WHAT'S NEW IN MEDICINE: DIABETES IN 2019

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09-07-19
Disclosure:
There are no relevant financial relationships with commercial interests to disclose

Objectives

- To know and understand newer anti-hyperglycemic medications: evidence, risks and benefits
- To understand advances in blood glucose testing and the use of insulin pumps
- To review the perioperative care for patients with diabetes including risk assessment, glycemic goals and choice of medications.

A clinical scenario

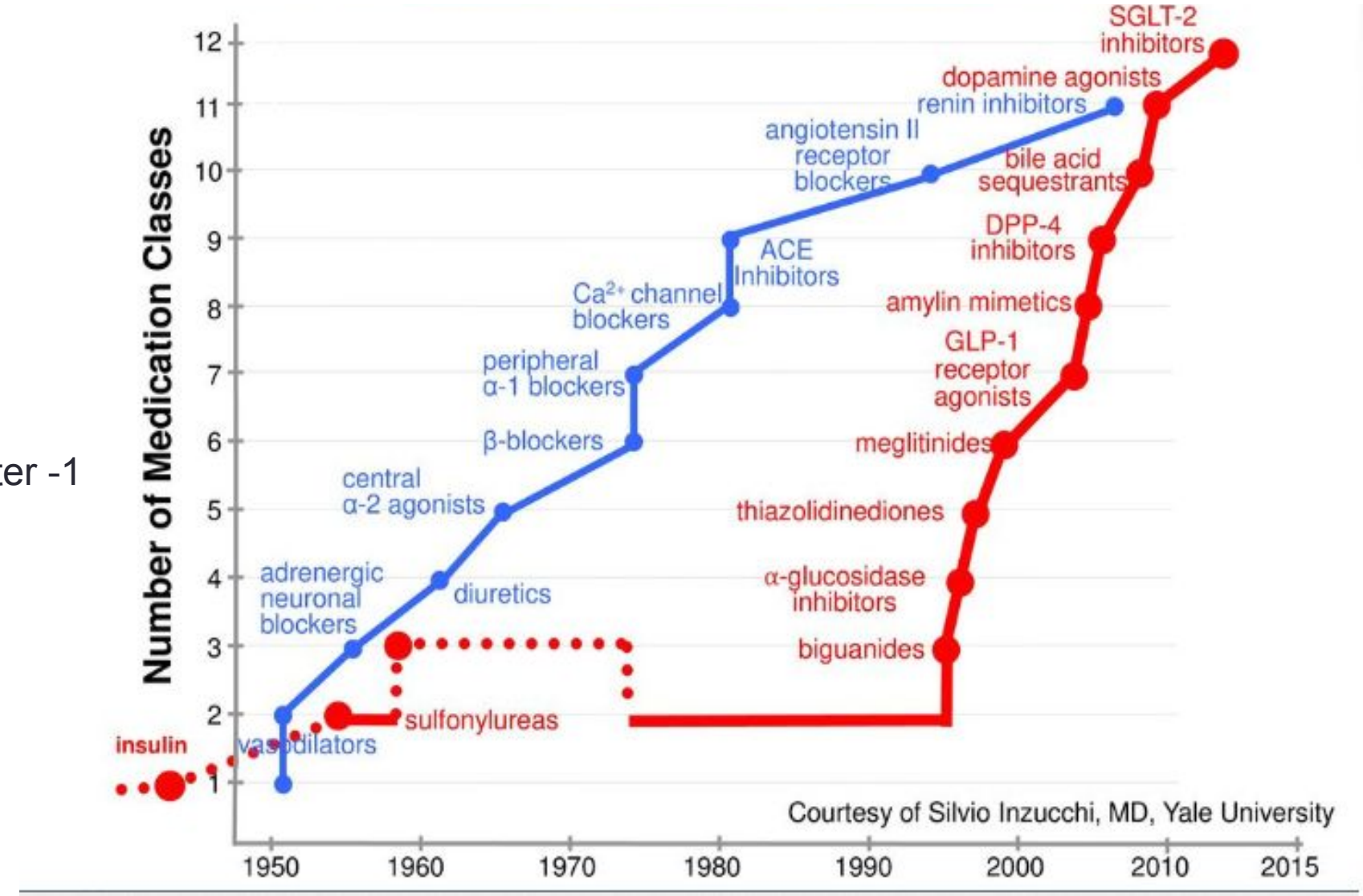
- 64 year old male
- Type 2 diabetes for 8 years
- CAD, had 2 stents placed 3 years ago after a myocardial infarction; EF is 40%
- Has microalbuminuria, no retinopathy
- Takes metformin, aspirin, beta blocker, statin
- Has commercial insurance
- BP 132/76 mmHg, BMI 33 kg/m^2; eGFR 55 $ml/m^2/min$
- A1C 8.1% (previous results in past year were 7.9% and 8.1%)

You feel that you need to intensify therapy for diabetes. What is the next best step for management of his diabetes?

A. Start glipizide
B. Start pioglitazone
C. Start sitagliptin
D. Start empagliflozin
E. Start liraglutide

Half a century of hypertension and T2D medications in the US

DPP-4i = dipeptyl peptidase inhibitors
GLP-1 = glucagon-like peptide-1
SGLT2i = sodium glucose cotransporter -1



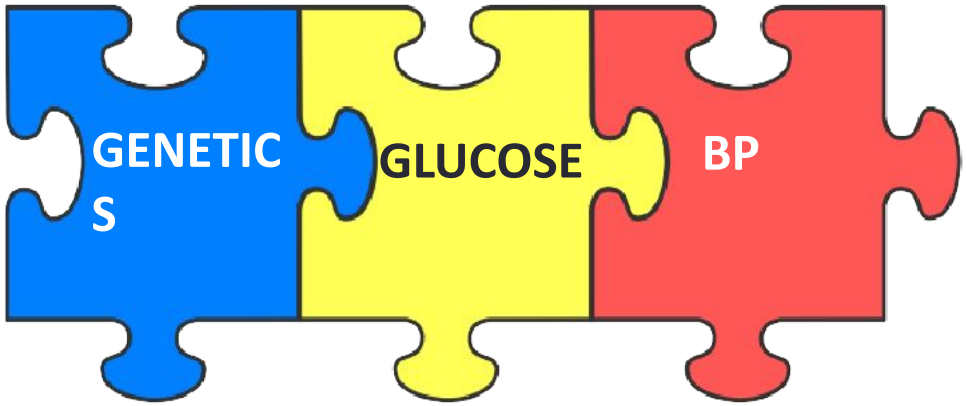
The list of new diabetes drugs is growing…

DPP4 inhibitors	SGLT2 inhibitors	GLP-1 analogs
Sitagliptin (Januvia)	Canagliflozin (Invokana)	Exenatide (Byetta)
Saxagliptin (Onglyza)	Dapagliflozin (Farxiga)	Liraglutide (Victoza)
Linagliptin (Tradjenta)	Empagliflozin (Jardiance)	Exenatide LAR (Bydureon)
Alogliptin (Nesina)	Ertugliflozin (Steglatro)	~~Albiglutide (Tanzeum)~~
		Dulaglutide (Trulicity)
		Lixisenatide (Adlyxin)
		Semaglutide (Ozempic)

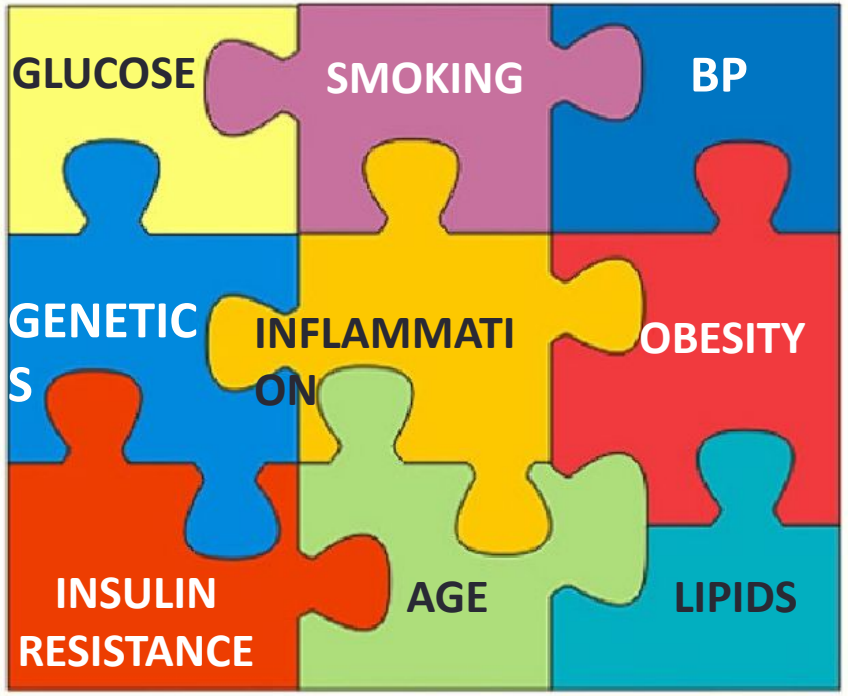
How can a clinician keep track?

Chronic complications in diabetes

MICROVASCULAR COMPLICATIONS



MACROVASCULAR COMPLICATIONS



Management of Type 2 diabetes in 2019

EFFICACY
A1C reduction

SAFETY
No hypoglycemia

CARDIOVASCULAR
risk reduction

Cardiovascular (CV) outcomes trials in diabetes: 2008 and beyond

- How did we get there?
  - Before 2008, no individual drug had shown **cardiovascular** benefit
    - **All diabetes medications were approved because… they lower blood glucose**
    - No prohibitive safety signals
  - Off-target effects - TZDs

- Where are we headed?

