patient has T2DM, CV risk and you need to start a GLP or GLP/GIP
  - Enter the Drug: Trulicity, Ozempic, Mounjaro (TZP), etc
  - Enter your State
  - Enter the insurance, ie, Commercial, MCaid, MCare
  - To your neighbor (the patient)
    - Explain the MOA/benefits: ie, Thermostat, **G**ut, **L**iver, **P**ancreas. A1C ↓1-3%; wt ↓ 8-13 (25) lbs; CV, Renal protection etc
    - Explain Side effects and how to mitigate: GI; Snack for the first few days, eat ½ of what you usually eat, STOP eating when full, etc
    - Demo injection/Provide Sample and have pt self inject at the visit
  - Call pharmacy: verify eRX received and run the Rx. Get out of pocket cost for pt (you/ MA)
  - Print Co-Pay card if commercial insurance (you or MA)

How Does *Oral* Semaglutide Compare With Other GLP-1 RAs?

SEMA Formulation With SNAC: Protection and Absorption[1]



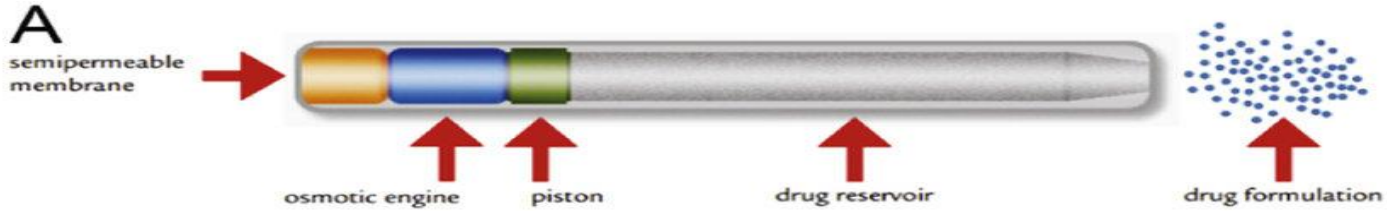


[a] Randomized trial; 26 weeks; N = 632; BL A1C 7.9%.
[b] Randomized trial; 52 weeks (26-week data, trial product estimand presented); N = 711; BL A1C 8.0%.
[c] *P* < .05 vs PBO.
[d] *P* < .05 vs PBO and LIRA.

1. Bucheit JD, et al. *Diabetes Technol Ther*. 2019 Oct 1. [Epub ahead of print];
2. Davies M, et al. *JAMA*. 2017;318:1460-1470; 3. Pratley R, et al. *Lancet*. 2019;394:39-50.

Exenatide Osmotic Pump (ITCA 650)

- Resubmitted New Drug Application has been accepted by the FDA[1]
- Exenatide delivered continuously via removable, subcutaneous, miniature osmotic pump[2]
  - Implanted during short office procedure
  - Predetermined delivery rate for up to 12 mc
- Pharmacokinetics[2,3]
  - Steady-state within ≈ 24 hours
  - , as for exenatide
- Efficacy vs EXN BID over 12 weeks[4]
  - A1C reduction
    - ITCA 20 μg/d: -0.98%
    - ITCA 40 μg/d: -0.95%
    - EXN BID: -0.72%
  - A1C ≤ 7%
    - ITCA 20 μg/d: 63%
    - ITCA 40 μg/d: 65%
    - EXN BID: 50%



1. Intarcia. https://www.intarcia.com/media/press-releases/intarcia-provides-2019-corporate-update1.html;
2. Henry RR, et al. *Clin Ther*. 2013;35:634-645;
3. Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/;
4. Henry RR, et al. *Diabetes Care*. 2013;36:2259-3565.

Use of GLP-1 RAs Across T2DM Progression: GLP-1 RAs vs Prandial Insulins for Intensifying Basal Insulin Therapy

Combining basal insulin and GLP1-RA therapy offers potent glucose-lowering action, less weight gain, and lower risk of hypoglycemic events than prandial insulin.[1]

Compared with insulin and basal-plus/basal-bolus insulin regimens, GLP-1 RA with basal insulin demonstrated[2]:

A1C reduction	***Weight loss***	***Less hypoglycemia***
Similar	**-3.72 kg**	**54% fewer events[a]**

Use with prandial insulin has been investigated for DULA, but there are limited data regarding the general use of GLP-1 RAs in combination with prandial insulin.[3]

[a] $P < .001$.

1. ADA. *Diabetes Care*. 2019;42(suppl 1):S1-S193;
2. Castellana M, et al. *Diabetes Metab* ResRev. 2019;35:e3082;
3. Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/.

CVOTs for GLP-1 RAs Have Been Completed per FDA Guidance[1]

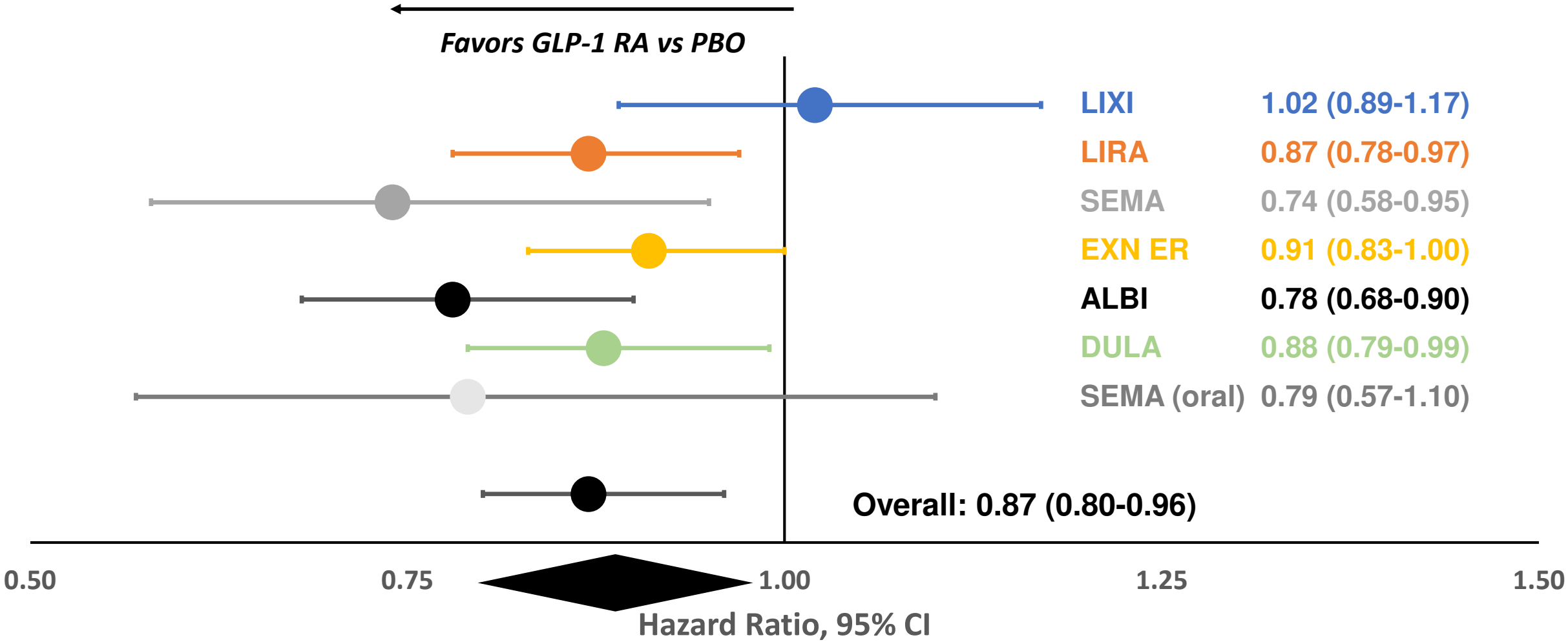
Varying trial designs across CVOTs may contribute to outcome differences[2]

Trial Characteristic	LIXI[2,3,a]	LIRA[2,4,a]	SEMA[2,5,a]	EXN ER[2,6,a]	ALBI[2,7,a]	DULA[2,8,a]	SEMA (oral)[2,9,a]
Participants, N	6068	9340	3297	14,752	9463	9901	3183
Mean age, y	60.3	64.3	64.6	62.0	64.1	66.2	66
Diabetes duration, y	9.2-9.4	12.8-12.9	13.9	12.0	14.1-14.2	10.5-10.6	14.9
Mean A1C, %	7.6-7.7	8.7	8.7	8.0	8.7-8.8	7.3-7.4	8.2
Established CVD, %	100	72.4	83	73.1	100	31.4	84.7
HF history, %	20.3	17.8	23.6	16.2	20.3	8.6	12.2
eGFR < 60,[b] %	23.2	23.1	28.5	21.6	NR	22.2	26.8
Mean follow-up, y	2.1	3.8	3.1	3.2	1.6	5.4	1.3

[a] Agent (CVOT acronym): LIXI (ELIXA), LIRA (LEADER), SEMA (SUSTAIN 6), EXN ER (EXSCEL), ALBI (HARMONY), DULA (REWIND), SEMA (oral) (PIONEER 6);
[b] mL/min/1.73 m^2.

1. FDA. https://www.fda.gov/media/71297/download; 2. Giugliano D, et al. *Diabetes Obes Metab*. 2019;21:2576-2580; 3. Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257; 4. Marso SP, et al. *N Engl J Med*. 2016;375:311-322; 5. Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844; 6. Holman RR, et al. *N Engl J Med*. 2017;377:1228-1239; 7. Hernandez AF, et al. *Lancet*. 2018;392:1519-1529; 8. Gerstein HC, et al. *Lancet*. 2019;394:121-130; 9. Husain M, et al. *N Engl J Med*. 2019;381:841-851.

GLP-1 RA CVOTs: MACE[a] Outcomes[1]



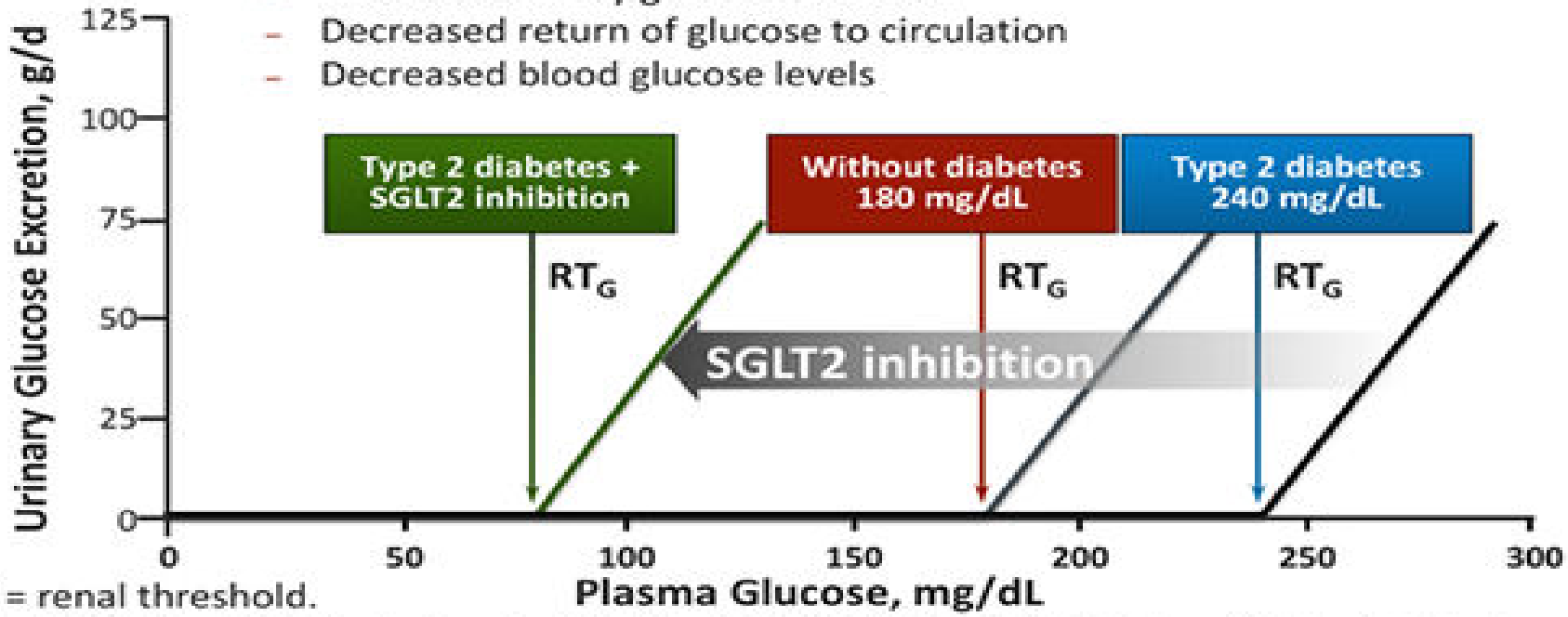
[a] CV death, nonfatal myocardial infarction, and nonfatal stroke in all 7 trials, plus hospitalization for unstable angina in ELIXA.[2-8]

1. Giugliano D, et al. *Diabetes Obes Metab*. 2019;21:2576-2580; 2. Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257; 3. Marso SP, et al. *N Engl J Med*. 2016;375:311-322; 4. Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844; 5. Holman RR, et al. *N Engl J Med*. 2017;377:1228-1239; 6. Hernandez AF, et al. *Lancet*. 2018;392:1519-1529; 7. Gerstein HC, et al. *Lancet*. 2019;394:121-130; 8. Husain M, et al. *N Engl J Med*. 2019;381:841-851.

SGLT2 inhibitors

Inhibiting SGLT2 Promotes Urinary Glucose Excretion

- SGLT2 inhibitors lower the threshold at which glucose is excreted, leading to
  - Increased urinary glucose excretion
  - Decreased return of glucose to circulation
  - Decreased blood glucose levels

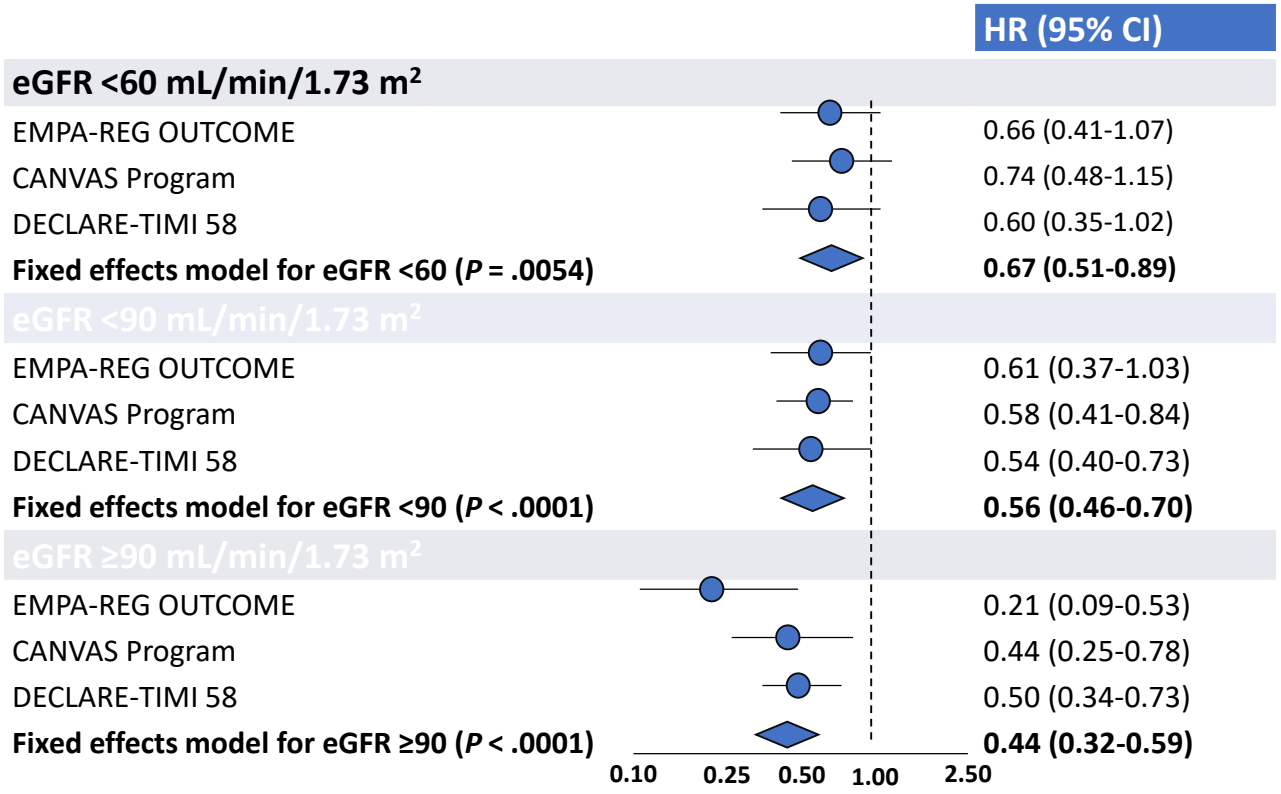


RT = renal threshold.

Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34-42[6]; Abdul-Ghani MA, et al. *Endocr Pract*. 2008;14:782-790[10]; Chao EC, et al. *Nat Rev Drug Discov*. 2010;9:551-559.[11]

In CVOTs, SGLT2 Inhibitors Improved Renal Outcomes

Composite of Worsening Renal Function, ESKD, or Renal Death



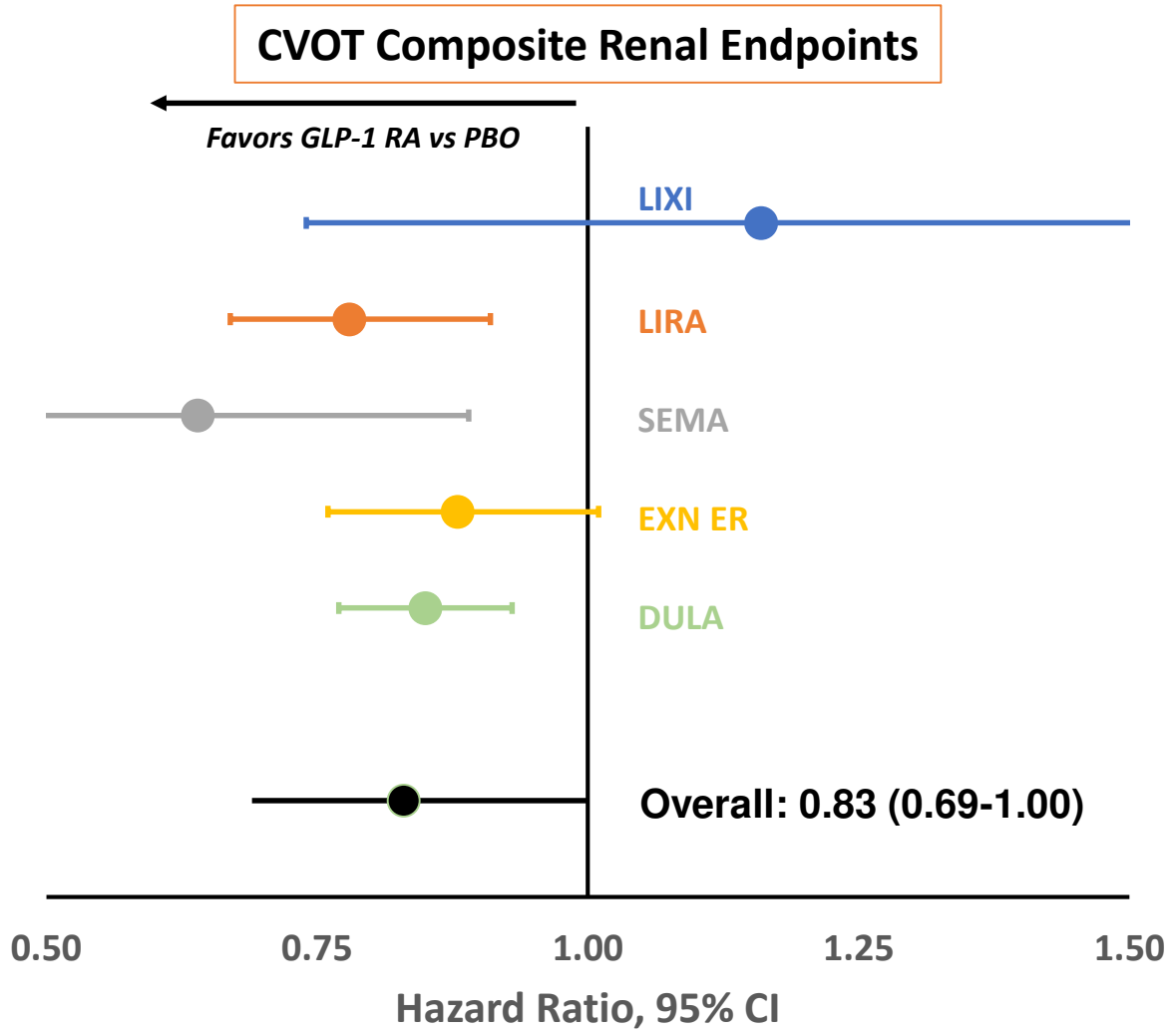
Zelniker TA et al. *Lancet*. 2019;393(10166):31-39.

- Most participants in CVOTs had eGFR ≥60 mL/min/1.73 m² and albuminuria <30 mg/g
- Renal function decline was slowed with SGLT2is by 33% to 66%
- Led to trials specific to kidney disease: Credence, DAPA-CKD, and EMPEROR-Renal (ongoing)

Heart Failure and Renal Function Effects in GLP-1 RA CVOTs

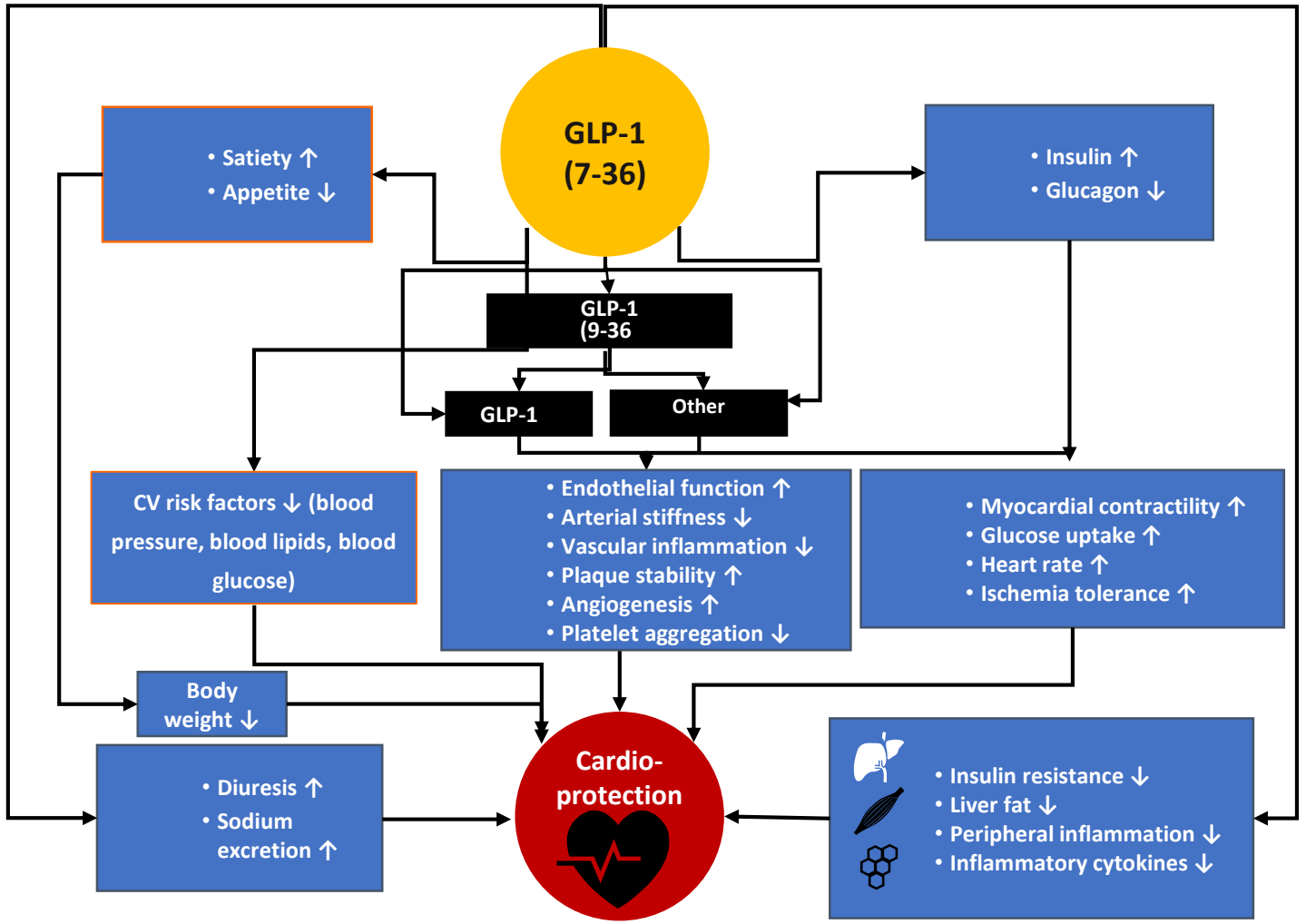
- HF
  - Meta-analysis demonstrated a 9% reduction in the risk of hospitalization for HF for GLP-1 RAs as a class
  - No significant effects on HF were identified in individual trials

- Renal effects
  - Meta-analysis demonstrated a 17% reduction in composite kidney outcomes for GLP-1 RAs as a class
  - Renal benefit driven by reduction in macroalbuminuria (HR, 0.76 [0.68-0.86])



Giugliano D, et al. *Diabetes Obes Metab*. 2019;21:2576-2580.

Multiple Actions of GLP-1 Could Contribute to Reduced Risk of CV Events With GLP-1 RAs



Nauck MA, et al. *Circulation*. 2017;136:849-870.

2022 ADA: Advancing Therapy

Independent of Metformin use, baseline A1C

If High Risk for ASCVD: GLP-1RA or SGLT2 (add the other for additional protection)

If HF: SGLT2

If CKD: SGLT2

GLP-RA before insulin

If insulin: Basal 10u/d or 0.1-0.2u/d increase 2u every 3 days, if hypo ↓ 10-20%

hard stop: 0.5u/kg ~ 50u (or elevated Bedtime v morning)

Rationale:

- Similar or greater A1C improvement with GLP-1 RA than with basal insulin[1,2]
- Potential body weight and CV benefits[1,2]
- Lower hypoglycemia risk with GLP and SGLT2[1,2]
- Potentially easier to use (eg, less need for BG monitoring to adjust dose; multiple dosing frequency options)[3]

1. ADA. *Diabetes Care*. 2022;42(suppl 1):S134-136.
2. Abd El Aziz MS, et al. *Diabetes Obes Metab*. 2017;19:216-227.
3. Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/.

GLP-1 RA or SGLT2 Inhibitor? Consider Clinical Status and Patient Preference

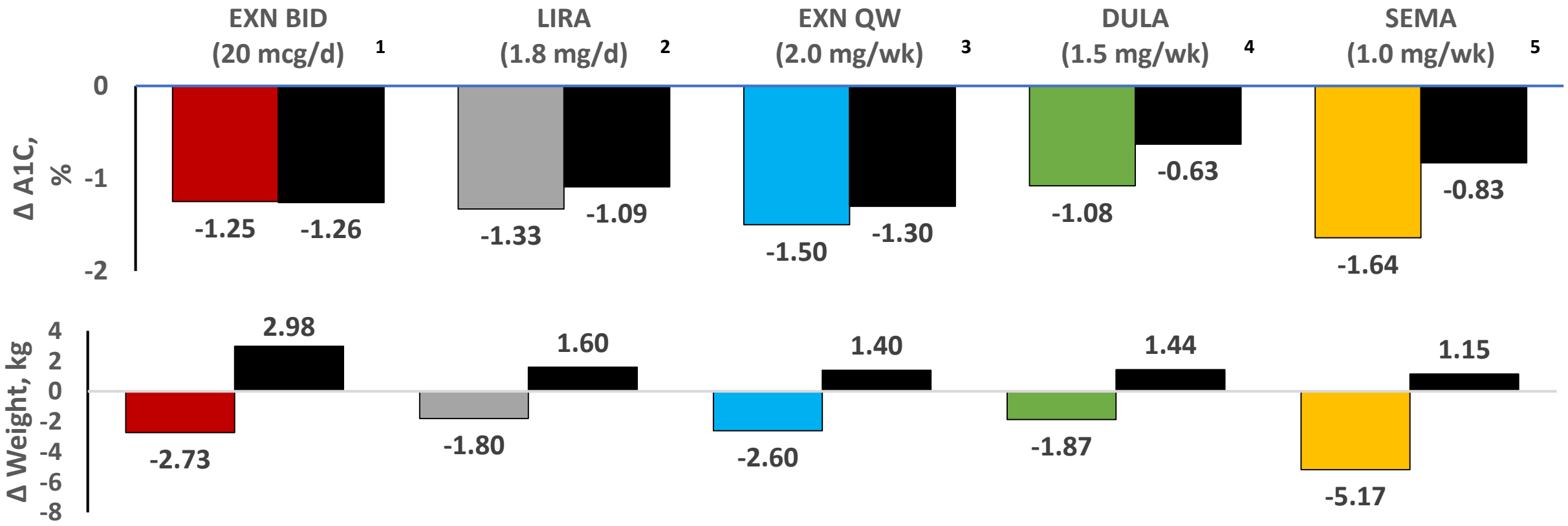
Characteristic	GLP-1 RAs	SGLT2 inhibitors
A1C reduction, %[1]	0.7-1.7 (3.2)[a]	0.3-1.2 (1.5)[a]
Weight loss, kg[1,b]	2-5[a]	2-3[a]
Systolic BP reduction, mm Hg[1]	2-5	3-5
Glucose-lowering action[1]	Insulin/glucagon, hepatic glucose production; incretin, satiety	Renal glucose excretion
Hypoglycemia risk[1]	Low	Low
Common adverse effects[2]	Gastrointestinal upset	Genital, urinary tract infections
Administration[1,2]	SC injections (weekly to twice daily) or oral (daily)	Oral (daily)
Indicated to reduce CV event risk[2,3]	Liraglutide, semaglutide SC, dulaglutide[c] (MACE); *preferred in patients with ASCVD*	Canagliflozin (MACE), dapagliflozin (hHF[c], CV death)[d], empagliflozin (CV death); *preferred in patients with HF*
Indicated for renal benefit[2]	Dulaglutide has a primary prevention indication for people with T2D and with multiple CV risk factors	Dapagliflozin: reduced risk of kidney function decline, kidney failure, CV death, and hHF in CKD; Canagliflozin: reduced risk of ESRD or creatinine doubling in patients with DKD and albuminuria

- **Meta-analyses, head-to-head trial support larger A1C reduction with GLP-1 RAs**[4-7]
- **Consider patient risk factors (eg, urinary tract infections, pancreatitis history) and preferences**[1,2]

[a] When used as a second-line therapy; [b] Not approved for weight loss at assessed doses; [c] In patients with established CVD or with multiple CV risk factors; [d] In patients with HFrEF +/- T2D.
DKD, diabetic kidney disease; ESRD, end-stage renal disease; HFrEF, heart failure with reduced ejection fraction; hHF, hospitalization for heart failure; MACE, major adverse CV events.

