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Editorial assistance: L Regier, B Jensen - Oct, 2013

SAVOR-TIMI 53

CV Outcomes Trial Summary

Saxagliptin and Cardiovascular (CV) Outcomes in Patients with Type 2 Diabetes Mellitus

SAVOR-TIMI 53 evaluated drug intervention (saxagliptin ONGLYZA vs. placebo) effects on CV outcomes in patients with Type 2 Diabetes Mellitus (T2DM) & history of CV disease or multiple risk factors for vascular disease.[1]

Trial Background: n=16,492 patients with T2DM.

- Randomized (stratification based on qualifying CV disease established CV disease vs. multiple risk factors only & renal function), concealed allocation, double-blind, multicenter 788 sites in 26 countries (N. America, Europe, Asia, etc.); industry sponsored (AstraZeneca & Bristol-Myers Squibb)
- Placebo-controlled phase IV trial – **Saxagliptin 5mg daily (or 2.5mg daily if GFR ≤50 ml/min)** to evaluate CV outcome (CV death, MI, or ischemic stroke) in T2DM; physicians could adjust T2DM and CV medications at their discretion.
- INCLUSION: T2DM, A1c of 6.5% to 12% & established CV disease ≥ 40yrs & hx of clinical event associated with atherosclerosis or multiple risk factors for vascular disease ♂≥ 55 yrs; ♀≥ 60 yrs; plus ≥ 1 of: dyslipidemia, hypertension, or active smoking
- EXCLUSION: receiving incretin-based therapy currently or past 6 months, end stage renal disease & undergoing long-term dialysis, previous renal transplant, or SCr > 530μmol/L
- POPULATION @baseline: ♂ ~67%; ethnicity ~75% white race & ~21.5% hispanic; age: 65 mean; weight mean ~88 kg ~64% > 80 kg; BMI 31.1kg/m^2 mean, BMI>30kg/m^2 ~53%; duration of diabetes 10.3 yrs median ; A1c 8% mean (**<6.5%**=7.8%, **6.5 to <7%**=17.6%, **7 to <8%**=33.4%, **8 to <9%**=19.4%, **≥9%**=21.8%); estimated GFR mean 72.6 ± 22.6 (**<30ml/min**=2%, **30-50ml/min**=14%, **>50ml/min**=84%); ACR median 1.8 (**<3.4**=61.5%, **3.4 to 33.9**=28.1%, **>33.9**=10.4%); established atherosclerotic disease 79%: hypertension 82%, dyslipidemia 71%, prior MI 38%, prior heart failure 13%, prior coronary revascularization 43%, no significant differences between CV & T2DM medications at baseline

Table 1: Results: 1° & 2° Endpoints - over the median 2.1 years of follow-up {ITT analysis}

Clinical Endpoints {see trial for additional 2° endpoint data}	Saxagliptin n=8280	Placebo n=8212	Hazard Ratio	Comments
1° Composite major vascular events **CV death, nonfatal MI, or nonfatal ischemic stroke**	7.4% {n=613}	7.4% {n=609}	1.00 (NS) (95% CI: 0.89-1.12)	**Primary (1°) composite endpoint:** saxagliptin neither reduced nor increased the risk of the primary composite endpoint from occurring **Overall**: no outcome benefit, some harm **A1c**: statistically significantly lower in saxagliptin vs. placebo throughout & at end of tx (7.7% vs. 7.9%) & more patients in saxagliptin group had a level < 7% (36.2% vs. 27.9%) at the end of the tx period
Death from any cause	5.1% {n=420}	4.6% {n=378}	1.11 (NS) (95% CI: 0.96-1.27)	
Hospitalization for Heart Failure	3.5% {n=289}	2.8% {n=228}	1.27 95% CI: 1.07-1.51 **NNH=143 /2.1 years**	

*Note: % based on raw data instead of 2 year Kaplan-Meier estimates reported in trial. CV= cardiovascular; MI=myocardial infarction; NNH=number needed to harm; NS= non-significant; Tx=treatment.

Table 2: Adverse Events - over the median 2.1 years of follow-up

Safety Endpoint	Saxagliptin n=8280	Placebo n=8212	Significant Harms p value	Comments
Opportunistic Infection	0.3% (n=21)	0.4% (n=35)	(NS) 0.06	Of note: fewer people in the saxagliptin group than in placebo needed an ↑ in the dose of antihyperglycemic medications or initiation of insulin therapy for more than 3 months. Other safety endpoints reported on that were not statistically significant include: thrombocytopenia, lymphocytopenia, severe infection, hypersensitivity reaction, bone fracture, skin reaction, & any liver abnormality. Rate of all "Serious Adverse Events" (SAEs): (Saxagliptin 24.2%, placebo 23.7% data requested) (Renal abnormality = 5.8% vs 5.1%, p=0.04; data requested.)
Renal Abnormality	5.8% (n=483)	5.1% (n=418)	NNH=142/2yrs p=0.04	
Any hypoglycemia	15.3% (n=1264)	13.4% (n=1104)	NNH= 53/2yrs p<0.001	
Major hypoglycemia	2.1% (n=177)	1.7% (n=140)	NNH=250/2yrs p=0.047	
Minor hypoglycemia	14.2% (n=1172)	12.5% (n=1028)	NNH=59/2yrs p=0.002	
Pancreatitis, any	0.3% (n=24)	0.3% (n=21)	(NS) p=0.77	
Acute: definite/possible	0.3% (n=22)	0.2% (n=16)	(NS) p=0.42	
Acute: definite	0.2% (n=17)	0.1% (n=9)	(NS) p=0.17	
Acute: possible	0.1% (n=6)	0.1% (n=7)	(NS) p=0.79	
Chronic	<0.1% (n=2)	0.1% (n=6)	(NS) p=0.18	
Cancer, any	3.9% (n=327)	4.4% (n=362)	(NS) p=0.15	
Pancreatic cancer	0.06% (n=5)	0.15% (n=12)	(NS) p=0.95	

NNH=Number needed to harm; NS= not significant.

