Type 2 Diabetes Management Update:
CGM, Cardiovascular & Renal Risk Management, Oh My!

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Disclosure

Consultant: AstraZeneca; Bayer; Corcept Therapeutics; Diasome; Eli Lilly; Novo Nordisk; Merck; Sanofi

Research Support: Bayer; Novo Nordisk; Merck; Twinhealth

Speaker Bureau: AstraZeneca; Corcept Therapeutics; Merck; Novo Nordisk

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Objectives

- For your patients with T2D, apply the results of landmark diabetes trials that established improved glycemic control reduces the risk of diabetes-related complications
- In patients with T2D and CVD, treat patients using an evidenced-based approach based on the results of CV, HF, and CKD outcome trials
- For your patients with T2D, apply the evolving paradigm by which the treatment of T2D (A1C reduction) has shifted to an outcome-based approach focused on risk reduction, particularly in older patients with established CVD, HF, or CKD
- Review Continuous Glucose Monitors and how they may provide additional information to assist in managing your patients with T2D

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7 Out of 10 Patients with T2D…..

DIE

of

Cardiovascular Causes

Laakso M. J Intern Med 2001; 249: 225– 235.

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CKD and CV Risk

- Patients with CKD are 5X more likely to die from CV causes than develop ESKD

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Reduce CV Risk!

- PCPs manage 90% of patients with T2D
- We need their help to help reduce the risk of adverse CV events and CVD in patients with T2D

Shrivastav M et al. Diabetes Spectrum 2018 Aug; 31(3): 279-287.
Davidson JA et al. Mayo Clin Proc 2010;85(Suppl.12:S3-S4).

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T2D and CV Risk

1) Glycemic control and CV Risk

2) GLP-1RA and CV (and Renal) Risk

3) SGLT-2i and CV (and Renal) Risk

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Which Randomized Controlled Trial Demonstrated Cardiovascular Risk (CV) Reduction with Improved (Intensive) Glycemic Control in Patients with T2D at High CV Risk?

A. ADVANCE
B. ACCORD
C. VADT
D. None of the above

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1) Glycemic Control and CV Risk

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Impact of Intensive Therapy in DM: Summary of Major RCTs

Study	Microvascular		CVD		Mortality	
	RCT	Follow-up	RCT	Follow-up	RCT	Follow-up
DCCT (DM-1) (A1c 7.2 vs. 9.1%)	↓	↓	↔	↓	↔	↓
UKPDS 33 (A1c 7.0 vs. 7.9%)	↓	↓	↔	↓	↔	↓
ACCORD (A1c 6.4% vs. 7.5%)	↓		↔		↑	
ADVANCE (A1c 6.3% vs. 7.0%)	↓		↔	↔	↔	↔
VADT (A1c 6.9% vs. 8.4%)	↓		↔	↔	↔	↔

Kendall DM, Bergenstal RM. ©International Diabetes Center 2009, 2015
UKPDS Group. *Lancet* 1998;352:854; Holman RR. *NEJM* 2008;359:1577; DCCT Group. *NEJM* 1993;329;977; Nathan DM. *NEJM* 2005;353:2643. Gerstein HC. *NEJM* 2008;358:2545; Patel A. *NEJM* 2008;358:2560; Duckworth W. *NEJM* 2009;360:129. (*erratum*:361:1024); DCCT Group. JAMA 2015;313:45; Hayward RA. NEJM 2015;372:2197; Reaven PD. NEJM 2019;380:2215.

RCT: Initial Randomized Controlled Trial
Follow-up: Observational Studies Post RCT

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

FDA NEWS RELEASE

For Immediate Release: Nov. 25, 2013
Media Inquiries: Morgan Liscinsky, 301-796-0397, morgan.liscinsky@hhs.fda.gov
Consumer Inquiries: 888-INFO-FDA, druginfo@fda.hhs.gov

FDA requires removal of certain restrictions on the diabetes drug Avandia

The U.S. Food and Drug Administration today announced it is requiring the removal of certain restrictions on prescribing and use of the diabetes drug Avandia (rosiglitazone) to reflect new information regarding the cardiovascular risk of the medicine. Today's actions are consistent with the recommendations of expert advisory committees.

Results from the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) clinical trial showed no elevated risk of heart attack or death in patients being treated with Avandia when compared to standard-of-care diabetes drugs. These data do not confirm the signal of increased risk of heart attacks that was found in a meta-analysis of clinical trials first reported in 2007.

Nissen SE and Wolski K. N Engl J Med. 2007 Jun 14;356(24

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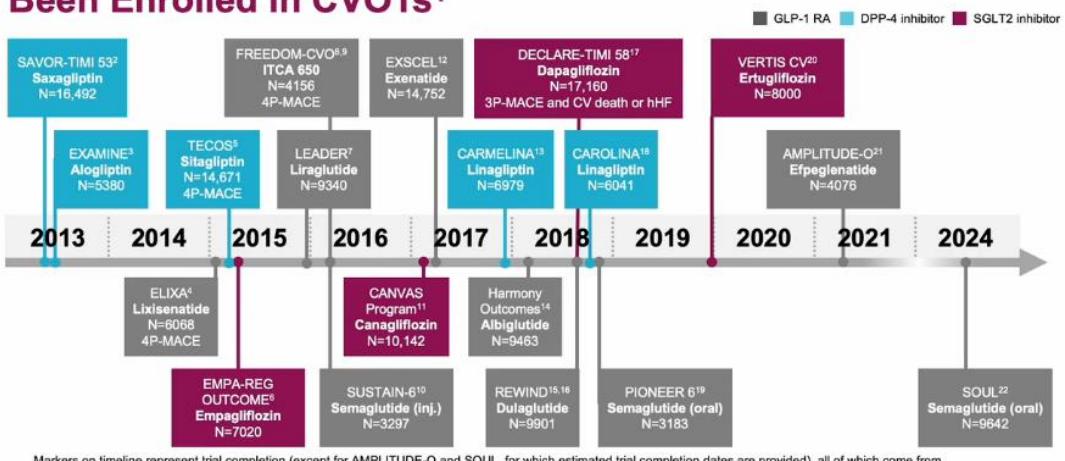
Since the 2008 FDA Mandate, >190,000 Patients Have Been Enrolled in CVOTs[1]



Markers on timeline represent trial completion (except for AMPLITUDE-O and SOUL, for which estimated trial completion dates are provided), all of which come from ClinicalTrials.gov. Primary endpoint is 3P-MACE unless indicated otherwise.
DPP-4=dipeptidyl peptidase-4; FDA=Food and Drug Administration; GLP-1 RA=glucagon-like peptide 1 receptor agonists; MACE=major adverse CV events.
See slide notes for full list of references.

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Question 2

A 62-year-old man presents for management of type 2 diabetes mellitus, which was diagnosed 6 years ago. His hemoglobin A1c has been well controlled on metformin therapy. He was initially only taking 500 mg daily, but the dosage has been slowly titrated to 1000 mg twice daily. His most recent A1C measurement was 6.4% (46 mmol/mol). Coronary artery disease was diagnosed 3 years ago, and he has had 3 coronary artery bypass grafts. He has no symptoms of chest pain, or shortness of breath. He recently underwent transthoracic echocardiography, and his left ventricular ejection fraction was 50%.

He has 45 pack-year history of cigarette smoking, but he quit 3 years ago. He has hypertension and hyperlipidemia controlled with atenolol 50mg once daily, lisinopril/hydrochlorothiazide, 20 mg/12.5 mg once daily, and atorvastatin, 80 mg daily.

Question 2 (Continued)

On physical examination, his blood pressure is 136/78 mm Hg and pulse rate is 66 beats/min. His height is 63 in (160cm), and weight is 176 lb (80 kg) (BMI = 31 kg/m2).

Laboratory Test results:

Total cholesterol = 112 mg/dL
LDL cholesterol = 45 mg/dL (<100 mg/dL) (SI: 1.61 mmol/L [<2.59 mmol/L])
HDL cholesterol = 35 mg/dL (>60 mg/dL) (SI: 0.91 mmol/L [>1.55 mmol/L])
Triglycerides = 105 mg/dL (<150 mg/dL) (SI: 1.63 mmol/L [<1.70 mmol/L])

Estimated glomerular filtration rate = 63 mL/min per 1.73 m2 (>60mL/min per 1.73 m2)

Which of the Following Is the Best Next Step to Reduce this Patient's Cardiovascular Risk?

