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At the Heart of Diabetes Management:

Incorporating New Evidence to Optimize Cardiovascular Safety

LMC

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Cardiovascular (CV) risk factors should be treated as aggressively in patients with Type 2 diabetes mellitus (T2DM) as in those with a prior myocardial infarction (MI). The Canadian Diabetes Association (CDA) recommends vascular protection in all patients living with diabetes because of the significantly increased risk of cardiovascular disease (CVD). In a series of presentations at LMC Diabetes & Endocrinology sites, LMC researchers and specialists discussed the impact of CVD on patients living with type 2 diabetes, as well as reviewed the results and clinical implications of a large randomized, controlled trial—Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infraction **(SAVOR-TIMI)** 53 Study.

CV RISK FACTORS IN DIABETES

The United Kingdom Prospective Diabetes Study (UKPDS) evaluated risk factors for coronary heart disease (CHD) and Dr. Harpreet Bajaj reviewed the rank order of these factors for patients developing a cardiovascular event. Elevated Low-Density Lipoprotein (LDL) Cholesterol was the highest risk factor followed by High-Density Lipoprotein (HDL) Cholesterol, Hemoglobin A1c (HbA1c), Systolic Blood Pressure, and then smoking. While HbA1c was statistically significant, so were the conventional CV risk factors like LDL and HDL (see Figure 1).

Figure 1

Stepwise Selection of Risk Factors : UKPDS
Coronary Artery Disease (n=280)

Position in Model	Variable	P Value
First	Low-Density Lipoprotein Cholesterol	<0.0001
Second	High-Density Lipoprotein Cholesterol	0.0001
Third	Hemoglobin A_{1c}	0.0022
Fourth	Systolic Blood Pressure	0.0065
Fifth	Smoking	0.056

* Adjusted for age and sex.
Turner Rc, et al. BMJ. 1998;316:823-828.

From the Endocrinology & Diabetes Specialists of LMC Endocrinology & Diabetes. The opinions expressed in this paper are those of the authors and do not necessarily reflect the opinions of LMC Endocrinology & Diabetes or the editorial board of Clinical Practice Update.

To achieve the target HbA1c in patients living with diabetes, the CDA has not outlined a stepwise approach when it comes to prescribing antihyperglycemic agents—there is much debate over which agents should be started initially as well as which agents should be added on. Dr. Bajaj highlighted the importance of individualizing therapy by looking at both the patient-related factors as well as the agent-related factors to determine the type of therapy to recommend for each patient.

Patient-Related Factors include:

- Hyperglycemia
- Hypoglycemia
- Weight
- Comorbidities
- Preferences
- Access to treatment

✓ Check Yourself:

Agent-Related Factors include:

- Glucose-lowering efficacy & durability
- Risk of hypoglycemia
- Effect on weight
- Contraindications, interactions and side effects
- Cost and coverage

ARE THERE CV BENEFITS OF DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS?

Drs. Bajaj, Ronald Goldenberg, and Samantha Sandler each in turn reviewed the results of SAVOR-TIMI 53 which was a prospective, randomized, controlled trial to determine the impact of saxagliptin [Onglyza] on cardiovascular events. Dr. Sandler pointed out that the US Food and Drug Administration (FDA) requires a CV trial for any new antihyperglycemic agent and SAVOR-TIMI 53 was one of the first studies to comply with this regulation. The study was designed to test the safety of saxagliptin as a treatment for patients living with type 2 diabetes who are also at high risk for CV complication–designed to illustrate that it was not increasing CV harm vs placebo, but also designed to potentially be able to show that it could reduce CV events more than placebo.

The study involved 16,492 patients (mean age 65 years) with documented type 2 diabetes (mean duration of 10.3 years) and had an HbA1c ≥6.5% and ≤12.0%. These patients also had either established CVD (78-79%) or multiple risk factors (21-22%). The primary endpoint of the study was the composite of CV death, non-fatal MI, or non-fatal ischemic stroke.

The study found that saxagliptin did not increase the risk of CV death, MI, or ischemic stroke thereby proving cardiovascular safety, however the results did not show cardiovascular benefit. There were many other clinical implications which have emerged out of the SAVOR-TIMI 53 study which will be further explored in follow-up analyses, and in the several ongoing trials also examining the cardiovascular benefit of both DPP-4 inhibitors & glucagon-like-peptide-1 (GLP-1) agonists.

