

## Treating Diabetes in Older Adults:

What the Cardiovascular Outcomes Trials (CVOT) are telling us

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University of  
Pittsburgh

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## Mary Korytkowski Disclosure of ABIM Service

- I am a member of the Endocrine Exam Committee (July 2014 – present)
- As is true for any ABIM candidate who has taken the certification exam, I have signed a Pledge of Honesty in which I have agreed to keep the ABIM exam confidential
- No exam questions will be disclosed in my presentation



### Patient Case: The older adult with diabetes

83 yo male with > 25 yr history T2D  
Seen following a severe hypoglycemia event 3 months earlier prompting DC of glimepiride  
He stopped taking Lantus 8 units at HS due to AM hypoglycemia  
DM complications: neuropathy, retinopathy, TIA  
PMH: HTN, OSA, RBBB  
DM Rx at presentation:  
Metformin XR 1000 mg in AM, 500 mg in PM  
Insulin: Novolog 6 units acb and acs  
Home BG: 198-304 No recent hypoglycemia events  
PE: BP 121/81 BMI 26 kg/m<sup>2</sup>  
Venous stasis changes both LE Decreased DP/PT  
Wide based gait  
Absent AJ, Vibration absent, proprioception/ MF decreased

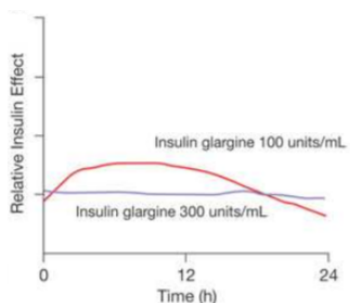
### Patient Case: The older adult with diabetes

Labs: A1c 7.9% Creat 0.94 LDL 65  
He was concerned about the elevated BG levels as he is concerned about his neuropathic symptoms  
Recommendations made at time of OV:  
Resume Lantus 8 units SQ and move dosing to AM  
Novolog instructions before meals:  

For BG <150	No Novolog
For BG 150-200	2 units Novolog
For BG 200-250	4 units Novolog
For BG >250	5 units Novolog

Use of glucagon discussed but not prescribed – pt lives with his wife who has dementia  
Rx given for glucose gel along with instructions for use  
B12 supplementation recommended

## Pharmacokinetics of Glargine U100 vs. U300

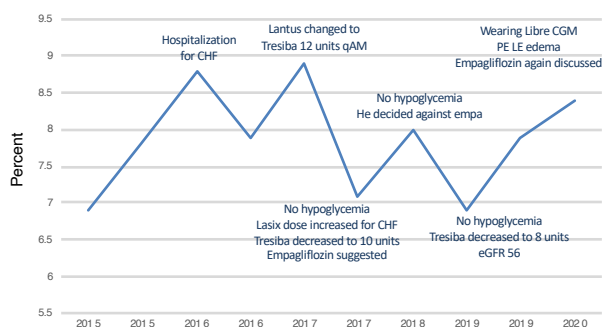


Pettus J et al. Diab Metab Res Rev 32:478 2016

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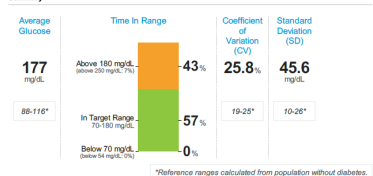
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## Patient Case: A1c over time



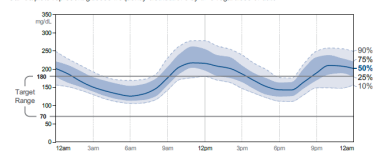
CGM Device: FreeStyle Libre [N/A] Compliant w/Calibration\* 97% Time Worn  
\*Not applicable to FreeStyle Libre or FreeStyle Libre Pro which do not require calibration.

### Summary



### Ambulatory Glucose Profile

Curves/plots represent glucose frequency distributions by time regardless of date



## Patient Case: The older adult with diabetes

OV January 2020

He is now 88 yrs old

Creatinine 1.9 mg/dl eGFR 31 ml/min

### Current medications:

Tresiba 7 units in AM Novolog 2 units with bkfst  
Aspirin EC 81 mg Avodart  
MetFORMIN 500 mg BID Losartan 50 mg  
Lasix 40 mg BID Coreg 12.5 mg bid

He and his family member decide against adding and SGLT2i following discussion of risks and benefits

2 days later he is started on empagliflozin 10 mg once a day by another physician

2 weeks later... Creatinine 2.04 eGFR 28 ml/min

### For discussion

What level of glycemic control is recommended for this particular patient?

