

Summary of CVD Trials – SGLT-2 inhibitors

	MACE	MI	CVA	CV death	HHF	All Death
Empagliflozin	0.86	0.87	1.18	0.62	0.65	0.68
Canagliflozin	0.86	0.85	0.90	0.90	0.67	0.87
Dapagliflozin	0.93	0.89	1.10	0.98	0.73	0.93

1. Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128.
2. Neal B, et al. *N Engl J Med.* 2017; DOI: 10.1056/NEJMoa161192
3. Wiviott SD et al. *N Engl J Med.*

Patient Characteristics of GLP-1 RA CV Outcomes Trials

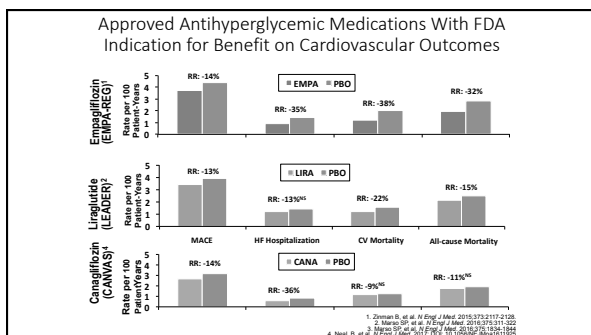
	ELIXA	LEADER	SUSTAIN	EXSCEL	REWIND	HARMONY
Mean age, y	60	64	65	62	66	64
Diabetes duration, y	9	13	14	12	NR	14
% with prior HF	22	14	24	16	8.6	20
% with prior CVD	100	81	83	73	31	100
% with CKD 3	23	25	25	22	22	23
HbA1c, %	7.6	8.7	8.7	8.0	7.3	8.7
Statin use, %	64	75	73	73	66	84
Premature discontinuation (%)	25	NR (17)	20	44	NA	13
Antihyperglycemic therapy, %	-MET 66 -SU 33 -TZD 2 -INS 39	-MET 76 -SU 50 -TZD 9 -INS 45	-MET 73 -SU 43 -TZD 2 -INS 20	-MET 77 -SU 37 -TZD 4 -INS 46	-MET 81 -SU 57 TZD 2 -INS 24	-MET 73 -SU 28 -TZD 2 -INS 60

Adapted from: Standl E, et al. *Circ Res.* 2016;118:1830-1843.

Patient Characteristics of SGLT-2 CV Outcomes Trials

	EMPA-REG	CANVAS/R	DECLARE	VERTIS-CV
Mean age, y	63	63	64	64
Diabetes duration, y	12	14	9	13
% with prior HF	10	14	10	23
% with prior CVD	100	66	41	100
% with CKD 3	26	20	9	22
HbA1c, %	8.1	8.2	8.3	8.3
Statin use, %	77	75	64	81
Premature discontinuation (%)	25	29 (but 40% in CANVAS)	25	NA
Antihyperglycemic therapy, %	-MET 77 -SU 43 -TZD 4 -INS 69	-MET 77 -SU 43 -TZD NR -INS 50	-MET 66 -SU 33 -TZD 2 -INS 39	-MET 76 -SU 41 -TZD 2 -INS 47

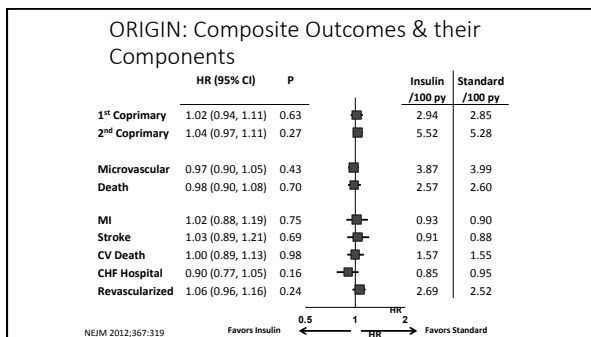
Adapted from: Standl E, et al. *Circ Res.* 2016;118:1830-1843.

