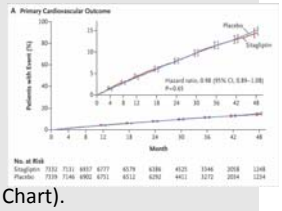
TECOS: Sitagliptin JANUVIA CV Outcomes Trial Summary [1]

Sitagliptin: Cardiovascular (CV) Outcomes and Mortality in Patients with Type 2 Diabetes Mellitus (T2DM)

In patients with T2DM and at high risk of CV events, does sitagliptin reduce CV risk compared to placebo when added to standard care?

BOTTOM LINE

***Sitagliptin* versus *placebo plus standard care:* not too bad but nothing really good either.**



- Neutral CV results. Achieved non-inferiority, but no indication of any particular CV outcome benefit.
- No increase in heart failure is reassuring given concerns with other DDP4-I saxagliptin SAVOR-TIMI 53 (see RxFiles Trial Summary) and alogliptin. EXAMINE
- Some rare safety concerns still remain (e.g., pancreatic cancer & pancreatitis), see uncertainties, page 2.
- Neutral CV results with **TECOS** and **ELIXA** trials somewhat disappointing now given recent trials with positive CV results (i.e. **LEADER, EMPA-REG, SUSTAIN-6**) (see related RxFiles Trial Summaries & Outcome Comparison Chart).
- Given the neutral effect on CV and other outcomes, the cost impact in **TECOS** is ~$100 per month (over $300 per 100 day fill) Canadian dollars for a reduction in HbA1c of ~0.3%. (Note: HbA1c is a surrogate outcome associated primarily with a reduction in microvascular endpoints; however, these endpoints were not specifically examined in this study and not statistically different from placebo. The potential for impact over longer term is unknown).

BACKGROUND

- Sitagliptin (JANUVIA ☎ ✆ $328/100days) is a dipeptidyl peptidase-4 inhibitor (DPP4-I) approved for use in T2DM 2008 CDN with inadequate blood glucose control as monotherapy when metformin contraindicated or as an add-on to metformin alone, metformin + SU, pioglitazone +/- metformin, or insulin +/- metformin.[2]
- Non-inferior outcome trial mandated by the FDA to ensure CV safety in the "post-rosiglitazone era".[3]

TRIAL BACKGROUND [1,4-6]

DESIGN: Randomized (allocation concealed), double-blind, placebo-controlled, international (38 countries), multi-centre (673 sites) trial. Non-inferiority analysis (PP population) for primary efficacy outcome followed by superiority analysis (ITT population). Funding: MerckSharp & Dohme (JANUVIA manufactuer). Enrollment/Follow-up period: 2008-2015.

INTERVENTION: Sitagliptin 100 mg PO daily (50mg if eGFR ≥30ml/min/1.73m^2 and <50ml/min/1.73m^2) **vs. placebo, added to existing therapy.**
-open label anti-hyperglycemic agents were used as required to achieve individually appropriate HbA1c targets according to local guidelines.

INCLUSION: T2DM, Age ≥50yrs, **eGFR ≥ 30 mL/min/1.73 m^2**, **established CVD (coronary artery disease, ischemic cerebrovascular disease, atherosclerotic peripheral arterial disease)**, with HbA1c of 6.5 to 8.0% when treated with stable doses of one or two oral anti-hyperglycemic agent(s) or insulin +/- metformin.

EXCLUSION: Patients taking a DPP4-I, glucagon-like peptide 1 receptor agonist or thiazolidinedione (except pioglitazone) during the preceding 3 months, patients who had 2 or more episodes of severe hypoglycemia during the preceding 12 months.

POPULATION baseline n= **14,671:** age 65.5 ± 8.0yrs; eGFR ~74.9± 21.1(mL/min/1.73m^2); ♂ 70.7%, SBP135 ± 17mmHg; DBP77 ± 10.5 mmHg

CV comorbidity/risk factors: single/multi-vessel CAD 57%, coronary stenosis 52.4%, MI 42.6%, PCI 39.5%, CABG 25%, cerebrovascular disease 24.5%, HF 18%, PAD 16.6%, **smoking (**never 48.7%, prior 38.9%, current 11.4%) **HbA1c** 7.2% ± 0.5; BMI 30.2 ± 5.6 kg/m^2, eGFR < 50 mL/min/1.73 m^2 9.4%, **duration of diabetes** 11.6 ± 8.1yrs

Race: White 67.9%; Asian 22.3%; African-American/Black 3.0%; Hispanic/Latino 12.3%; Other 6.8%

Medications: metformin 81.6%; insulin 23.2%; SU 45.3%; pioglitazone 2.7%
ACEI/ARB 78.8%; BB 63.5%; diuretic 41%; CCB 33.8%, statin 79.9%; ezetimibe 5.2%, aspirin 78.5%, other antiplatelet 21.7%

RESULTS [1,6]

follow-up: median 3 yrs

TABLE 1: EFFICACY/SAFETY NON-INFERIORITY DATA {NNT/H = number needed to treat for Benefit / Harm}