CLINICAL IMPLICATIONS OF THE SAVOR-TIMI 53 STUDY

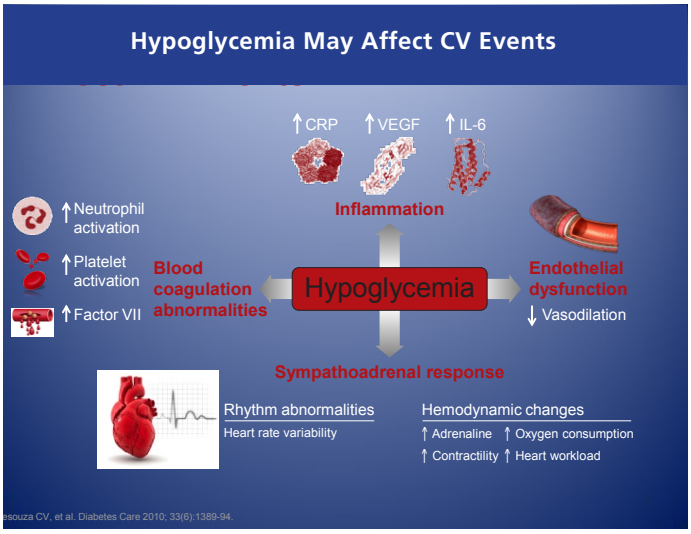
Hypoglycemia May Affect CV Events

Dr. Bajaj discussed some of the physiological abnormalities triggered by hypoglycemia that may increase the risk for CV events in patients living with diabetes (see Figure 2). The results of the SAVOUR-TIMI 53 study did show an increased rate of both major and minor hypoglycemia in the saxagliptin treated arm when compared to placebo, however, when stratified by antihyperglycemic use and by A1C, the increased risk largely occurred in therapy

combinations that included either a sulfonylurea and/or insulin (see Figure 3). Dr. Sandler reiterated that saxagliptin only significantly increased the risk of hypoglycemia in patients treated with sulfonylureas as well as significantly increased major hypoglycemic events in patients treated with insulin if the HbA1c was < 7.0%. Major hypoglycemic events were defined as those which required the assistance of another person. Of note, there was no increase in hospitalization for hypoglycemia in patients treated with saxagliptin.

These findings raised a question of whether we should more consistently be prioritizing incretins as a second line agent because of the increased side effect of hypoglycemia shown in individuals being treated with sulfonylureas. Another important question was raised during the sessions: "should we be considering incretins early in the treatment continuum because of their reduction in hyperglycemia & weight gain as well as their prevention of hypoglycemia?" The hypoglycemia findings of the SAVOR study also highlight the importance of reassessing the doses of the baseline antihyperglycemic agents like sulfonylureas or insulin when medications like saxagliptin are being added to the treatment plan.

Figure 2



Hazard Ration for Hypoglycemia in Saxagliptin vs. Placebo treated patients Stratified by Diabetic Medication Use and HbA1c

	The entire population	Patients with HbA1c<7%	Patients with HbA1c≥7%
No Baseline Diabetes Med. Use	(1.44)	(NA)	(1.54)
Meformin alone	(0.92)	(0.71)	(1.03)
Sulfonylurea	1.42	1.86	1.29
Insulin alone	(1.00)	1.39	(0.93)
Insulin in combination	(1.03)	1.42	(0.98)

ITT population
Raz I and Bhatt DL. Presented at: EASD; September 2013, Barcelona, Spain.

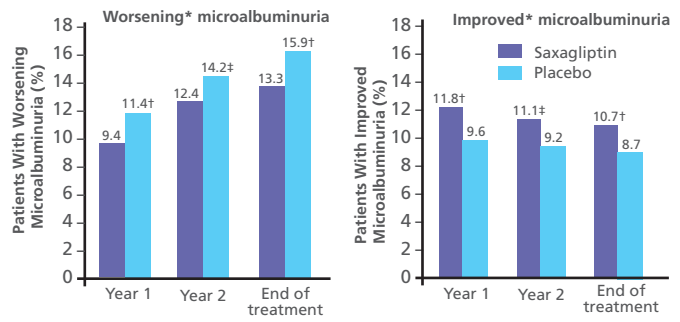
Figure 3

A FOCUS ON GLYCEMIC CONTROL

A significant improvement in glycemic control with saxagliptin compared to the placebo arm was demonstrated. As Dr. Bajaj pointed out, there is a need to remember that saxagliptin is a diabetes therapy and therefore, our focus generally should also be on glycemic control that was shown in patients treated with saxagliptin. Dr. Sandler also reviewed that there was a 23% reduction in the intensification of other antihyperglycemic medications with saxagliptin compared to placebo and there was also a decline in the initiation of insulin therapy with saxagliptin use.