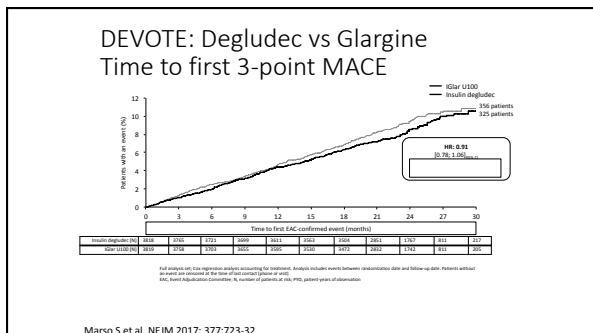


Comparison of Changes in CVD Risk Factors

	LEADER	EMPA-REG	CANVAS/-R
Weight (kg)	-2.3	-2	-1.6
SBP (mmHg)	-1.2	-3.0	-3.9
DBP (mmHg)	+0.6	0	-1.4
HR (BPM)	+3	0	0
A1c (%)	-0.4	-0.6	-0.6
HDL (mg/dl)	0	+4	+2.1
LDL (mg/dl)	0	0	+4.6

1. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128. 2. Marso SP, et al. *N Engl J Med*. 2016;375:311-322. 3. Neal B et al. *N Engl J Med* 2017





Microvascular Outcomes

Microvascular Complications in the CVOT studies

STUDY	Nephropathy (HR)	Retinopathy (HR)	Amputation (HR)
EMPA-REG	0.61	NR	0 [†]
CANVAS	0.60	NR	1.97 [‡]
LEADER	0.78	1.15*	NR
SUSTAIN-6	0.64	1.76*	NR

- In the SUSTAIN study: 79 events/3297 pts. 83% gave hx of DR, 29% hx of PDR
- In the CANVAS study: 125 events/10,142 pts. 71% "minor". Highest with hx of amputation & PVD

* Enrolled patients with higher A1c – monitored retinopathy as event of interest
 † Events/1000 patient years 6.5/1000 in treatment groups in both studies. Differences noted in placebo event rate.
 EMPA – not collected during study

Other
Adverse Events of Interest

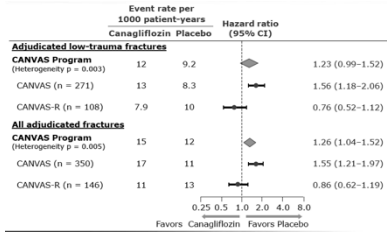
Hypoglycemia

- Despite all studies showed a lower A1c with active treatment, only LEADER reported lower risk of hypoglycemia:
 - Confirmed: HR 0.80
 - Severe: HR 0.69

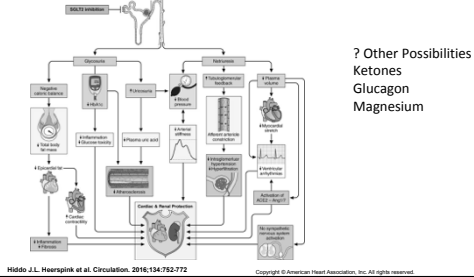
Other Adverse Events of Interest

- In the studies with GLP-1 RA, the adverse profile was as expected: GI SE, injection site reactions (n = 27,389) .
 - In LEADER, there was increase in gallbladder disease
 - Despite increases in lipase and amylase, there was no evidence of increase in risk for pancreatitis nor pancreatic cancer.
 - There was no evidence of increased risk for medullary cancer of the thyroid
- In the studies with SGLT-2 inhibitors, there was increased risk for genital mycotic infections and symptoms of volume depletion (n = 17,162)
 - Volume depletion was reported in 26 and 17/1000 pt-years in CANVAS and EMPA-REG respectively
 - There was no increase in risk for UTI, DKA, acute kidney injury, hyperkalemia.

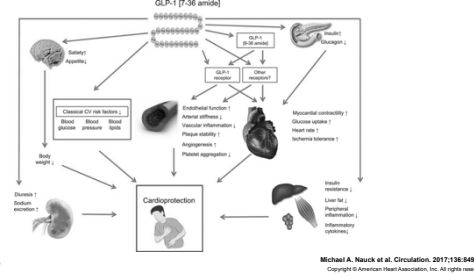
CANVAS Program: Fractures



Physiologic mechanisms implicated in the cardiovascular and renal protection with SGLT2 inhibition.

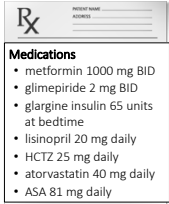


Potential mechanisms of beneficial effect of glucagon-like peptide-1 (GLP-1) receptor agonists on reducing cardiovascular



Janice

- A 69-year-old woman with a 14 year history of T2D is seen for diabetes management. She has history of Right CVA 6 months ago. She has a 40 pack-year history of smoking, but quit after CVA.
- BP 142/90, BMI 36 kg/m²
- PE: unremarkable
- Labs: HbA_{1c} 8.5%, eGFR 40 mL/min/1.73m², LDL 90, HDL 37, TG 224; ALT normal; UACR 45
- SMBGs high 100s AM, 200s rest of the day



Medications

- metformin 1000 mg BID
- glimepiride 2 mg BID
- glargine insulin 65 units at bedtime
- lisinopril 20 mg daily
- HCTZ 25 mg daily
- atorvastatin 40 mg daily
- ASA 81 mg daily

What is your A1c goal for Janice?