Regulatory response and FDA requirements: a paradigm shift

- **International agencies now require that all new hyperglycemic agents demonstrate glucose lowering response AND exclude clinically meaningful increases in major adverse CV outcomes**

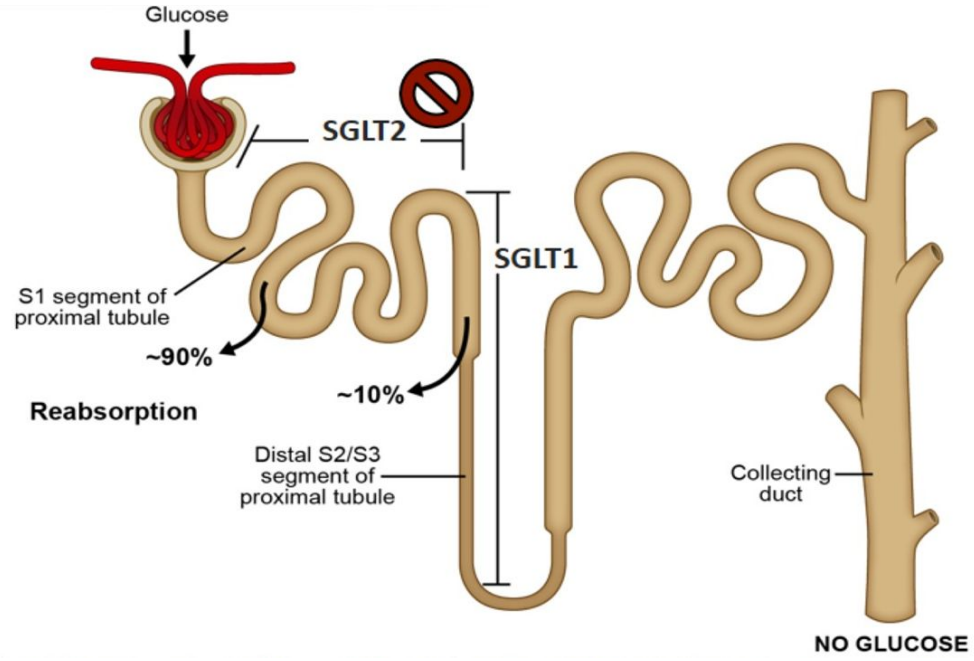
- "Guidance for industry" by FDA in 2008
- Trials to show CV safety
- Include higher CV risk patients
- Be of adequate duration to detect adverse CV events
- Include independent CV endpoint committees
- ~15,000 patient year exposure

Cardiovascular outcomes trials (CVOTs) of newer antihyperglycemic drugs

- SGLT2 inhibitors
- GLP-1 analogs
- DPP-4 inhibitors

SGLT-2 inhibitors - the “flozins”

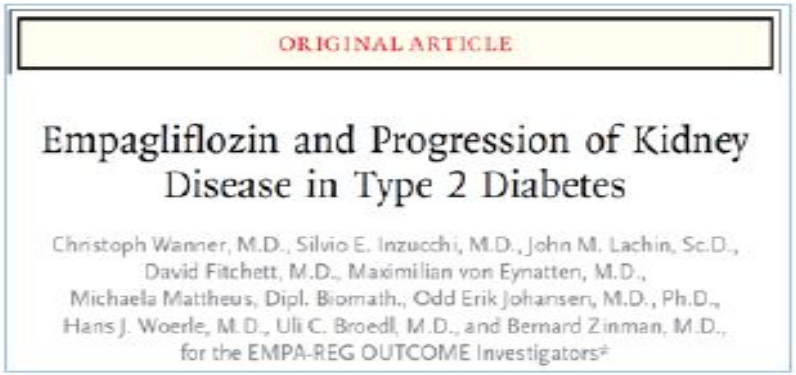
- Reduce A1c upto 0.7-1%
- **Not dependent on insulin secretion**
- Can be used combination with other glucose lowering agents in type 2 diabetes
- FDA approved for treatment of type 2 diabetes



CVOTs of SGLT2 inhibitors

Study	SGLT2 inhibitor	Study phase	Completion
EMPA-REG	empagliflozin	3	2015
CANVAS	canagliflozin	3	2017
CANVAS-R	canagliflozin	4	2017
DECLARE TIMI-58	dapagliflozin	3	2019
CREDENCE	canagliflozin	3	~~2020~~ 2019
Ertugliflozin CVOT	ertugliflozin	3	2020

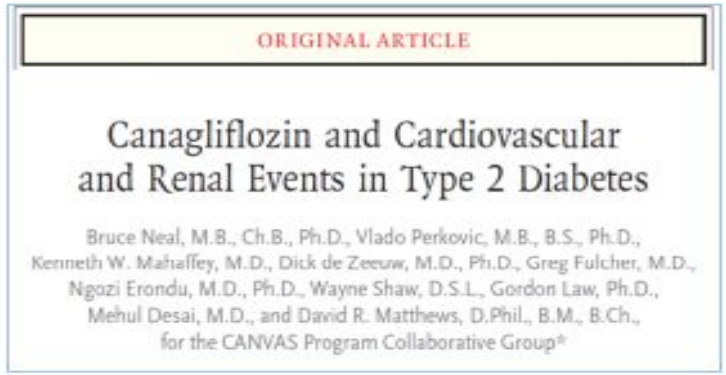
SGLT-2 inhibitors and cardiovascular outcomes



ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

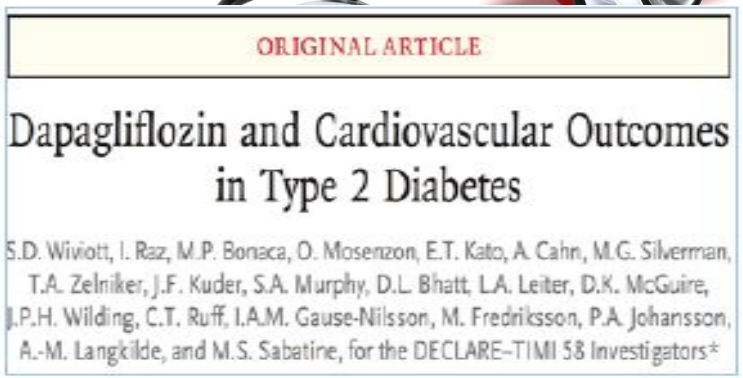
Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*



ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*



ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

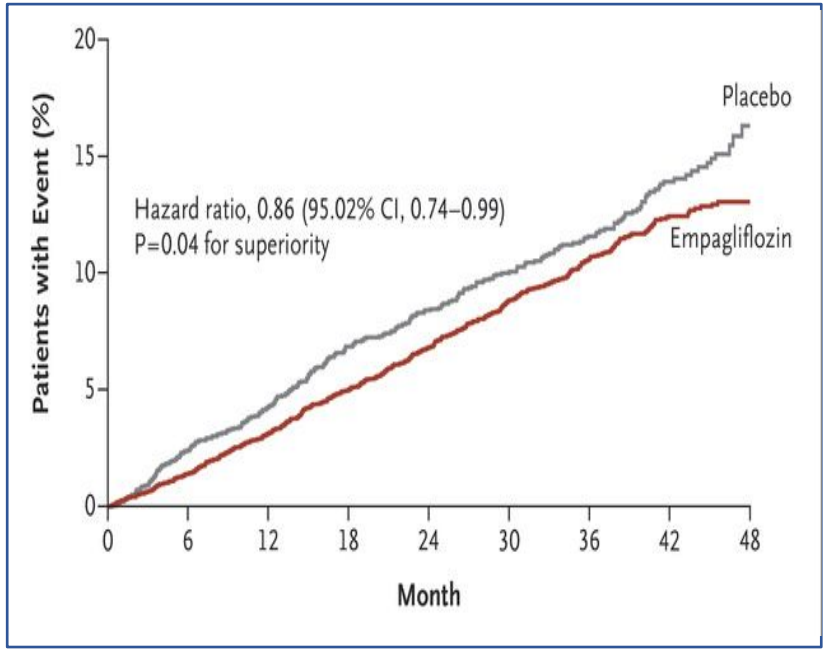
S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

EMPA-REG OUTCOME 2015 empagliflozin	CANVAS 2017 canagliflozin	DECLARE-TIMI58 2019 dapagliflozin
N=7020	**N=10,142**	**N= 17160**
T2D with ASCVD	T2D with ASCVD or with risk factors – diabetes >10y, HTN, albuminuria	T2D with ASCVD or multiple risk factors
A1C 7-10%	A1C 7.5-10.5%	
3 years	2 years	4.2 years

Zinman B et al NEJM 2015; Neal B et al. N Engl J Med 2017; Wiviott SD et al NEJM 2019; Zelniker T et al Lancet 2019

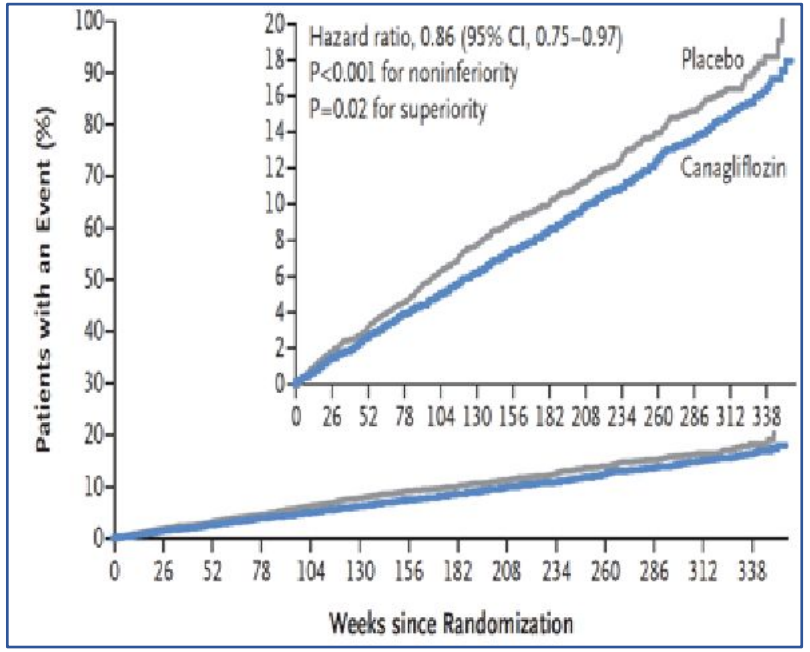
Primary outcome: 3-point MACE (CV death, MI, stroke)

EMPA-REG (Empagliflozin)