Is this patient truly a candidate for an SGLT2i?

Would a Glucagon like peptide receptor agonist be a better choice?

What about metformin?

Is it reasonable to use a continuous glucose monitoring device in an 88 year old patient with diabetes?

What other questions are there?

### CLINICAL PRACTICE GUIDELINE

#### Treatment of Diabetes in Older Adults: An Endocrine Society\* Clinical Practice Guideline

Derek LeRoith,<sup>1</sup> Geert Jan Blesse,<sup>2</sup> Susan S. Braithwaite,<sup>3,4</sup> Felipe F. Casanueva,<sup>5</sup> Boris Draznin,<sup>6</sup> Jeffrey B. Halter,<sup>7,8</sup> H. B. Hirsch,<sup>9</sup> Marie E. McDonnell,<sup>10</sup> Mark E. Molitch,<sup>11</sup> M. Hassan Murad,<sup>12</sup> and Alan J. Sinclair<sup>13</sup>

*J Clin Endocrinol Metab* May 2019 110(5):1-55

### Framework for Considering Health and Patient Values in Determining Clinical Targets in Adults Aged ≥ 65 y

Overall Health Category	Group 1: Good Health	Group 2: Intermediate Health	Group 3: Poor Health
Patient characteristics	No comorbidities or 1-2 non-diabetes chronic illnesses and No ADL* impairments and ≤1 IADL impairment	3 or more non-diabetes chronic illnesses** and/or Any one of the following: mild cognitive impairment or early dementia ≥2 IADL impairments	Any one of the following: End-stage medical condition(s)** Moderate to severe dementia ≥2 ADL impairments Residence in a long-term nursing facility
	Reasonable glucose target ranges and HbA1c by group		
	Shared decision-making: individualized goal may be lower or higher		
	Use of drugs that may cause hypoglycemia (e.g., insulin, sulfonylureas, glinides)	No	Fasting: 90-130 mg/dL Bedtime: 100-150 mg/dL Fasting: <7.5%
Yes†		Fasting: 90-150 mg/dL Bedtime: 100-180 mg/dL Fasting: ≥7.0 and <7.5%	Fasting: 100-150 mg/dL Bedtime: 150-180 mg/dL Fasting: ≥7.5 and <8.0%

LeRoith D et al *J Clin Endocrinol Metab* 104:1520, 2019

### Factors contributing to health status in older adults:

#### Instrumental Activities of Daily Living (ADL)

Ability to use the telephone  
Shopping  
Doing housework  
Doing laundry  
Preparing meals  
**Driving**  
**Taking medications**  
Managing money

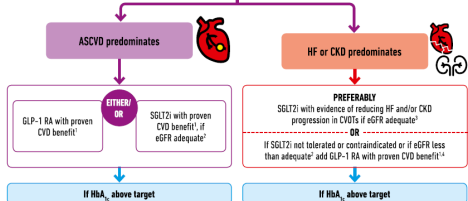
#### Comorbidities

Arthritis, HTN  
Cancer, MI, CVA  
Chronic heart failure  
Chronic kidney disease (CKD)  
COPD  
Falls  
Urinary incontinence



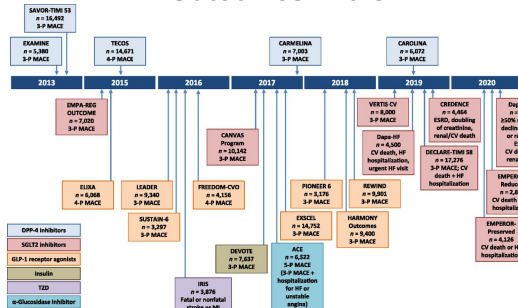
## Glucose lowering medications for patients with Type 2 Diabetes and ASCVD or CKD

A1C above goal on metformin / intolerance to metformin



Davies MJ et al. Diabetes Care 41:2668, 2018

## Completed and Ongoing Cardiovascular Outcomes Trials



Cefalu WT et al. Diabetes Care 2018;41:14-31



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

For Immediate Release December 12, 2018

The U.S. Food and Drug Administration today approved a new indication for Jardiance (empagliflozin) to reduce the risk of cardiovascular death in adults with type 2 diabetes and established cardiovascular disease.