A. <6.0%
 B. <6.5%
 C. <7.0%
 D. <7.5%
 E. <8.0%

What is the best next step to improve glycemic control?

A. Increase glimepiride to 4 mg BID
 B. Add linagliptin 5 mg daily
 C. Add lispro with each meal
 D. Add canagliflozin 100 mg daily
 E. Add liraglutide up to 1.8 mg daily

Treatment Considerations for Janice

- Due to age and serious comorbidities, I would be satisfied with an A1c in the 7's.
- With her low GFR, I would opt for substituting liraglutide for glimepiride
 - Ensure up to date on eye exam.
 - Advise about GI SE: slow titration
 - Advise about risk for gallbladder disease
- Lower insulin dose by at least 20%
- With history of CVA, lower target BP might be indicated, if tolerated
 - Consider an orthostatic BP/P
 - Helpful to know the carotid anatomy
- Consideration for increasing atorvastatin vs adding ezetimibe

Cost of Liraglutide vs SGLT-2 Inhibitors

Drug	Lowest cost for 30 days
Liraglutide 1.8 mg	\$950/633 (1.2 mg)
Empagliflozin 25 mg	\$476/238 (1/2 tab)
Canagliflozin 300 mg	\$514/257 (1/2 tab)

Source: GoodRx.com for zip 99203, accessed 4/1/19

Liraglutide – to Minimize Side Effects

- Nausea/Vomiting – start low and titrate slowly. Encourage to start with smaller servings and eat more slowly
- Consider decreasing insulin (prandial and basal) by 20% and/or glimepiride
- Label warnings that were not seen in excess in CVOT
 - Acute Kidney Injury
 - Pancreatitis
 - Medullary Thyroid CA (is primarily restricted to rodents)
- Cholelithiasis – new signal seen in the LEADER trial
 - Educate patients of symptoms

SGLT-2 Inhibitors: Minimizing Adverse Events

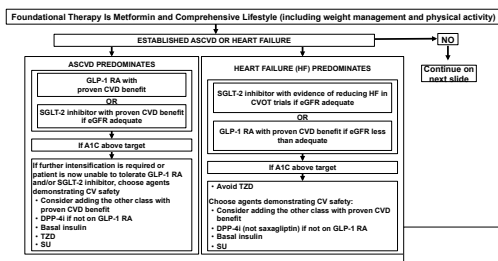
- Not to be used with GFR < 45 (due to poor glycemic efficacy). This might change (discussed later)
- Genital mycotic infections in 6 – 10% of women (75% of which only have one) – usual OTC treatments effective without stopping/holding the medication
- Fournier's gangrene reported, but extremely rare, no clear cause/effect
- Volume Depletion – advise to drink 16 – 32 oz of additional water daily
- Orthostasis – if BP is at target, then lower or discontinue one medication (usually the diuretic)
- Amputations (canagliflozin) – likely related to decreased perfusion - avoid hypotension and volume depletion
- Fractures (canagliflozin) - avoid hypotension and volume depletion
- Label Warnings that were not seen in excess in the CVOT
 - AKI
 - UTI
 - DKA

Treatment Recommendations Specify Multiple Individualized Goals for Patients With T2DM

<p>Weight loss: ≥ 5%¹ For overweight or obese patients, based on achievement of individualized <u>health</u> goals</p> <p>Weight loss based on BMI² For all patients</p>	<p>A1C: < 7.0%¹ or ≤ 6.5%² More stringent (eg, < 6.5%) for some, if safely achievable.^{1,2} Higher (eg, < 8.0%) may be appropriate for others.^{1,2}</p>
<p>BP: < 140/90¹ mm Hg or < 130/80² mm Hg Lower targets (eg, < 130/80 mm Hg) may be appropriate for high-risk patients, if achievable without undue treatment burden¹</p>	<p>Statin therapy according to CVD risk^{1,2}</p> <p>Combination therapy according to LDL-C and CVD risk¹ - < 70 mg/dL on statin therapy</p> <p>LDL-C based on CVD risk² - High risk: < 100 mg/dL - Very high risk: < 70 mg/dL - Extreme risk: < 55 mg/dL</p>

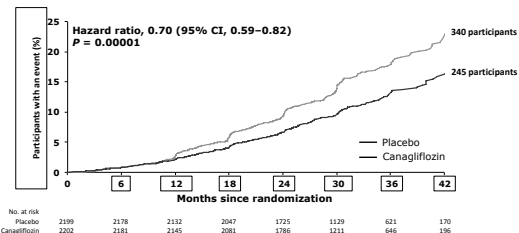
1. ADA. Diabetes Care. 2019;42(suppl 1):S1-S155.
2. Collier AC, et al. Endocrinol Pract. 2018;24:91-120.

