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CLINICAL PRACTICE UPDATE IN
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Clinical Controversies in Diabetes Management:

An Interactive Evening for Endocrinologists at Vascular 2013
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Part 2 – Glycemia Management in the Diabetes Patient


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As new therapies emerge, the risk/benefit profile of each comes under scrutiny, creating a flood of sometimes conflicting data. The role of each emerging therapy also becomes more challenging to define as each takes its place in our list of indications, and eventually in our practice guidelines. Dr. Alice Cheng, the evening's moderator, tackled these issues through a series of questions.

QUESTION 1 - Do incretin agents increase the risk of pancreatitis or pancreatic cancer?

Drs. Remi Rabasa-Lhoret and Goldenberg debated the pre-clinical literature to date – conflicting at best. Some studies have documented GLP-1 receptors in both the endocrine and exocrine pancreas and animal models exposed to incretins have sometimes shown ductal inflammation. Although there have been post-marketing reports of pancreatitis amongst incretin users, Dr. Goldenberg outlined the flaws and bias in the FDA Adverse Reporting System. Dr. Rabasa-Lhoret also criticized a recently publicized autopsy study of incretin users which recently found pre-malignant lesions in DPP4-i users who had died of unrelated causes. Unfortunately, the study was too unbalanced to lead to any reliable

conclusions. Lipase levels may be higher on average in incretin users, potentially due to low-level pancreatic inflammation.

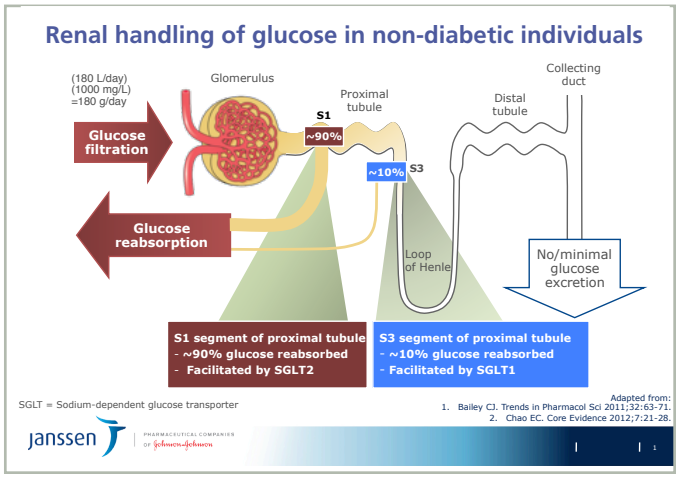
However, simply having type 2 diabetes in itself carries a significant risk of pancreatitis. Dr. Rabasa-Lhoret outlined a recent meta-analysis of seven observational studies which suggested a pancreatitis risk that is 84% higher in diabetes patients compared to those without diabetes. Although registry studies have reported increased incidences of pancreatitis in incretin users, many were not adequately controlled and did not correct for important other contributors such as alcohol use, cystic fibrosis, gallstone disease, and others. Large controlled trials like the recently published SAVOR and EXAMINE trials, have shown no increase in pancreatitis nor pancreatic cancer, in users of saxagliptin or alogliptin.

To rule out even a 25% increased risk of pancreatitis, one would need a randomized controlled trial with 89 000 patients-years follow up per group. Given the natural history of pancreatic carcinoma, a controlled surveillance would need at least a 12-year duration.

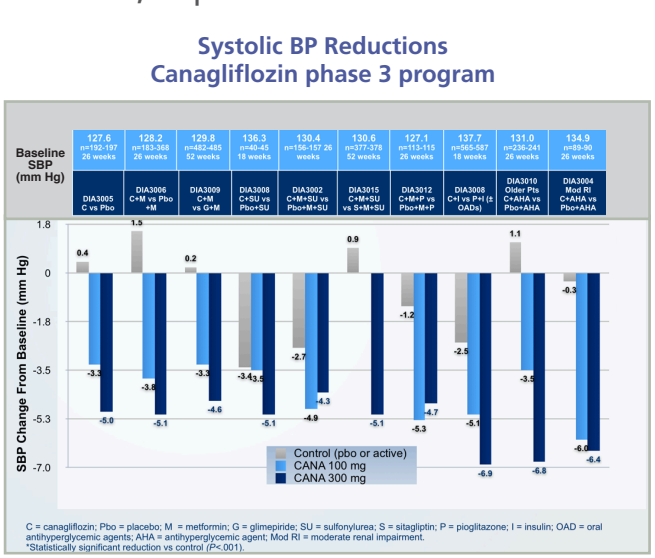
QUESTION 2 - Are SGLT2 inhibitors safe for the kidney?

Dr. Cheng introduced this new class of blood sugar (BS) lowering therapies with the confession that the mechanism – clearance of glucose through intentional glycosuria – took her by surprise. The extensive evidence to date shows them to be effective in BS lowering – what is their impact on GFR and albuminuria in diabetes patients? And in diabetes patients with CKD?