**Newsroom** - Published on October 31, 2018

#### FDA Approves Dapagliflozin to Cut Risk of Hospitalization for Heart Failure in Type 2 Diabetes

Mary Gaffney

Results are based on the DECLARE-TIMI 58 cardiovascular outcomes trial, which compared dapagliflozin to placebo in patients with type 2 diabetes and established cardiovascular disease.

The FDA today approved AstraZeneca's dapagliflozin (Farxiga) to reduce hospitalization for heart failure in patients with type 2 diabetes (T2D) and cardiovascular disease or multiple cardiovascular risk factors.

### U.S. FDA Approves INVOKANA® (canagliflozin) to Reduce the Risk of Heart Attack, Stroke or Cardiovascular Death in Adults with Type 2 Diabetes and Established Cardiovascular Disease

INVOKANA is now the only oral diabetes treatment approved to reduce the risk of these cardiovascular events. Approval aligns with ADA and MACE treatment guidelines and supports use of INVOKANA across a broad range of patients.   
 INVOKANA is a trademark of Janssen Inc. The U.S. Food and Drug Administration (FDA) has approved INVOKANA (canagliflozin) to reduce the risk of major adverse cardiovascular (CV) events, including heart attack, stroke or death due to a cardiovascular cause in adults with type 2 diabetes (T2D) who have established CV disease. INVOKANA is the first and only oral diabetes treatment approved with this indication.

### FDA OKs Canagliflozin to Curtail Diabetic Kidney Disease

Megan Brooks  
DISCLOSURES | September 30, 2019

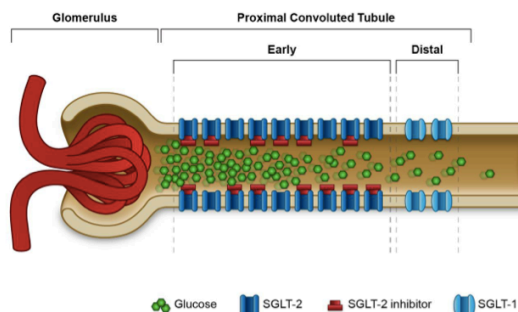
[Read Comment](#)

The US Food and Drug Administration (FDA) has approved canagliflozin (Invokana, Janssen) to reduce the risk of end-stage kidney disease, worsening of kidney function, cardiovascular death, and heart failure hospitalization, in adults with type 2 diabetes and diabetic kidney disease.

## Sodium glucose cotransporter 2 (SGLT2) Inhibitors

Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

### Mechanism of action

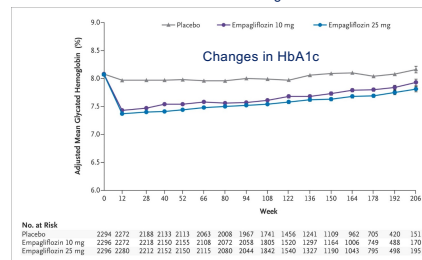


## Sodium Glucose Transporter Inhibitors (SGLT2i)

	dapagliflozin , canagliflozin, empagliflozin, ertugliflozin
Efficacy	Intermediate (Reduce A1C by ~ 0.8-1.0%)
Risk for hypoglycemia	Do not cause hypoglycemia when used alone or in combination with metformin
Weight	Weight loss
Side effects	Genito-urinary infections Dehydration Amputations (canagliflozin) Fracture risk (canagliflozin) AKI
Cost	High

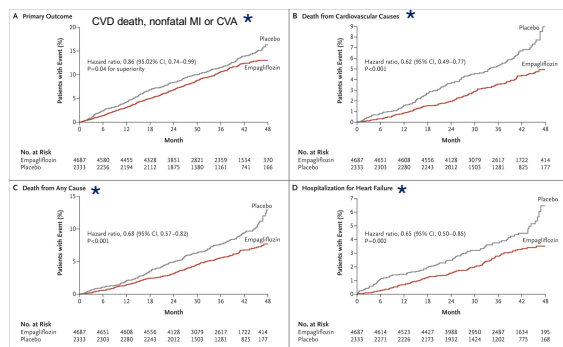
## 2015 Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