Many studies have demonstrated that improved HbA1c has been shown to reduce the risk of microvascular complications such as nephropathy. Dr. Goldenberg shared that the saxagliptin-treated arm showed slower progression of microalbuminuria and when compared to placebo, these patients showed improved albumin to creatinine ratios (11.1% versus 9.2%, respectively) and were also less likely to have a worsening ratio (12.4% versus 14.2%, respectively) (see Figure 4).

Figure 4

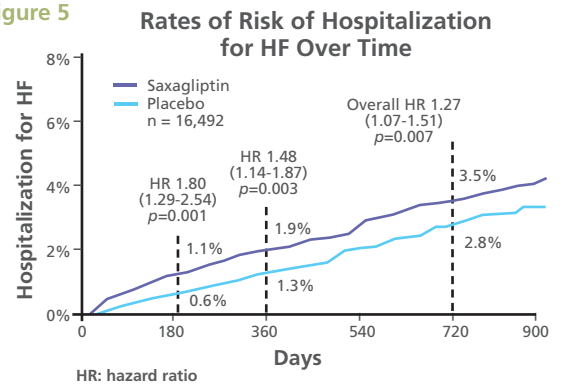


*Treatment difference in the number and proportion of patients with albumin/creatinine rations that worsened, did not change, or improved is defined as a shift from baseline category (<3.4, ≥3.4 to ≤33.9, or >33.9 mg/mmol).
†p<0.001 vs placebo; ‡p = 0.0058 vs placebo.
Scirica BM et al. *N Engl J Med.* 2013.10.1056/NEJMoa1307684.

INCREASED RISK OF HEART FAILURE

The rate of hospitalization for heart failure (HF) was increased in the saxagliptin group compared to placebo (3.5% versus 2.8%, respectively). Dr. Sandler pointed out that the increased risk of hospitalization for HF occurred particularly in the first six months of therapy and that these patients had measurable risk factors for HF already (see Figure 5). Dr. Goldenberg pointed out that after the initial 6 months, the rate of HF in each group was identical. The biological mechanism contributing to this imbalance has not been identified and it may turn out to be related to chance, given the number of outcomes being analyzed. This outcome is being investigated in more detail however; the general consensus amongst the presenters is that caution should be used in prescribing DPP-4 inhibitors like saxagliptin in patients with HF or at high risk of developing HF.

Figure 5



Scirica BM, et al. *American Heart Association Scientific Sessions.* Novermber 2013.

PANCREATIC OUTCOMES

Dr. Goldenberg also highlighted that there were similar rates of pancreatitis and pancreatic cancer between the two groups. Saxagliptin did not increase the overall risk or severity of pancreatitis nor did it increase the risk of pancreatic cancer.

SUMMARY

The SAVOR-TIMI 53 study resulted in a number of clinical learnings which included the proof of cardiovascular safety for saxagliptin since it did not increase the risk of CV death, MI, or ischemic stroke. The other clinical implications of the DPP-4 inhibitor, saxagliptin, include:

- Did not show any cardiovascular benefit (did not reduce risk of CV outcomes)
- Increased risk of hypoglycemia
- Significantly improved glycemic control
- Prevented of deterioration of microalbuminuria
- Increased risk of hospitalization for heart failure in at-risk patients
- Rates of pancreatitis and pancreatic cancer not different than placebo

The CDA advocates for the importance of vascular protection and making it a priority for all patients living with diabetes. Large randomized trials like SAVOR-TIMI are demonstrating that DPP-4 inhibitors like saxagliptin have many benefits and are safe in the context of CV risk in the management of T2DM.

[i] Scirica BM, et al. Saxagliptin and cardiovascular outcomes in type 2 diabetes mellitus. N Engl J Med. 2013.10.1056/NEJMoa1307684.
[ii] Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study. BMJ 1998;316:823-828.
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[iv] Scirica BM, et al. N Engl J Med 2013; [epub ahead of print].
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[vi] Raz I and Bhatt DL. Presented at: EASD; September 2013; Barcelona, Spain.
[vii] Raz I and Bhatt DL. Presented at: EASD; September 2013; Barcelona, Spain
[viii] Raz I and Bhatt DL. Presented at: EASD; September 2013; Barcelona, Spain.
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