1. Gurgle H, et al. *Vasc Health Risk Manag*. 2016;12:236-249. 2. Drugs@FDA. Accessed June 4, 2021. https://www.accessdata.fda.gov/scripts/cder/daf/. 3. American Diabetes Association. *Diabetes Care*. *Diabetes Care*. 2021;44(suppl 1):S1-S232; 4. Lorenzi M, et al. *Diabetes Ther*. 2017;8:85-99. 5. Sharma R, et al. *Curr Med Res Opi*n. 2018;34:1595-1603; 6. Kanters S, et al. *BMJ Open*. 2019;9:e023458. 7. Rodbard HW, et al. *Diabetes Care*. 2019;42:2272-2281.

Glycemic Control and Weight Effects in Available Head-to-Head Studies of GLP-1 RAs and Insulin Glargine[a]

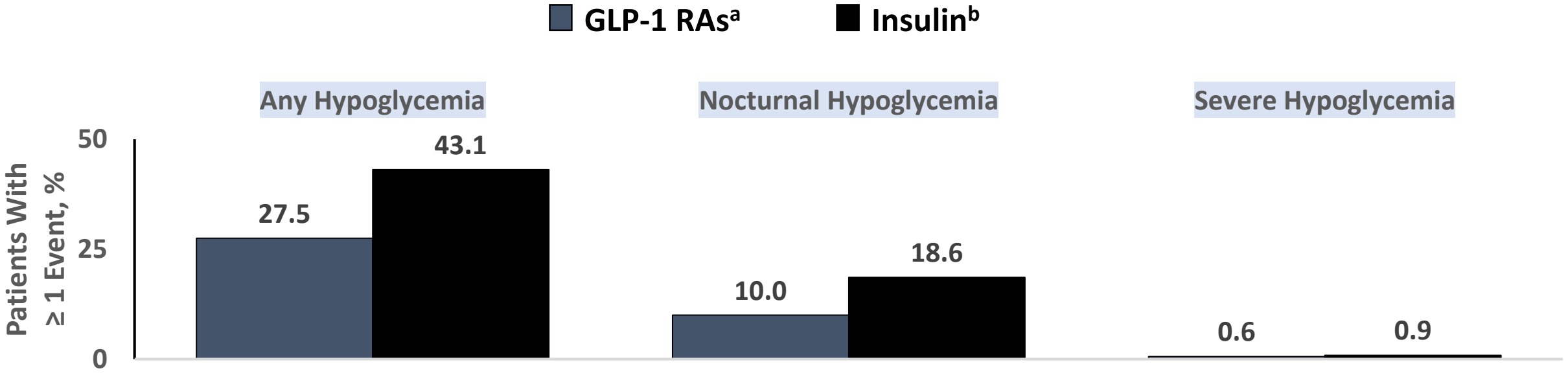


All A1C and weight outcomes were significantly better ($P < .05$) with GLP-1 RA than with insulin glargine, except no significant difference was seen in A1C change with EXN BID vs insulin glargine.[1-5]

[a] Results with insulin glargine represented by gray bars; 26 weeks (EXN BID, EXN QW, LIRA), 52 weeks (DULA), or 30 weeks (SEMA); baseline A1C 8.1% to 8.6%; T2DM duration 7.8 to 9.7 years across studies.

1. Davies MJ, et al. *Diabetes Obes Metab*. 2009;11:1153-1162; 2. Russell-Jones D, et al. *Diabetologia*. 2009;52:2046-2055; 3. Diamant M, et al. *Lancet*. 2010;375:2234-2243; 4. Giorgino R, et al. *Diabetes Care*. 2015;38:2241-2249; 5. Aroda VR, et al. *Lancet Diabetes Endocrinol*. 2017;5:355-366.

Hypoglycemia: GLP-1 RAs vs Insulin plus Orals

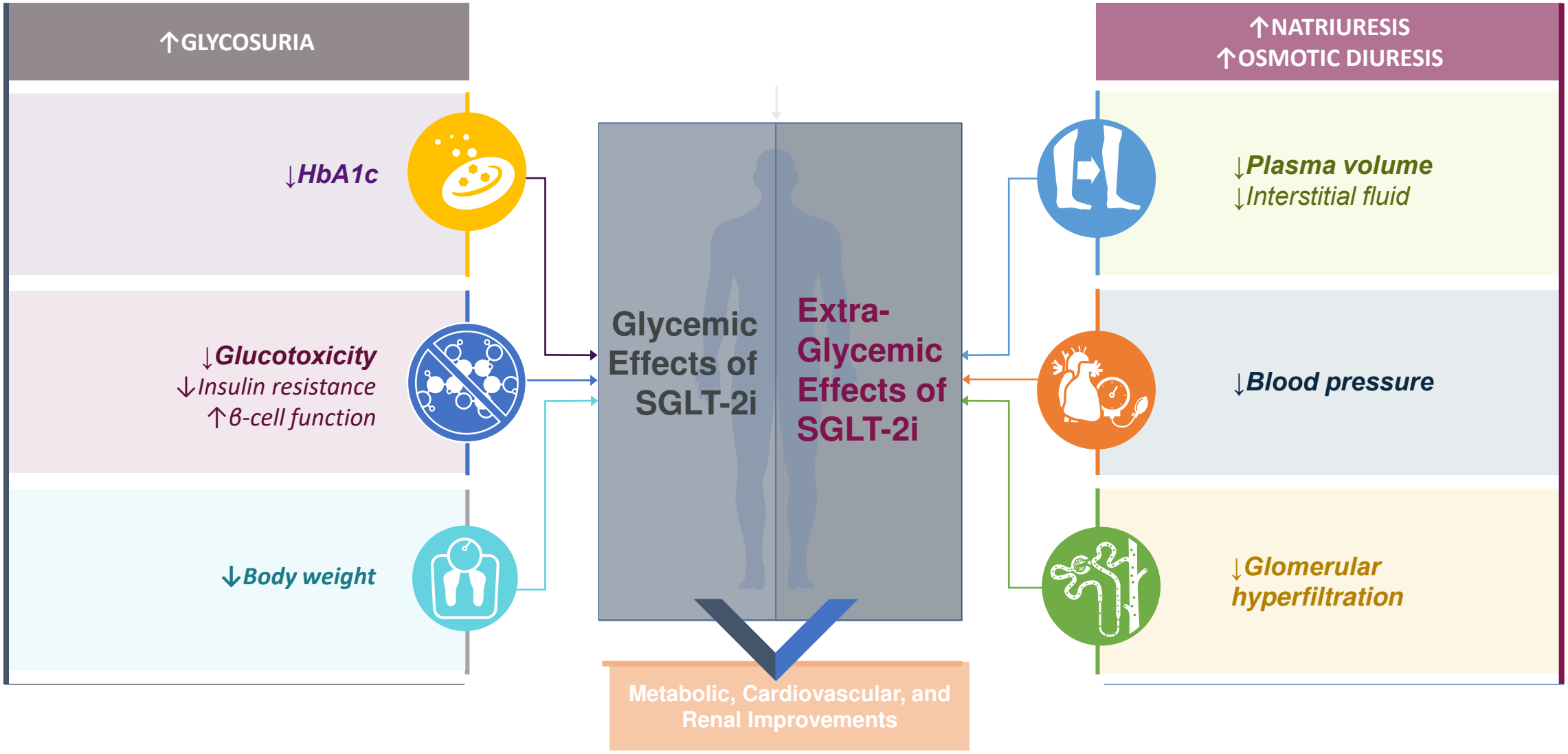


- Any hypoglycemia and nocturnal hypoglycemia were significantly lower with GLP-1 RA than with insulin; rates of severe hypoglycemia were low (< 1%) across all groups[1]
- Rates of severe or blood glucose–confirmed hypoglycemia were significantly lower with SEMA (4% to 6%) than with insulin glargine (11%; *P* < .05), with most episodes occurring in patients taking an SU[2]

[a] GLP-1 RAs in meta-analyses: ALBI, DULA, EXN BID, EXN ER, LIRA.
[b] Insulin glargine or biphasic insulin aspart vs short-acting GLP-1 RA; insulin glargine vs long-acting GLP-1 RAs.

1. Abd El Aziz MS, et al. *Diabetes Obes Metab*. 2017;19:216-227.
2. Aroda VR, et al. *Lancet Diabetes Endocrinol*. 2017;5:355-366.

Key Physiological Effects of SGLT-2 Inhibition



HbA1C=hemoglobin A1C; SGLT-2=sodium-glucose co-transporter 2; SGLT-2i=sodium-glucose co-transporter 2 inhibitor.

1. Heerspink HJL, et al. *Kidney Int*. 2018;94(1):26-39. 2. van Baar MJB, et al. *Diabetes Care*. 2018;41(8):1543-1556. 3. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32.

Potential Effects of SGLT-2 Inhibition to Improve Renal Outcomes

SGLT-2 INHIBITION

Reduce Glomerular Pressure[1]
↑Afferent vasoconstriction
↓Glomerular hyperfiltration

Neurohormonal Improvement
↓Intrarenal RAAS activity[3]
↓SNS activity[4]

Inflammation/Fibrosis Reductions[1,2]
↓Inflammatory markers
↓Fibrotic markers

Decreased Renal Workload and Hypoxia[1,2]
↓Solute transport
↓Oxygen demand

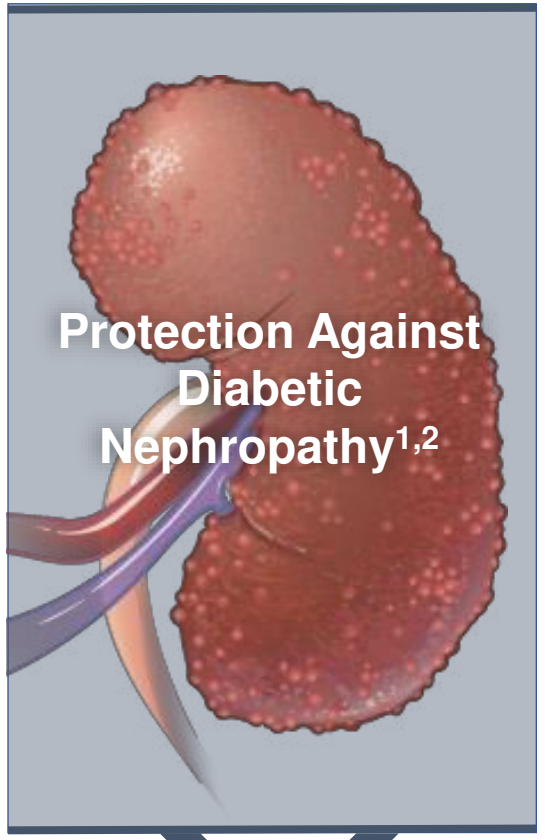
CLINICAL EFFECTS

Stabilization of eGFR[2]

↓Blood Pressure[1]

↓Tubular/Glomerular Injury[1,2]
↓Albuminuria

↓Renal Ischemic Injury[1]
↑Hb/hematocrit[2]



Preserved Renal Function[2]

eGFR=estimated glomerular filtration rate; Hb=hemoglobin; RAAS=renin angiotensin aldosterone system; SNS=sympathetic nervous system.

1. Heerspink HJL, et al. *Kidney Int*. 2018;94(1):26-39. 2. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32. 3. Shin SJ, et al. *PLoS One*. 2016;11:e0165703. 4. Sano M. *J Cardiol*. 2018;71(5):471-476.

SGLT-2 Inhibition Restores Tubuloglomerular Feedback and Reduces Glomerular Hypertension

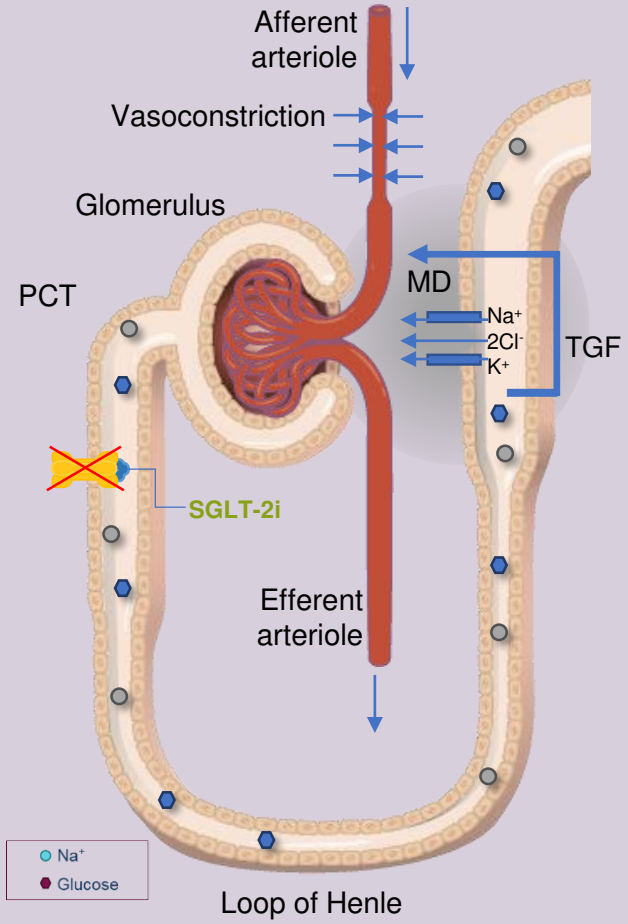
SGLT-2 INHIBITION

Reduce Glomerular Pressure
↑Afferent vasoconstriction
↓Glomerular hyperfiltration

Neurohormonal Improvement
↓Intrarenal RAAS activity
↓SNS activity

Inflammation/Fibrosis Reductions
↓Inflammatory markers
↓Fibrotic markers

Decreased Renal Workload and Hypoxia
↓Solute transport/
↓Oxygen demand



- In patients with diabetes, increased glucose and Na^+ reabsorption in the proximal tubule via SGLT-2, decreases Na^+ delivery to the macula densa, causing afferent arteriolar vasodilation and hyperfiltration[1,2]
- SGLT-2i reduce Na^+ reabsorption in the proximal tubule and increase its distal delivery to the macula densa (natriuresis)[1-3]
- This restores tubuloglomerular feedback, producing afferent arteriolar vasoconstriction and reducing intraglomerular pressure/hyperfiltration[1-3]
- These effects are clinically manifested as acute reductions in eGFR, followed by stabilization in eGFR in the longer term[3,4]
- SGLT-2i are complementary to ACE inhibitors which reduce intraglomerular pressure and hyperfiltration by inducing vasodilation of efferent renal arterioles[5]