7070 subjects with T2D at high risk for CVD  
Randomized to Placebo, Study Drug 10 or 25 mg for ~ 3.1 years  
Mean age of subjects ~63 ± 9 years  
Mean BMI ~30 ± 5 kg/m<sup>2</sup>



THE NEW ENGLAND JOURNAL OF MEDICINE 373(22):2117-2128 2015

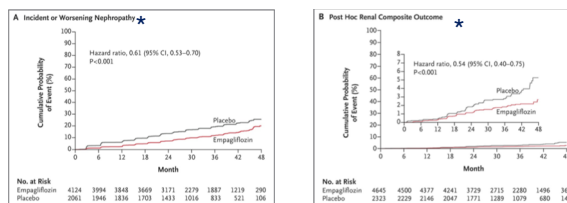
## Cardiovascular Outcomes and Death



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

THE NEW ENGLAND JOURNAL OF MEDICINE

## Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes



Primary outcomes:

Progression to macroalbuminuria, doubling serum creatinine, renal replacement therapy, renal death

12.7 with empagliflozin vs. 18.8% with placebo (HR 0.61 95% CI: 0.53-0.70)

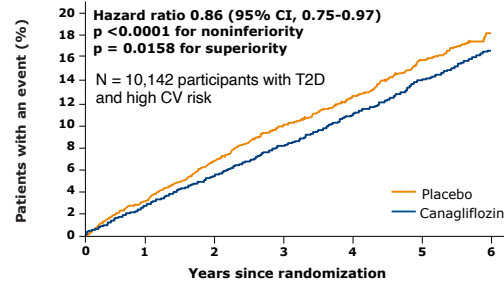
Wanner C et al. 375:323 2016

THE NEW ENGLAND JOURNAL OF MEDICINE

## CANagliflozin cardioVascular Assessment Study

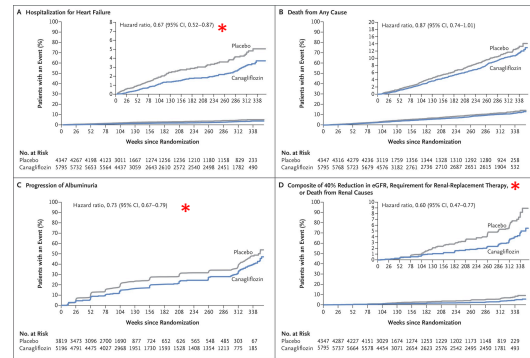
### Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



Neal B et al. *N Engl J Med* ;377:644-657, 2017

## CVD and Renal Outcomes with Canagliflozin

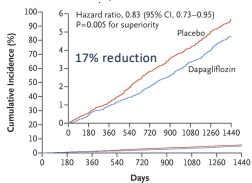


Neal B et al. *N Engl J Med* ;377:644-657, 2017

## ORIGINAL ARTICLE

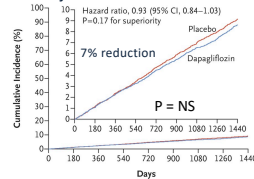
### Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

#### CV Death or Hospitalization for HF\*



No. at Risk  
 Placebo 8578 8485 8387 8259 8127 8003 7880 7367 5362  
 Dapagliflozin 8582 8517 8415 8322 8224 8110 7970 7497 5445

#### Major Adverse CV Events



No. at Risk  
 Placebo 8578 8483 8281 8129 7969 7805 7649 7137 5158  
 Dapagliflozin 8582 8466 8303 8166 8017 7873 7708 7237 5225