CLINICAL ENDPOINTS ITT ANALYSIS UNLESS OTHERWISE SPECIFIED	SITAGLIPTIN + USUAL CARE n=7332		PLACEBO + USUAL CARE n=7339		HR (95% CI)		P VALUE		ARR/ARI	NNT/NNH /3 YRS	COMMENTS
PRIMARY ENDPOINT											
CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina	ITT n=7332	PP n=7257	ITT n=7339	PP n=7266	ITT	PP	ITT	PP	P value – statistically significant only for non-inferiority. Thus no NNT for benefit or NNH for harm calculation.		-Sitagliptin was non-inferior (PP analysis), but not superior (ITT analysis) to placebo for the primary composite CV endpoint .
	11.4% (n=839)	9.6% (n=695)	11.6% (n=851)	9.6% (n=695)	0.98 (0.89-1.08)	0.98 (0.88-1.09)	NS	<0.001			
SECONDARY COMPOSITE ENDPOINT CV death, nonfatal MI, nonfatal stroke	10.2% (n=745)	8.4% (n=609)	10.2% (n=746)	8.3% (n=602)	0.99 (0.89-1.10)	0.99 (0.89-1.11)	NS	<0.001			
SECONDARY ENDPOINTS											
Fatal or nonfatal MI	4.1% (n=300)		4.3% (n=316)		0.95 (0.81-1.11)		0.49		--	--	• **mean HbA1c** ↓ by 0.29% (-0.32 to -0.27) more with sitagliptin than placebo (least-squares mean difference).
Fatal or nonfatal stroke	2.4% (n=178)		2.5% (n=183)		0.97 (0.79-1.19)		0.76		--	--	
All-cause death	7.5% (n=547)		7.3% (n=537)		1.01 (0.90-1.14)		0.88		--	--	
CV death	5.2% (n=380)		5.0% (n=366)		1.03 (0.89-1.19)		0.71		--	--	
Hospitalization for HF	3.1% (n=228)		3.1% (n=229)		1.00 (0.83-1.20)		0.98		--	--	
Hospitalization for HF; CV death	7.3% (n=538)		7.2% (n=525)		1.02 (0.90-1.15)		0.74		--	--	

TABLE 2: ADVERSE EVENTS-PP ANALYSIS

CLINICAL ENDPOINTS	SITAGLIPTIN + USUAL CARE n=7332	PLACEBO + USUAL n=7339	HR (95%)	P VALUE	ARR/ARI	NNT/NNH /3 YRS	COMMENTS
Acute pancreatitis	0.3% (n=20)	0.2% (n=11)	1.80 (0.86-3.76)	NS	↑0.1%	--	-NS microvascular outcomes: blindness due to DM, retinopathy, renal failure (includes dialysis or transplant),
Charter-defined cancer	3.4% (n=248)	3.6% (n=260)	0.93 (0.78-1.10)	NS	↓0.2%	--	
Pancreatic cancer	0.1% (n=9)	0.1% (n=10)	0.91 (0.37-2.25)	NS	↓0%	--	

Severe hypoglycemia	2.0% (n=144)	1.7% (n=125)	1.13 (0.89-1.44)	NS	↑ 0.3%	--	microalbuminuria, diabetic neuropathy, amputation, PAD (See Table S5).[6] -NS for hospitalization due to hyperglycemia, DM complications etc. (See Table S5).[6]
Use of additional ant-hyperglycaemic agents	22% (n=1591)	28% (n=2046)	0.72 (0.68-0.77)	<0.001	↓6%	17	
Initiation of chronic insulin	9.7% (n=542)	13.2% (n=744)	0.70 (0.63-0.79)	<0.001	↓3.5%	29	
eGFR (ml/min/ 1.73m^2)	-4.0 ± 18.4	-2.8 ± 18.3	-1.76 to -0.91	<0.001	--	--	

STRENGTHS, LIMITATIONS, & UNCERTAINTIES [1]

STRENGTHS:

- Large trial size.
- Longest duration of follow-up for published DPP4-I CV outcome trials.
- Well-designed RCT (properly randomized [allocation concealment, balanced baseline demographics]; registered; appropriately powered; all CV outcomes were pre-specified, adjudicated, & clinically relevant).
- 95.1% in sitagliptin group and 94.1% in placebo group completed study; vital status not confirmed for <2.5% of patients.
- ITT and PP analyses were performed for the primary composite endpoint. Results are mostly reassuring.
- Primary composite endpoint consistent (homogeneous) among subgroups.
- Decreased use of anti-hyperglycaemic agents and insulin initiation in sitagliptin group.
- No increased HF risk with or without adjustment for baseline HF history (previously uncertain given increase with drugs from the same class, saxagliptin [SAVOR-TIMI 53] alogliptin [EXAMINE]).[7-11]

LIMITATIONS:

- 26.1% of all sitagliptin patients and 27.5% of all placebo patients prematurely discontinued study medication (reasons for discontinuation NR).
- The sponsor- Merke, Sharpe and Dohme- involved in the study (e.g., reviewed the data, revised the manuscript).
- Reporting bias: not all pre-specified outcomes reported (e.g., change in weight) and overall SAE not reported. Of the SAE that were reported (those at least 1%), sitagliptin generally similar to placebo: (Composite SAE of those ≥1% [calculated by RxFiles] : sitagliptin 11% vs placebo 10.6%; components: neoplasms 4.7% vs 5.1%; injury, poisoning or procedural complication 2% vs 1.8%; GI disorder 1.8% vs 1.4%; musculoskeletal or connective tissue disorder 1.6% vs 1.3%; resp, thoracic, or mediastinal disorder 0.9% vs 1%).
- No adjustments made for multiplicity of secondary outcomes (risk of false-positive result [type 1 error]).
- Non-inferiority margin of 1.3 was arbitrarily set by the FDA, and thus may not represent a minimally-clinically important difference to clinicians or patients.

