Safety of New Antihyperglycemics in Patients with Cardiovascular Disease

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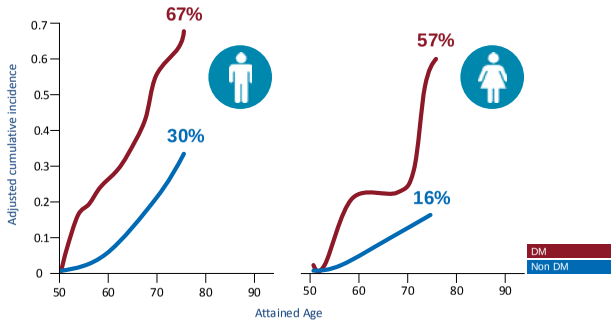
@RPhDiabetes

Diabetes and Lifetime Risk for CVD



Circulation. 2006;113:791-799.

Individualizing Treatment

Add another agent best suited to the individual by prioritizing patient characteristics:	
PATIENT CHARACTERISTIC	**CHOICE OF AGENT**
Degree of hyperglycemia	Consider relative A1C lowering
Risk of hypoglycemia	Rare hypoglycemia
Overweight or obesity	Weight loss or weight neutral
CV disease or multiple risk factors	Effect on cardiovascular outcome
Comorbidities (renal, CHF, hepatic)	See therapeutic considerations
Preferences & access to treatment	See cost column; consider access

CDA CPG 2016 Interim Update

CV Safety Trial Design

- No increased CV risk vs placebo
- Dose adjustment to maintain A1C the same in both groups
- Test for non-inferiority +/- test for superiority

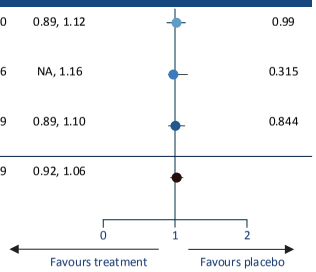
CV Trials – DPP-4 Inhibitors

	EXAMINE[1] N = 5,380	SAVOR-TIMI[2] N = 16,492	TECOS[3] N ~ 14,671-
	Alogliptin vs Placebo	**Saxagliptin vs Placebo**	**Sitagliptin vs Placebo**
Population	ACS within 15 to 90 days	Established CVD and/or multiple risk factors	Pre-existing CVD
Median duration of diabetes, yrs	≈7.2	10.3	11.6
Baseline HbA_{1c} %	8.0	8.0	7.2
Number of events	621	1,222	>1,300
Median duration of exposure, yrs	1.5	2.1	~3.0
Primary end point	CV death, Nonfatal MI, or Nonfatal stroke	CV death, Nonfatal MI, or Nonfatal stroke	CV death, Nonfatal MI, Nonfatal stroke, or UA req. hospitalization

[1]N Engl J Med. 2013;369:1327–1335.
[2]N Engl J Med. 2013;369:1317–1326.
[3]N Engl J Med. 2015;373:232–242.

Composite CV Primary Endpoint

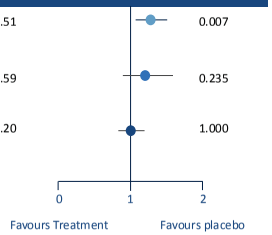
	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	*P* value
SAVOR-TIMI 53[1] (saxagliptin vs. placebo)	613/8280 (7.4%)	609/8212 (7.4%)	1.00	0.89, 1.12	0.99
EXAMINE[2] (alogliptin vs. placebo)	305/2701 (11.3%)	316/2679 (11.8%)	0.96	NA, 1.16	0.315
TECOS[3] (sitagliptin vs. placebo)	745/7332 (10.2%)	746/7339 (10.2%)	0.99	0.89, 1.10	0.844
SAVOR + EXAMINE + TECOS	1663/18313 (9.1%)	1671/18230 (9.2%)	0.99	0.92, 1.06	



[1]N Engl J Med. 2013;369:1327–1335.
[2]N Engl J Med. 2013;369:1317–1326.
[3]N Engl J Med. 2015;373:232–242.
Peterson ED. Results from the Trial to Evaluate Cardiovascular Outcomes after Treatment with 6 Sitagliptin (TECOS). American Diabetes Association, 75th Scientific Sessions, June 5-9, 2015, Boston, MA.