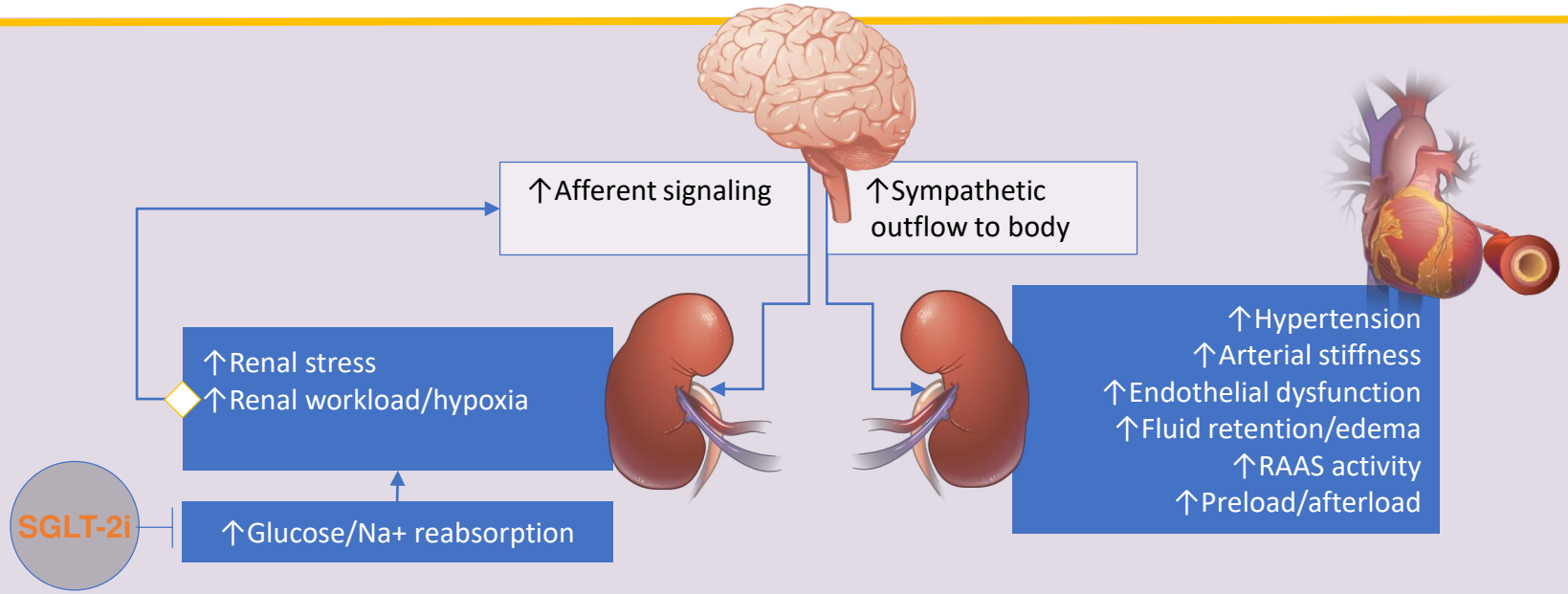
ACE=angiotensin-converting enzyme; K^+=potassium; MD=macula densa; Na^+=sodium; PCT=proximal convoluted tubule; TGF=tubuloglomerular feedback.

1. Heerspink HJL, et al. *Kidney Int.* 2018;94(1):26-39. 2. Thomas MC, et al. *Diabetologia*. 2018;61:2098–2107. 3. Wanner C, *Am J Cardiol*. 2017;120(1S):S59-S67.
4. Heerspink HJL, et al. *J Am Soc Nephrol*. 2017;28(1):368-375. 5. DeFronzo RA et al. *Nat Rev Neprhol*. 2016;13:11-26.

SGLT-2 Inhibitors May Provide Benefits by Reducing Central Sympathetic Overactivity and Intrarenal RAAS Activation

SGLT-2 INHIBITION

Neurohormonal Improvement
↓Intrarenal RAAS activity[2]
↓SNS activity[3]



- Chronic activation of the SNS has been identified in many conditions, including T2D, HF, and kidney disease[1]
- Sympathetic overactivity triggers the development of hypertension, increases arterial stiffness, causes endothelial dysfunction, and alters renal sodium and water homeostasis to promote fluid retention and edema[1]
- Excess renal glucose reabsorption may contribute to renal stress, stimulating the sympathetic center in the brain and enhancing sympathetic outflow to the whole body; inhibition of SGLT-2 may have a protective effect by reducing renal afferent nervous activity and suppressing central reflex mechanisms[1,2]
- In addition, inappropriate activation of RAAS is critical in the pathogenesis of cardiovascular and renal diseases[3]
- Evidence suggests that intrarenal RAAS is not activated by SGLT-2i as in rodent models of diabetes; treatment with dapagliflozin significantly lowered urinary angiotensin II and angiotensinogen levels, both regulators of RAAS activity[3,4]

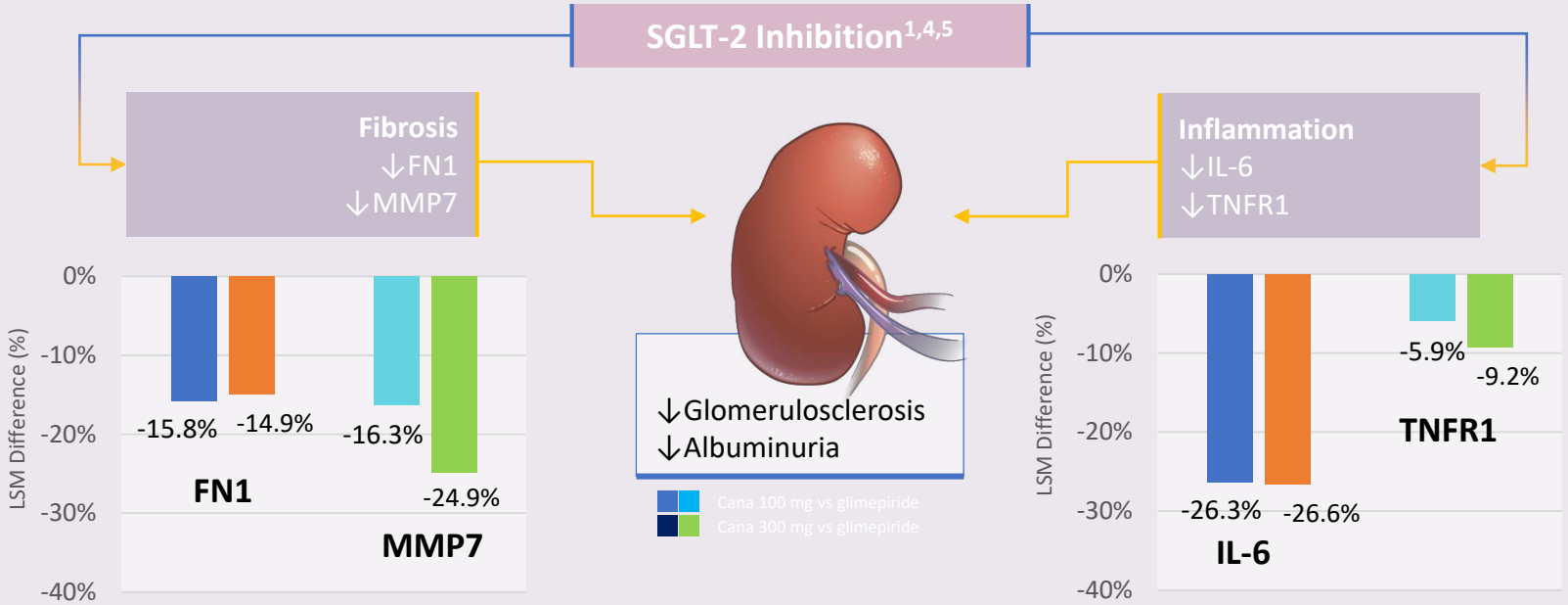
HF=heart failure; RAAS=renin angiotensin aldosterone system; SNS=sympathetic nervous system; T2D=type 2 diabetes.

1. Sano M. J Cardiol. 2018;71(5):471-476. 2. Heerspink HJL, et al. *Kidney Int.* 2018;94(1):26-39. 3. Ansary TM, et al. *Int J Mol Sci*. 2019;20:629; doi:10.3390/ijms20030629. 4. Shin SJ, et al. *PLoS One*. 2016;11:e0165703.

SGLT-2 Inhibitors May Protect Against Inflammatory and Fibrotic Responses[1]

SGLT-2 INHIBITION

Inflammation/Fibrosis Reductions[2,3]
↓Inflammatory markers
↓Fibrotic markers



- Patients with diabetes and/or CKD can have thickening of the tubular basement membrane, tubular atrophy, interstitial fibrosis, and chronic inflammation[6,7]
- During chronic hyperglycemia, an increase in glucose trafficking through proximal tubule cells, as well as increased secretion of inflammatory and profibrotic cytokines, can promote inflammation and fibrosis[6]
- SGLT-2i have been shown in clinical trials to have anti-inflammatory and antifibrotic effects as evidenced by decreases in plasma concentrations of markers of fibrosis (FN1, MMP7) and inflammation (IL-6, TNFR1)[6-8]

CKD=chronic kidney disease; FN1=fibronectin-1; IL-6=interleukin-6; LSM=least square mean; MMP7=matrix metalloproteinase-7; TNFR1=tumor necrosis factor receptor-1.

1. Heerspink HJL, et al. *Diabetologia*. 2019;62:1154-1166. 2. Heerspink HJL, et al. *Kidney Int*. 2018;94(1):26-39. 3. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32. 4. Kawanami D, et al. *Int J Mol Sci*. 2017;18(5):E108. 5. Ke B, et al. *Front Physiol*. 2017;8:21. doi: 10.3389/fphys.2017.00021. 6. Fioretto P, et al. *Diabetes Care*. 2016;39(suppl. 2):S165-S171. 7. Liu Y. *J Am Soc Nephrol*. 2010;21:212-222. 8. Terami N, et al. *PLoS One*. 2014;9:e100777.

Let's help your patient get started

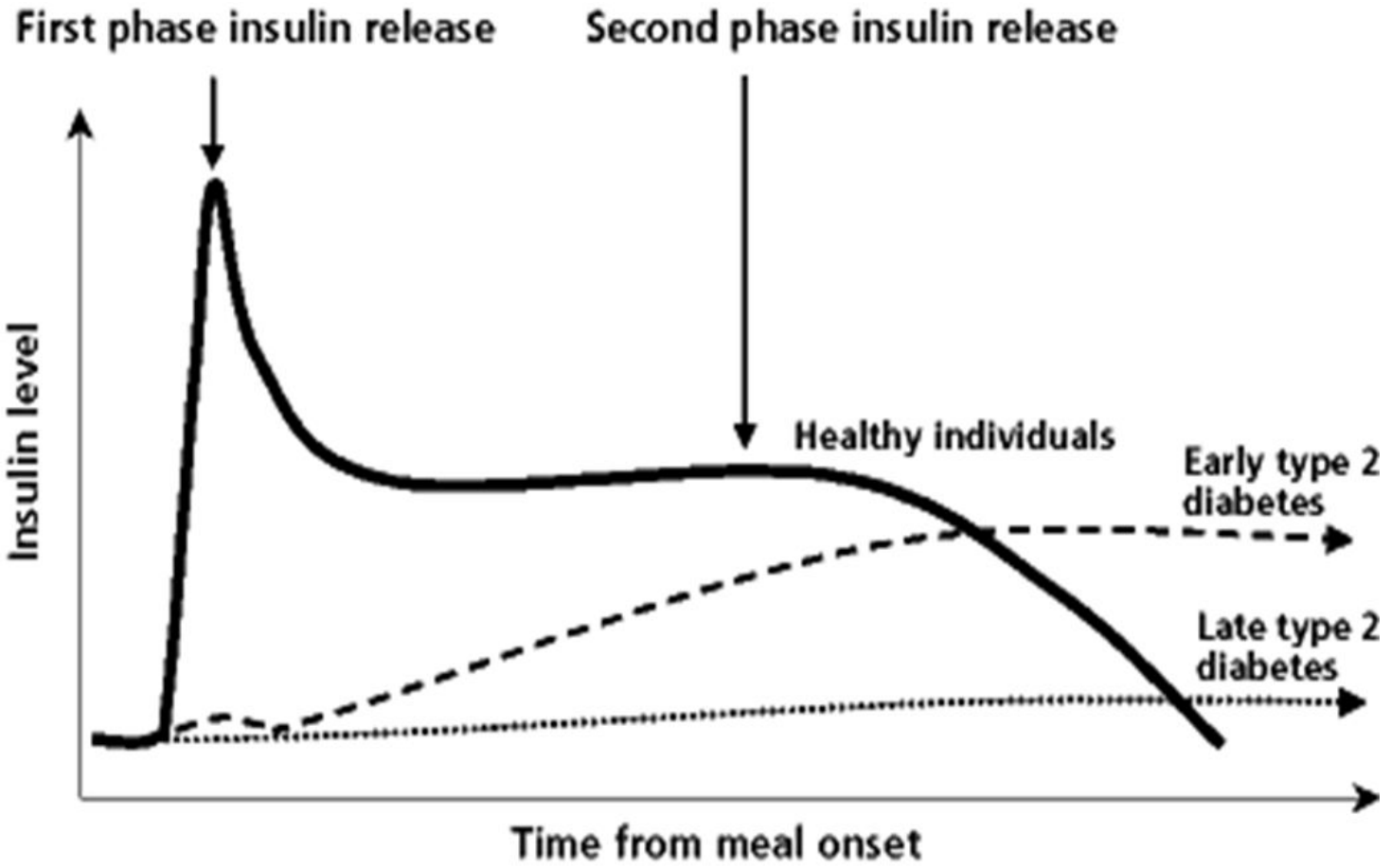
Bilateral edema and DM…You want to start an SGLT2

- Open *Coverage Search* on your phone 
- Enter the (Trade name)Drug: Emapgliflozin (Jardiance), Dapagliflozin (Farxiga), Canagliflozin (Invokana), Ertugliflozin (Steglatro)
- Enter your state:
- Enter the category of insurance
- To your neighbor (the patient)
  - Explain the MOA/Benefits: ie; Pushes glucose out the urine when blood sugars ≥ 100mg; ↓A1C 1-1.5% ↓BP, ↓Wt-8-10lbs; Renal, CV protection and HF treatment.
  - Explain side effects and how to mitigate: UTI 6-8%; GMI 6-11%: Good hygiene, clean and dry; drink 1 extra glass of water/d.
- Provide sample and Co-Pay card (commercial insurance)
- Call pharmacy to verify eRX and request they run Rx for out of pocket $

