Should Empagliflozin and Liraglutide be Included in Cardiovascular Guidelines?

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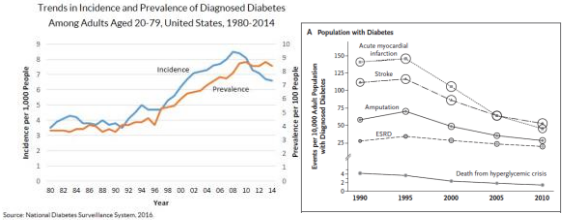
Objectives

- Describe the cardiovascular benefits of empagliflozin and liraglutide
- Design a regimen for a patient with diabetes and cardiovascular disease that optimizes care of both disease states

Cardiovascular disease is the leading cause of death in diabetes

29.1 million people have diabetes

50% higher risk of death

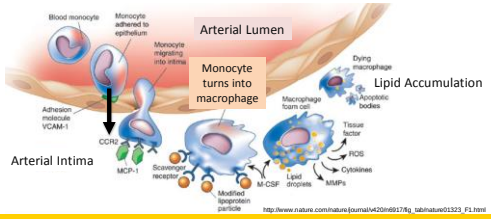


N Engl J Med. 2014;370:1514-23
CDC Diabetes Data and Statistics at https://www.cdc.gov/diabetes/data/

Pathogenesis of atherosclerosis

Endothelial Injury

- Physical stress or trauma – hypertension
- Turbulent blood flow (artery branching)
- Reactive oxygen species (smoking)
- Hyperlipidemia
- Hyperglycemia
- Homocysteinemia



Nature 2002;420:868-74

Hyperglycemia promotes atherosclerosis

- DM accelerates the natural time course of atherosclerosis involving greater number of vessels and diffuse disease
- Glycosylation of proteins to form advanced glycosylation end products (AGEs)
  - Impaired clearance of low-density lipoprotein (LDL), increased recognition by macrophages → foam cell formation
  - Increased endothelial cell permeability and smooth muscle cell proliferation
- Formation of reactive oxygen species

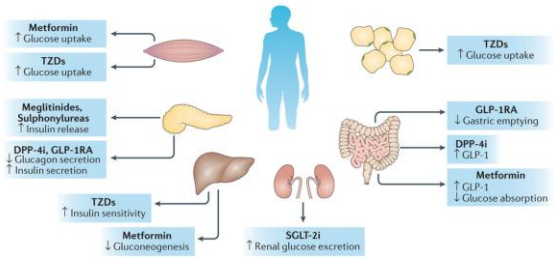
Cardiovasc Diabetol. 2002;1:1

Current recommendations for glycemic goals: A1c < 7%

- Lower HbA1c = ↓ microvascular complications
  - Can consider targeting A1c <6.5%
- More intensive treatment in newly diagnosed patients may reduce long-term CVD rates
  - UKPDS – ↓ MI & SCD in intensive glycemic control arm (p=0.052)
  - 10-year observational f/u significant ↓ MI and all-cause mortality
- Intensive treatment in patients with advanced DM is controversial – consider less stringent goal?
  - ACCORD – increased CV mortality and all-cause mortality
  - ADVANCE – no evidence of benefit or harm
  - VADT – reduction in CV events but not mortality

Diabetes Care 2009;32(1):187-192.
Diabetes Care 2017;40(Suppl 1):S48-S56
Lancet 1998;352:837-53

Let's reduce hyperglycemia and lower cardiovascular risk!



Nature Reviews 2016;12:370-346

However, antidiabetic agents should not be considered interchangeable

TZDs
- Rosiglitazone – ↑ MI & HF risk
- Pioglitazone – ↑ HF risk

Repaglinide?
Tolbutamide

FDA releases guidance for completion of CV trials

DPP-4 Inhibitors
- Saxagliptin – ↑ HF hospitalization
- Sitagliptin, alogplitin – no CV benefit

N Engl J Med 2015;373:232-42
Lancet 2015;385:2067-76.
JAMA 2007;298(10):1189-95.
N Engl J Med. 2013;369:1317-26

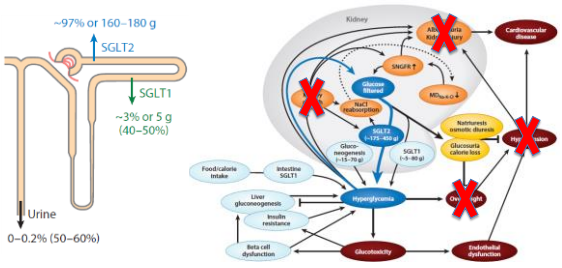
FDA. Guidance for industry diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. 2008
JAMA 2007;298(10):1180-88.
Lancet 2005;366:1279-89

Need safe and efficacious therapy

↓CV risk
↓Microvascular complications

Hypoglycemia risk
Side effects

Sodium Glucose Transporter – 2 (SGLT-2)



Annu Rev Med. 2015;66:255-70

Is there additional benefit of SGLT-1 inhibition?