A. Increase lisinopril
B. Add once weekly subcutaneous semaglutide
C. Add spironolactone
D. Add icosapent ethyl
E. Add ezetimibe

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2) GLP-1RA and CV Risk (and Renal Risk)

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Characteristics of GLP-1RA CVOTs[a,b]

	ELIXA[c]	LEADER[d]	SUSTAIN 6[d]	EXSCEL[d]	HARMONY[d]	REWIND[d]	PIONEER[d]
N	6068	9340	3297	14752	9463	9901	3183
Drug Tested	Lixisenatide 20 mcg/day	Liraglutide 1.8 mg/day	Semaglutide 0.5 or 1 mg/week	Exenatide LAR 2 mg/week	Albiglutide 30 or 50 mg/week	Dulaglutide 1.5 mg/week	Semaglutide (oral) 14 mg
Prior CVD	100%	81%	83%	73%	100%	31%	85%
Mean Age	60 y	64 y	54 y	62 y	64 y	66 y	66 y
Women	30%	36%	39%	38%	31%	46%	32%
Median F/U	2.1 y	3.8 y	2.1 y	3.2 y	1.6 y	5.4 y	1.3 y
DM Duration	9.2 y	12.8 y	13.9 y	13.1 y	14.2 y	10.5 y	14.9 y
Baseline A1c	7.7%	8.7%	8.7%	8.1%	8.8%	7.3%	8.2%
Baseline eGFR	76	~75	~75	76	79	77	74
Insulin Use	39%	45%	58%	46%	59%	24%	61%

[a]Definitions of CV disease vary by study, making cross-trial comparisons difficult
[b]Only data form published articles are included
[c]MACE[4]: nonfatal MI, nonfatal stroke, hospitalization for angina or unstable angina, or CV death
[d]MACE[3]: nonfatal MI, nonfatal stroke, or CV death

Pfeffer MA et al. N Engl J Med 2015; 373:2247-2257.
Marso SP et al. N Engl J Med. 2016 Jul 28;375(4):311-22.
Marso SP et al. N Engl J Med. 2016 Nov 10;375(19):1834-1844.
Holman RR et al. N Engl J Med. 2017 Sep 28;377(13):1228-1239.
Hernandez AF et al. Lancet. 2018 Oct 27;392(10157):1519-1529.
Gerstein HC et al Lancet. 2019 Jul 13;394(10193):121-130.
Husain M et al. N Engl J Med 2019; 381:841-851.

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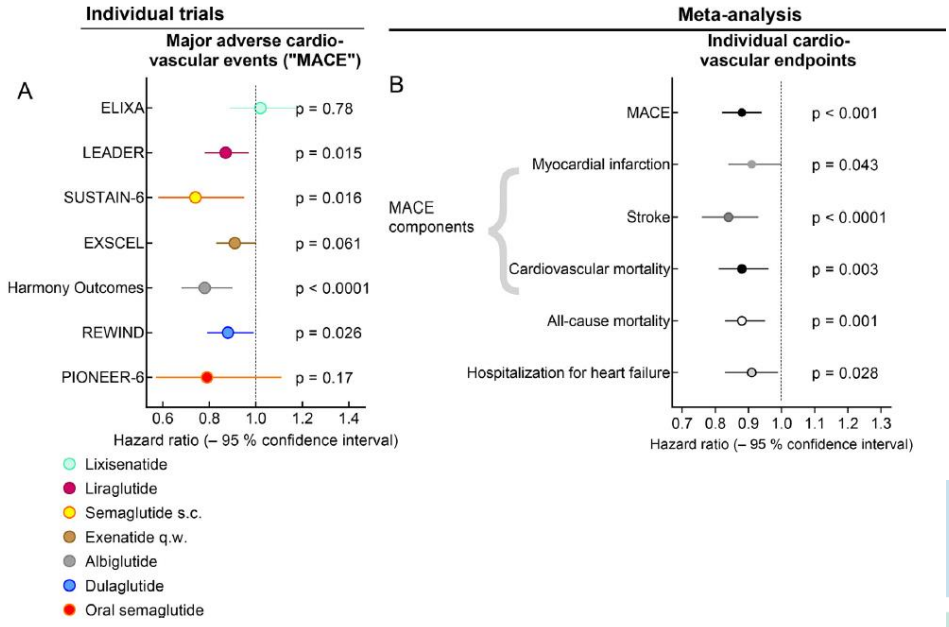

Nauck MA et al. Mol Metab. 2021 Apr;46:101102.

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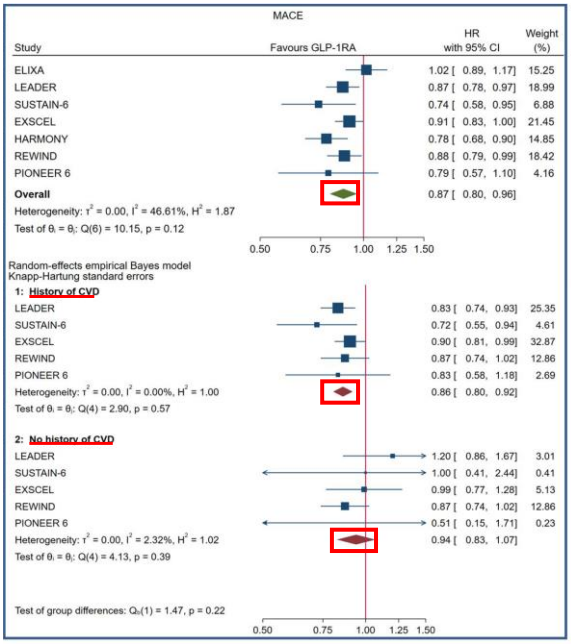

Giugliano D et al. Diabetes Obes Metab. 2019 Nov;21(11):2576-2580.

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GLP-1RA and Renal Benefit?

Table 1
CV and kidney outcomes of GLP1-RA CVOT trials.

Trial	Drug	Population	CV outcomes	Kidney outcomes
ELIXA	lixisenatide	Patients with T2D and recent MI or unstable angina	Noninferior to placebo for primary end point including CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina	Reduced risk of developing macroalbuminuria
LEADER	liraglutide	Patients with T2D and high CV risk	• Reduced risk of 3-point MACE[a] • Reduced risk of CV death • Reduced risk of all-cause mortality	Reduced risk of composite kidney outcome[b]
SUSTAIN-6	subcutaneous semaglutide	Patients with T2D and CVD, chronic heart failure, or CKD with a CV risk factor	• Reduced risk of 3-point MACE[a] • Reduced risk of non-fatal stroke	Reduced risk of composite kidney outcome[c]
PIONEER 6	oral semaglutide	Patients ≥50 years old with CVD or CKD, patients ≥60 years old with CV risk factors	• Reduced risk of CV death • Reduced risk of all-cause mortality	Not available
EXSCEL	exenatide	Patients with T2D with or without CVD	Noninferior to placebo for primary end point including CV death, non-fatal MI, non-fatal stroke	Reduced risk of composite kidney outcome[d]
Harmony Outcomes	albiglutide	Patients ≥40 years old with CVD	• Reduced risk of 3-point MACE[a] • Reduced risk of fatal or non-fatal MI	Not available
REWIND	dulaglutide	Patients ≥50 years old with T2D and CVD or CV risk factors	• Reduced risk of 3-point MACE[a] • Reduced risk of non-fatal stroke	Reduced risk of composite kidney outcome[e] Reduced risk of worsening kidney function
AMPLITUDE-O	efpeglenatide	Patients with T2D and CVD or CKD	• Reduced risk of 3-point MACE[a] • Reduced risk of fatal or non-fatal MI • Reduced risk of hospital admission for heart failure	Reduced risk of composite kidney outcome[f]

CV, cardiovascular; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiac events; MI, myocardial infarction; T2D, type 2 diabetes.
[a] Three-point MACE was comprised of CV death, MI, and stroke.
[b] Composite kidney outcome was comprised of development of macroalbuminuria, doubling of serum creatinine or an eGFR of ≤40 mL/min/1.73 m², kidney replacement therapy, or death due to kidney disease.
[c] Composite kidney outcome was comprised of persistent macroalbuminuria, doubling of serum creatinine or an eGFR of ≤45 mL/min/1.73 m², or kidney replacement therapy.
[d] Composite kidney outcomes included kidney replacement therapy or death due to kidney disease.
[e] Composite kidney outcome included development of macroalbuminuria, a sustained ≥30% decline in eGFR, or kidney replacement therapy.
[f] Composite kidney outcome included development of macroalbuminuria, increase in albumin-to-creatinine ratio of >30%, a sustained ≥40% decline in eGFR, end-stage kidney disease, or death due to any cause.

Michos ED et al. American Journal of Preventive Cardiology 14 (2023) 100502.