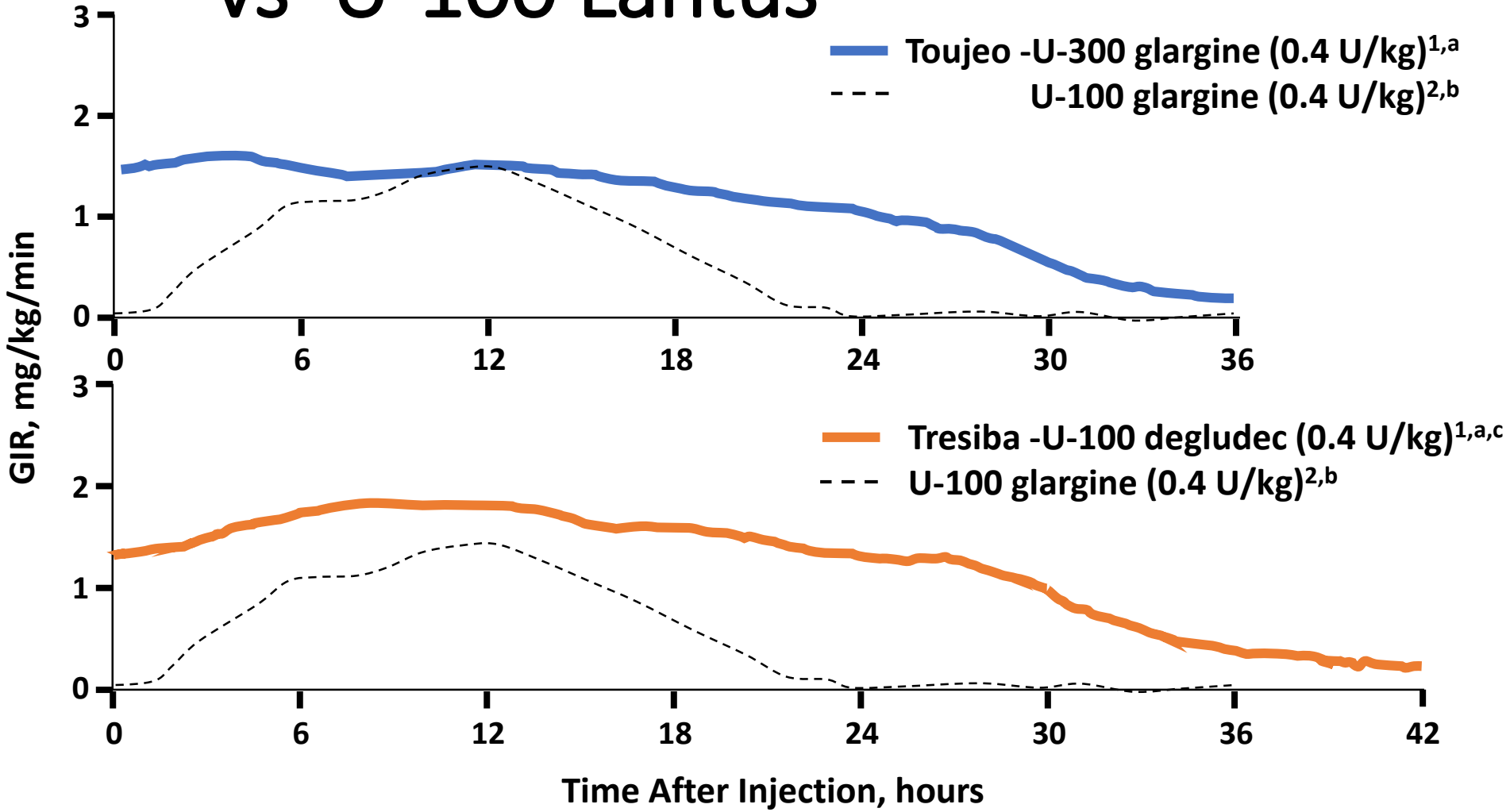
Time Action of Insulins

Insulin	Starts (m-hr)	Peak (hr)	Duration (hrs)
Aspart,Lispro,Gulisine Novolog, Humalog, Apidra	10-15m	1–1.5	3-4
Lyumjev, FiAsp Ultra fast	1-5 m	30-90m	3
Afrezza(inhaled rapid)	12-15	53min	180min
Regular	30+m	2–3	4–6
NPH (Walmart $25 no Rx)	2–4h	6–8	10–12
Glargine (Lantus) u-100 (Toujeo) - U300	2+h	~Flat VERY flat	24+/- 32 hr
Detemir (Levemir)	2+h	6+/-	20-24
Degludec (Tresiba)	2+ hr	VERY flat	42 hr

Impaired Insulin Secretion



Time Action of Ultralong-Acting Insulins vs U-100 Lantus



[a] Results shown for individuals with T1DM; [b] Individuals with and without T1DM; [c] U-200 degludec curve is similar.[3]

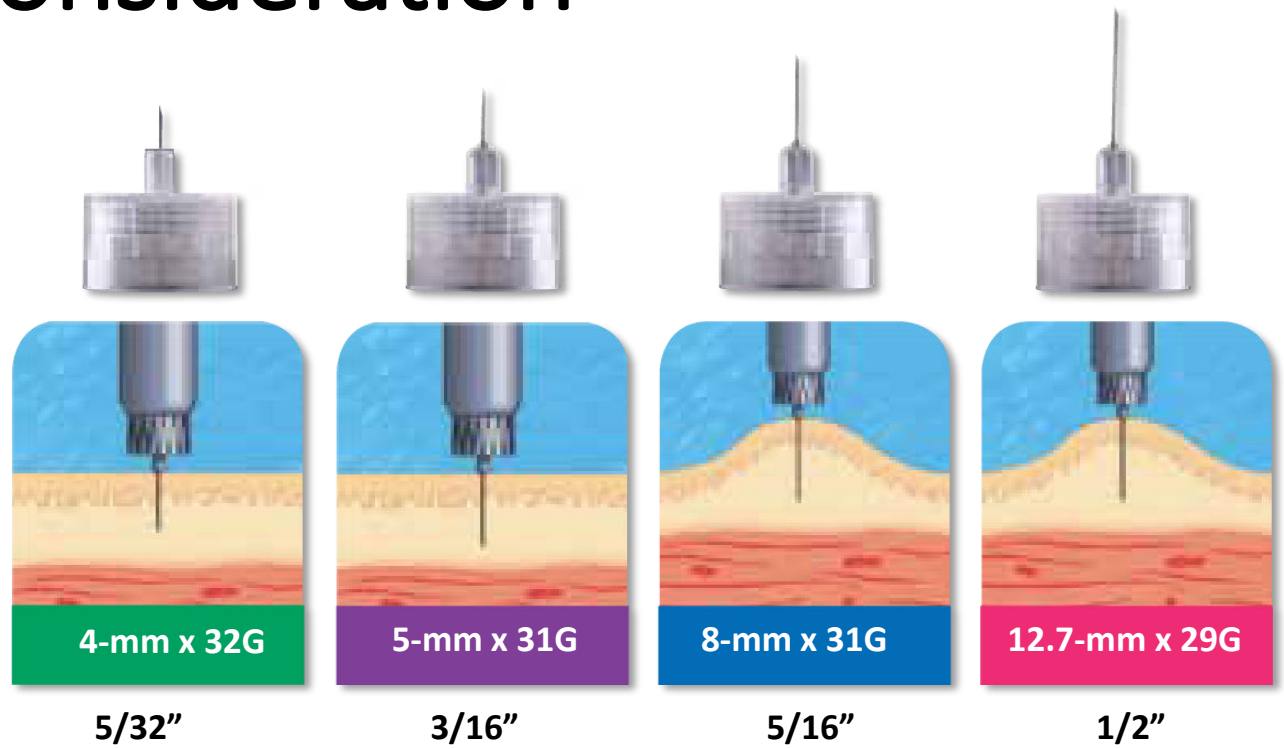
1. Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/daf/.
2. Google Patents. http://www.google.com/patents/US20120122774.
3. Heise T, et al. *Diabetes*. 2012;61(suppl 1):A91 [abstract 349-OR].

Insulin Delivery Devices

- Whenever possible, insulin should be self-administered
- Pen devices (durable or disposable) may improve the accuracy of insulin administration
- Insulin dosers may be useful for individuals with limited vision or manual dexterity

ADA. *Diabetes Care.* 2022;27(Suppl 1):S106–S109.

Needle Size Consideration



- Use the shortest needle possible when initiating insulin therapy
- There is no medical reason to use a needle longer than 8-mm

Becton Dickinson Diabetes. *Step by step injection guide.* 2012; www.bd.com/us/diabetes.
Becton Dickinson Diabetes. BD pen needles fit these pens. http://www.bd.com/us/diabetes/hcp/main.aspx?cat=3067&id=3156
Frid A, et al. *Diabetes Metab*. 2010;36(suppl 1):S3-S18.

Fixed-Ratio Coformulations of GLP-1 RAs and Basal Insulin

- **Insulin degludec and liraglutide (DEG-LIRA)**
  - Fixed-ratio (1 U DEG : 0.036 mg LIRA)
  - Once daily, same time each day
  - Start at 16 U (≈ 0.6 mg/d LIRA); titrate biweekly to maximum 50 U (1.8 mg LIRA)
- **Insulin glargine and lixisenatide (GLAR-LIXI)**
  - 3:1 ratio (30-60 U GLAR : 10-20 mg LIXI)
  - Once daily, within 1 hour before first meal
  - Start at same dose as prior insulin dose, titrate weekly to maximum 60 U (20 mcg LIXI)

Basal insulin/GLP-1 RA coformulations are indicated for adults with T2DM inadequately controlled on basal insulin or the respective GLP-1 RA.

Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

Clinical Characteristics of Basal Insulins vs U-100 Glargine in T2DM

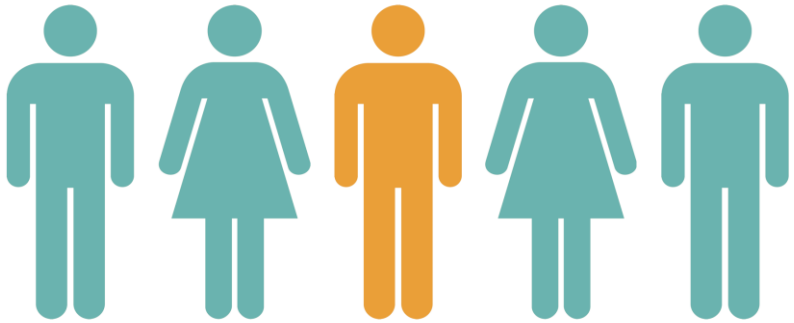
	U-100 NPH[1]	U-100 Detemir[1]	U-100 Glargine Equivalent[2]	U-300 Glargine[3]	U-100 Degludec[4,5]
Insulin dose			=	⇑ 12%	⇑ 4%
A1C	=	=	=	=	=
Weight	=	⇓ 0.77 kg	=	⇓ 0.28 kg	=
Overall hypoglycemia	=	=	=	⇓ 14%	⇓ 19%
Nocturnal hypoglycemia	⇑	=	=	⇓	⇓
Severe hypoglycemia	=	=	=	=	⇓ 40%

Statistically significant differences indicated by arrows.

1. Rys P, et al. *Acta Diabetol*. 2015;52:649-662.
2. Rosenstock J, et al. *Diabetes Obes Metab*. 2015;17:734-741;
3. Ritzel R, et al. *Diabetes Obes Metab*. 2015;17:859-867.
4. Zhang XW, et al. *Acta Diabetol*. 2018 Feb 8. [Epub ahead of print].
5. Marso SP, et al. *N Engl J Med*. 2017;377:723-732.

HYPOGLYCEMIA IS A COMMON COMPLICATION OF DIABETES MANAGEMENT

- **Most people** with T1D experience hypoglycemia[1,2]
- **30% to 40%** of people with T1D experience **1-3 severe** hypoglycemia events per year[3]
- **50 %** of people with T2 Diabetes experience hypoglycemia[4]
- **1 in 5** people with T2D experience ≥**1 severe** hypoglycemic event per year[5]



T1D, Type 1 diabetes; T2D, Type 2 diabetes

1. Spanakis EK et al. *NCBI Bookshelf*. 2018.
2. Cryer PE. *Diabetes.* 2008;57:3169-3176.
3. International Hypoglycaemia Study Group. *Diabetes Care.* 2015; 38: 1583-1591.
4. Gehlaut RR et al. *J Diabetes Sci and Technol.* 2015;9(5):999-1005.
5. Edrige CL et al. *PLOS One*. 2015.

Classification of Hypoglycemia

BG ≤ 70 mg/dL

BG < 54 mg/dL

Assistance Required

Level 1

Hypoglycemia alert: ≤ 70 and ≥ 54 mg/dL

- **Treat with rule of 15**

Level 2

Clinically significant hypoglycemia < 54mg/dL

- **Neuroglycopenic symptoms occur, cognitive impairment**
- **Treat with rule of 15**
- ***Have Glucagon available***

Level 3

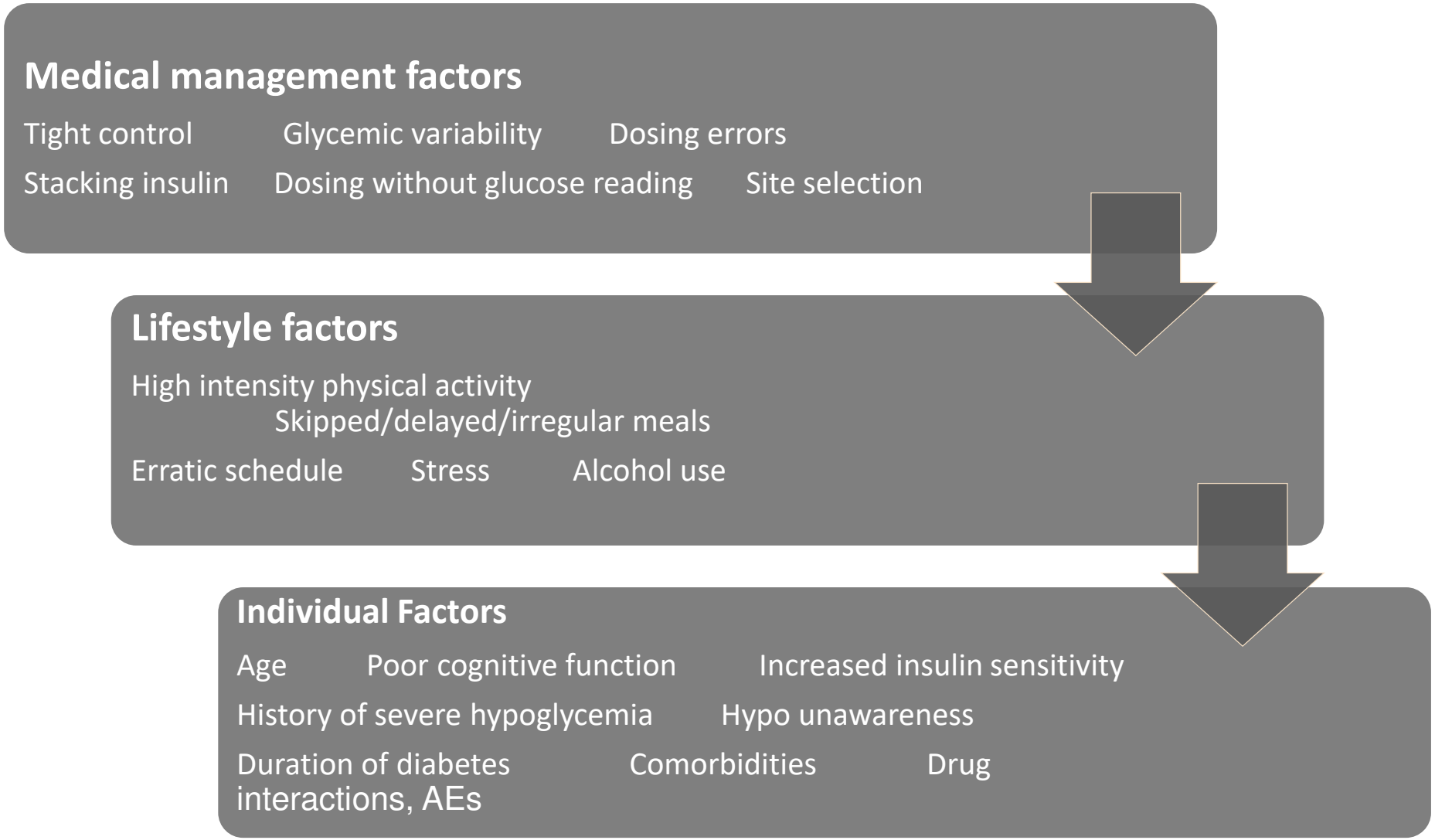
Severe hypoglycemia

- **No specific glucose threshold**
- **Associated with severe cognitive and/or physical impairment**
- **Requires assistance for recovery**