Delayed intestinal glucose absorption

↓

Increased glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP)

↓

↑insulin release (glucose-dependent manner), ↓pancreatic glucagon secretion, ↓appetite

Annu Rev Med. 2015;66:255-70

Empagliflozin is the 3rd agent to become available in this class

- SGLT-2 inhibition only
- Dosing: 10 mg once daily, can increase to 25 mg
  - CrCl 30-45 ml/min: Not recommended for use
  - CrCl < 30 ml/min: Contraindicated
- Lowers A1c ~0.5-0.8%
- SBP reduction ~3-5 mmHg
- Weight loss ~1-2 kg
- Others: dapagliflozin, canagliflozin

Jardiance [package insert] Boehringer Ingleheim Inc; 2016

What factors may limit blood glucose lowering effect of SGLT2 inhibitors?

- Increased endogenous glucose production (likely hepatic gluconeogenesis)
- Reduced GFR (less filtered glucose)
  - Canagliflozin and empagliflozin reduce A1c in GFR as low as 30 mL/min/1.73m²
  - Small reduction in GFR in CKD stage 3 patients, but also reduction in albuminuria
  - Increased adverse events and no reduction in A1c in CKD stage 4

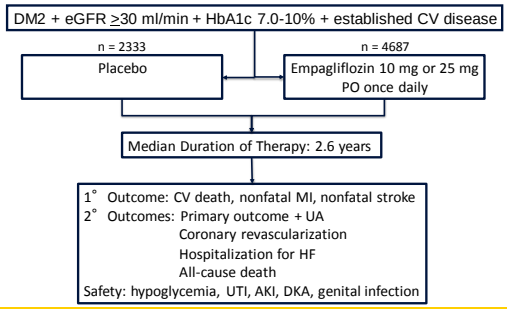
Annu Rev Med. 2015;66:255-70
Lancet Diabetes Endocrinol 2014;2:369-84

Safety concerns with SGLT-2 inhibitors

- Urinary tract infections
- Fungal genital infections
- Ketoacidosis
- Hypotension/Volume depletion
- Increased LDL

Jardiance [package insert] Boehringer Ingleheim, Inc; 2016
Lancet 2014;2:369-84

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME)



N Engl J Med. 2015;373:2117-28.

Baseline characteristics were well balanced between groups

	Placebo (%)	Empagliflozin - Pooled (%)
Age, years ± SD	63.2 ± 8.8	63.1 ± 8.6
Race		
White	1678 (71.9)	3403 (72.6)
Asian	511 (21.9)	1006 (21.5)
Black/African-American	120 (5.1)	237 (5.1)
CAD	1763 (75.6)	3545 (75.6)
MI	1083 (46.4)	2190 (46.7)
CABG	563 (24.1)	1175 (25.1)
Stroke	553 (23.7)	1084 (23.1)
PAD	479 (20.5)	982 (21.0)
Glycated Hemoglobin, %	8.08 ± 0.84	8.07 ± 0.85
Time since diagnosis of DM		
<5 years	423 (18.1)	840 (17.9)
5-10 years	571 (24.5)	1175 (25.1)
>10 years	1339 (57.4)	2672 (57.0)
Metformin	1734 (74.3)	3459 (73.8)
Insulin	1135 (48.6)	2252 (48.0)
Sulfonylurea	992 (42.5)	2014 (43.0)
Monotherapy	691 (29.6)	1380 (29.4)
ACEI/ARB	1868 (80.1)	3798 (81.0)
Statin	1773 (76.0)	3630 (77.4)
Acetylsalicylic Acid	1927 (82.6)	3876 (82.7)
Systolic blood pressure, mmHg	135.8 ± 17.2	135.3 ± 16.9
Low-density lipoprotein, mg/dL	84.9 ± 35.3	85.9 ± 36.0
High-density lipoprotein, mg/dL	44 ± 11.3	44.6 ± 11.9
Estimated GFR, ml/min/1.73m²	73.8 ± 21.1	74.2 ± 21.6