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Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes The Flow Trial

- Randomly assigned patients with type 2 diabetes and chronic kidney disease (defined by an estimated glomerular filtration rate [eGFR] of 50 to 75 ml per minute per 1.73 m2 of body-surface area and a urinary albumin-to-creatinine ratio [with albumin measured in milligrams and creatinine measured in grams] of >300 and <5000 or an eGFR of 25 to <50 ml per minute per 1.73 m2 and a urinary albumin-to-creatinine ratio of >100 and <5000) to receive subcutaneous semaglutide at a dose of 1.0 mg weekly or placebo.
- The primary outcome was major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes.
- Prespecified confirmatory secondary outcomes were tested hierarchically.

Perkovic V et al. NEJM 2024 Jul 11;391(2):109-121. doi: 10.1056/NEJMoa2403347. Epub 2024 May 24.

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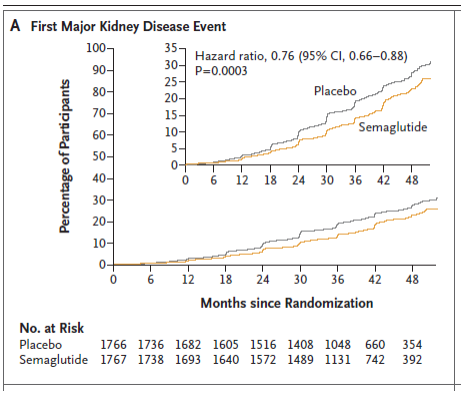
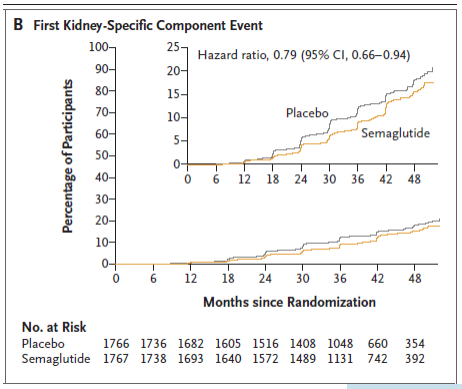
The Flow Trial

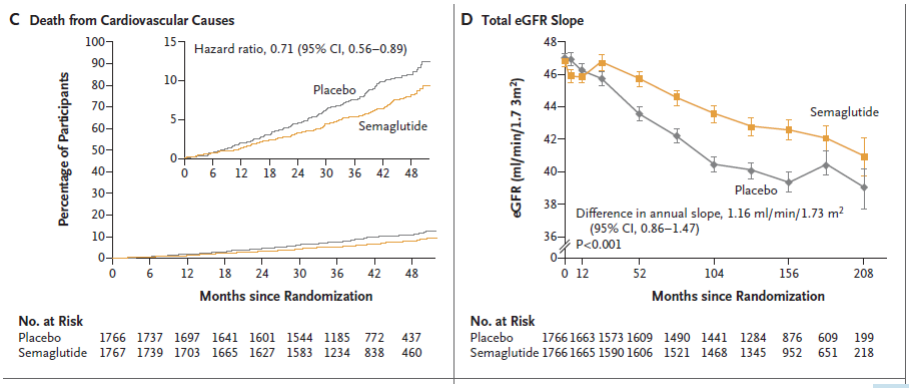




Perkovic V et al. NEJM 2024 Jul 11;391(2):109-121. doi: 10.1056/NEJMoa2403347. Epub 2024 May 24.

22

The Flow Trial



CONCLUSIONS

Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease.

Perkovic V et al. NEJM 2024 Jul 11;391(2):109-121. doi: 10.1056/NEJMoa2403347. Epub 2024 May 24.

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3) CV (and Renal) Risk Reduction and SGLT-2i

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Baseline characteristics of patient populations by trial

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]	CREDENCE[4]	VERTIS CV
SGLT2 inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
N	7020	10,142	17,160	4401	8246
Duration of follow-up, median, years	3.1	2.4	4.2	2.6	3.0
Age, mean ± SD, years	63.1 ± 8.6	63.3 ± 8.3	63.9 ± 6.8	63.0 ± 9.2	64.4 ± 8.1
Female, %	28.5	35.8	37.4	33.9	30.0
HbA1c, mean ± SD, %	8.1 ± 0.8	8.2 ± 0.9	8.3 ± 1.2	8.3 ± 1.3	8.2 ± 1.0
Diabetes duration, mean ± SD, years	NA	13.5 ± 7.8	11.8 ± 7.8	15.8 ± 8.6	13.0 ± 8.3
Established CV disease, %	100	65.6	40.6	50.4	100
History of HF, %	10.1	14.4	10.0	14.8	23.7
Reduced kidney function (eGFR <60 mL/min/1.73 m^2), %	25.9	20.1	7.4	59.8	21.9

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; NA, not available; SD, standard deviation.
1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657. 3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.
4. Perkovic V et al. *N Engl J Med* 2019; 380:2295-306.

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SGLT-2i Landmark CVOT Summary in T2D

	EMPA-REG[16] (empagliflozin vs placebo, n=7020)	DECLARE-TIMI[9] (dapagliflozin vs placebo, n=17 160)	CANVAS[15] (canagliflozin vs placebo, n=10 142)	VERTIS[41] (ertugliflozin vs placebo, n=8246)
Main inclusion criteria	Established cardiovascular disease, eGFR >30 mL per min per 1·73 m^2	Established cardiovascular disease (40·6%) or multiple cardiovascular risk factors (59·4%)	Established cardiovascular disease	Aged older than 40 years, established cardiovascular disease
Key cardiovascular outcome: major adverse cardiovascular events				
Placebo	43·9	24·2	31·5	40·0
SGLT2 inhibitor	37·4	22·6	26·9	39·0
HR (95% CI)	0·86 (0·74–0·99)	0·93 (0·84–1·03)	0·86 (0·75–0·97)	0·97 (0·85–1·11)
Key cardiovascular outcome: cardiovascular death				
Placebo	20·2	7·1	12·8	19
SGLT2 inhibitor	12·4	7·0	11·6	18
HR (95% CI)	0·62 (0·49–0·77)	0·98 (0·82–1·17)	0·87 (0·72–1·06)	0·92 (0·77–1·11)
Key cardiovascular outcome: cardiovascular death or admission to hospital for heart failure				
Placebo	30·1	14·7	20·8	27·0
SGLT2 inhibitor	19·7	12·2	16·3	23·0
HR (95% CI)	0·66 (0·55–0·79)	0·83 (0·73–0·95)	0·78 (0·67–0·91)	0·88 (0·75–1·03)
Key cardiovascular outcome: all-cause mortality				
Placebo	28·6	16·4	19·5	26·0
SGLT2 inhibitor	19·4	15·1	17·3	24·0
HR (95% CI)	0·68 (0·57–0·82)	0·93 (0·82–1·04)	0·87 (0·74–1·01)	0·93 (0·80–1·08)
Key cardiovascular outcome: admission to hospital for heart failure				
Placebo	14·5	8·5	8·7	11·0
SGLT2 inhibitor	9·4	6·2	5·5	7·0
HR (95% CI)	0·65 (0·50–0·85)	0·73 (0·61–0·88)	0·67 (0·52–0·87)	0·70 (0·54–0·90)
Key cardiovascular outcome: myocardial infarction				
Placebo	19·3	13·2	12·6	17·0
SGLT2 inhibitor	16·8	11·7	11·2	18·0
HR (95% CI)	0·87 (0·70–1·09)	0·89 (0·77–1·01)	0·89 (0·73–1·09)	1·04 (0·86–1·26)
Key cardiovascular outcome: stroke				
Placebo	10·5	6·8	9·6	9·0
SGLT2 inhibitor	12·3	6·9	7·9	10·0
HR (95% CI)	1·18 (0·89–1·56)	1·01 (0·84–1·21)	0·87 (0·69–1·09)	1·06 (0·82–1·37)

Brown E et al. The Lancet 2021;398.10296(2021):262-276.