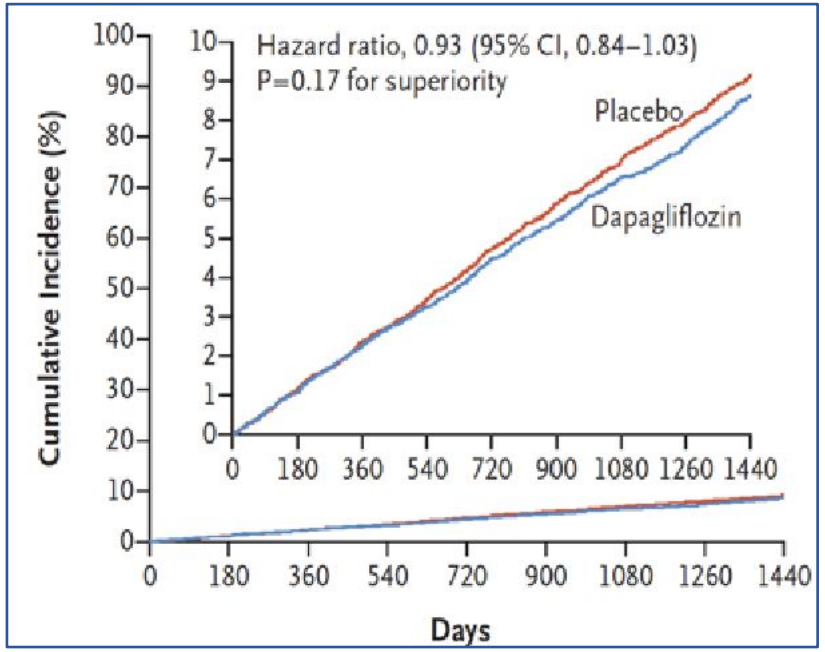
EMPA: 10.5% vs. PBO: 12.1% event per 1000 patient-years (hazard ratio, 0.86; 95% CI, 0.74 to 0.99)

CANVAS (Canagliflozin)



CANA: 26.9% vs. PBO: 31.5% event per 1000 patient-years (hazard ratio, 0.86; 95% CI, 0.75 to 0.97)

Dapagliflozin (DECLARE –TIMI58)

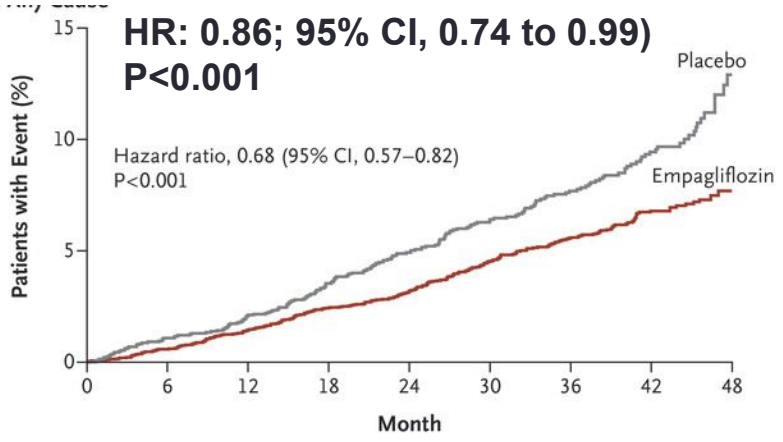


DAPA: 8.8% vs. PBO: 9.4% event per 1000 patient-years (hazard ratio, 0.93; 95% CI, 0.84 to 1.03)

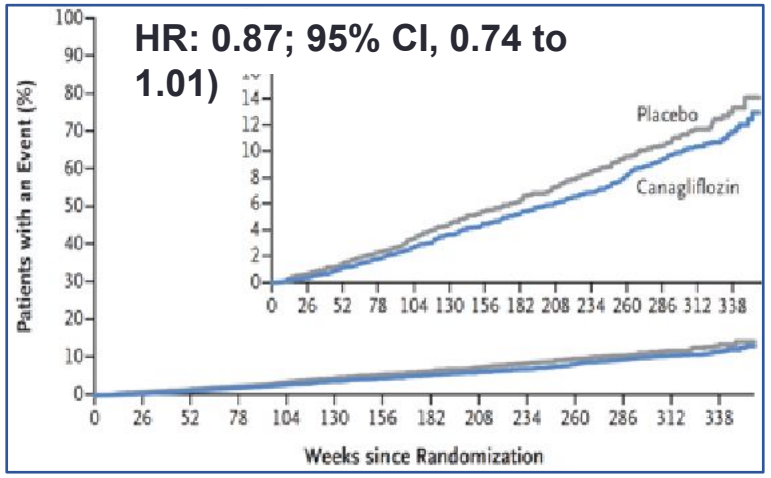
1. Zinman B et al. *N Engl J Med.* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med.* 2017;377:644-657. 3. Wiviott et al. NEJM 2018

Mortality (any cause) SGLT2i CVOTs

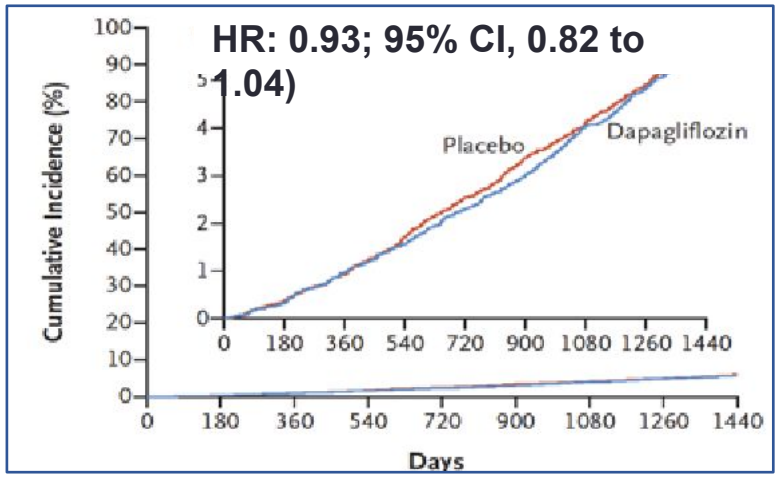
EMPA-REG (Empagliflozin)



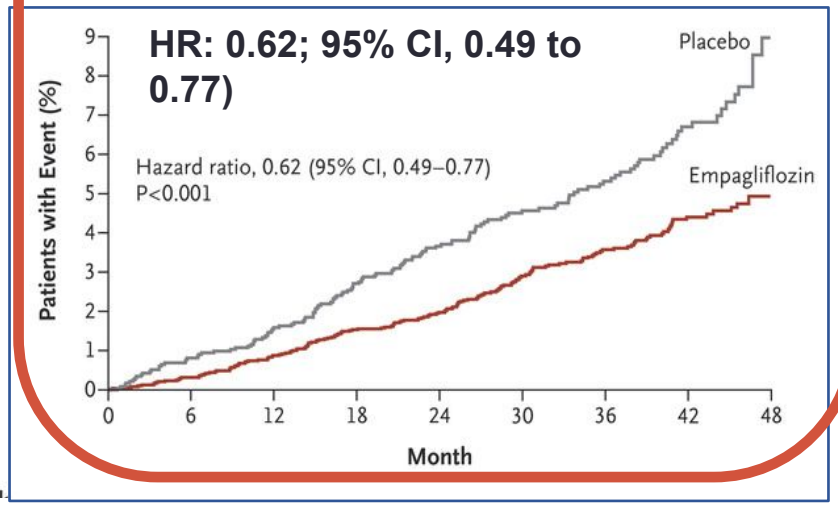
CANVAS (Canagliflozin)

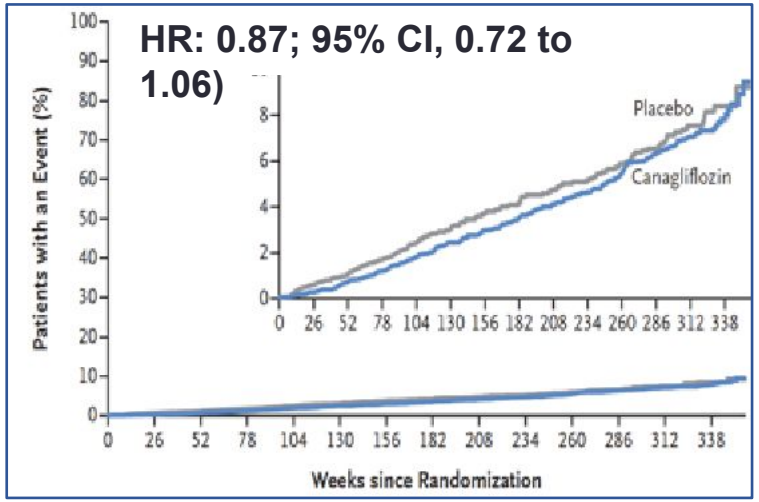


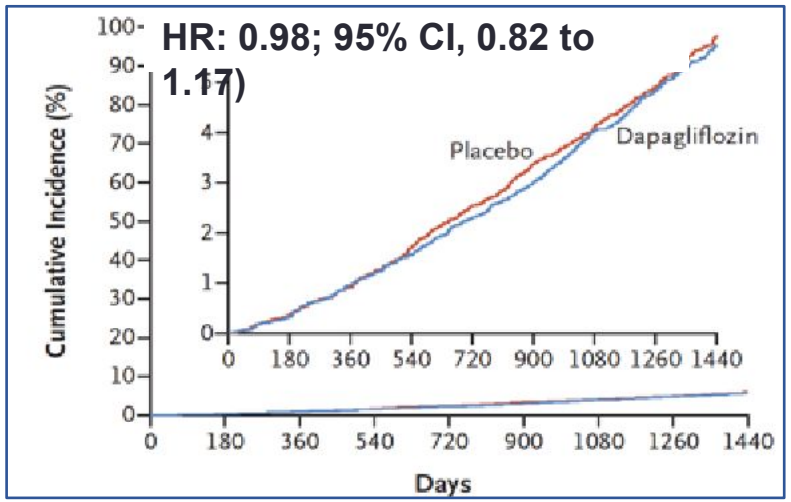
Dapagliflozin (DECLARE –TIMI58)