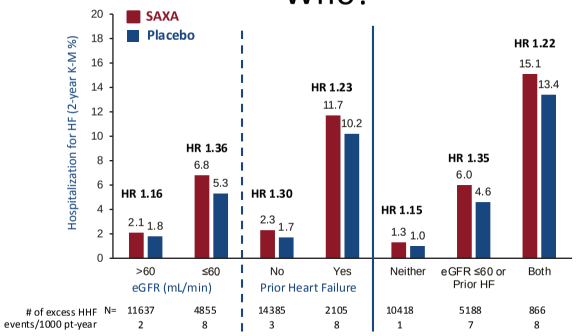
Hospitalization for Heart Failure

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	P value
SAVOR-TIMI 53[1] (saxagliptin vs. placebo)	289/8280 (3.5%)	228/8212 (2.8%)	1.27	1.07, 1.51	0.007
EXAMINE[2] (alogliptin vs. placebo)	106/2701 (3.9%)	89/2679 (3.3%)	1.19	0.89, 1.59	0.235
TECOS[3] (sitagliptin vs. placebo)	228/7332 (3.1%)	229/7339 (3.1%)	1.00	0.84, 1.20	1.000



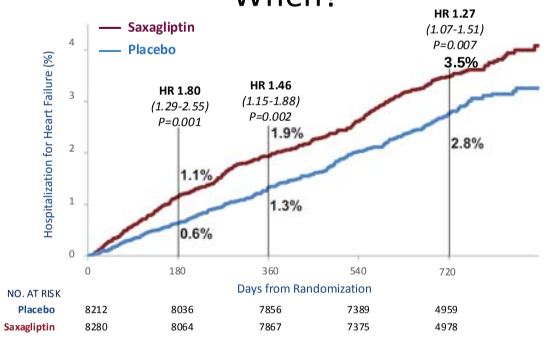
[1]N Engl J Med. 2013;369:1317–1326.
[2]N Engl J Med. 2013;369:1327–1335.
[3]N Engl J Med. 2015;373:232–242.
JAMA Cardiol. 2016;E1–E10.

Hospitalization for Heart Failure – Who?



Circulation. 2014;130:1579-88.

Hospitalization for Heart Failure – When?



Circulation. 2014;130:1579-88.

Potential Reasons for Differences in Heart Failure

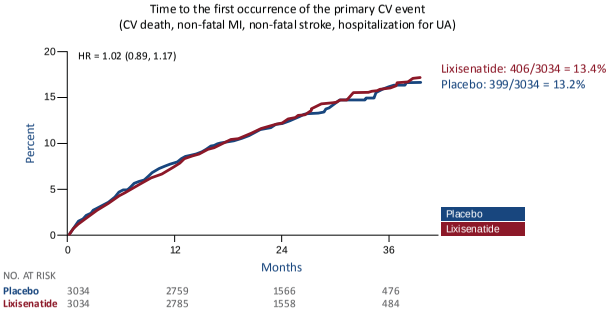
- Play of chance
- Differences in patients enrolled
- Differences in background care provided
- Variation in acquisition/definition of HF events among trials
- Intrinsic pharmacologic differences among the DPP-4 inhibitors

Baseline Characteristics

	DPP-4 Inhibitors			GLP-1RA
	SAVOR-TIMI 53[1]	EXAMINE[2]	TECOS[3]	ELIXA[4]
STUDY DRUG	Saxagliptin	Alogliptin	Sitagliptin	Lixisenatide
CV Risk	Established CVD/MRF	ACS within 15-90 days	Preexisting CVD	ACS within 180 days
Sample size, N	16,492	5,380	14,671	6,068
Mean duration of diabetes, years	10	7	12	9
Mean A1C,%	8.0	8.0	7.2	7.7
Mean age, years	65	61 (median)	66	60
BMI, kg/m²	31	29 (median)	30	30

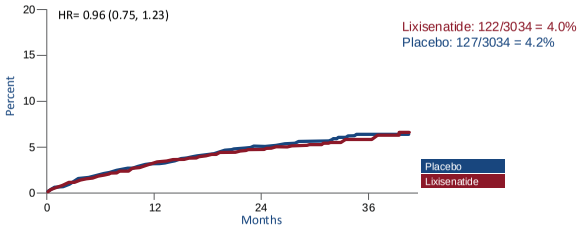
[1]N Engl J Med. 2013;369:1317–1326.
[2]N Engl J Med. 2013;369:1327–1335.
[3]N Engl J Med. 2015;373:232–242.
[4]N Engl J Med. 2015;373:2247–2257.

Primary Endpoint: ELIXA



N Engl J Med. 2015;373:2247–2257.

Hospitalizations for Heart Failure: ELIXA



N Engl J Med. 2015;373:2247–2257.

Bottom Line

- In patients with established CV disease or multiple CV risk factors, the DPP-4 inhibitors, sitagliptin, saxagliptin, alogliptin demonstrated CV safety vs placebo
- In patients with CV disease, GLP-1 agonist lixisenatide demonostrated CV safety vs placebo
- Saxagliptin increased the risk of hospitalization for heart failure
  - Particularly in first 12 months
  - Incremental risk was greatest in patients at high risk of heart failure
    - History of heart failure, impaired renal function
  - Confirmation is required

FDA Update April 5, 2016

- Consider discontinuing medications containing saxagliptin and alogliptin in patients who develop heart failure and monitor their diabetes control.
- Patients taking these medicines should contact their health care professionals right away if they develop signs and symptoms of heart failure.