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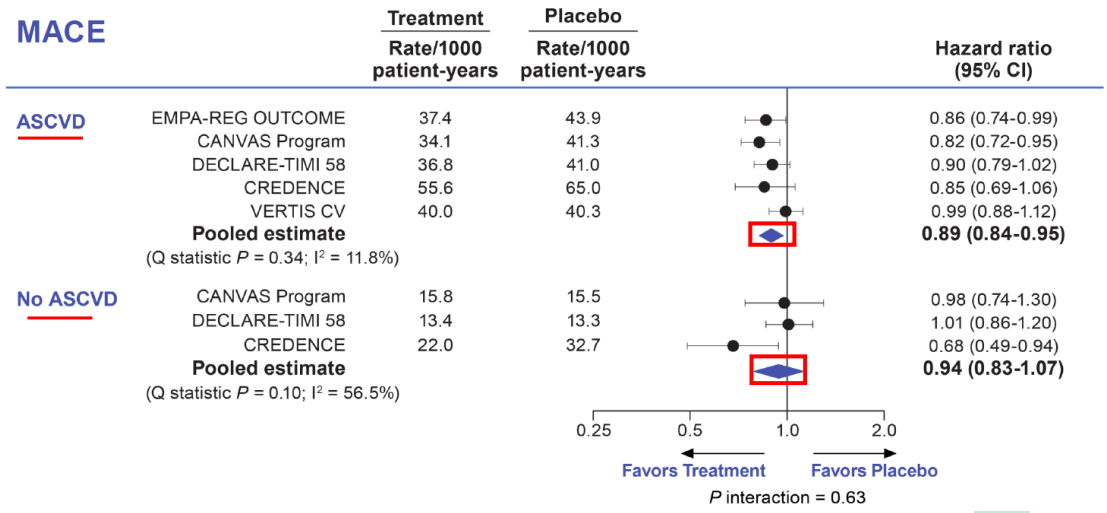
Time to first MACE – subgroup analysis by ASCVD



https://www.acc.org/latest-in-cardiology/clinical-trials/2020/06/16/11/24/vertis

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SGLT-2i and HF

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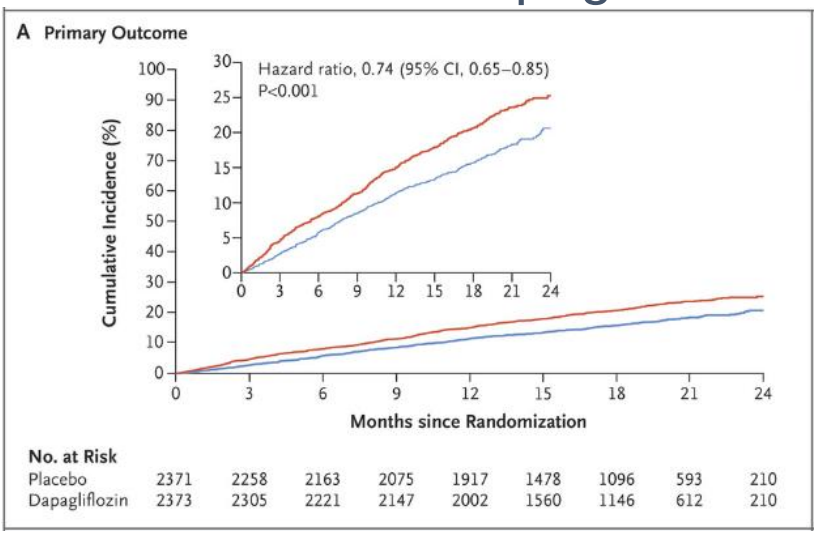
DAPA-HF*
Dapagliflozin



Primary Outcome:
Composite of worsening heart failure or death from cardiovascular causes

Primary Endpoint
Without T2D:HR 0.73, 95% CI 0.60-0.88
With T2D: HR 0.75, 95% CI 0.63-0.85

McMurray J et al. N Engl J Med. 2019 Nov 21;381(21):1995-2008.

*Included patients with and without T2D

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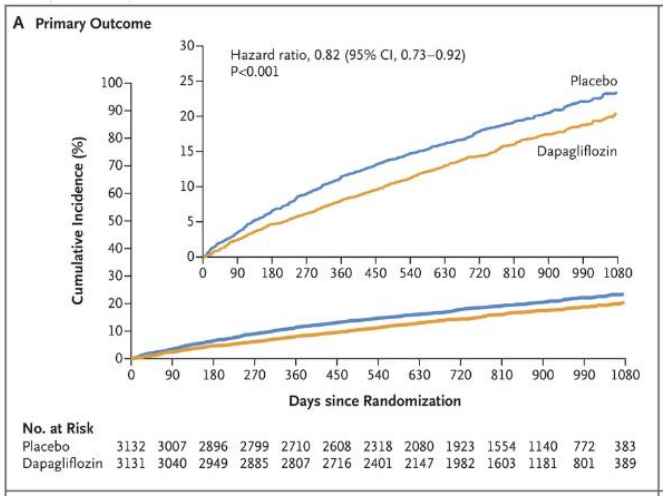
DELIVER*
Dapagliflozin



- Reduction in risk of CV death or worsening heart failure
- Patients with mildly reduced or preserved EF (HFpEF)

Soloman SD et al. N Engl J Med August 27, 2022. E pub ahead of print

*Included patients with and without T2D

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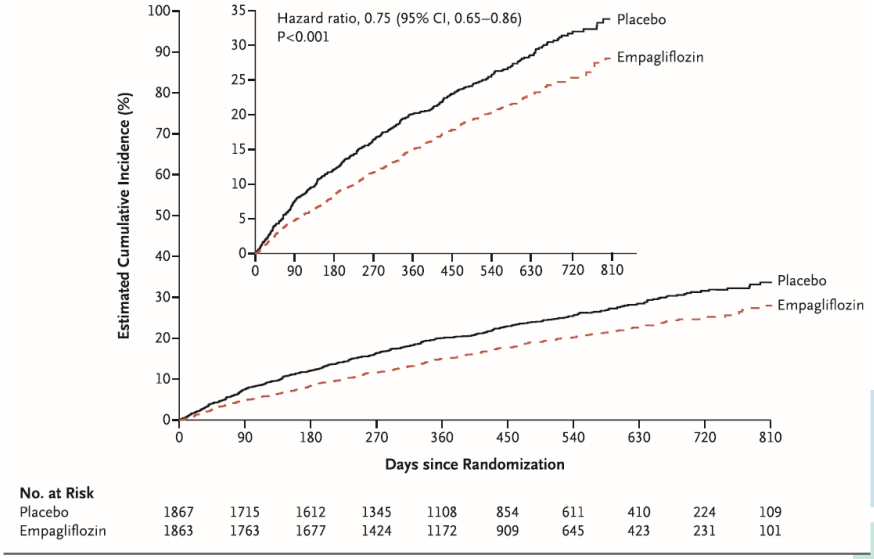
EMPEROR-Reduced*

Primary Outcome: Composite of CV death or hospitalization for heart failure



Packer M et al. N Engl J Med 2020; 383:1413-1424.

***Included patients with and without T2D**

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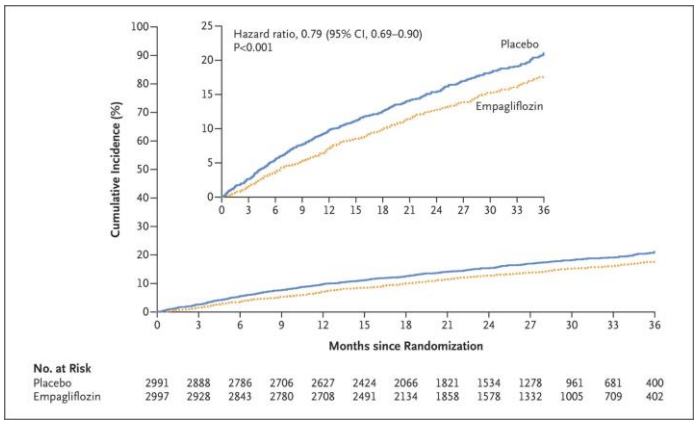
EMPEROR-Preserved*

The Primary Outcome Was a Composite of CV Death or Hospitalization for Heart Failure



Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes

Anker SD et al. N Engl J Med 2021; 385:1451-1461.

*Included patients with and without T2D

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Question 3

A 59-year-old man returns for continued management o ftype 2 diabetes mellitus, which was diagnosed 15 years ago. He was initially treated with oral agents, but he has been receiving insulin therapy for the past 5 years. He currently takes metformin, 1000 mg twice daily, and administers 20 units of insulin aspart before meals (3 times daily) in addition to 40 units of insulin degludec at bedtime. His hemoglobin A1C level has ranged from 7.0% to 9.0% (53-75 mmol/mol) over the past few years, and his most recent hemoglobin A1C measurements was 8.4% (68 mmol/mol)

He has a history of coronary artery disease and had 2 coronary drug eluting stents placed 2 years ago for recurrent angina, which has since resolved. He has chronic kidney disease and macroalbuminuria. He notes peripheral neuropathy that is well controlled with pregabalin. He also has hypertension and hyperlipidemia. His current medications are aspirin; clopidogrel; metoprolol; lisinopril, 20 mg daily; chlorthalidone; and rosuvastatin.