Cardiovascular Death

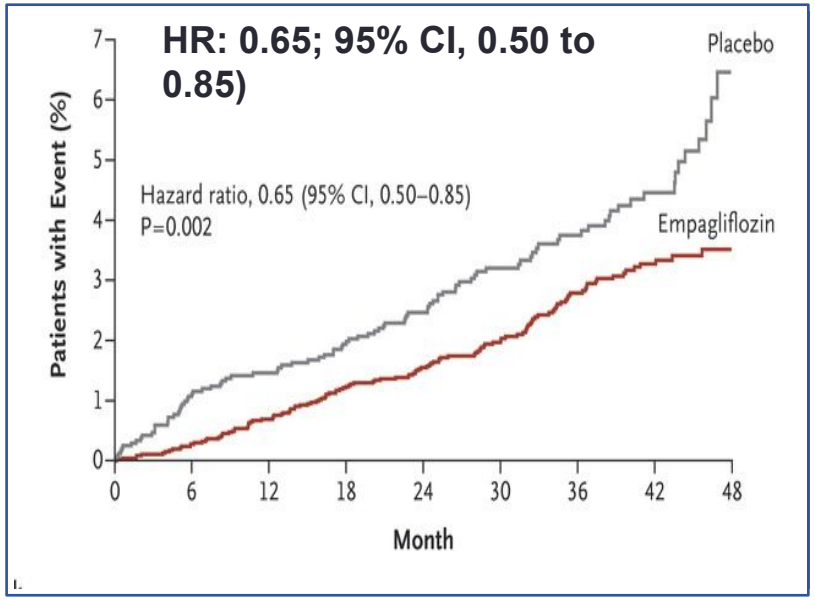




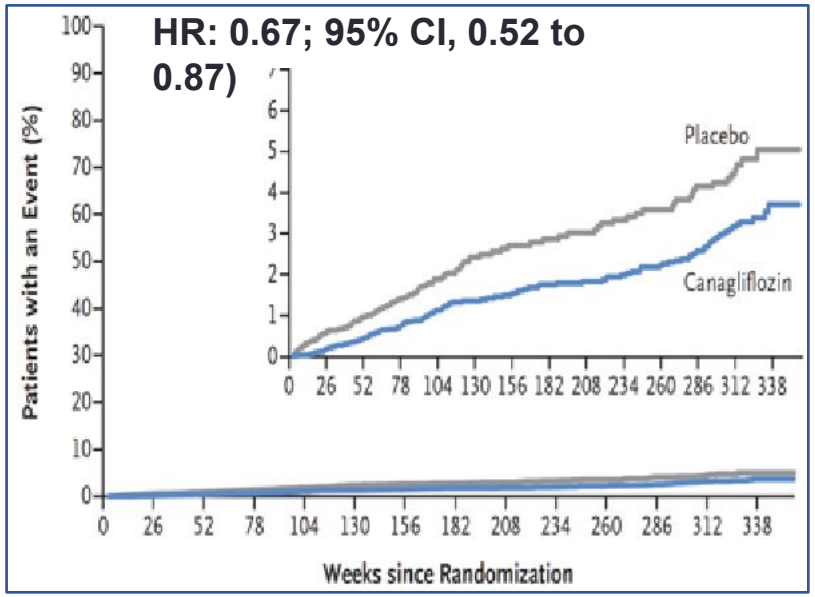


Hospitalization from Heart Failure, SGLT2-i CVOTs

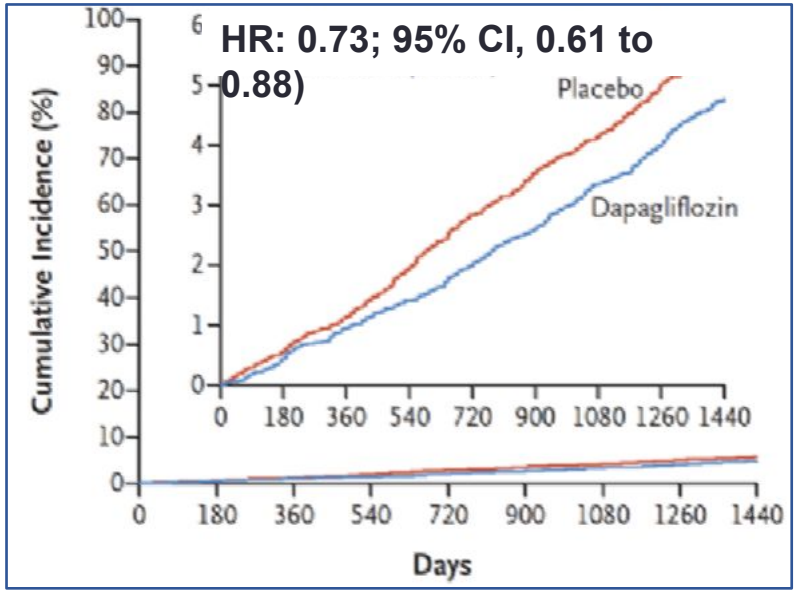
EMPA-REG (Empagliflozin)



CANVAS (Canagliflozin)



Dapagliflozin (DECLARE TIMI58)



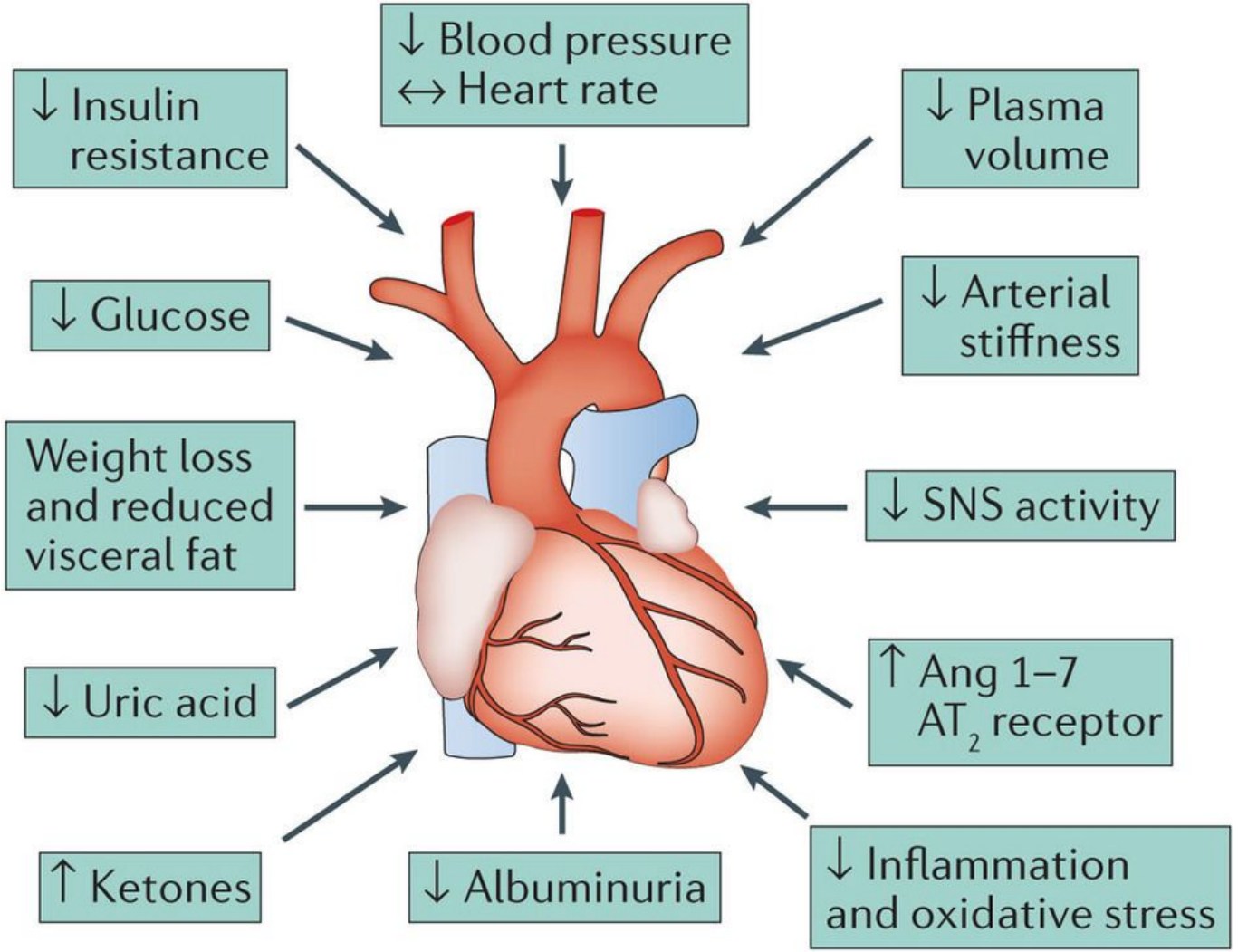
1. Zinman B et al. *N Engl J Med.* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med.* 2017;377:644-657. 3. Wiviott et al. NEJM 2018

Summary of completed SGLT2 inhibitor CVOTS

	EMPA-REG	CANVAS	DECLARE
SGLT2 inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin
CV safety endpoint	Achieved (non-inferior to placebo)	Achieved (non-inferior to placebo)	Achieved (non-inferior to placebo)
3-P MACE	0.86 (95% CI 0.74-0.99), p=0.04	0.86 (95% CI 0.75-0.97), p<0.02	0.93 (95% CI 0.84-1.03), p=0.17
Cardiovascular death	0.62 (95% CI 0.49-0.77), p=<0.001	0.87 (95% CI 0.72-1.06, p=0.04)	0.98 (95% CI 0.82-1.17), p= NS
Heart Failure Hospitalization	0.65 (95% CI 0.50-0.85), p<0.001	0.67 (95% CI 0.52-0.87), p<0.001	0.73 (95% CI 0.61-0.88), p=0.005
Death from any cause	0.68 (95% CI 0.57-0.82), p<0.001	0.87 (95% CI 0.74-1.01), p=0.04)	0.93 (95% CI 0.82-1.04), p=0.17
Percent with Baseline ASCVD	**99%**	**66%**	**40%**

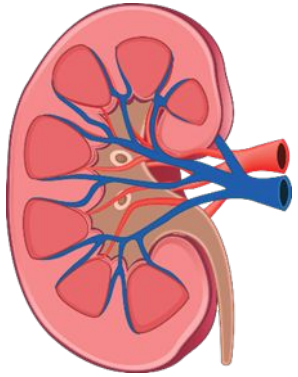
1. Zinman B et al. *N Engl J Med.* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med.* 2017;377:644-657. 3. Wiviott et al. NEJM 2018, on line November 2018

How do SGLT2 inhibitors provide CV benefit?