MACE defined as CV death, MI, or ischemic stroke

Wiviott SD et al. *N Engl J Med* 2019;380:347-357

Not all SGLT2 inhibitors are the same



## Summary: Diabetes CVOT with SGLT2i

	CVD Death	All Cause Mortality	Nonfatal MI	Nonfatal CVA	Renal Outcomes
Empagliflozin (EMPA-REG)	↓38%	↓32%	NSD	NSD	↓39%
Canagliflozin (CANVAS, CREDENCE)	↓20%		NSD	NSD	↓40%
Dapagliflozin (DECLARE)	NSD	NSD	NSD	NSD	↓24%
Ertugliflozin (VERTIS-CV)	In progress				

All SGLT2i agents were associated with significant reductions in hospitalizations for heart failure, weight, BP and a composite of renal outcomes

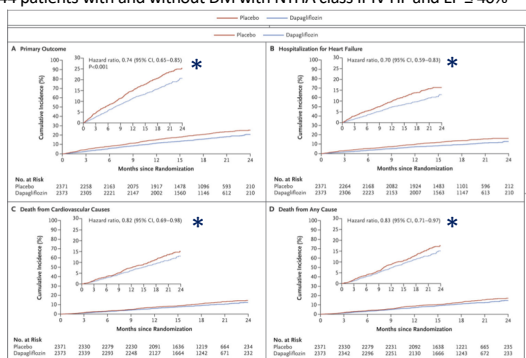
## CVOT with SGLT2i

### Relevance to Older Adults with Type 2 DM

	Age (y)	% Subjects > age 75	HR for Primary Outcome Age ≥65	HR for CVD Death Age ≥65
Empagliflozin (EMPA-REG)	63 ± 8.6	9%	0.71 (0.5-0.87)	0.54 (0.4-0.73)
Empagliflozin (EMPA-REG Outcome)	67 ± 8		0.61 (0.53-0.7)	
Canagliflozin (CANVAS, CREDENCE)	63 ± 8 63 ± 9		0.8 (0.67-0.95) 0.77 (0.6-1.0)	
Dapagliflozin (DECLARE)	64 ± 7	6.4%	P = NS	

## Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

4744 patients with and without DM with NYHA class II-IV HF and EF ≤ 40%



McMurray JJV et al. N Engl J Med September 2019

## Sodium Glucose Transporter (SGLT) 2 Inhibitors

### Disadvantages:

- ✓ Increase in risk for "euglycemic DKA"
- ✓ High risk for volume depletion, hypotension, and dehydration
  - ✓ Use carefully in the elderly or those receiving diuretics
- ✓ Contraindicated in advanced kidney disease (eGFR ≤ 30 ml/min)
  - Glycemic benefit declines with eGFR < 60 ml/min
- ✓ Increase in fracture risk observed with canagliflozin
- ✓ Increase risk of amputations observed with canagliflozin
- ✓ Postmarketing reports of acute kidney injury (cana, dapa)
- ✓ Personal note: Use with caution in men with prostatic hyperplasia
- ✓ Cost!

## ORIGINAL RESEARCH

Annals of Internal Medicine

**Fournier Gangrene Associated With Sodium-Glucose Cotransporter-2 Inhibitors**

June 4, 2019

**A Review of Spontaneous Postmarketing Cases**

Susan J. Bersoff-Matcha, MD; Christine Chamberlain, PharmD, CDE; Christian Cao, MPAS, PA-C; Cindy Kortepeter, PharmD; and William H. Chong, MD

FDA Adverse Event Reporting System (FAERS) database

Report of 55 cases of patients receiving SGLT2i from 5 days – 49 months

Age 33-87: 39 men / 16 women

Comparator: FDA reports 19 cases associated with other DM agents 1984-2019:

- 8 treated with metformin
- 8 treated with insulin
- 2 treated with sitagliptin + metformin
- 1 treated with dulaglutide

**Avoid use of SGLT2i in the following conditions**

- Type 1 diabetes
- eGFR <45 ml/min/1.73m<sup>2</sup> (<60 ml/min/1.73m<sup>2</sup> for ertu)
- Frequent bacterial UTI or genitourinary yeast infections.
- Low bone mineral density
- High risk for fracture and falls.
- Foot ulceration (e.g. neuropathy, foot deformity, vascular disease, and/or history of previous foot ulceration)
- Factors predisposing to DKA (e.g. ketosis-prone T2D, pancreatic insufficiency, drug or alcohol addiction)