Question 3 (Continued)

On physical examination, his height is 68 in (172.7 cm) and weight is 225 lb (102.3 kg) (BMI = 34 kg/m2). His blood pressure is 136/82 mm Hg, and pulse rate is 74 beats/min. He has 1+ pitting edema in the bilateral lower extremities. His lungs are clear on auscultation, and his heart has a regular rate and rhythm with no audible murmur. There is decreased sensation to 10-g monofilament testing on the distal plantar aspect of his feet bilaterally.

Laboratory test results:

Electrolytes, normal

Creatinine = 1.5 mg/dL (0.7-1.3 mg/dL) (SI: 132.6 µmol/L [61.9-114.9 µmol/L])

Estimated glomerular filtration rate = 50 mL/min per 1.73 m2 (>60 mL/min per 1.73 m2)

Hemoglobin A1C = 8.4% (4.0%-5.6%) (68 mmol/mol [20-38 mmol/mol])

Albumin-to-creatinine ratio = 520 mg/g creat (<30 mg/g creat)

Which of the Following Is The Best Next Step in This Patient's Treatment?

A. Start liraglutide
B. Start aliskiren
C. Start pioglitazone
D. Start canagliflozin
E. Start losartan

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SGLT-2i and CKD

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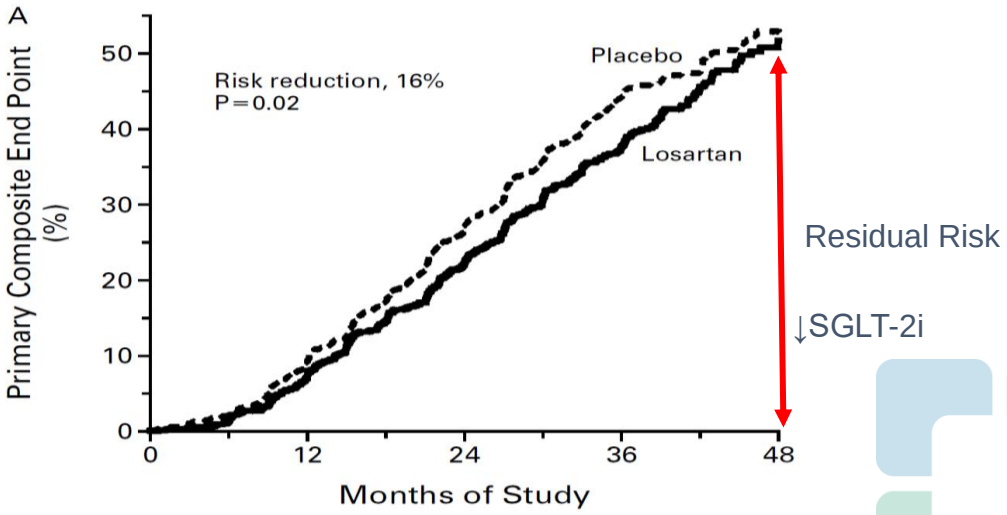
Effects of Losartan on Renal and Cardiovascular Outcomes in T2D with Nephropathy (RENAAL)

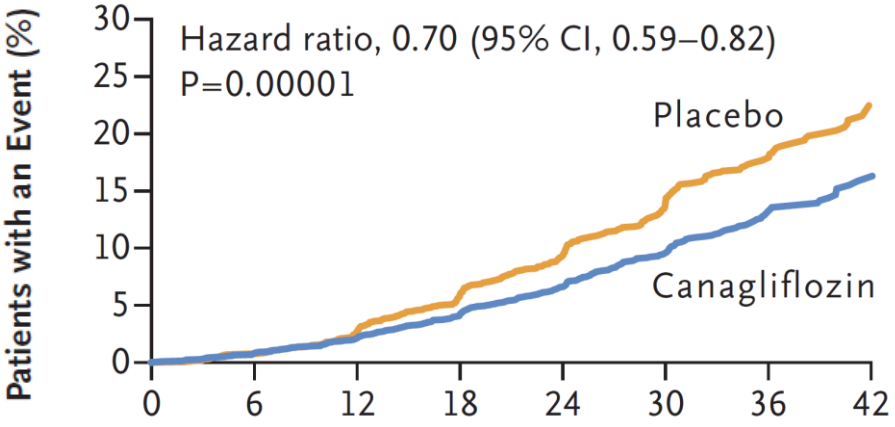


Brenner BM et al. NEJM 2001;345(12):861-9.

37

CREDENCE-Renal Outcomes*

Primary Outcome: ESKD, Doubling of Serum Cr, Renal Death, CV Death



All patients had T2D, eGFR 30-90 mL/min/1.73m^2 and urinary albumin:Cr > 300 to 5000 mg/g, and were treated with renin-angiotensin system blockade (ACE/ARB)

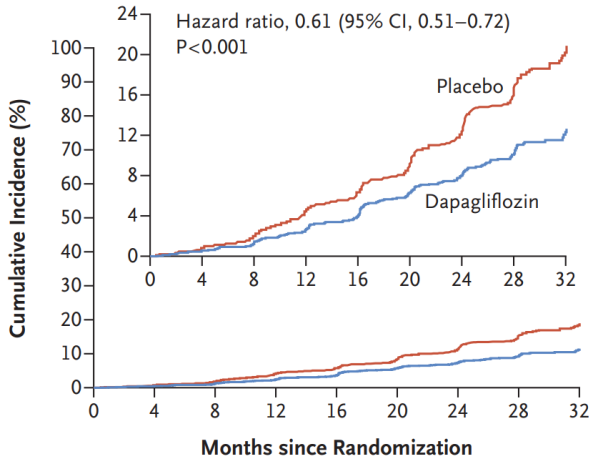
Perkovic V et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.

* Included only patients with T2D

38

DAPA-CKD*

A Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death



All patients had eGFR 25-75 mL/min/1.73m^2 and urinary albumin:Cr ratio > 200 to 5000 mg/g

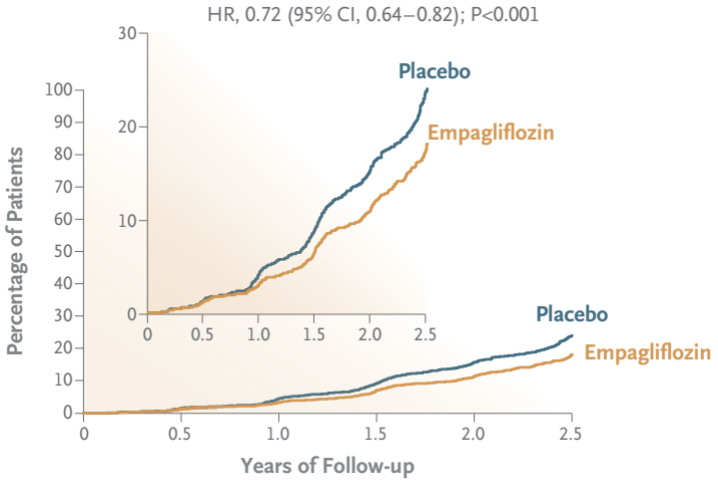
Heerspink HJL et al. N Engl J Med 2020; 383:1436-1446.

*Included patients with and without T2D

39

EMPA-Kidney*

Primary Outcome: ESKD (Sustained eGFR <10 mL/min/1.73 m^2), Sustained of ≥40% eGFR, Renal or CV Death



All patients had eGFR 20-45 mL/min/ 1.73m^{2}eGFR or of 45 but less than 90 mL/min 1.73 m^2 and urinary alb:Cr ratio of at least 200 mg/g

Empa-Kidney Collaborative Group. 2023 Jan 12;388(2):117-127.