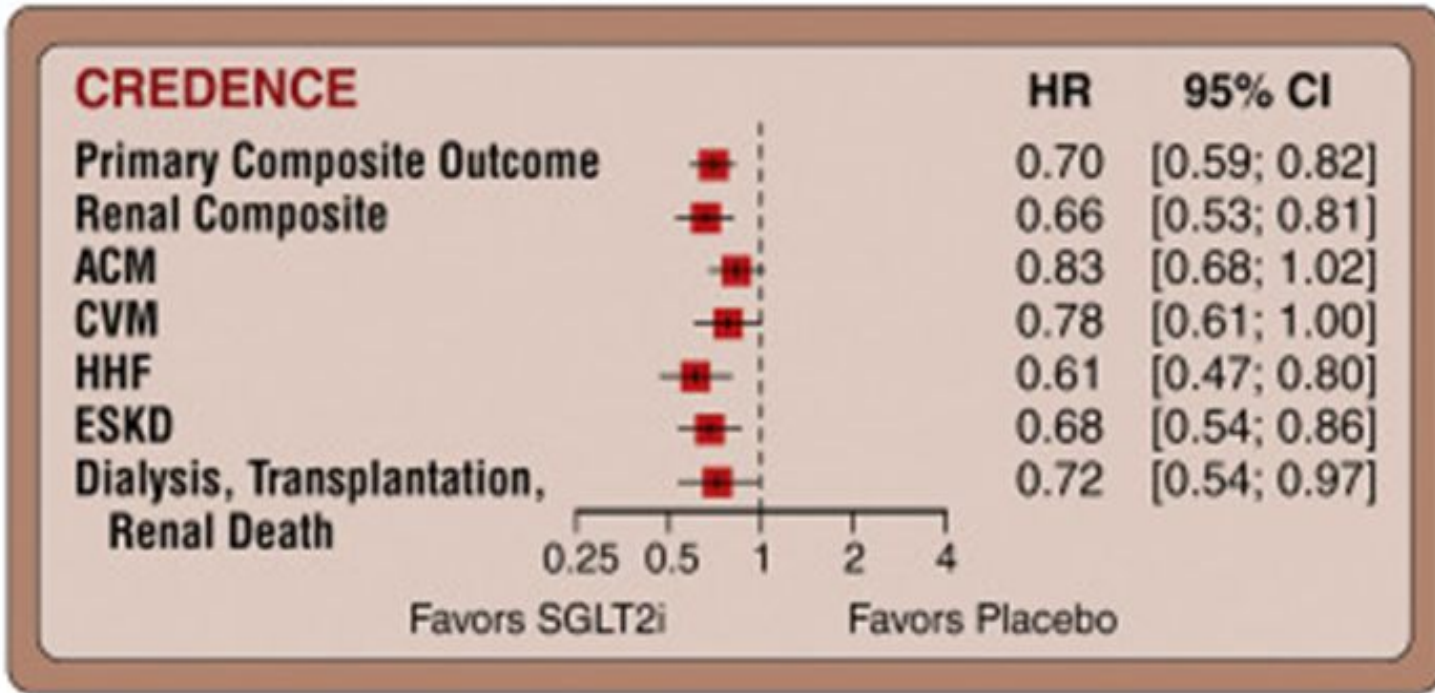
Defronzo et al Nat Reviews Nephrology 2017