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MEDICINE<https://www.uptodate.com/contents/sodium-glucose-co-transporter-2-inhibitors>**Patient Case: The older adult with diabetes**

February 2020

2 weeks later... Creatinine 2.04 eGFR 28 ml/min

Actions taken:

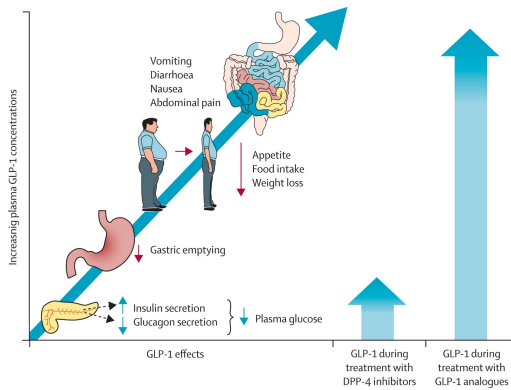
Metformin discontinued for CKD Stage 4

Recommendation made to stop Jardiance

**Patient Case: The older adult with diabetes**

Would a GLP1-RA be a better  
choice for this  
patient?

## Incretin Therapy: GLP1 RA and DPP4i



## Dipeptidyl Peptidase IV Inhibitors

Sitagliptin / Saxagliptin / Alogliptin / Linagliptin

<b>Efficacy</b>	Intermediate (Reduce A1C by ~ 0.8-1.0%)
Risk for hypoglycemia	Low
Weight	Weight neutral
Side effects	Infrequent Increase in nasopharyngitis/URI/UTI Headache, myalgias / arthralgias Rarely LFT elevations Case reports of acute pancreatitis Rare case reports severe hypersensitivity reactions with anaphylaxis, angioedema, exfoliative skin conditions
Cost	High

CVOT with DPP4i consistently neutral

Increase in hospitalizations for HF with saxagliptin and alogliptin

Renal dosing for all DPP4i except linagliptin

## Glucagon Like Peptide 1 (GLP1) Receptor Agonists

	exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, semaglutide
Efficacy	High - Reduces A1c by 0.7-1.1%
Risk for hypoglycemia	Low
Weight	Weight loss
Side effects	Gastrointestinal (nausea, vomiting) Post-marketing reports of pancreatitis and acute renal failure
Cost	High

Reductions in CVD and renal outcomes with GLP1RA are similar in older and younger patient populations  
Nausea occurs in up to 50% of study participants receiving study drug.

Costs are high with these agents

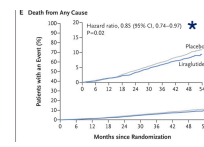
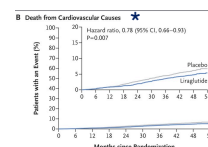
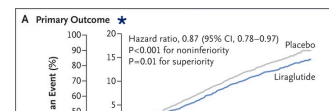
## Liraglutide and CV Outcomes in T2DM

N = 9340  
81% of subjects with prior CVD  
Followed for 3.8 years  
Primary outcome  
CVD death, nonfatal MI and CVA

### Subgroup analysis:

Age < 60 (n = 2321) HR for primary outcome 0.78 (0.62 – 0.97)

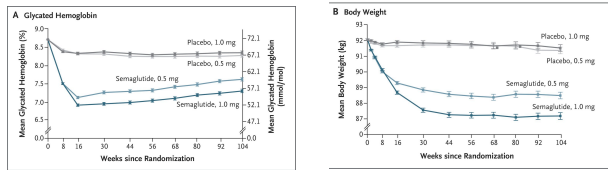
Age ≥ 60 (n = 7019) HR for primary outcome 0.9 (0.79 – 1.02)



Marso SP et al. N Engl J Med 2016;375:311-322

### Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

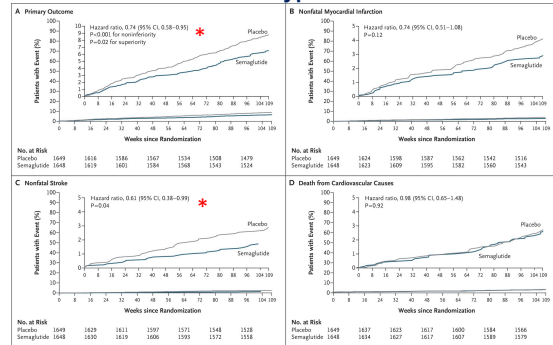
N = 3297 (mean age 65)  
83% of subjects with prior CVD, CKD or both  
Followed for 2.1 years  
Weekly GLP-1RA