CGM Goal: <4% time <70mg/dL and <1% <54mg/dL

ADA. *Diabetes Care*. 2019;41(suppl 1):S1-S193;
Seaquist ER et al. Diabetes Care 2013 May; 36(5): 1384-1395.
IHSG

Review the multiple factors that can increase risk of hypoglycemia – assess the specific factors affecting the PWD



Standards of Medical Care in Diabetes– 2020. Diabetes Care. 2020;43(suppl 1): S66-S76

Preventing Hypoglycemia

- Patient education
- Dietary intervention
- Exercise management
- Glucose monitoring
- Medication adjustment
- Clinicians asking about hypoglycemia at every visit

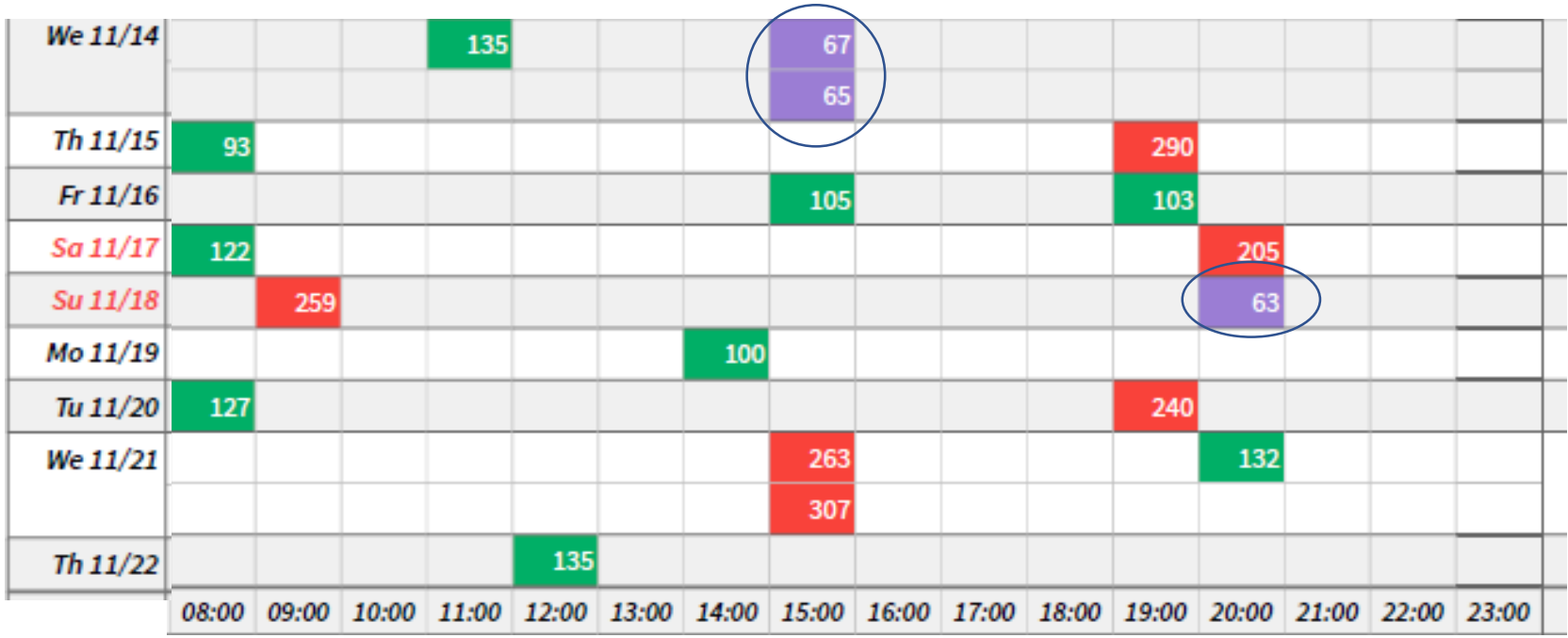
Seaquist ER et al. Diabetes Care 2013 May; 36(5): 1384-1395.

Recognizing Hypoglycemia From Glucose Data

Handwritten SMBG Diary

Date	Time	BG
Mon	6:00 AM	57
	6:00 PM	140
Tue	4:40 AM	45
	7:20 AM	92
	12:45 PM	110
	10:20 PM	87
Weds	6:00 AM	160

Downloaded Glucose Meter



Hypoglycemia in CGM Downloads

Summary

Average Glucose

151 mg/dL

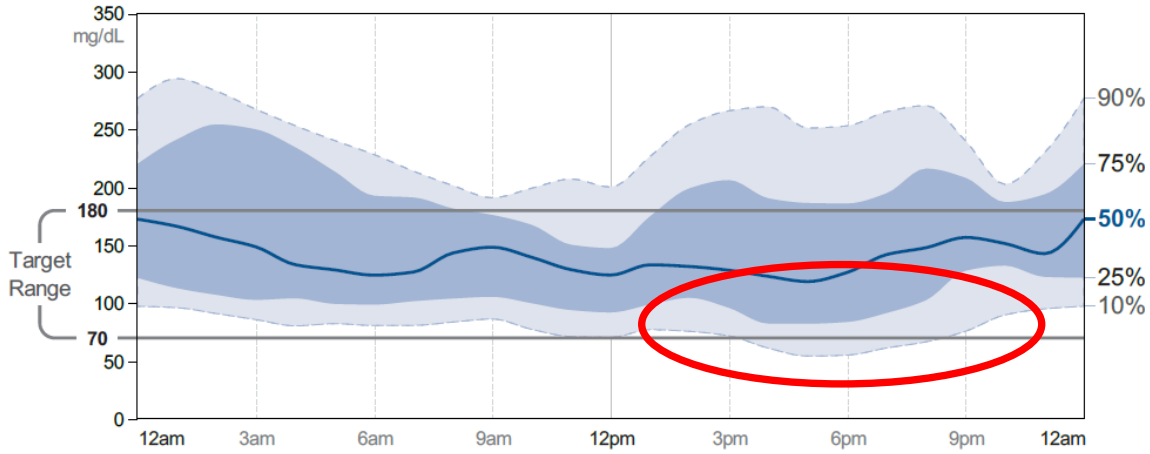
*88-116**

Time In Range

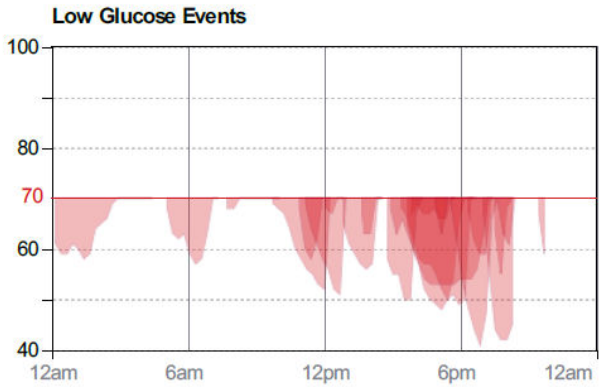
Above 180 mg/dL (above 250 mg/dL: 10%) — 31 %

In Target Range 70-180 mg/dL — 62 %

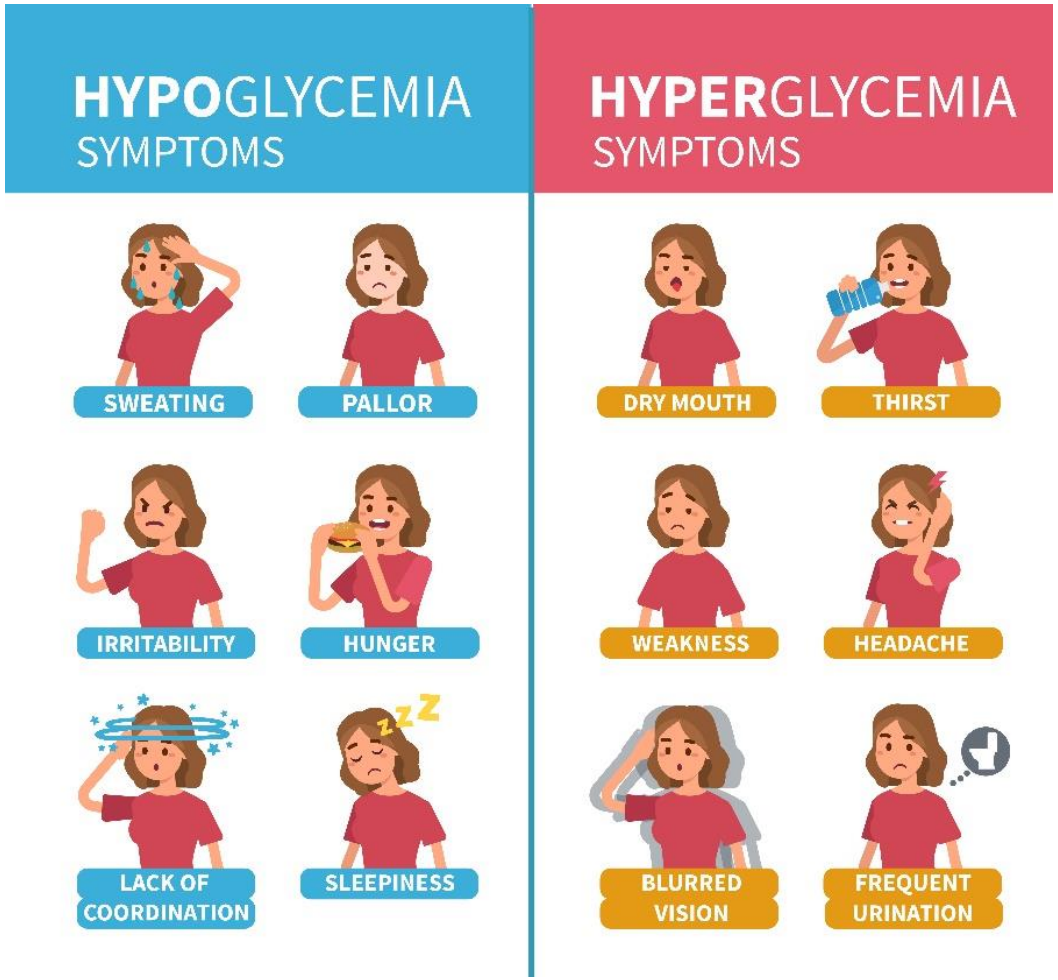
Below 70 mg/dL (below 54 mg/dL: 2%) — 7 %



LOW GLUCOSE EVENTS	20
Average duration	114 Min



Proactively Discuss Hypoglycemia at *Every* Visit



- How many times have you had glucose < 70 mg/dL in the past 2 weeks?
- How low is your glucose when you feel symptoms?
- How do you treat low glucose?
- What do you carry with you *at all times* in case you need to treat low glucose?
- What do you do to prevent low glucose?

1. Seaquist ER, et al. *Diabetes Care*. 2013;36:1384-1395.
2. Unger J. *Diabetes Metab Syndr Obes.* 2011;4:253-261.

TREATMENT OPTIONS FOR HYPOGLYCEMIA:

15 GRAMS CHO→ "SWEET BITE"…WHAT CAN PATIENTS CARRY *ALL* THE TIME

SEVERE HYPOGLYCEMIA OCCURS AT *ALL* LEVELS OF GLYCEMIC CONTROL AND ALL AGES

The risk of severe hypoglycemia increases with age

% Persons With Type 1 Diabetes Experiencing ≥1 Severe Hypoglycemic Event[a] In Prior 3 Months By Recent HbA1C (N=11,060)[b]

HbA1C-recent	6-12 years old N=1313	13-17 years old N=3183	18-25 years old N=2445	26-49 years old N=2143	>50 years old N=1976
<7%	4%	5%	4%	6%	10%
7.0-7.5%	3%	3%	4%	5%	11%
7.5-8%	4%	4%	4%	7%	8%
8-9%	5%	4%	6%	7%	9%
>9%	7%	6%	7%	14%	9%

[a]Severe hypoglycemic event defined by loss of consciousness or seizure.

[b]Management practices and health outcomes were reported for 22,697 patients (ages 1 to 93 years) enrolled in the T1D Exchange Registry from 2016 to 2018. Foster NC et al. *Diabetes Technol & Ther.* 2019;21(2):66-72.

Patients and Care Partners Need to Know How to Use Glucagon for Severe Hypoglycemia

When?

- Unconscious and/or having seizure
- Unable to eat or drink a sugar-sweetened product
- Sugar does not improve condition

Where?

- Available by prescription fro local pharmacies
- Inject in buttocks, arm or thigh (SC or IM)

How?

- Require powder to be reconstituted and drawn up
- Downloadable app has audio instructions to talk care partners through the process of injection

HypoKit

Glucagon Emergency Kit and App

Glucagon.Package insert, Glucagon APP: http://myhealthapps.net/app/details/228/glucagon.

….New Glucagon Delivery

- Lilly: Nasal Glucagon (BAQSIMI) 3mg
  - Nasal glucagon, no reconstitution
  - >4y/o

- Xeris, Glucagon injection (G-Voke hypopen)0.5mg and 1mg
  - Re-constituted. pre-filled (PFS) and
  - Hypo pen, Auto injector 2021

- Zeland: Dasiglucagon (Zegalogue), 0.6mg/0.6ml
  - Approved 3-22-21, available 6-21
  - Auto injector and prefilled >6 y/o

Glucagon Nasal Powder

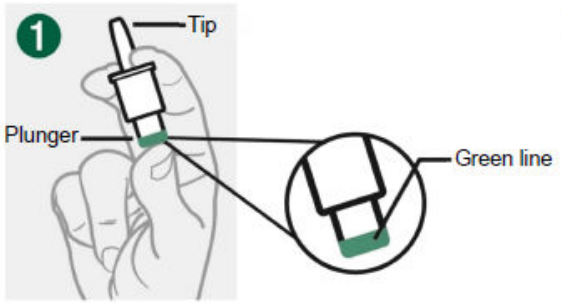
- Nasal powder dosing: delivers into patient's nose
- Nasal cavity has a large surface area and rich vascular bed for absorption
- No need to inhale=consistent dosing
- Found equally effective to 1mg injectable glucagon in a cross-over study with 75 participants
  - Mean time to recovery: 16 min (IN) vs 13 min (IM) ($P<0.001$)
- Studied in patients with nasal congestion: dosing found to be consistent
- Non trained individuals could successfully administer >90%, ~ 48 seconds
- Single-use dose 3mg

Rickels MR et al. . Diabetes Care. 2016;39: 264–270.
Guzman CB et al. Diabetes Obes Metab. 2018 Mar;20(3):646-653

Nasal Glucagon

- Indicated for severe hypoglycemia in PWD over 4 years old
- Can be carried in high and low temps
- Stable at room temp

Giving the Dose



- Hold Device between fingers and thumb.
- Do not push Plunger yet.