SGLT2i and the kidney



- SGLT2 inhibitors –CREDENCE 2019
- Stopped early for efficacy

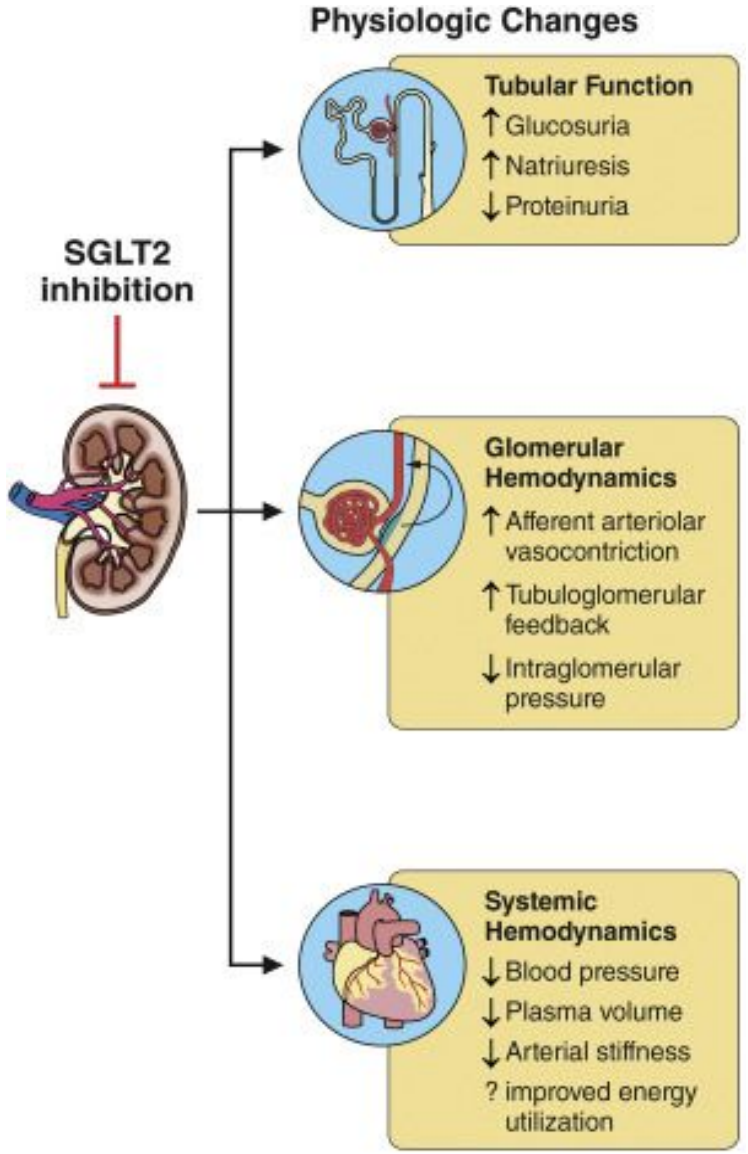
Primary Renal Outcome Trials



Cherney and Verma Cell Metabolism 2019

SGLT2i and the kidney

- Tubuloglomerular feedback

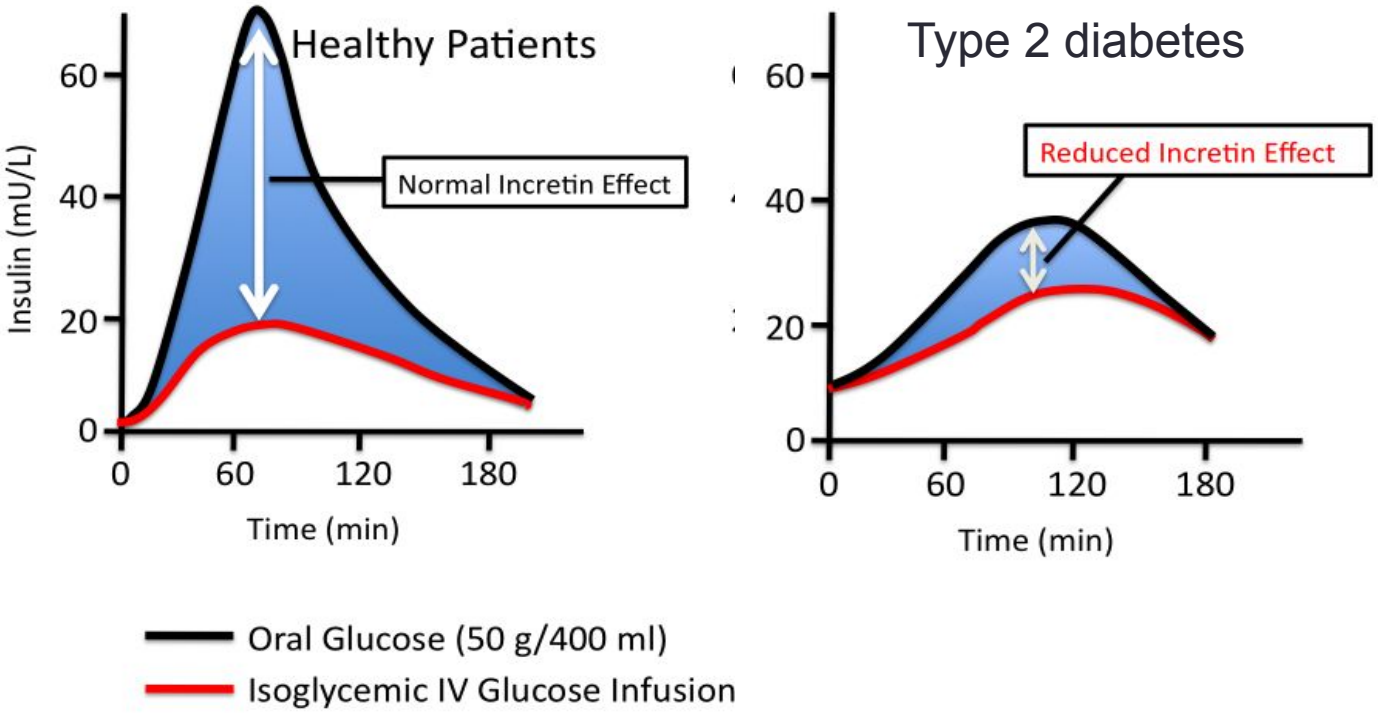


Cherney and Verma Cell Metabolism 2019

Cardiovascular outcomes trials (CVOTs) of newer antihyperglycemic drugs

- SGLT2 inhibitors
- GLP-1 analogs
- DPP-4 inhibitors

Diabetes and the incretin effect



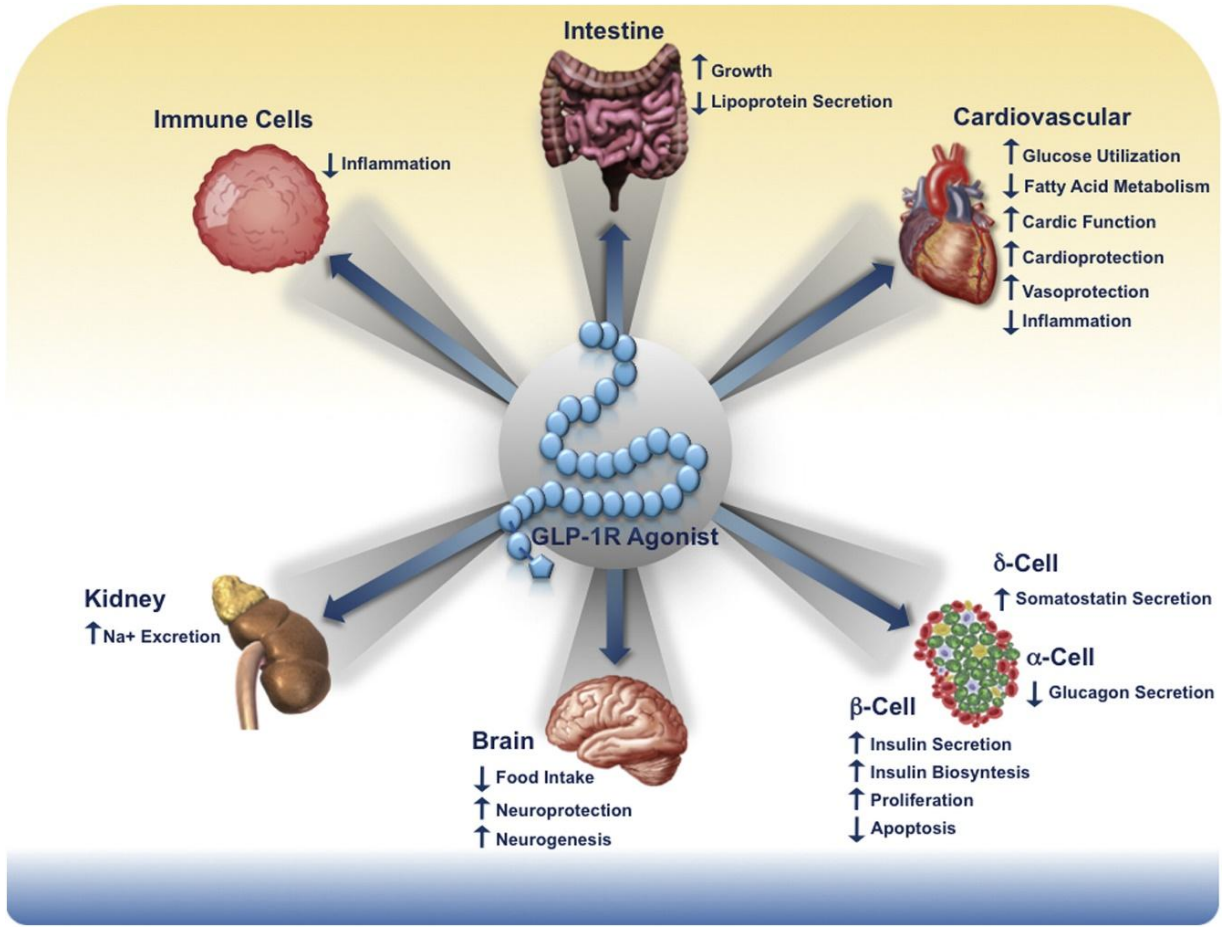
<u>Incretins</u>

Glucagon like peptide 1 (GLP-1)

Gastric inhibitory peptide (GIP)

Nauck M et al. Diabetologia 1986

GLP1 receptor analogs



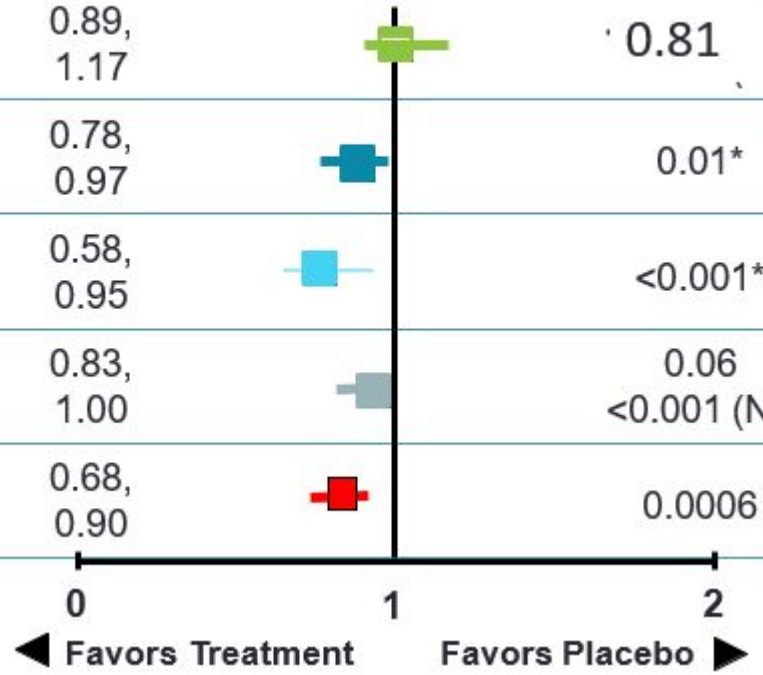
Campbell & Drucker 2013 Cell Metabolism

Cardiovascular outcomes trials of GLP1 receptor analogs

Study	Drug	Completion
ELIXA	lixisenatide	2015
LEADER	liraglutide	2015
SUSTAIN 6	semaglutide	2016
EXSCEL	exenatide	2018
REWIND	dulaglutide	2019
HARMONY Outcomes	albiglutide	2019

Summary of completed GLP1-agonist CVOTS

MACE Outcomes	Hazard Ratio	95% CI	P-Value (superiority)
ELIXA (lixisenatide vs PBO)	1.02	0.89, 1.17	0.81
LEADER (liraglutide vs PBO)	0.87	0.78, 0.97	0.01*
SUSTAIN-6* (semaglutide vs PBO)	0.74	0.58, 0.95	<0.001*
EXSCEL (exenatide vs PBO)	0.91	0.83, 1.00	0.06 <0.001 (NI)
Harmony Outcomes (albiglutide vs PBO)	0.78	0.68, 0.90	0.0006



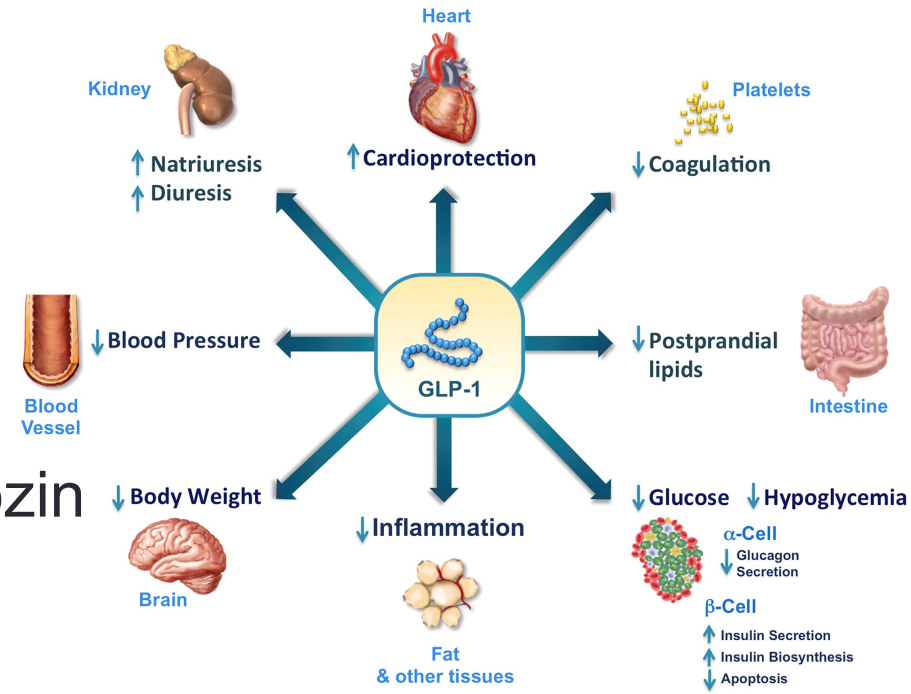
REWIND 2019 - Dulaglutide and CV outcomes

- REWIND – dulaglutide 1.5mg weekly
- N=9,901
- International study
- T2D ~10y, A1C 7.3%
- Higher proportion of women
- 31% with ASCVD

- Decreased 3 point MACE; demonstrated superiority

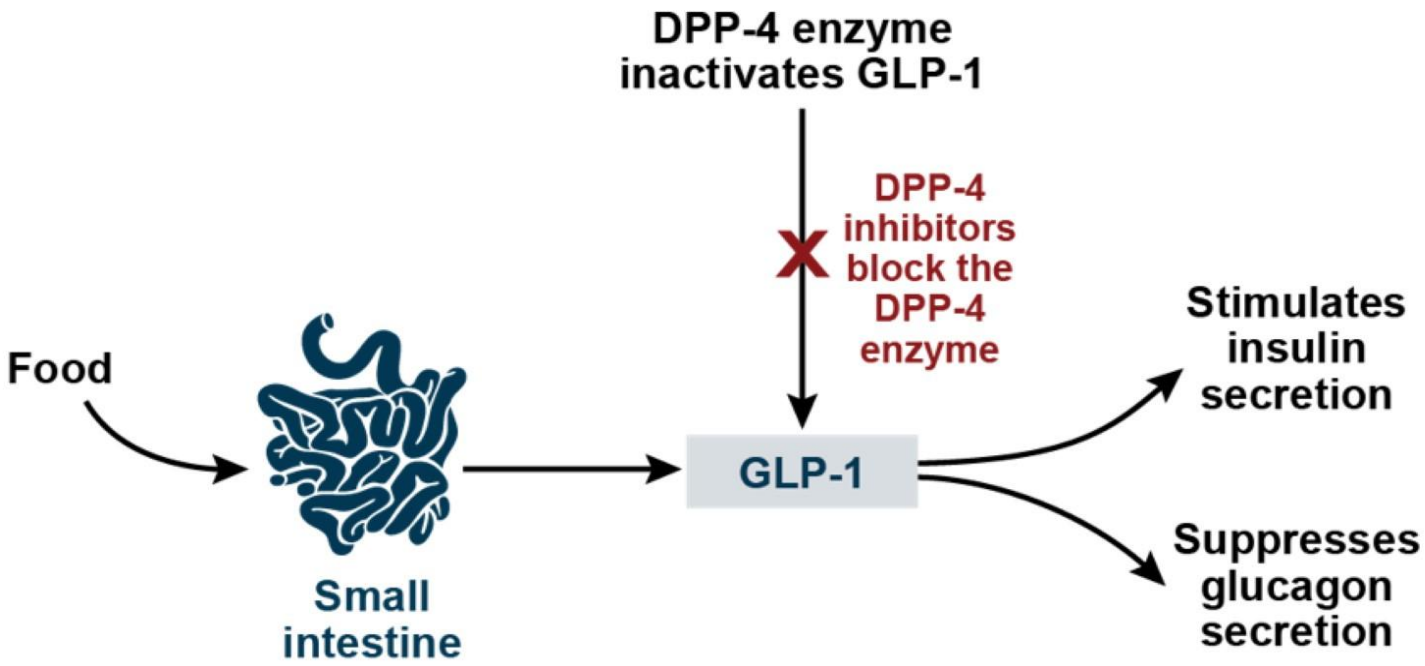
GLP1 receptor agonists: do they decrease CV risk?