Health Canada

WARNINGS AND PRECAUTIONS

Saxagliptin
- Caution in patients with history of congestive heart failure (especially in those patients who also have renal impairment and/or history of myocardial infarction [MI])

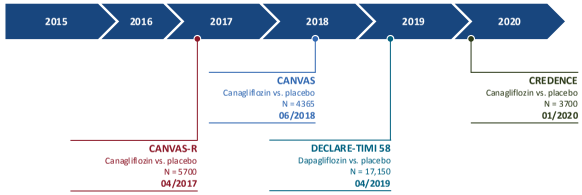
Sitagliptin
- NYHA class I, II, III, IV – not recommended

Alogliptin
- NYHA class III and IV – caution

Sodium-Glucose Co-transporter 2 Inhibitors

- Inhibition of the sodium glucose co-transporter 2 (SGLT2) in the kidney
- Glucose reduction occurs by reducing renal glucose reabsorption and thus increasing urinary glucose excretion
- In patients with type 2 diabetes, leads to:
  - Significant reductions in HbA1c
  - Weight loss
  - Reductions in blood pressure without increases in heart rate

SGLT2 Inhibitors CV Safety Trials Currently In Progress



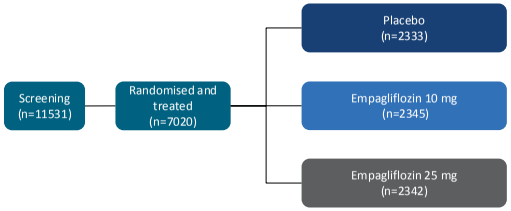
Baseline Characteristics

	DPP-4 Inhibitors			GLP-1RA	SGLT2 Inhibitor
	SAVOR-TIMI 53[1]	EXAMINE[2]	TECOS[3]	ELIXA[4]	EMPA-REG[5]
STUDY DRUG	Saxagliptin	Alogliptin	Sitagliptin	Lixisenatide	Empagliflozin
Sample size, N	16492	5380	14671	6068	7020
CV background	Established CVD and/or multiple risk factors*	ACS within 15 to 90 days	Pre-existing CVD	ACS within 180 days	Pre-existing CVD
Females, %	33	32	29	31	29
Mean age, y	65	61 (median)	66	60	63
Duration of diabetes, y	10	7	12	9	≈ 57% had DM for >10 years
Mean A1C, %	8.0	8.0	7.2	7.7	8.1
Mean BMI, kg/m²	31	29 (median)	30	30	31

*≥55 years old (men) or ≥60 years old (women) with ≥1 of the following additional risk factors: dyslipidemia, hypertension, or active smoking.

[1]N Engl J Med. 2013;369:1317–1326. [2]N Engl J Med. 2013;369:1327–1335. [3]N Engl J Med. 2015;373:232–242. [4]N Engl J Med. 2015;373:2247–2257. [5]N Engl J Med. 2015;373:2117-2128.

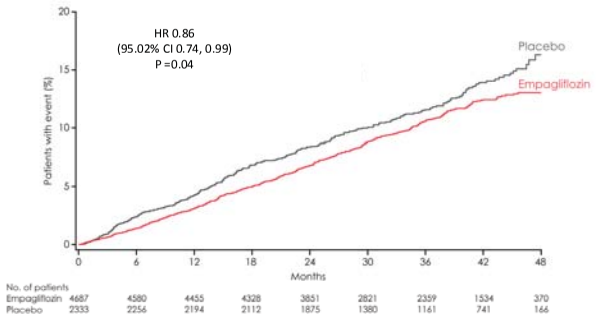
Empa-reg Outcome Trial Design



- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

Cardiovasc Diabetol. 2014;13:102.

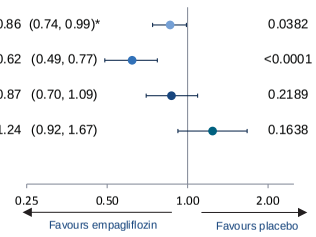
Cardiovascular Death, Non-Fatal MI or Non-Fatal Stroke



N Engl J Med. 2015;373:2117-2128.