Empagliflozin significantly reduced the primary CV outcome compared to placebo

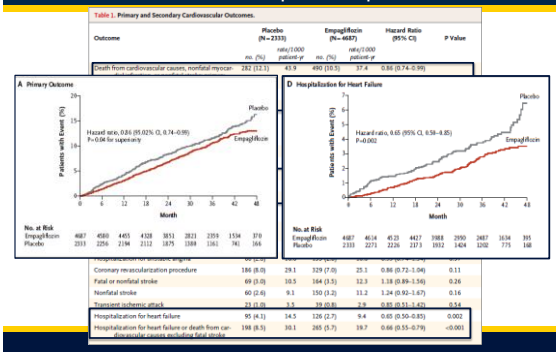


Table 1. Primary and Secondary Cardiovascular Outcomes.

Outcome	Placebo (N = 2333) no. (%)	Placebo (N = 2333) rate/1000 patient-yr	Empagliflozin (N = 4687) no. (%)	Empagliflozin (N = 4687) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Death from cardiovascular causes, nonfatal myocar-	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74–0.99)	
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from car- diovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001

N Engl J Med. 2015;373:2117-28.

The primary outcome was driven by a reduction in CV death

Table S5. Categories of cardiovascular death.

	Placebo (N = 2333)	Empagliflozin 10 mg (N = 2345)	Empagliflozin 25 mg (N = 2342)	Pooled empagliflozin (N = 4687)
	no. (%)			
Patients with cardiovascular death	137 (5.9)	90 (3.8)	82 (3.5)	172 (3.7)
Sudden death	38 (1.6)	30 (1.3)	23 (1.0)	53 (1.1)
Worsening of heart failure	19 (0.8)	7 (0.3)	4 (0.2)	11 (0.2)
Acute myocardial infarction	11 (0.5)	6 (0.3)	9 (0.4)	15 (0.3)
Stroke	11 (0.5)	9 (0.4)	7 (0.3)	16 (0.3)
Cardiogenic shock	3 (0.1)	1 (<0.1)	2 (0.1)	3 (0.1)
Other cardiovascular death*	55 (2.4)	37 (1.6)	37 (1.6)	74 (1.6)

*Includes fatal cases that were not assessable due to a lack of information and were presumed to be cardiovascular deaths as per conventional definition.

Table 1. Primary and Secondary Cardiovascular Outcomes.
Hospitalization for heart failure 95 (4.1) 14.5 126 (2.7) 9.4 0.65 (0.50–0.85) 0.002
Hospitalization for heart failure or death from car- diovascular causes excluding fatal stroke 198 (8.5) 30.1 265 (5.7) 19.7 0.66 (0.55–0.79) <0.001
N Engl J Med. 2015;373:2117-28.

Increased incidence of urinary tract infections in females and genital infections with empagliflozin

Table 2. Adverse Events.*

Event	Placebo (N = 2333)	Empagliflozin, 10 mg (N = 2345)	Empagliflozin, 25 mg (N = 2342)	Pooled Empagliflozin (N = 4687)
		number of patients (percent)		
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2)†
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5)‡
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2)†
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8)§
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3)§
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection‖	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4)‡
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection††	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4)†
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0)†
Female patients	17 (2.6)	64 (9.2)	71 (10.8)	135 (10.0)†
Event consistent with volume depletion‡‡	115 (4.9)	111 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure§§	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2)§
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0)‡
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event‖‖	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture***	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

How did empagliflozin have such an immediate impact on outcomes?

Hemodynamic Hypothesis
- BP reduction
- Osmotic diuresis and natriuresis
  - Reduction in vascular pressure, ventricular preload and afterload
  - Support: 5%↑ HCT, similar time course of events with rosiglitazone except opposite effect (increased volume and HF exacerbation)

Other
- Cardiorenal protection
- ↑Glucagon
  - Inotropic actions
  - Regulation of myocardial glucose uptake
  - Anti-arrhythmic action

J Diabetes Complications 2016;30(1):3-4
N Engl J Med. 2015;373:2117-28
Kidney International 2016;89:524-26

Who would most likely benefit? (Cardiovascular risk reduction)

Type 2 diabetes with A1c greater than 7.0%
- Majority had diabetes greater than 5 years

+ Established CV disease
- Known CAD (>50% stenosis), history of ACS, stroke, or PAD

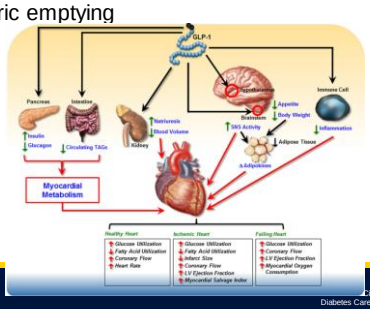
+ Combination therapy w/ other anti-diabetic agents
- Monotherapy?