Strengths, Limitations & Uncertainties

Strengths

- large sample size; important clinical endpoints; double-blinded; outcomes adjudicated by cardiovascular & pancreatic medicine specialists who were unaware of the study-group assignments; final vital status assessed in 99.1% of patients (28 patients lost to follow-up)

Limitations

- the short trial duration 2.1 year $_{\text{median}}$ limits ability to comment on long term benefits vs harms
- the population studied had longer-standing T2DM with high CV risk. Therefore the trial provides minimal insight into potential cardiovascular benefits vs harms in newly diagnosed T2DM & those with lower cardiovascular risk
- drug company assisted in trial design, provided the drug & monitoring support (analysis was completed independently of the sponsor)
- Per protocol analysis was not completed as originally designed as a superiority trial. As intention to treat analysis results in a bias towards "no difference", per protocol analysis is recommended when the design is for non-inferiority

Uncertainties- hospitalizations for heart failure

The Bottom Line

When considering the primary composite endpoints of cardiovascular death, non-fatal myocardial infarction & non-fatal ischemic stroke, saxagliptin (in addition to standard care) was non-inferior to placebo in patients at high risk for experiencing cardiovascular events. Overall, considering secondary & safety endpoints, none are positive & some, such as admissions for heart failure raise concern of increased harm.

This is the largest RCT examining cardiovascular & safety outcomes for agents that target the incretin system. At best, currently published trials (EXAMINE, SAVOR-TIMI 53) regarding DPP-4 Inhibitors, show neutral effects on major CV outcomes & some potential harm. Additional trial data is required before the long term balance of benefits & harms is known. In the context of previous trials, metformin still has the best evidence for outcome benefit overall[UKPDS-34]. See RxFiles Diabetes Landmark Outcome Trials for an evidence summary in this area.[2]

Other Recent outcome Trials of interest (2013)

The **EXAMINE** trial[3] was a smaller, randomized, double-blind, multi-center (international) trial assessing **CV outcomes** using **alogliptin** vs. placebo. It randomized 5380 patients with T2DM who had either a MI or unstable angina requiring hospitalization in the previous 15 to 90 days. The purpose was to address concern regarding elevated cardiovascular risk related to new antihyperglycemic drugs used to treat T2DM. The primary outcome end point was a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke, in which alogliptin proved to be non-inferior vs. placebo (11.8% vs. 11.3%) with a median trial duration of 18 months. There were no statistically significant findings on other safety or outcome endpoints.

The **Look AHEAD** trial[4] was an American multi-center, randomized clinical trial evaluating CV outcomes when comparing the intervention of an intensive **lifestyle** vs. control in 5145 T2DM overweight or obese patients. The intensive lifestyle intervention aimed for weight loss of at least 7% through strict caloric restriction & increased physical activity, whereas the control group received diabetes support & education. At the end of the follow-up period that weight loss reported was 6% for the intervention group & 2.5% for the control group. The primary composite endpoint included death from cardiovascular causes, nonfatal MI, nonfatal stroke & hospitalization for angina. The primary outcome results were 1.83 vs. 1.92 events per 100 person years for the intervention & control groups respectively over the median follow-up time of 9.6 years. There were no significant differences in other endpoints of safety measures other than self-reported fracture rates, but no significant difference was found between adjudicated rates of fractures. Intensive lifestyle intervention in comparison to diabetes education & support did not decrease the risk of cardiovascular morbidity & mortality in patients with T2DM who were overweight or obese.

(Previous lifestyle intervention trials have shown benefit in preventing diabetes. The DPP (Diabetes Prevention Program)[5] was a trial that compared lifestyle intervention program vs. metformin (850mg twice daily) vs. placebo to delay or prevent the development of diabetes. The primary outcome was development of diabetes, which cumulatively over three years occurred in 14.4%, 21.7%%, & 28.9% in the **lifestyle**, metformin, & placebo groups respectively. There were significant increases in musculoskeletal symptoms (24.1 vs. 21.1 events per 100 patient years) with lifestyle intervention & gastrointestinal symptoms (77.8 vs. 30.7 events per 100 patient years) with metformin in comparison to placebo. Both lifestyle & metformin interventions were superior to placebo & lifestyle interventions are superior to metformin in delaying or preventing the onset of diabetes.)

See also: Diabetes Agents: Outcomes Summary Table: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf

[1] Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al; the **SAVOR-TIMI** 53 Steering Committee and Investigators. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. N Engl J Med. 2013 Sep 2.

[2] RxFiles Diabetes Trials Chart: accessed online at http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf

[3] White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al; the **EXAMINE** Investigators. Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes. N Engl J Med. 2013 Sep 2.

[4] **Look AHEAD** Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM,Coday M, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013 Jul 11;369(2):145-54.

[5] Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program (**DPP**) Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002 Feb 7;346(6):393-403.