Marso SP et al. (SUSTAIN-6 Investigators) *N Engl J Med* 375(19):1834, 2016



### Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes



Marso SP et al. (SUSTAIN-6 Investigators) *N Engl J Med* 375(19):1834, 2016



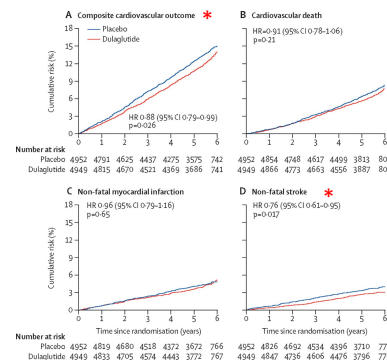
### Semaglutide and Microvascular Complications in Type 2 Diabetes

- Nephropathy**
  - ✓ Rates of new or worsening nephropathy were lower in the semaglutide groups (3.8 vs. 6.1% of patients)
- Retinopathy**
  - ✓ Rates of vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation were significantly higher with semaglutide (3.0 vs. 1.8%, HR: 1.76; 95% CI, 1.11 to 2.78; P=0.02)
- Other side effects**
  - ✓ More patients treated with semaglutide discontinued treatment due to adverse events (mainly GI) (13 vs. 6.7%)

Marso SP et al. (SUSTAIN-6 Investigators) *N Engl J Med* 375(19):1834, 2016



### REWIND: Dulaglutide and CV Outcomes in Type 2 Diabetes



Gerstein HC et al. *The Lancet* Published: June 09, 2019

Not all GLP1-RA  
are the same



**Summary Table: CVOT with GLP1RA**

	CVD Death	All Cause Mortality	Nonfatal MI	Nonfatal CVA	Renal Outcomes
Liraglutide (LEADER)	↓ 22%	↓ 15%	NSD	NSD	↓ 22%
Semaglutide SQ (SUSTAIN)	NSD	NSD	NSD	↓ 39%	↓ 36%
Semaglutide PO (PIONEER)	↓ 51%	↓ 49%	NSD	NSD	NR
Albiglutide (HARMONY)	NSD	NSD	↓ 25%**	NSD	NR
Dulaglutide (REWIND)	NSD	NSD	NSD	↓ 24%	↓ 15%

\*\*Fatal or nonfatal MI    NSD No significant difference    NR Not reported

All GLP1RA agents were associated with improved A1c, decreased body weight, and high frequency of nausea

### Patient Case: The older adult with diabetes

February 2020

2 weeks later... Creatinine 2.04 eGFR 28 ml/min

Actions taken:

Metformin discontinued for CKD Stage 4

Recommendation made to stop Jardiance

A GLP-RA can be considered  
However, the beneficial effect is not primarily on CHF

### Patient Case: The older adult with diabetes

#### What about metformin?

<b>Efficacy</b>	Reduces A1c by 1.5-2.0%
<b>Renal Dosing</b>	eGFR ≥ 60 ml/min Max dose 2 – 2.5 G/day CKD Stage 3A (eGFR 45-60 ml/min) max dose 1.5 G/day CKD Stage 3B (eGFR 30-45 ml/min) max dose 1 G/day
<b>Risk for hypoglycemia</b>	Low
<b>Weight</b>	Neutral / Mild weight loss
<b>Side effects</b>	B12 Deficiency (monitor B12 levels periodically) Gastrointestinal (5% of patients)* Lactic acidosis (rare)
<b>Cost</b>	Low

\*Can be minimized by using extended release formulations and taking after a meal

**Contraindications:**

- Intolerance to metformin
- eGFR <30 ml/minute
- Concurrent active or progressive liver disease
- Active alcohol abuse
- Unstable or acute HF with risk of hypoperfusion / hypoxemia
- PMH of lactic acidosis during metformin therapy
- Decreased tissue perfusion or hemodynamic instability

**For discussion**

Is it reasonable to use a continuous glucose monitoring device in an 88 year old patient with diabetes?