- **Insert Tip** gently into one nostril until finger(s) touch the outside of the nose.

- **Push Plunger** firmly all the way in.
- **Dose is complete when the Green Line disappears.**

www.baqsimi.com

Glucagon Hypo Pen

- Room temperature stable, non-aqueous liquid form of glucagon
- Proprietary formulation technology (XeriSol™)
- Long-term stability at room temperature
- Pre-mixed solution in auto-injector
  - Doses: 0.5mg, 1mg
- Phase 2 trials for other indications
  - Post-bariatric hypoglycemia, exercise induced hypoglycemia

https://www.xerispharma.com/pipeline/

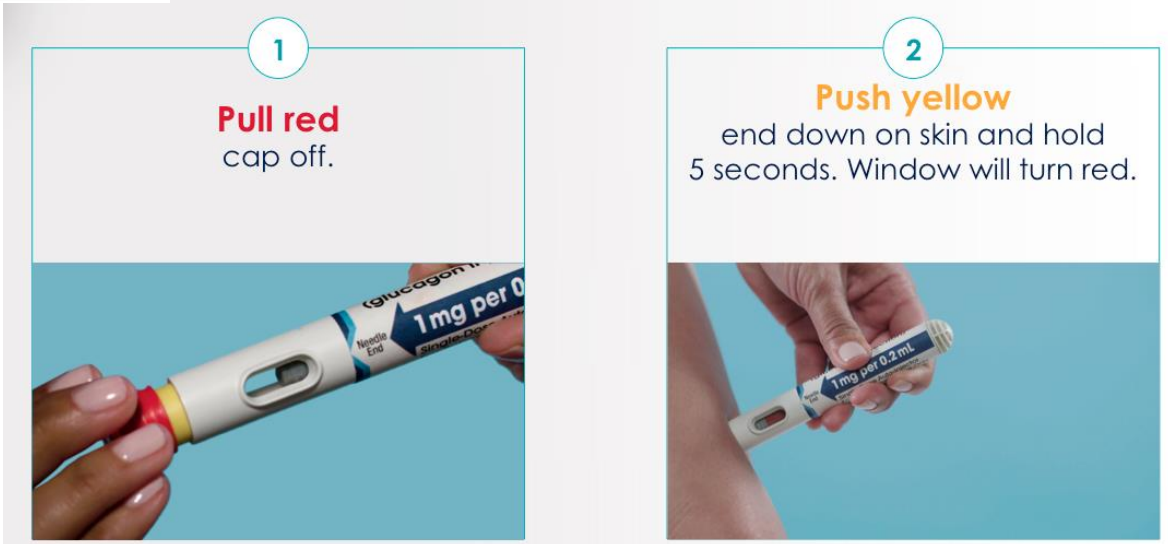
Glucagon: instructions

PreFilledSyringe

$0 savings card for commercial insurance patients at: https://www.gvokeglucagon.com/savings-and-support

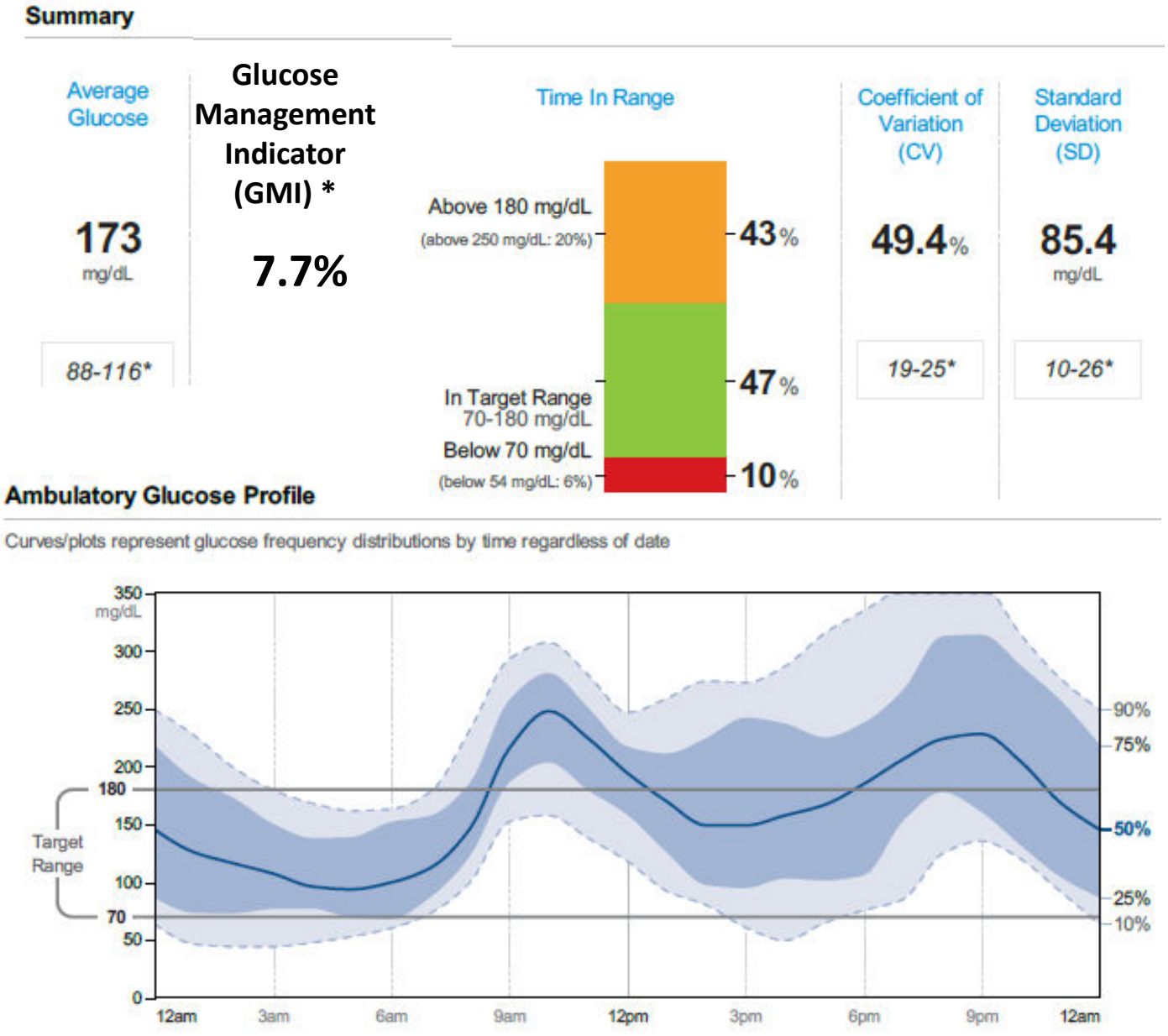
Patient assistance program also available: 1-877-myGvoke

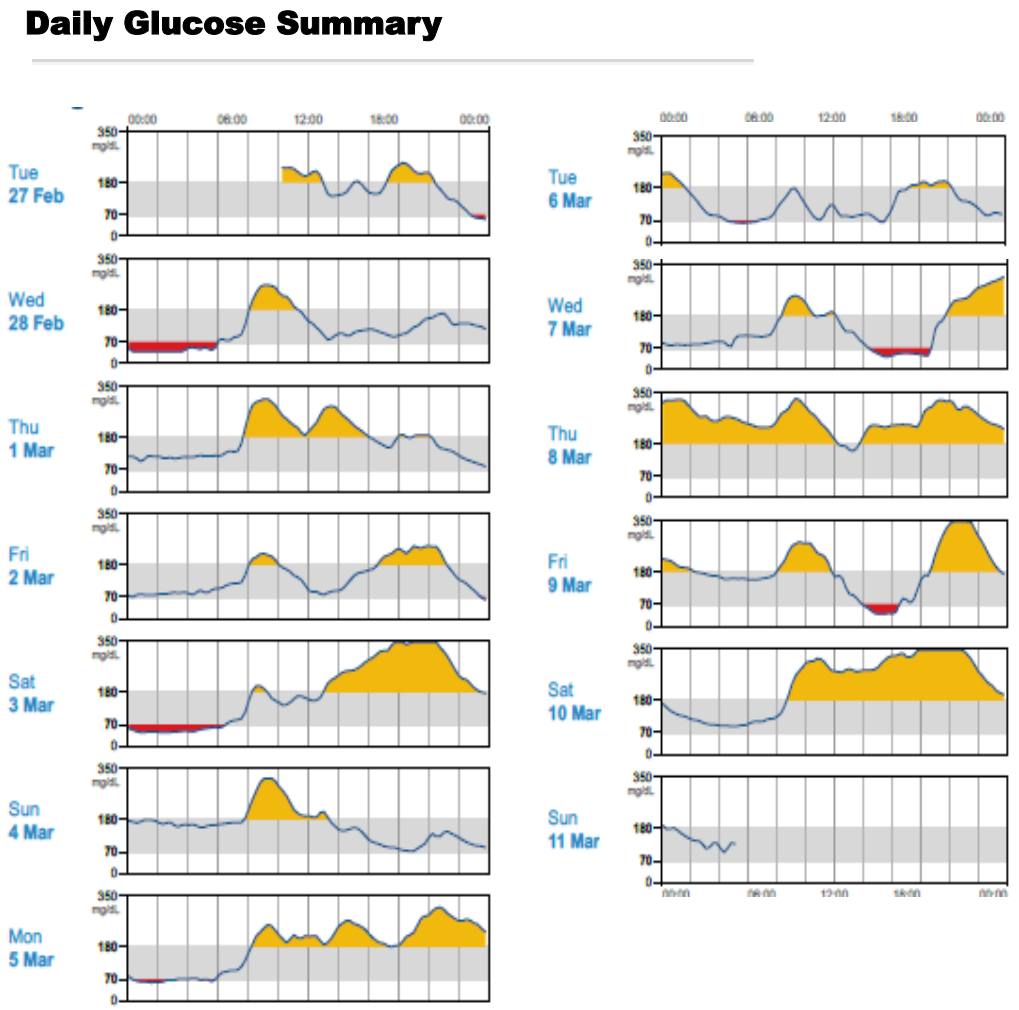
Patients can request rx online/home delivery: https://www.gvokeglucagon.com/ordering-gvoke



www.gvokeglucagon.com

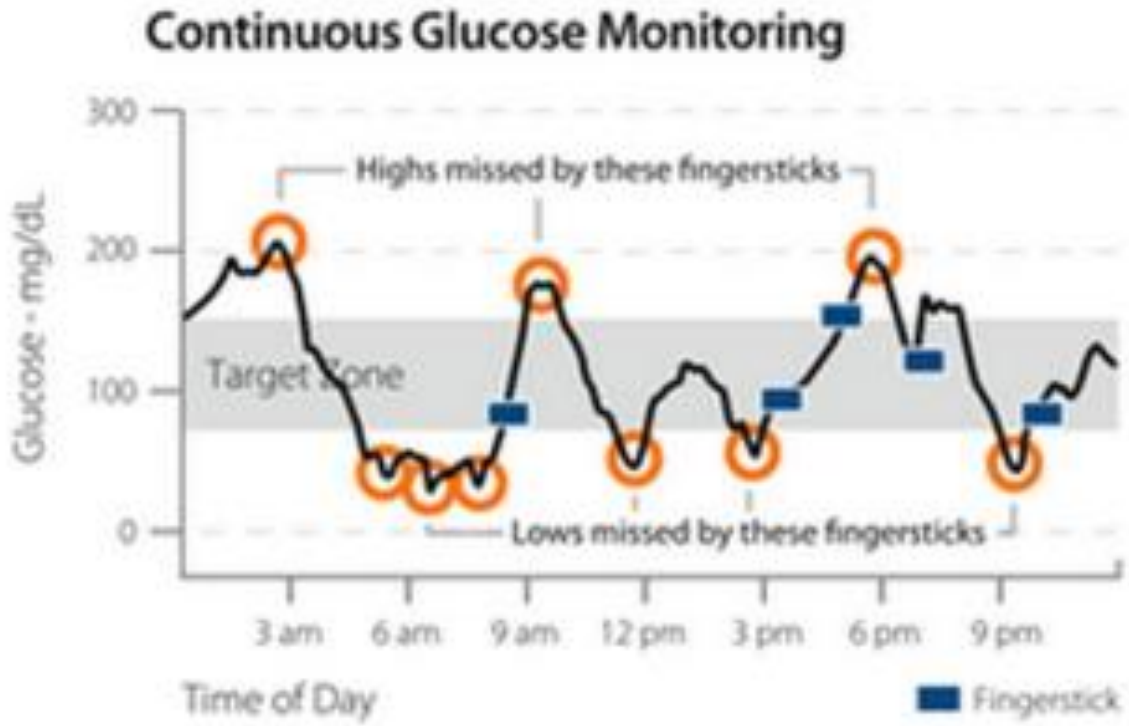
PATTERN MANAGEMENT WITH THE AGP:AMBULATORY GLUCOSE PROFILE





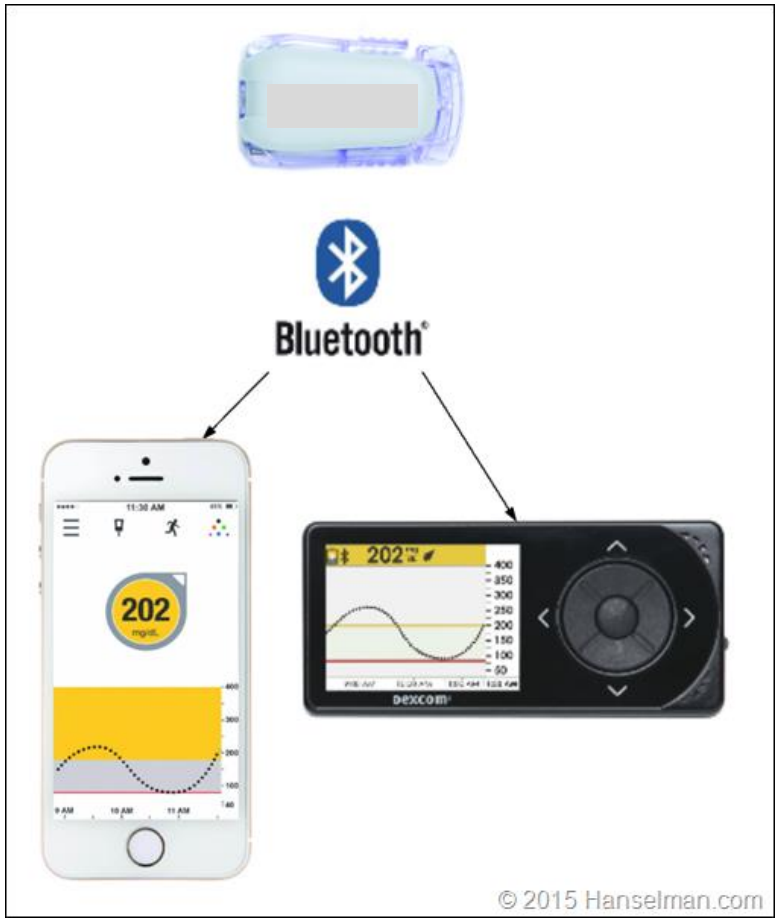
Carlson AL, Mullen DM, Bergenstal RM. Clinical use of continuous glucose monitoring in adults with type 2 diabetes. *Diabetes Technol Ther*. 2017;19(Suppl. 2):S4–S11.