*Included patients with and without T2D

40

SGLT-2i Landmark Trial Summary

Trial	Year Published	Treatment (s)	Primary or Secondary End-Point	Composite Kidney Outcome	Hazard Ratio (95% CI)
EMPA-REG OUTCOME [24]	2015	Empagliflozin vs. placebo	Secondary	Doubling of serum creatinine, initiation of kidney replacement therapy or death from renal disease	0.54 (0.40–0.75)
CANVAS [25]	2017	Canagliflozin vs. placebo	Secondary	Sustained 40% reduction in eGFR, need for kidney replacement therapy, or death from renal cause	0.6 (0.47–0.77)
CREDENCE [26]	2019	Canagliflozin vs. placebo	Primary	End-stage kidney disease, doubling of the serum creatinine level, or death from renal or cardiovascular causes	0.70 (0.59– 0.82)
DECLARE-TIMI [27]	2019	Dapagliflozin vs. placebo	Secondary	Sustained ≥40% reduction in eGFR to <60 mL/min/1.73 m^2, new end-stage kidney disease or death from renal cause	0.53 (0.43–0.66)
DAPA-CKD [28]	2020	Dapagliflozin vs. placebo	Primary	Sustained ≥50% reduction in eGFR, end-stage kidney disease, or death from renal or cardiovascular cause	0.61 (0.51–0.72)
EMPEROR-Reduced [29]	2020	Empagliflozin vs. placebo	Secondary	Sustained ≥40% reduction in eGFR, chronic dialysis, renal transplant or sustained eGFR < 10–15 mL/min/1.73 m^2	0.50 (0.32–0.77)
EMPA-KIDNEY	2022	Empagliflozin vs. placebo	Primary	End-stage kidney disease, a sustained reduction in eGFR to <10 mL/min/1.73 m^2, renal death, or a sustained decline of ≥40% in eGFR	0.72 (0.64 to 0.82)

Sawaf H et al. J Clin Med 2022;11(2):378. Empa-Kidney Collaborative Group. 2023 Jan 12;388(2):117-127.

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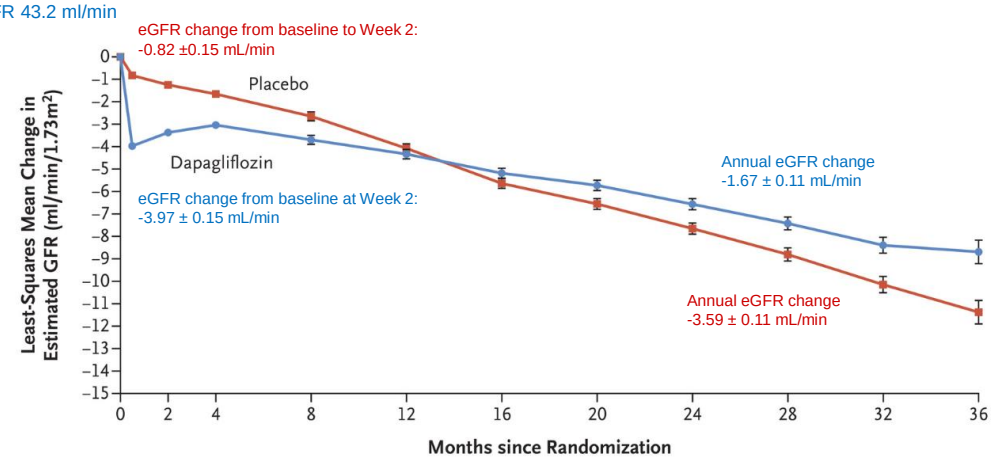
Baseline

Placebo eGFR 43.0 ml/min

Dapagliflozin eGFR 43.2 ml/min



No. of Participants

Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157
Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157

Heerspink HJL et al. N Engl J Med 2020; 383:1436-1446.

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GLP-1RA and SGLT-2i

Additional Benefits and Risks

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GLP-1RA Therapy

- Benefits
  - Weight loss
  - Low (no) risk of hypoglycemia
  - Improved glycemic control
  - Reduction in systolic BP
  - Reduce CV risk (MACE)
    - FDA Approved Labels of liraglutide, sc semaglutide, dulaglutide in patients with established CVD
    - Dulaglutide (primary and secondary prevention)
  - Kidney protection, FLOW Study (sc semaglutide)-Awaiting full results
  - ? In-vivo increase B-cell growth/replication

- Side Effects/Adverse Reactions/Warnings
  - Nausea, vomiting, diarrhea, injection site reactions
  - Acute pancreatitis
  - Thyroid C-cell tumors, including medullary thyroid carcinoma (MTC)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022341s027lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125469s033lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209637s003lbl.pdf

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GIP/GLP-1RA Receptor Agonist Tirzepatide

- Similar side effect profile to GLP-1RA
  - Tolerability is slightly lower, but patient specific
  - Generally greater A1C reductions and weight loss vs. GLP-1RA
- CVOT in process (SURPASS-CVOT)

Dutta P et al. Cureus. 2023 May; 15(5): e38379.
Chavda VP et al. Molecules. 2022 Jul; 27(13): 4315.
Nicholls SJ et al. Am Heart J 2024 Jan:267:1-11.

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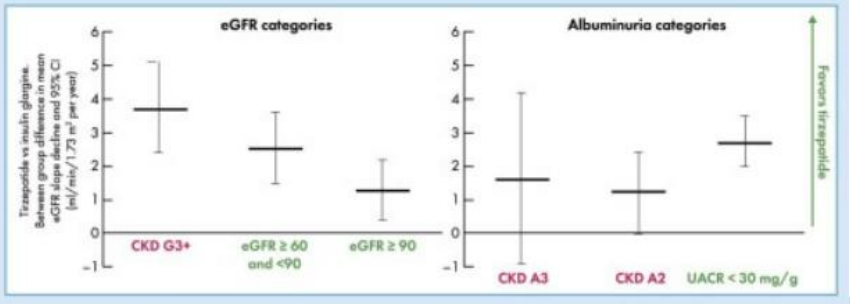
Post-hoc Renal Outcomes Tirzepatide

In SURPASS-4 post-hoc analyses, tirzepatide offered kidney protection as compared with insulin glargine for T2DM participants with CKD and also for participants with eGFR G1–G2 or with albuminuria A1



Bosch C et al. Clin Kidney J. 2023 May; 16(5): 797–808.
Heerspink HJL. Lancet Diabetes Endocrinol 2022;10:774–85.
Del Prato S et al. Lancet North Am Ed 2021;398:1811–24.

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SGLT-2 Inhibitors

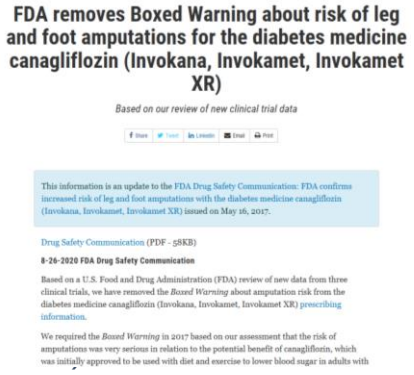
- Benefits
  - Weight loss
  - Low (no) risk of hypoglycemia
  - Improved Glycemic control
  - Reduction in systolic BP (~ 5 mmHg)
  - Renal risk reduction
  - CV risk reduction (CVD and HF)

Zinman B et al. N Engl J Med. 2015 ;373(22):2117-2128.
Neal B et al N Eng J Med. N Engl J Med 2017; 377:644-657.
Wiviott SD et al. N Engl J Med. 2019 Jan 24;380(4):347-357.
https://www.acc.org/latest-in-cardiology/clinical-trials/2020/06/16/11/24/vertis

McMurray J et al. N Engl J Med. 2019 Nov 21;381(21):1995-2008.
Percovik V et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.
https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-type-heart-failure

SGLT-2 Inhibitors

- Risks/Negatives
  - Slight increase in LDL cholesterol
  - Hypotension
    - Intravascular volume contraction
  - UTIs, genital mycotic infections
  - Fournier's gangrene (???)
  - Bladder Cancer (???) Breast Cancer (???)
  - Increase risk of DKA
  - Bone loss and increase in fracture risk (Canagli
  - Amputations (Canagliflozin ????)
  - Retinal Vein Occlusion (???)



FDA removes Boxed Warning about risk of leg and foot amputations for the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR)

Based on our review of new clinical trial data

This information is an update to the FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) issued on May 16, 2017.

Drug Safety Communication (PDF - 58KB)

8-26-2020 FDA Drug Safety Communication

Based on a U.S. Food and Drug Administration (FDA) review of new data from three clinical trials, we have removed the *Boxed Warning* about amputation risk from the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) prescribing information.