- Pattern different from that of SGLT2 inhibitors
- Associated with
  - Modest ↓ in A1C, BP and body weight
  - Slight ↓ in LDL-c
  - Slight ↑ in heart rate
- Time to benefit emerged earlier than with empagliflozin
  - Different patient populations
  - Modified progression of atherosclerotic CVD
- Mechanism are unclear – pre-clinical studies suggest anti-inflammatory, anti-oxidant and pro-survival pathways
- Heterogeneity with agents: lack of a class effect
  - Liraglutide, semaglutide benefit CVD and albuminuria benefit



Drucker DJ 2016 Cell metabolism

What about the DPP4 inhibitors and cardiovascular safety?



CVOT of DPP4 inhibitors: what do we know in 2019?

- Cardiovascular neutral – no benefit
- All 4 DPP4 inhibitors demonstrated cardiovascular safety in >50,000 patients with T2D
- Non-inferior to placebo in all CVOTs
- Cost is an issue

Summary of CVOTs

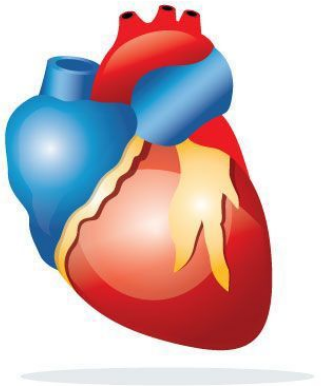
Drug class	Trial	Trial	Trial
DPP4 inhibitor	SAVOR-TIMI53	EXAMINE	TECOS
	neutral	neutral	neutral
	CARMELINA	CAROLINA	
	neutral	TBD	
SGLT2 inhibitor	EMPA-REG	CANVAS	DECLARE-TIMI 58
	beneficial	beneficial?	beneficial?
GLP1 R agonist	LEADER	ELIXA	SUSTAIN-6
	beneficial	neutral	beneficial
	EXSCEL	REWIND	HARMONY
	neutral	beneficial	beneficial

“I prefer Sulfonylureas because they are low cost”

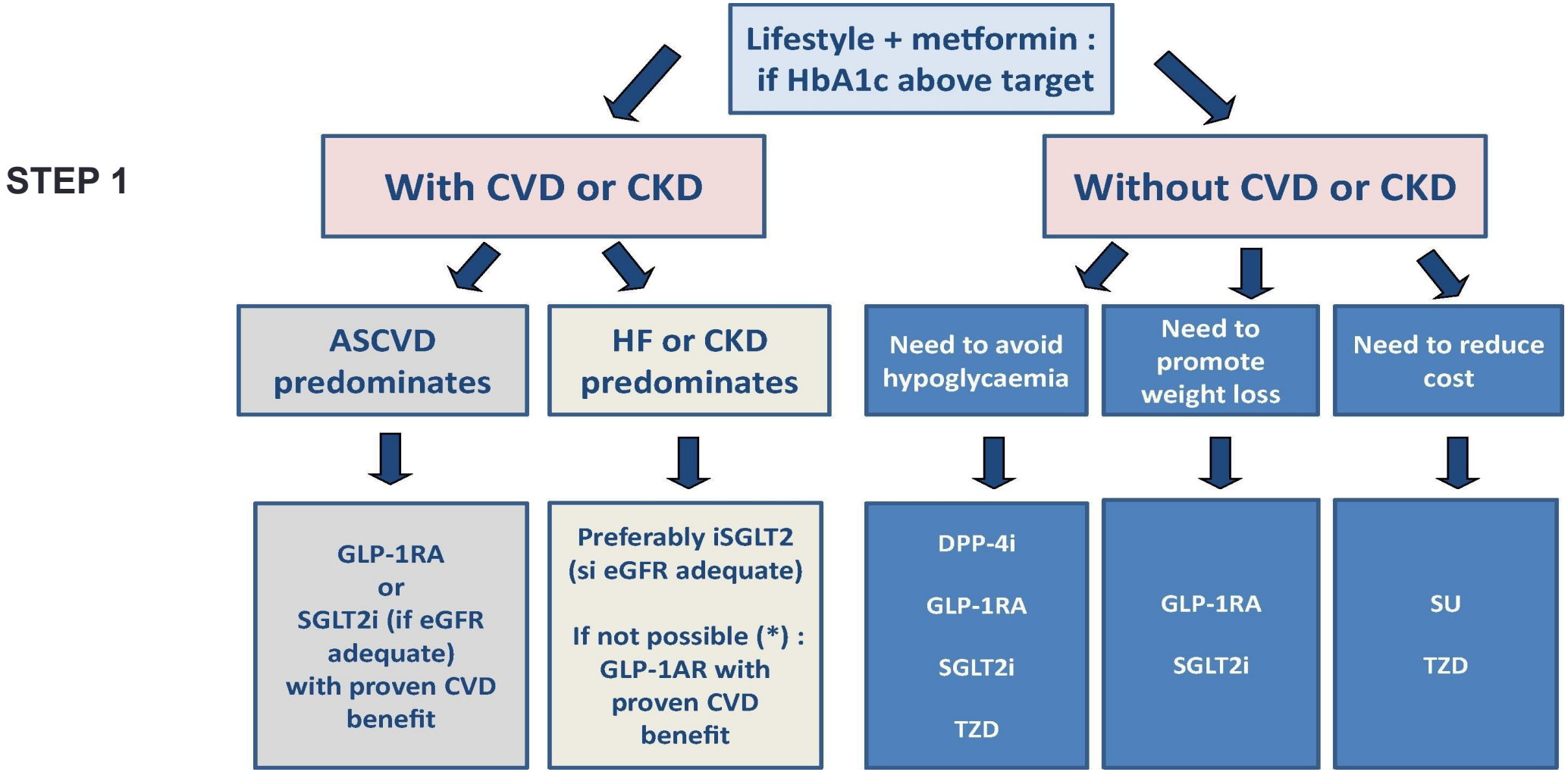
- Increased cardiovascular mortality (tolbutamide, UGDP 1970)
- Other observational studies show similar results
  - ? Impairment of ischemic preconditioning

- CAROLINA trial – completed September 2018
- Comparison of DPP4 inhibitor linagliptin and sulfonylurea
  - largest head-to-head comparison of an SU and DPP4i
  - N=6033 with ASCVD or increased CV risk
  - 6 years follow up; no safety signals

How to incorporate newer drugs in practice?



Summary of new ADA/EASD guidelines 2019



Remember this guy?

- 64 year old male
- Type 2 diabetes for 8 years
- CAD, had 2 stents placed 3 years ago after a myocardial infarction; EF is 40%
- Has microalbuminuria, no retinopathy
- Currently takes metformin, aspirin, beta blocker, statin
- BP 132/76 mmHg, BMI 33 kg/m^2; eGFR 55 $ml/m^2/min$
- A1C 8.1%

64 y/o male with known CAD

- Started on empagliflozin 10mg
- A1C in 3 months now 7.3%
- No side effects so far

- GLP-1 analog is also a reasonable option
- Better A1C lowering with weight loss

- Newer anti-hyperglycemic medications: evidence, risks and benefits
- Advances in blood glucose testing and the use of insulin pumps
- Perioperative care for patients with diabetes including risk assessment, glycemic goals and choice of medications.

Glucose monitoring technologies

- Self monitoring of blood glucose (SMBG)
- ADA – Standards of Care 2019 –
- When prescribed as part of a broad education program,… helps guide treatment decisions and/or self-management for patients