Should empagliflozin be added to heart failure guidelines?

- Sudden death and worsening heart failure helped drive the reduction in CV death but the majority of reduction was labeled “other” CV death
- Significant reduction in HF hospitalizations
- Questions from EMPA-REG OUTCOME
  - # of HF patients
  - HFrEF versus HFpEF
- Need future trials in heart failure patients!

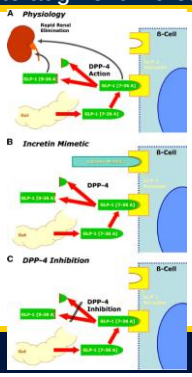
Incretin hormones are part of normal physiology

- Released from gut endocrine cells
- Potentiate meal-stimulated insulin secretion, slow gastric emptying



Circ Res. 2014;114:1788-1803
Diabetes Care 2009;32(Suppl 2):S223-231

Endogenous administration or degradation inhibition to augment incretin actions



Diabetes Care 2009;32(Suppl 2):S223-231

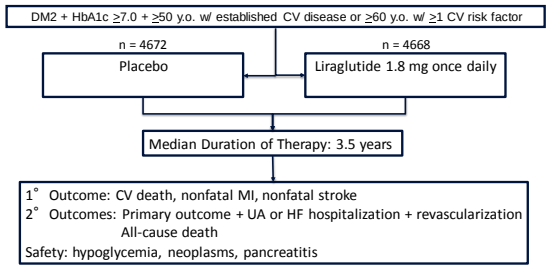
Liraglutide is a GLP-1 receptor agonist

- Longer half-live than endogenous GLP-1
- Dosing: 0.6 mg inject subcutaneously once daily, titrate to 1.8 mg once daily

Advantages	Disadvantages
Lowers A1c ~0.4-1.2%	Significant N/V/D
Reduces SBP ~2-8 mmHg	Unclear relationship w/ pancreatitis
Reduces TG ~15-20%	Potential for anti-liraglutide antibodies
Weight loss ~2-3 kg	Subcutaneous dosing only

Diabetes Care 2007;30(6):1608-10
Diabetes Care 2009;32(Suppl 2):S223-231
Victoza [package insert], Novo Nordisk; 2016

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER Trial)



N Engl J Med. 2016;375(4):311-22

Baseline characteristics were well balanced between groups

	Liraglutide (%)	Placebo (%)
Age, years ± SD	64.2 ± 7.2	64.4 ± 7.2
CVD risk factors (Age ≥60)		
Microalbuminuria/Proteinuria	1678 (71.9)	3403 (72.6)
HTN + LV hypertrophy	511 (21.9)	1006 (21.5)
LV systolic or diastolic dysfunction	120 (5.1)	237 (5.1)
Established CVD (Age ≥50)	3831 (82.1)	3767 (80.6)
MI	1464 (31.4)	1400 (30.0)
Revascularization	1835 (39.3)	1803 (38.6)
Stroke	730 (15.6)	777 (16.6)
CKD	1185 (25.4)	1122 (24.0)
Glycated Hemoglobin, %	8.7 ± 1.6	8.7 ± 1.5
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
Metformin	3540 (75.8)	3604 (77.1)
Insulin	2038 (43.7)	2131 (45.6)
Sulfonylurea	2370 (50.8)	2362 (50.6)
Monotherapy	691 (29.6)	1380 (29.4)
ACEI/ARB	3905 (83.7)	3836 (82.1)
BB	2652 (56.8)	2529 (54.1)
Statin	3405 (72.9)	3336 (71.4)
Acetylsalicylic Acid	2977 (63.8)	2899 (62.1)
Systolic blood pressure, mmHg	135.9 ± 17.8	135.9 ± 17.7
eGFR >90	1620 (34.7)	1655 (35.4)
60-89	1932 (41.4)	1975 (42.3)
30-59	999 (21.4)	935 (20.0)
<30	117 (2.5)	107 (2.3)