## Medicare Coverage of Diabetes Supplies & Services

CENTERS FOR MEDICARE & MEDICAID SERVICES

**Criteria for approval of a CGM Device:**

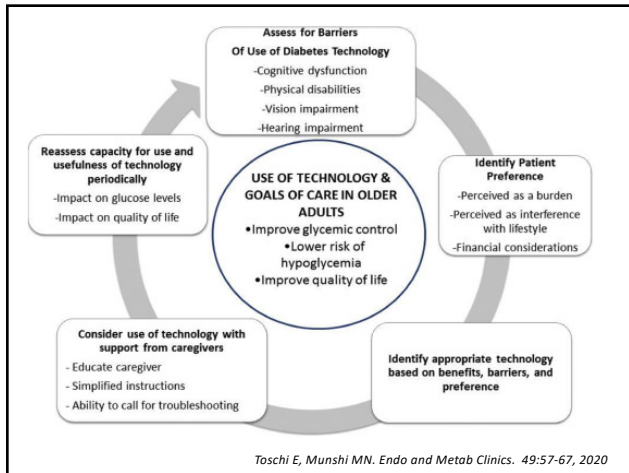
- The patient is receiving  $\geq 3$  daily insulin injections (MDI) or uses an insulin infusion pump
- There is documentation of 30 days of home blood glucose monitoring  $\geq 4$  times a day
- There is a need for frequent adjustments by the patient on the basis of therapeutic testing results.

<https://www.medicare.gov/Pubs/pdf/A1022-Medicare-Diabetes-Coverage.pdf> (accessed 11-19-2018)

### Treatment of Diabetes in Older Adults: An Endocrine Society\* Clinical Practice Guideline

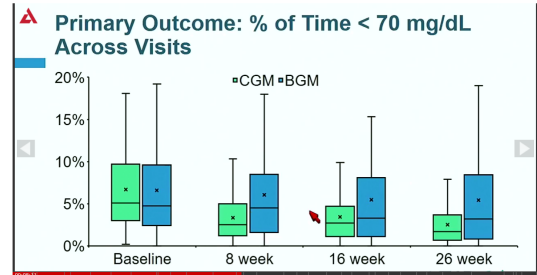
**Assessing glycemia in older adults with diabetes**

- 4.2 In patients aged 65 years and older with diabetes who are treated with insulin, we recommend frequent fingerstick glucose monitoring and/or continuous glucose monitoring (to assess glycemia) in addition to HbA1c. (1 |  $\oplus\oplus\oplus$ )



### WSDM: Wireless Innovation for Seniors with DM

198 subjects with intermediate health status randomized to real time CGM or masked CGM with conventional BG monitoring  
Mean Age 68 56% using CSII Therapy Mean A1c 7.5%

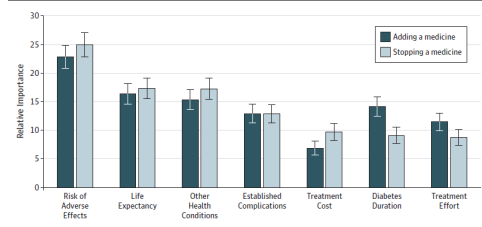


JAMA Internal Medicine | Original Investigation

### Patient Perceptions of Diabetes Guideline Frameworks for Individualizing Glycemic Targets

838 participants with Type 2 DM Mean Age 74

Figure. Relative Importance of the 7 Factors in Diabetes Treatment Decisions



*Schoenborn NL et al. 2019*

### Patient Case: The older adult with diabetes

What level of glycemic control is recommended for this 88 year old man with insulin treated type 2 diabetes?

Answer: HbA1c 7.5-8.4% (Average ~BG 165-195 mg/dl)

Is this patient truly a candidate for an SGLT2i?

Not at this time based on eGFR < 30 ml/min

Would a GLP1-RA be a better choice?

Reasonable choice if needed for glycemic control

What about metformin?

This was DC'ed once eGFR dropped to <30 ml/min

Is it reasonable to use CGM in this patient?

It makes him and his family more confident about his DM management

**Thank you for your attention**

**Questions?**

**Comments?**