- Many patients struggle with fingerstick checks

Continuous glucose monitoring

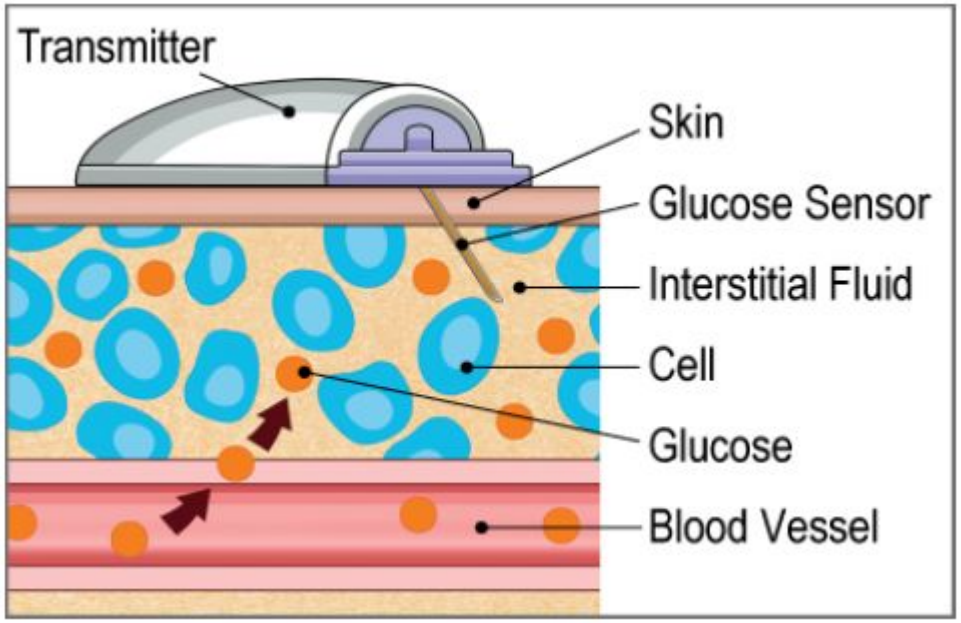
Continuous glucose monitoring

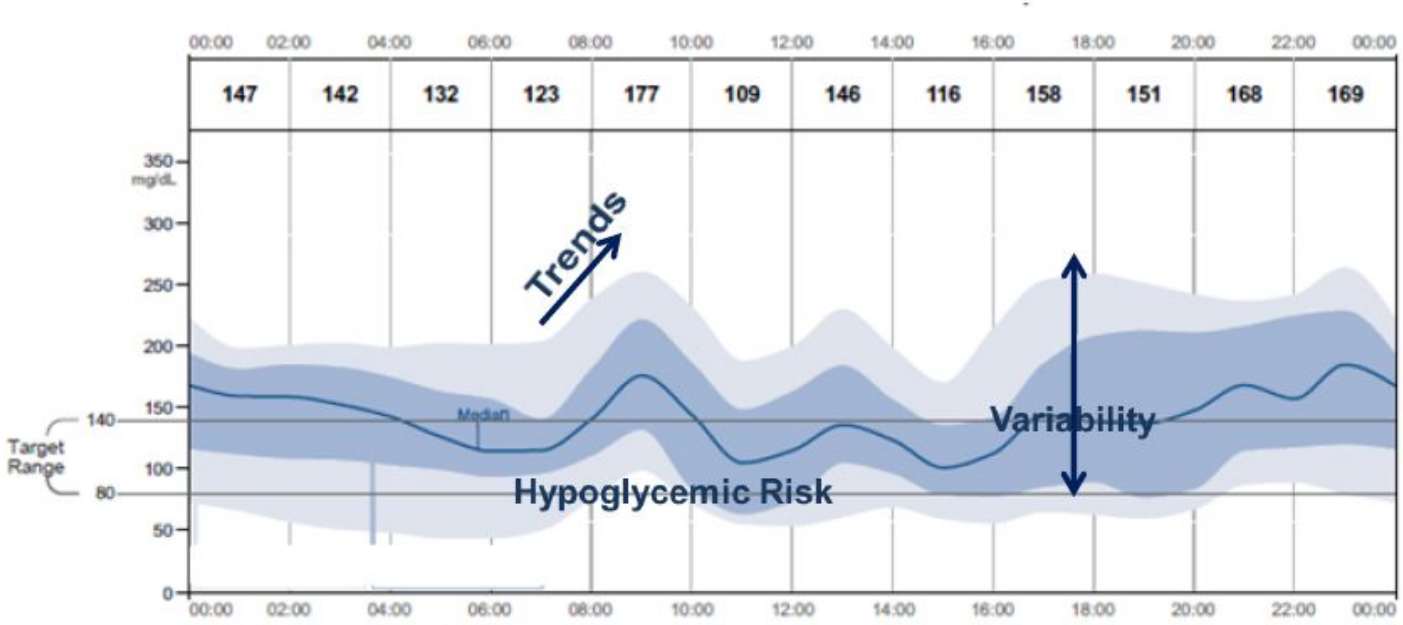
IMPLANTABLE SENSOR

Why do we need this?

- **Patients are asking**
- Behavioral changes; patient engagement
- Personalized care
- Pattern recognition; therapy advancement

How does CGM measure blood glucose?





- Flash glucose monitoring available for personal or professional use
- Available by prescription – one for reader, one for sensors

CGM Glucose Pattern Summary

August 1, 2018 - August 28, 2018 (28 Days)

LibreView

CGM Device: FreeStyle Libre [N/A]% Compliant w/Calibration* 93% Time Worn

*Not applicable to FreeStyle Libre or FreeStyle Libre Pro which do not require calibration.

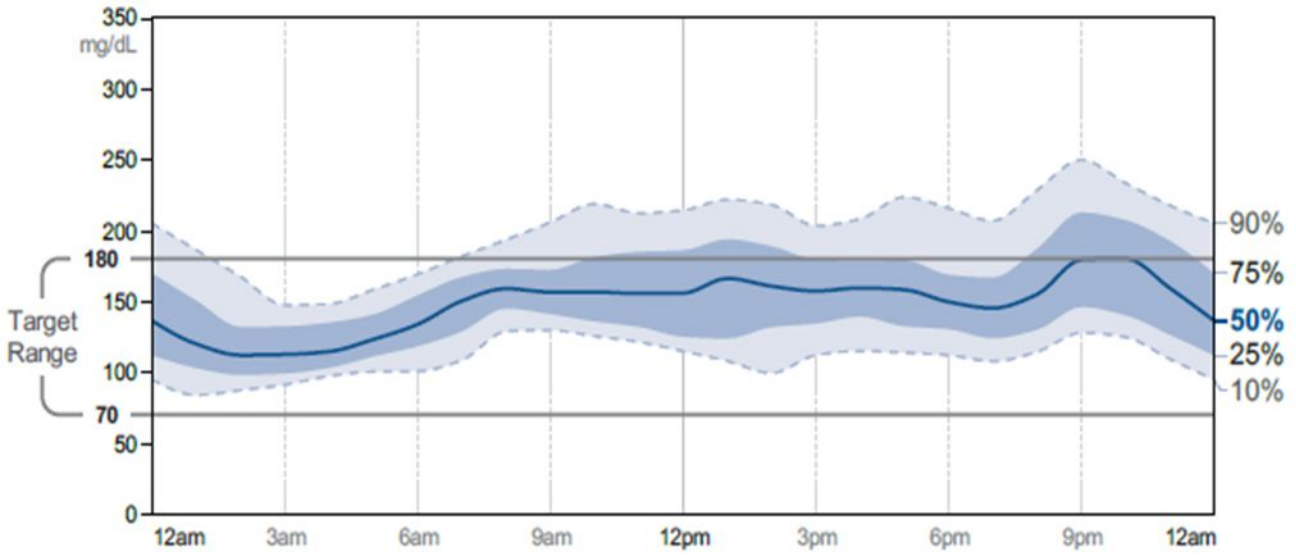
Summary

Average Glucose	Time In Range	Coefficient of Variation (CV)	Standard Deviation (SD)
151 mg/dL	Above 180 mg/dL (above 250 mg/dL: 2%) 22%	27.2%	41.1 mg/dL
88-116*	In Target Range 70-180 mg/dL 77%	19-25*	10-26*
	Below 70 mg/dL (below 54 mg/dL: 0%) 1%		

*Reference ranges calculated from population without diabetes.

Ambulatory Glucose Profile

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

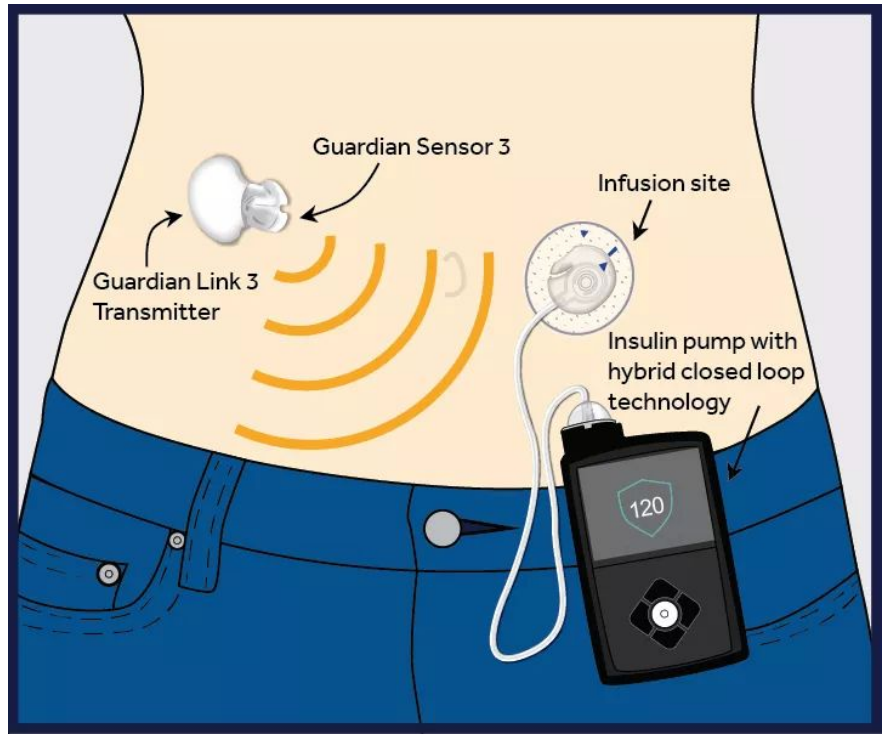


Insulin pens

- Reusable insulin pens - Inpen
- Aspart or lispro penfill cartridges
- ½ unit dose increments
- Pairs via Bluetooth to smartphone app
- Set reminders, track insulin doses
- Calculate insulin doses using individualized algorithms
- Share information with HCP

Insulin pump therapy

- Use is increasing in the US
- Majority are type 1 diabetes, but more in T2D also
- Closed loop therapy for Type 1 diabetes



- Newer anti-hyperglycemic medications: evidence, risks and benefits
- Advances in blood glucose testing and the use of insulin pumps
- Perioperative care for patients with diabetes including risk assessment, glycemic goals and choice of medications

Diabetes medications and elective procedures

- Mr. A has had T2D for 7 years needs to undergo elective surgery
- Current meds include metformin, dapagliflozin, glargine 35 units at bedtime

- What about if he was undergoing a colonoscopy?

Perioperative management of diabetes

- 1 year mortality associated with pre-op blood glucoses
- Increased post-op infection risk for A1C >7%
- Lack of RCTs for best pre-operative oral therapies blood glucose management

Oral medication use the day before and day of elective surgery

Medication	Day before surgery	Day of surgery if: 1. Normal oral intake 2. Minimally invasive surgery	Day of surgery if: 1. Decreased post-op oral intake OR 2. Extensive surgery, fluid shift etc
Metformin	Take	Take/hold	Hold
Sulfonylurea	Take	Hold	Hold
TZD	Take	Take	Hold
DPP4 inhibitors	Take	Take	Take
SGLT2 inhibitors	Hold	Hold	Hold

Insulin or non-insulin injectable use based on oral intake

For bowel prep – clear liquids only 12-24h before surgery

- GLP-1 analogs – daily dose HOLD when starting bowel prep
- Insulin –
- if dose taken in evening – basal insulin decrease by 20-30% of usual dose

Day of surgery and post operative insulin

- Glargine or detemir – 80% of usual dose, especially for twice daily regimens
- NPH or premixed insulin – 50% of usual dose
- Hold meal-time insulin
- Non-insulin injectables – hold

- Post operative for non-ICU patients – subcutaneous insulin can be continued
- Basal-bolus regimens continued
- Do not use correctional insulin only

What about patients on insulin pumps and CGMs?

- Patients with an insulin pump should continue insulin preoperatively and on the day of surgery
- Patient's home device may be used in the operating room
- Pre-operative planning to facilitate pump use in the operating room, especially for outpatient surgery, prevents interruption of the patient's normal insulin routine
- CGM can also be used similarly
- **Establishment of clear policies and procedures to guide patients and hospital staff in diabetes management with the use of insulin pumps**

Take away points

1. New trials in the past 4 years in patients with T2D show cardiovascular outcome benefit from use of SGLT2i and GLP1RA in patients with diabetes and known ASCVD
2. Addition of these agents after metformin should be strongly considered in patients with CVD/HF/CKD
3. SGLT2i but not GLP1-RA reduce the risk of heart failure
4. SGLT2i reduce the risk of worsening estimated glomerular filtration rate
5. DPP4 inhibitors are mostly safe, have no CV benefit and are costly

Take away points

6. New glucose monitoring technologies help with increased patient engagement, behavior change and improved glycemic management
7. Smart insulin pens can help with accurate pre-meal insulin dosing
8. SGLT2 inhibitors should be held for 48 hours before surgery
9. GLP-1 analogs should be held in hospitalized patients

Thank you

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