Liraglutide significantly reduced the primary CV outcome compared to placebo

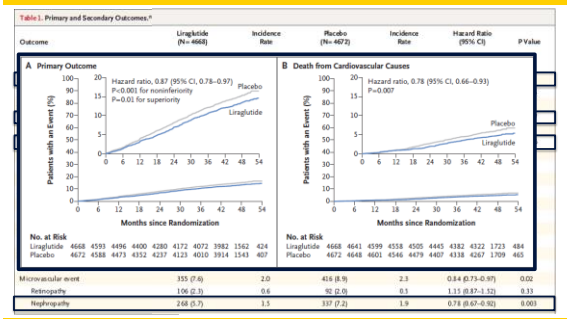


Table 1. Primary and Secondary Outcomes.*

Outcome	Liraglutide (N=4668)	Incidence Rate	Placebo (N=4672)	Incidence Rate	Hazard Ratio (95% CI)	P Value
Microvascular event	355 (7.6)	2.0	416 (8.9)	2.3	0.84 (0.73–0.97)	0.02
Retinopathy	106 (2.3)	0.6	92 (2.0)	0.5	1.15 (0.87–1.52)	0.33
Nephropathy	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67–0.92)	0.003

N Engl J Med. 2016;375(4):311-22

Increased incidence of adverse events and GI side effects with liraglutide

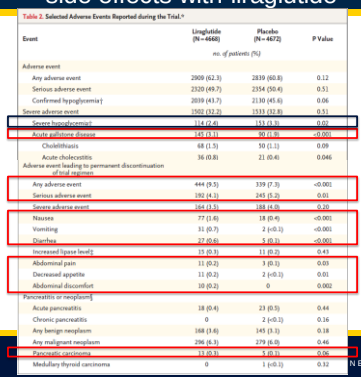


Table 2. Selected Adverse Events Reported during the Trial.*

Event	Liraglutide (N=4668)	Placebo (N=4672)	P Value
	no. of patients (%)		
Adverse event			
Any adverse event	2909 (62.3)	2839 (60.8)	0.12
Serious adverse event	2320 (49.7)	2354 (50.4)	0.51
Confirmed hypoglycemia†	2039 (43.7)	2130 (45.6)	0.06
Severe adverse event	1502 (32.2)	1533 (32.8)	0.51
Severe hypoglycemia‡	114 (2.4)	153 (3.3)	0.02
Acute gallstone disease	145 (3.1)	90 (1.9)	<0.001
Cholelithiasis	68 (1.5)	50 (1.1)	0.09
Acute cholecystitis	36 (0.8)	21 (0.4)	0.046
Adverse event leading to permanent discontinuation of trial regimen			
Any adverse event	444 (9.5)	339 (7.3)	<0.001
Serious adverse event	192 (4.1)	245 (5.2)	0.01
Severe adverse event	164 (3.5)	188 (4.0)	0.20
Nausea	77 (1.6)	18 (0.4)	<0.001
Vomiting	31 (0.7)	2 (<0.1)	<0.001
Diarrhea	27 (0.6)	5 (0.1)	<0.001
Increased lipase level§	15 (0.3)	11 (0.2)	0.43
Abdominal pain	11 (0.2)	3 (0.1)	0.03
Decreased appetite	11 (0.2)	2 (<0.1)	0.01
Abdominal discomfort	10 (0.2)	0	0.002
Pancreatitis or neoplasm¶			
Acute pancreatitis	18 (0.4)	23 (0.5)	0.44
Chronic pancreatitis	0	2 (<0.1)	0.16
Any benign neoplasm	168 (3.6)	145 (3.1)	0.18
Any malignant neoplasm	296 (6.3)	279 (6.0)	0.46
Pancreatic carcinoma	13 (0.3)	5 (0.1)	0.06
Medullary thyroid carcinoma	0	1 (<0.1)	0.32

N Engl J Med. 2016;375(4):311-22

How does the impact of liraglutide on outcomes compare to empagliflozin?

- Time to benefit emerged later with liraglutide – more related to reduction in atherosclerotic risk?
- Less heterogeneity in direction and impact on the components that make up the primary outcome
  - Numerically higher rates of stroke and no effect on nonfatal MI with empagliflozin
  - Consistent trends in reduction of stroke and MI with liraglutide
- Increased rates of discontinuation and adverse events with liraglutide

N Engl J Med. 2016;375(4):311-22

Who would most likely benefit? (Cardiovascular risk reduction)

Type 2 diabetes with A1c greater than 7.0%
- Majority had long-standing diabetes

+ Established CV disease
- Known CAD, history of ACS, revascularization, stroke, PAD, or CKD
- Significant risk reduction not seen in those with CV risk factor only

+ Combination therapy w/ other anti-diabetic agents
- Monotherapy?