Finger Stick Testing does NOT tell the Whole Story



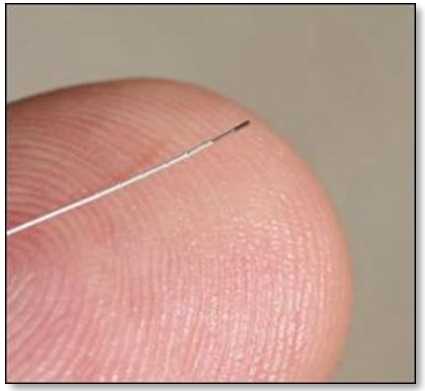
Slide courtesy of Daniel Desalvo, MD
Texas Children's Hospital

Continuous Glucose Monitor



* Body not included.

Continuous glucose Monitor



Sensor + Algorithm

No Calibration Required
10 Day Session Duration
Cannot Restart Sensor Session
Acetaminophen blocking
Intended For Use for Ages 2 and Older

Applicator

Less Painful, Simple, Push Button Sensor Applicator
Tiny Insertion Needle (26Ga)

Transmitter

~30% Thinner
Contoured Wearable
3 Month Life
20 Foot Transmission Range
Built in BLE for Direct Transmission of
CGM data to Receiver and Mobile Device

Receiver

Touchscreen Receiver
NEW Urgent Low Soon Alert
Firmwear upgradable
Customizable Alerts

Apps

Updated Apps:
New Dexcom G6 App
NEW Urgent Low Soon Alert
Upgradable
Clarity

Now available for Medicare

Continuous Glucose Monitor

14 day sensor *iPhone or Android phone for reader*

Continuous glucose monitor

Implantable

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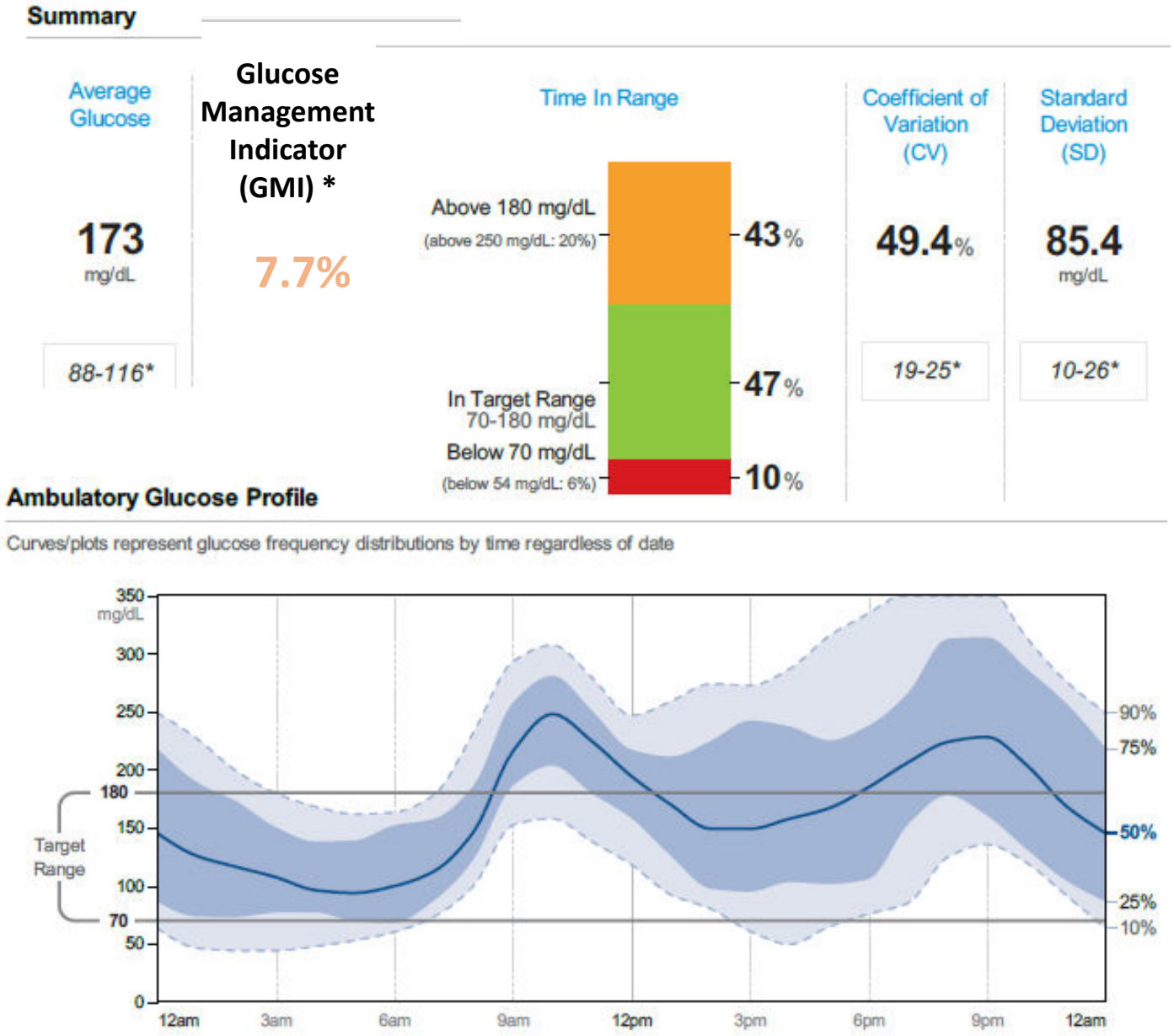

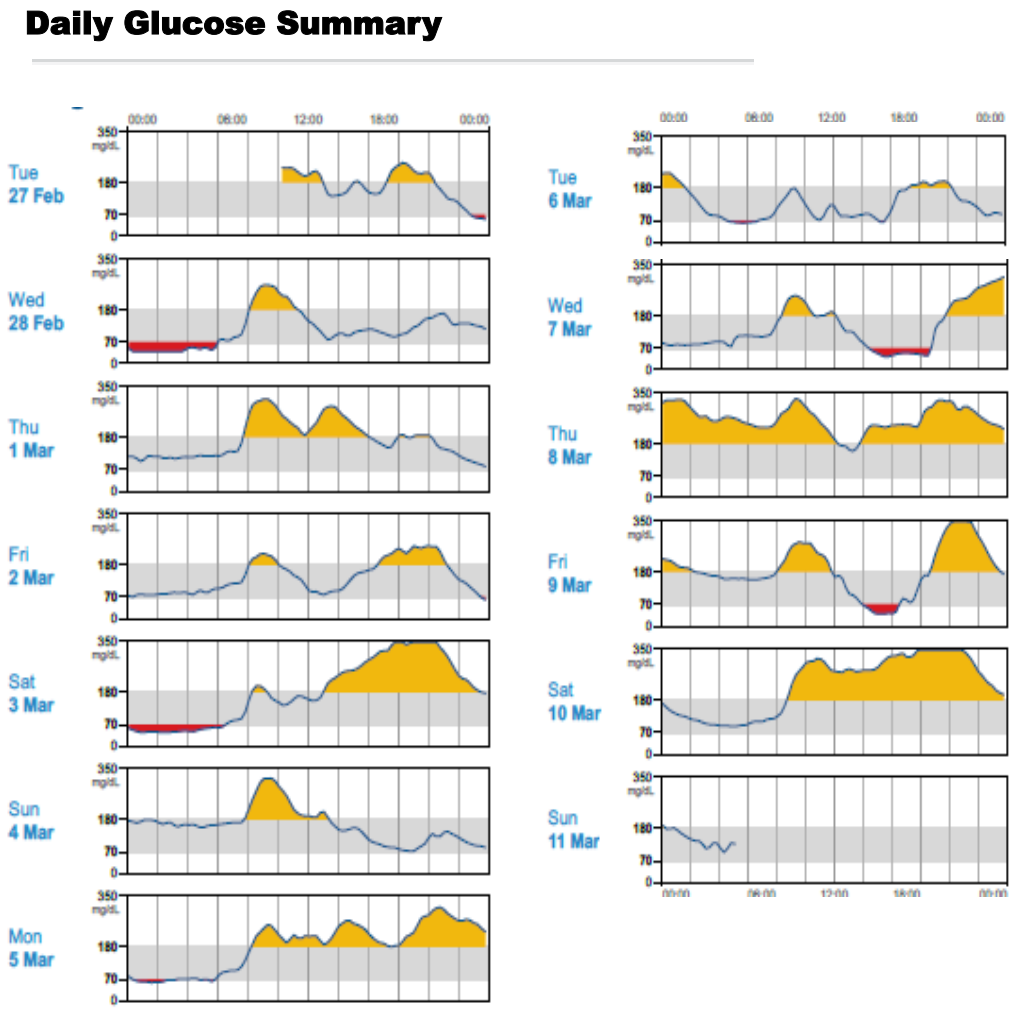

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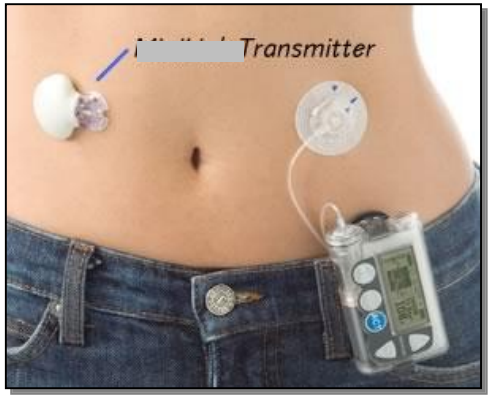
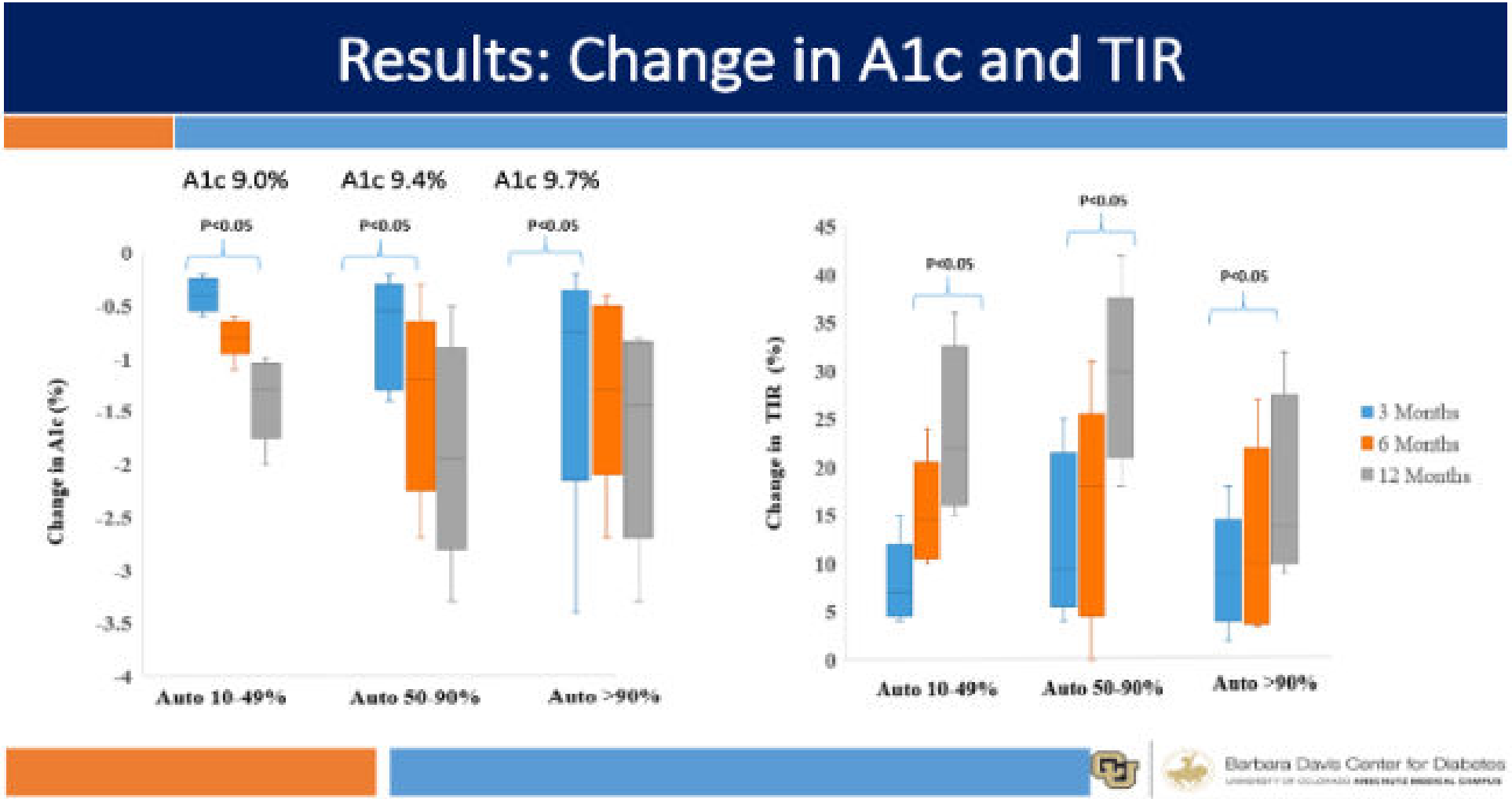
Integrated Insulin Pumps. Insulin and CGM
Automated Insulin Delivery (AID)



Control IQ→ A1C and Time in Range (TIR) *WITHOUT* user initiated bolus



- **Control-IQ was safe across all three cohorts.** There were very few changes in weight, total daily dose, and Time Below Range across all three arms of the study. Time Below Range was ~2% in each cohort, which is below the international consensus target of <4% time spent <70 mg/dL.

Target Population For AID Therapy

- **Strongly consider recommending AID systems to all people with T1D to improve glycemic control**
  - School aged children (7-14 years) (2,3,5,18,42,62-66) **A**
  - Adolescents/ Adults (3,6,67) **A**
- **Consider recommending to:**
  - Older Adults (above 65 years) (2,28,67,68) **B**
  - Preschool children (<7 years) (31,30,54,55,69-72) **B**
  - People with moderate/severe hypoglycemia and hypoglycemia unawareness (73-76) **C**
  - Pregnancy complicated with T1D (56,58,77-80) **C**
  - People with comorbidities: chronic renal failure and gastroparesis (81-83) **C**
- **Consider recommending appropriate AID systems to people with other types of diabetes treated with intensive insulin therapy:**
  - People with type 2 diabetes (58,59) **C**
  - People after pancreatectomy **E**
  - People with cystic fibrosis related diabetes (84, 85) **C**
- Use of AID under supervision should be allowed in hospital settings if not contraindicated by clinical status or treatment needs **E**

ADA evidence-grading system, Diabetes Care. 44, 2021

Summary

- Diabetes treatment can be more specific
  - *"We can now **treat** diabetes, not just **chase blood sugars**"*
- Diabetes medications provide not just glycemic benefit, but cardiovascular, renal and now can treat heart failure.
- Choose medications with lower hypoglycemia risks.
- Discuss hypoglycemia at ***every*** *visit:* ask questions and review glucose data
- New glucagon formulations make treatment easier, faster, safer…
- Monitoring glycemic trends is NOT done with an A1C.

  A1C is the ***OLD*** standard. CGM/TIR is the ***GOLD*** standard