We required the *Boxed Warning* in 2017 based on our assessment that the risk of amputations was very serious in relation to the potential benefit of canagliflozin, which was initially approved to be used with diet and exercise to lower blood sugar in adults with

Zinman B et al. N Engl J Med. 2015 ;373(22):2117-2128.
Neal B et al N Eng J Med. N Engl J Med 2017; 377:644-657.
Wiviott SD et al. N Engl J Med. 2019 Jan 24;380(4):347-357.
https://www.acc.org/latest-in-cardiology/clinical-trials/2020/06/16/11/24/vertis

McMurray J et al. N Engl J Med. 2019 Nov 21;381(21):1995-2008.
Percovik V et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.
https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-type-heart-failure
https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin

Summary: SGLT-2 Inhibitors

- **Renal Risk Reduction/Kidney Protection**
  - Canagliflozin-reduction in risk of ESKD, doubling of serum Cr, CV death, and hospitalization for heart failure (hHF) in adults with T2D and diabetic nephropathy, albuminuria > 300 mg/day
  - Dapagliflozin-to reduce the risk of sustained eGFR decline, end stage kidney disease cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease at risk of progression
  - Empagliflozin-to reduce the risk of sustained decline in eGFR, ESKD, CV death and hospitalization in adults with chronic kidney disease at risk of progression
- **CV Risk Reduction**
  - Reduction in CV death risk (Empagliflozin)
  - Reduction in CV events: CV death, nonfatal MI, nonfatal stroke (Canagliflozin)
  - Reduction in hHF (Dapagliflozin): Primary and secondary prevention
  - Reduction in CV death and hHF in patients with HFrEF or HFpEF with dapagliflozin
    - With or without diabetes
  - Reduction in hHF and CV death in patients with HFrEF or HFpEF with empagliflozin
    - With or without diabetes

Zinman B et al. N Engl J Med. 2015 ;373(22):2117-2128.
Neal B et al N Eng J Med. N Engl J Med 2017; 377:644-657.
Wiviott SD et al. N Engl J Med. 2018 Nov 10.
Anker SD et al. N Engl J Med 2021; 385:1451-1461.
McMurray J et al. N Engl J Med. 2019 Nov 21;381(21):1995-2008.
Percovik V et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.
Packer M et al. N Engl J Med 2020; 383:1413-1424.
Heerspink HJL et al. N Engl J Med 2020; 383:1436-1446.
Soloman SD et al. N Engl J Med August, 2022. E pub ahead of print
EMPA-KIDNEY Collaborative Group. N Engl J Med. November 2022. Epub ahead of print.

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How Have the CV, Renal, and HF Benefits with GLP-1RA and SGLT-2i Therapy Changed Guidelines?

50

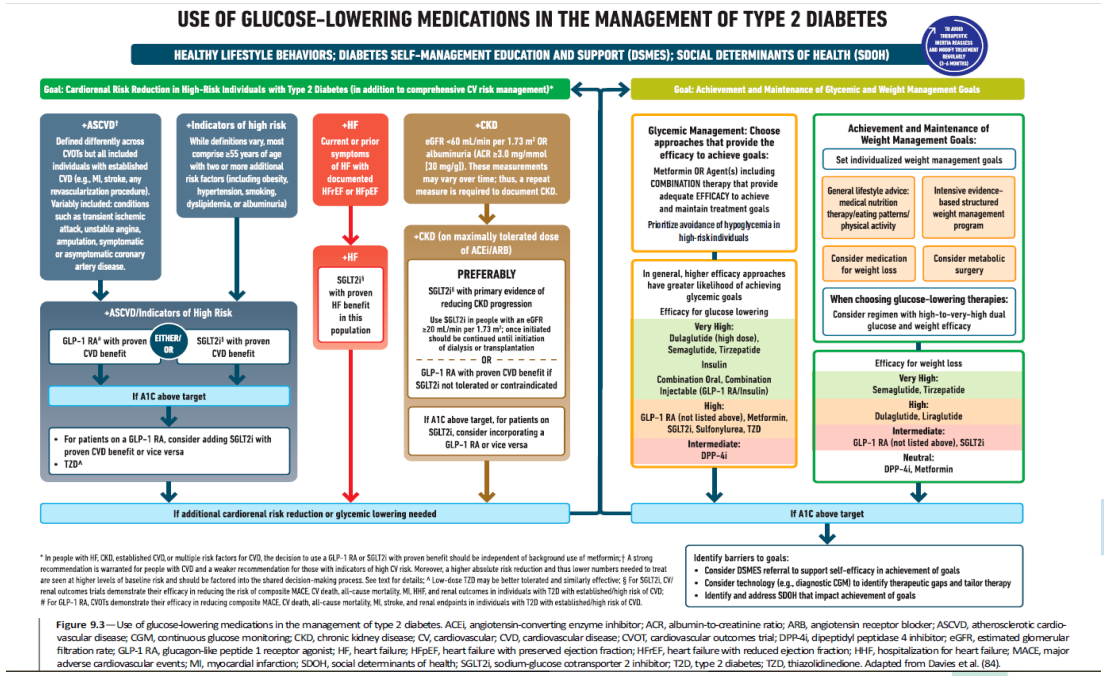

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (84).

American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2024. Diabetes Care 2024;47 (Suppl. 1):S158–S178.

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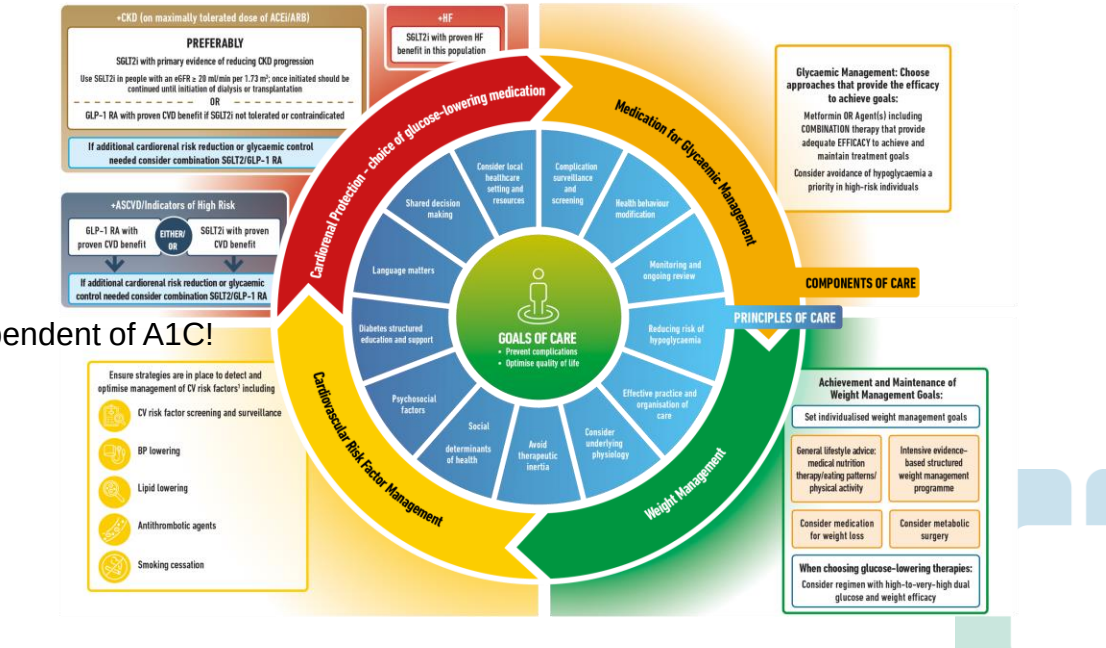

Independent of A1C!

American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2024. Diabetes Care 2024;47 (Suppl. 1):S158–S178.

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Glycemic Control Is Still Important!

- HbA1c: average glycemia during the past 3 months
- Continuous glucose monitors provide real-time feedback to patients in terms of their BG control, and often pick up more detailed information regarding overall BG control, via Time-in-Range, than the HbA1c alone

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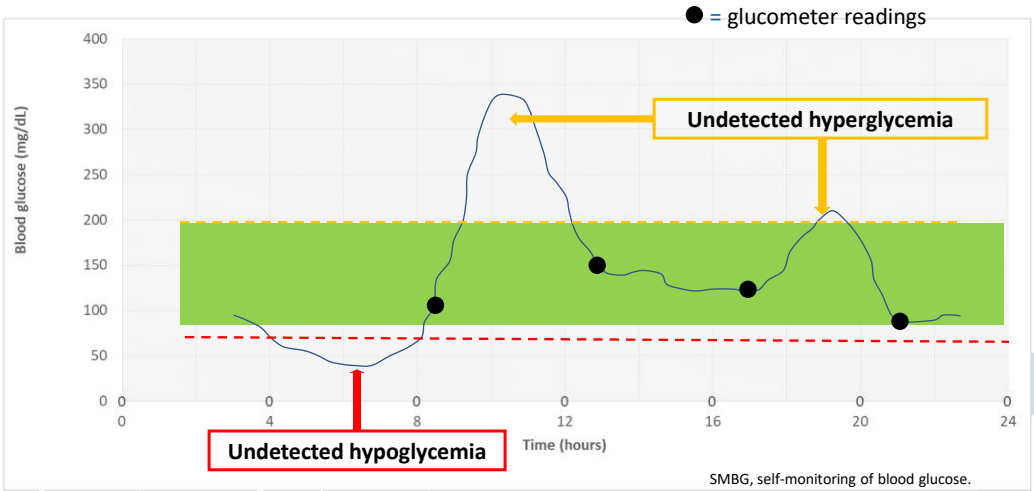
BGM vs CGM