Is the cardiovascular benefit consistent across the medication class of GLP-1 receptor agonists?

- Lixisenatide
  - DM2 + ACS in preceding 180 days
  - No significant differences compared to placebo in any CV endpoint
  - Mean HbA1c = 7.6 ± 1.3; lower weight and BMI; higher rates of ACEI, BB, statin, antiplatelet use
- Semaglutide
  - Same inclusion criteria as LEADER Trial, smaller trial
  - Baseline characteristics similar to patients in the LEADER Trial
  - CV death, MI, stroke: 6.6% (S) v. 8.9% (P), 0.74 [0.58-0.95] p=0.02
  - Increased risk of retinopathy compared to placebo
- CV trials with exenatide and dulaglutide are ongoing

N Engl J Med. 2016;375:1834-44
N Engl J Med. 2015;373:2247-57

2015 AHA/ADA Scientific Statement – Update on prevention of CV disease in adults with DM2

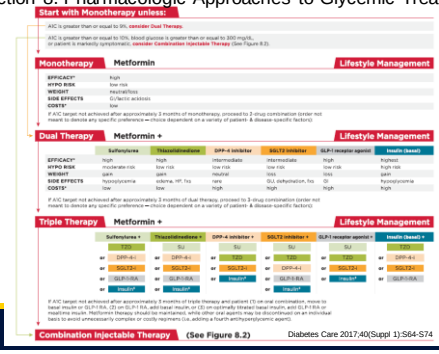
"To date, there are no convincing data to suggest that any single type of antihyperglycemic therapy in type 2 diabetes mellitus has a CVD advantage over another other than perhaps metformin."

Consider efficacy in glycemic control, adverse effects, cost and quality of life when selecting therapies

Circulation 2015;132:000-000

American Diabetes Association – Standard of medical care in diabetes 2017

Section 8. Pharmacologic Approaches to Glycemic Treatment



Diabetes Care 2017;40(Suppl 1):S64-S74

American Diabetes Association – Standard of medical care in diabetes 2017

Section 9. Cardiovascular Disease and Risk Management

- Diet and lifestyle modifications
- Hypertension
  - BP management w/ ACEI, ARB, thiazide, or DHP CCB to goal <140/90 or can consider 130/80 mmHg
- Lipid Management
  - High intensity statin for patients 40-75 y.o. with CV disease
- Antiplatelet Agents
  - Aspirin for secondary prevention of CV events and primary prevention in those with risk factors
- Coronary Heart Disease
  - Aspirin, statin, ACEI
  - BB post-MI
  - Avoid use of thiazolidinedione in HF

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Should empagliflozin and liraglutide be included in cardiovascular guidelines?

- In patients with DM2 and CV disease who are not at goal HbA1c, use liraglutide as part of combination therapy to reduce CV events
- In patients with DM2 and CV disease who are not at goal HbA1c, use empagliflozin as part of combination therapy to reduce CV events

Agent selection considerations: liraglutide v. empagliflozin

	Liraglutide	Empagliflozin
Place in therapy for patients w/ CV disease	Use as part of combination therapy to reduce CV events	Consider use as part of combination therapy to reduce CV events
Effect on CV risk factors	Reduction in weight, small reduction in SBP, increase in HR	Small reductions in weight, waist circumference, uric acid level, SBP and DBP. Small increases in LDL and HDL
Adverse effects	Nausea, vomiting, pancreatitis? (unclear)	UTI, genitourinary fungal infections, unusual DKA
1° outcome – CV death, nonfatal MI and stroke	↓Primary outcome ↓CV death Trend ↓ MI and stroke	↓Primary outcome ↓CV death ↔ MI and stroke
Other benefits	Lower risk of hypoglycemia than sulfonylureas and insulin	
		Benefit in HF patients?
Limitations	Subcutaneous dosing only $831/mo.	Contraindicated GFR < 30 ml/min $470/mo.

Questions that remain…

- Younger patients with a shorter duration of diabetes
- Patients without clinically evident CV disease (empagliflozin)
- CV outcomes with other SGLT-2 inhibitors

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