UNCERTAINTIES:

- Applicability of results to patients without established CVD or with more complicated coexisting illnesses.
- Applicability of results to patients with severe renal insufficiency (<30 ml/min/1.73m^2), as dose-adjusted sitagliptin (i.e., 25 mg daily) is recommended by the product monograph but these patients were excluded from the trial.[2]
- Effect of sitagliptin on microvascular outcomes (e.g., retinopathy, neuropathy, nephropathy) as these may take 5-10+ years to develop and median trial follow-up was 3 years.
- ? Greater efficacy in patients with higher BMI. BMI ≥30kg/m^2 subgroup demonstrated numerically greater reduction in the primary composite outcome (HR 0.88, 95% CI 0.76-1.01) vs BMI <30 kg/m^2 (HR 1.08, 95% CI 0.95-1.24).
- Since diabetes patients are more likely to develop adverse CV outcomes, agents with promising CV protection such as empagliflozin, [12 EMPA-REG] liraglutide, [13 LEADER] and semaglutide (not available in CAN) [14 SUSTAIN-6] may be preferred over sitagliptin. Since sitagliptin may have some acute pancreatitis concerns, lixisenatide [15 ELIXA] may be a safer agent. (Difficult to assess as diabetes may itself be a risk factor for pancreatitis). Note, patients in **ELIXA**[15] may have been higher risk than **TECOS** (e.g., higher rate of annual mortality rate).
- Several concerns regarding serious adverse effects with sitagliptin use have been raised outside of this trial:
  - Pancreatic cancer risk: there was no statistically significant difference in pancreatic cancer; in **TECOS**, 9 cases in sitagliptin group and 10 cases in placebo group.
  - Pancreatitis: there was no statistically significant difference in pancreatitis; in **TECOS**, 20 cases (0.0032%) in sitagliptin group and 11 cases (0.0015%) in control (P=0.12).
  - Unpublished meta-analysis of **TECOS**, **SAVOR-TIMI 53**, **EXAMINE** estimate pancreatitis risk for DPP4-I is low, but can occur with an estimated NNH=834/ 2.4yrs.[16]
- **Trials currently underway for DDP4-I: CARMELINA**(linagliptin)(2018).

Remember… for vascular protection, CDA 2013 (updated 2016) recommends: lifestyle (nutrition, exercise, smoking cessation); optimal HbA1c control (usually ≤ 7%), BP control (<130/80 mmHg), and cholesterol control (LDL ≤2 mmol/L); and lastly CV protective drugs (i.e., ACEI/ARB, statin, ASA [if indicated]).[17]

RELATED RxFiles LINKS

- RxFiles Diabetes Agents Outcomes Table: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf
- RxFiles Diabetes – Landmark Trials and Links: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf
- RxFiles Diabetes **ELIXA** trial summary http://www.rxfiles.ca/rxfiles/uploads/documents/Lixisenatide-ELIXA%20Trial%20Summary.pdf
- RxFiles Diabetes **LEADER** trial summary http://www.rxfiles.ca/rxfiles/uploads/documents/Leader-Liraglutide%20VICTOZA%20and%20Cardiovascular%20Outcomes%20in%20Type%202%20Diabetes.pdf
- RxFiles Diabetes **EMPA-REG** trial summary http://www.rxfiles.ca/rxfiles/uploads/documents/EMPA-REG%20Trial%20Summary.pdf

✗ =non-formulary in SK ⊗=not covered by NIHB ☎=Exceptional Drug Status in SK **♀**=female **♂**=male **AE**=adverse event **BMI**=body mass index **CABG**=coronary artery bypass graft **CAD**=coronary artery disease **CV**= cardiovascular **CVD**=cardiovascular disease **DBP**=diastolic blood **DPP4-I**=dipeptidyl peptidase-4 inhibitor **eGFR**= estimated glomerular filtration rate **FDA**= Food and Drug Administration **GI**=gastrointestinal **GLP1-A**=glucagon-like peptide-1 agonist **HbA1c**= hemoglobin A1c **HF**=heart failure **ITT**=intention to treat **MI**=myocardial infarction **NR**=not reported **NS**=not statistically significant **PAD**=peripheral artery disease **PCI**= percutaneous intervention **PP**= per protocol **SAE**=serious adverse events **SBP**=systolic blood pressure **SGLT2-I**=sodium glucose cotransporter 2 inhibitor **SU**=sulfonylurea **T2DM**=type 2 diabetes mellitus

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