Antihyperglycemic Medication in T2DM: Overall Approach

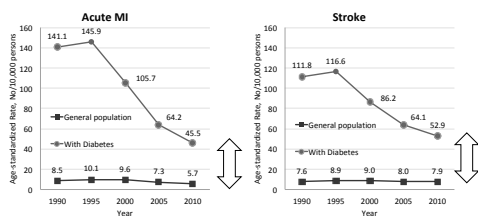


Diabetes Care reference

Credence Study: ESKD, Doubling of Serum Creatinine, or Renal or CV Death



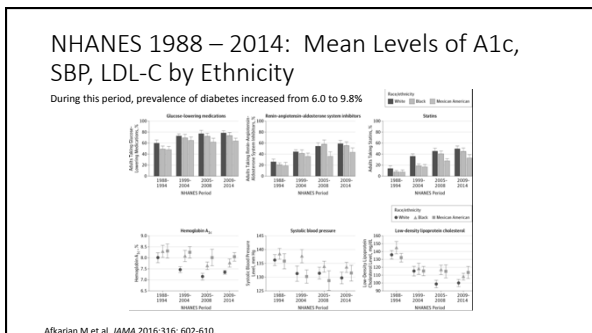
Impact of Diabetes on Vascular Disease



Gregg EW, Li Y, Wang J, Burrows NR, et al. *N Engl J Med.* 2014;370(16):1514-23.

Role of Nurses, Dieticians and Educators in Prevention of Cardiovascular Disease In Diabetes

- Emphasize the risk of cardiovascular disease in patients with diabetes
- Discuss the role (and limitations) of lifestyle modifications for prevention of CVD
- Educate patients on options for individualization of medical therapies for diabetes
- Identify high risk patients:
 - Long duration of diabetes
 - Known coronary artery disease
 - Known congestive heart failure
 - Known chronic kidney disease
 - Known retinopathy
 - Report of decreased exertional tolerance due to dyspnea, claudication or "fatigue"
- Act as liaison between patient and provider to advocate for appropriate therapies



Cardiovascular (CV) Risk Factor Targets and CV Disease Event Risk in Diabetes:

We are not getting the job done

Percent at target levels for any one, two, or all three factors among the 2018 persons with diabetes:

Any 1 of 3	Any 2 of 3	3 of 3
41.1%	26.5%	7.2%

Percent CVD risk reduction for being at target level among the 2018 persons with diabetes for each of the

Blood pressure	LDL-C	HBA1c
17%	33%	37%

Percent lower adjusted risk of CVD events with one, two, or three risk factors at target level:

Any 1 of 3	Any 2 of 3	3 of 3
36%	52%	62%

Wong, et al. Diabetes Care 2016 May; 39(5): 668-676.

- ### Summary: Lowering Risk for CVD events in Diabetes
- Clear evidence of CVD/mortality in T2DM over several decades, but there remains a large gap over the risk for patients without diabetes
 - Better management of CVD risk factors have a major role, but many sub-optimally treated
 - BP and LDL-C reduction > glucose reduction
 - Smoking reduction
 - Best time to prevent CVD with glucose control is at diagnosis of diabetes
 - Cardiovascular outcome trials show safety of DPP-4 inhibitors, insulin glargine, insulin degludec, lixisenatide and exenatide QW
 - Data from cardiovascular outcome trials support role of SGLT-2 inhibitors (empagliflozin and canagliflozin) and long-acting GLP-1 receptor agonists (liraglutide) for reduction of CVD events in patients with established CVD
 - For patients with heart failure, SGLT-2 inhibitors are preferred.
 - For now, patients with GFR < 45, Liraglutide is preferred (Credence will change this)

With a missionary zeal, one must convert not only the patient's mind and soul, but also his doctor to the realization that it is worth the effort to control the disease as shown by the sugar-free urine, normal blood sugar and cholesterol.

Elliott P. Joslin — 1959