Cardiovascular Death, MI and Stroke

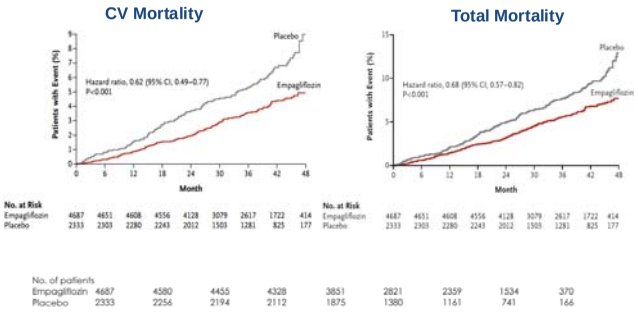
	Patients with event/analysed				*P* value
	Empagliflozin	Placebo	HR	(95% CI)	
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



*Cox regression analysis.

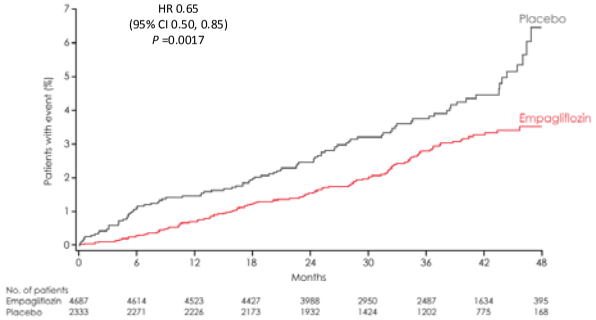
N Engl J Med. 2015;373:2117-2128.

Cardiovascular and Total Mortality



N Engl J Med. 2015;373:2117-2128.

Hospitalization for Heart Failure



N Engl J Med. 2015;373:2117-2128.

EMPA-REG OUTCOME®: Bottom Line

- *In people with type 2 diabetes and CVD,* empagliflozin
  - reduced risk for 3-point MACE by 14%
    - reduced CV death by 38%
  - reduced hospitalization for heart failure by 35%
  - reduced all-cause mortality by 32%

Reduction in MACE with Liraglutide LEADER to be presented at ADA

- Type 2 diabetes mellitus at *high risk of cardiovascular events*
- Liraglutide 1.2 mg and 1.8 mg versus placebo
- Primary endpoint: Time to occurrence of CVA, MI, CV death
- Met noninferiority and superiority

Results to be presented at the American Diabetes Association Annual Meeting in June 2016.

Add another class of agent best suited to the individual (*agents listed in alphabetical order*):

Class	Relative A1C Lowering	Hypo-glycemia	Weight	Effect in Cardiovascular Outcome Trial	Other therapeutic considerations	Cost
α-glucosidase inhibitor (acarbose)	↓	Rare	neutral to ↓		Improved postprandial control, GI side-effects	$$
Incretin agents: DPP-4 Inhibitors GLP-1R agonists	↓↓ ↓↓ to ↓↓↓	Rare Rare	Neutral to ↓ ↓↓	Neutral (alo, saxa, sita) Neutral (lixi)	**Caution with saxagliptin in heart failure** GI side-effects	$$$ $$$$
Insulin	↓↓↓	Yes	↑↑	Neutral (glar)	No dose ceiling, flexible regimens	$-$$$$
Insulin secretagogue: Meglitinide Sulfonylurea	↓↓ ↓↓	Yes Yes	↑ ↑		Less hypoglycemia in context of missed meals but usually requires TID to QID dosing Gliclazide and glimepiride associated with less hypoglycemia than glyburide	$$ $
SGLT2 inhibitors	↓↓ to ↓↓↓	Rare	↓↓	Superiority (empa in T2DM patients with clinical CVD)	Genital infections, UTI, hypotension, dose-related changes in LDL-C, caution with renal dysfunction and loop diuretics, dapagliflozin not to be used if bladder cancer, rare diabetic ketoacidosis (may occur with no hyperglycemia)	$$$
Thiazolidinediones	↓↓	Rare	↑↑	Neutral	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	$$
Weight loss agent (orlistat)	↓	None	↓		GI side effects	$$$

alo=alogliptin; glar=glargine; saxa=saxagliptin; sita=sitagliptin; lixi=lixisenatide; empa=empagliflozin

CDA Interim Update 2016

- *In people with clinical CV disease in whom glycemic targets are not met,* an SGLT2 inhibitor with demonstrated CV outcome benefit should be added to antihyperglycemic therapy to reduce the risk for CV and all cause mortality (Grade A, level 1A for empagliflozin)

Individualizing Treatment

Add another agent best suited to the individual by prioritizing patient characteristics:

PATIENT CHARACTERISTIC	CHOICE OF AGENT
PRIORITY: **Clinical Cardiovascular Disease** →	**SGLT2 inhibitor with demonstrated CV outcome benefit**
Degree of hyperglycemia Risk of hypoglycemia Overweight or obesity CV disease or multiple risk factors Comorbidities (renal, CHF, hepatic) Preferences & access to treatment	Consider relative A1C lowering Rare hypoglycemia Weight loss or weight neutral Effect on cardiovascular outcome See therapeutic considerations See cost column; consider access