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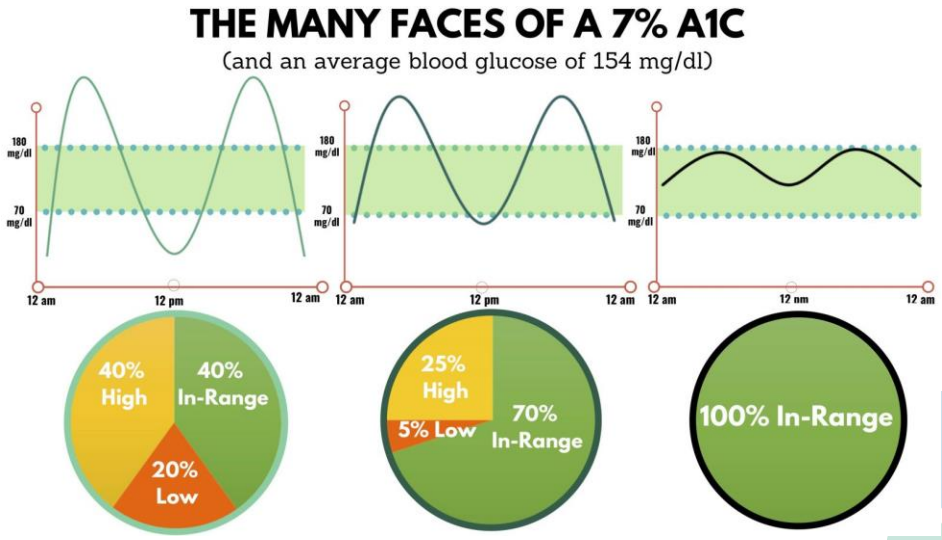
A1C Alone Is Not Enough



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Personal CGM Options

Owed by the person with diabetes

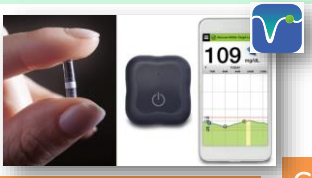
Typically used long term

Device options include real-time glucose monitoring (rtCGM) or intermittent scanning (isCGM)

Some options can be integrated with insulin pumps or connected insulin pens

Freestyle Libre 2 and Libre 2+

Freestyle Libre 3 and Libre 3+



Eversense E3

Guardian Connect or Guardian 3 or 4

Dexcom G6

Dexcom G7

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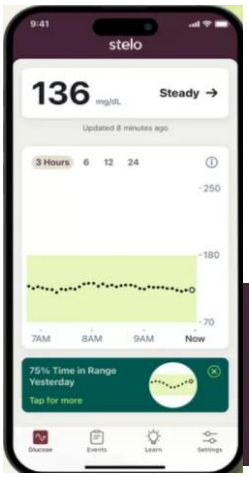
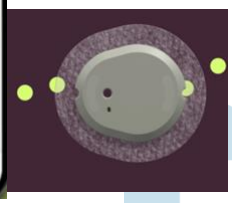
OTC CGMs

Abbott Lingo

Seems more geared to athletes or “health nuts”



Dexcom Stelo



- Can be purchased online without a prescription
- There are no real time alerts, price is ~$89-$99/month and they are meant for people not taking insulin
- The Abbot Rio will be coming out in the future, another OTC option for people with diabetes not taking insulin

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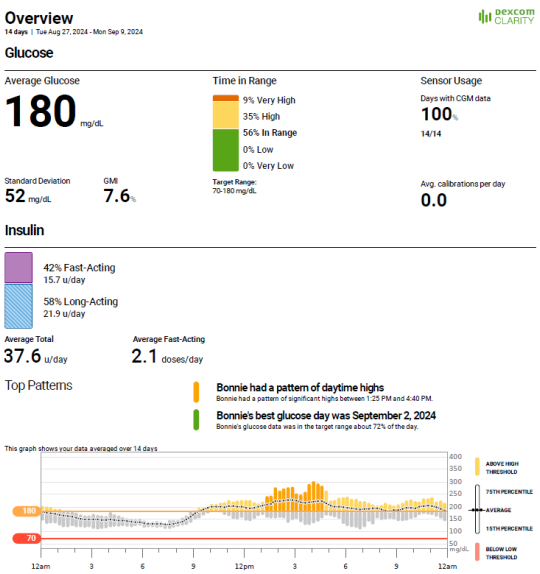
65-year-old Woman, T2D, on MDI, A1c 6.5%



Illustrates higher average glucose, time above range despite “well controlled A1c”

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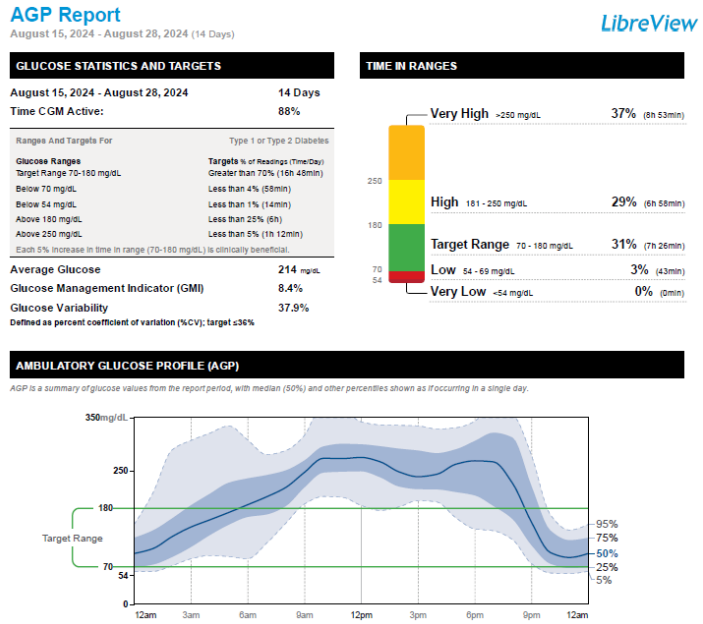
59-year-old Woman, T2D, on Basal Insulin, Metformin, SGLT-2i, Recently Started GLP-1RA, A1c 8.2%



Average glucose in CGM lines up with A1C, but illustrates that A1c cannot capture variability and hypoglycemia

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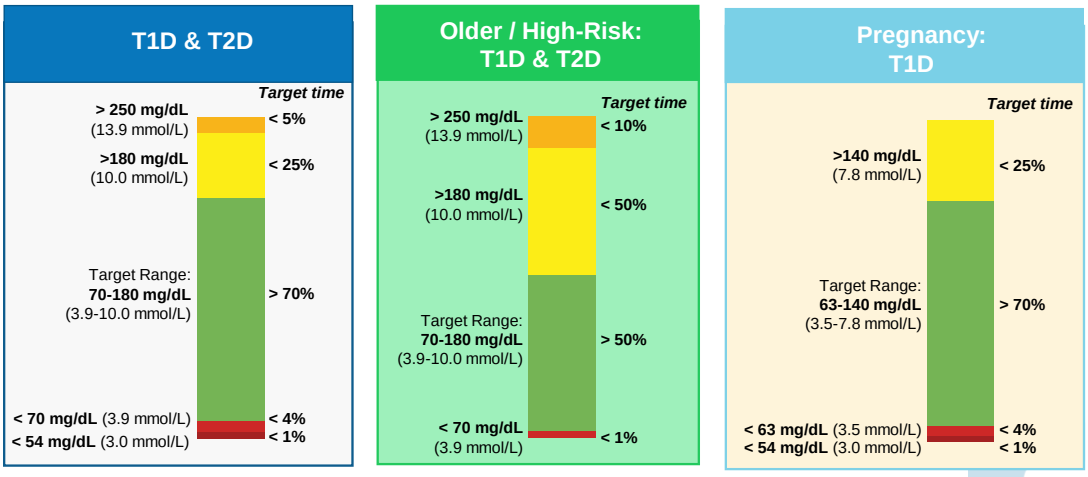
Time in Range



1% of the day is ≈15 minutes.

Battelino T et al. Diabetes Care. 2019;42(8):1593-1603.

60

Conclusions

1) A1C reduction/goal attainment is **STILL** important

2) CV (and Renal) Risk Reduction with GLP-1RA

3) CV, Renal, and HF risk reduction with SGLT-2i

4) CGM can assist patients and providers in improving glycemic control