Dr. Jordan Weinstein reviewed their mechanism – we naturally filter 180 mg/day of glucose through the proximal kidney (glomeruli). We then undergo an attempt at conserving that "lost" glucose by reabsorbing it in the distal kidney (tubules) via the work of the SGLT2 glucose-sodium cotransporters. If we inhibit the SGLT2 transporters, we prevent the re-absorption of the filtered glucose (and sodium) in the renal tubules. He further suggested that they resemble a diuretic in their effect – a modest loss of salt, sugar and water. The expected side effects then, would include a modest BP drop, urinary frequency and theoretical volume contraction.



Dr. Weinstein also pointed out that BP reduction is a lot like BS reduction:"…it depends where you start." Across studies to date with the first of this class, Canagliflozin, in patients with controlled hypertension, systolic BP drops were in the order of 3-6mm, vs placebo.



Addressing renal function specifically, Dr. Weinstein pointed out the Canagliflozin phase 3 research program, and the SGLT2 development programs in general, are the largest ever performed for a new therapy and they indicate that these therapies are entirely neutral in their effect on renal func

tion and on albuminuria. Overall, in regards to renal safety, he felt there was not much "signal for concern".

Dr. Ron Goldenberg, again in his role as Devil's Advocate, did point out that a small minority of patients might experience a more significant GFR decline (> 30%) – including the elderly, RAAS therapy users, and those already using loop diuretics, especially in patients with pre-existing moderate CKD. Dr. Goldenberg mused that when SGLT2 inhibitors do become available in Canada, the Clinical Practice Guidelines scientific committee would have to consider adding them to the list of "sick day" medications – therapies to be withheld during an acute illness.

A provocative audience question emerged: as we begin using this class of medications, should we be holding or discontinuing ACEi/ARB therapies and/or diuretics? Dr. Weinstein used the opportunity to remind the Endocrinologist audience that there is no proven cardioprotection with diuretics and went on to suggest that the SGLT2 class could conceivably replace current thiazide diuretic use. If a diuretic-user is showing very well-controlled BP as their baseline, then addition of an SGLT2i might suggest withholding the prior diuretic to avoid the risk of hypotension.

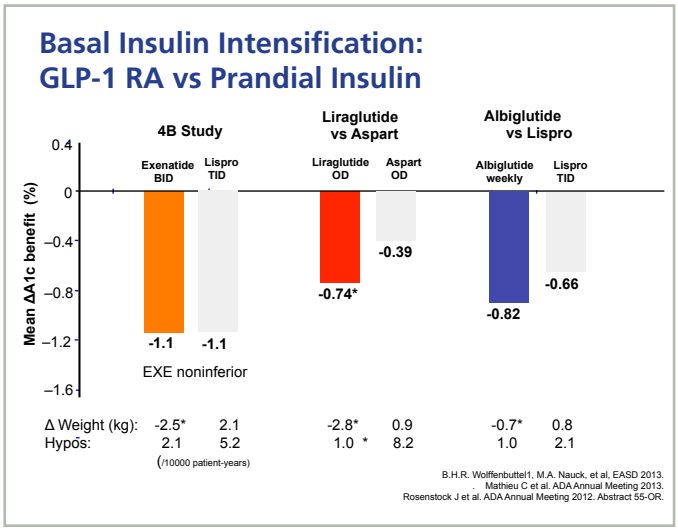
Dr. Goldenberg pointed out recent studies with empagliflozin, another SGLT2i, which showed that BP drops were dependent on the patient's own baseline – if they were already in the lower end of the normal range, they did not experience any further drop in BP. In contrast, recent posters have indicated that BP lowering was greater in antihypertensive users (with a history of hypertension) than in non-users – possibly related to loss of the adaptive response to BP changes. The general consensus was that our clinical experience would guide us as we begin using this important new class of therapies.

Dr. Cheng wrapped up the SGLT2i discussion by asking whether we know the implications of long-term exposure of the renal tubules to higher glucose levels. In the proximal kidney, the nephrons, the known pathophysiology of glomerular nephropathy is related to high blood levels of glucose, not to filtered tubular levels of glucose. In the distal kidney, the tubular portion, glucose is consistently accommodated as part of our natural physiology. The marginal increase in the amount of glucose in the distal kidney that would be produced by SGLT2i is unlikely to contribute to any known renal disease. Dr. Goldenberg further pointed out that, in fact, an existing rare genetic disease called "Familial Renal Glycosuria", with an autosomal dominant inheritance, produces a natural model of the SGLT2 effect and that these people live perfectly normal lives with no sign of chronic kidney damage.

QUESTION 3 - Intensification beyond basal insulin – prandial insulin or an incretin?

Dr. Cheng posed the question of the DM2 patient, optimized on basal insulin therapy with well-controlled fasting glucose levels, BUT with a persistent uncontrolled A1C.

Drs. Rabasa-Lhoret and Goldenberg discussed the evidence to date. Three trials have taken uncontrolled basal insulin-treated patients and randomly assigned them to addition of prandial insulin vs. an incretin agent. While full publications are still not available, the trials have been presented in abstract form at the ADA meeting over the past 2 years. The 4B study compared exenatide BID with prandial insulin TID and found them to be equal – exenatide was non-inferior and was actually associated with less hypoglycemia and with weight loss. Liraglutide similarly showed weight loss and less hypoglycemia, and was also significantly more effective than OD prandial insulin. Finally, the once-weekly GLP-1R agonist, albiglutide was non-inferior to TID prandial insulin, again with weight loss and a trend towards less hypoglycemia.

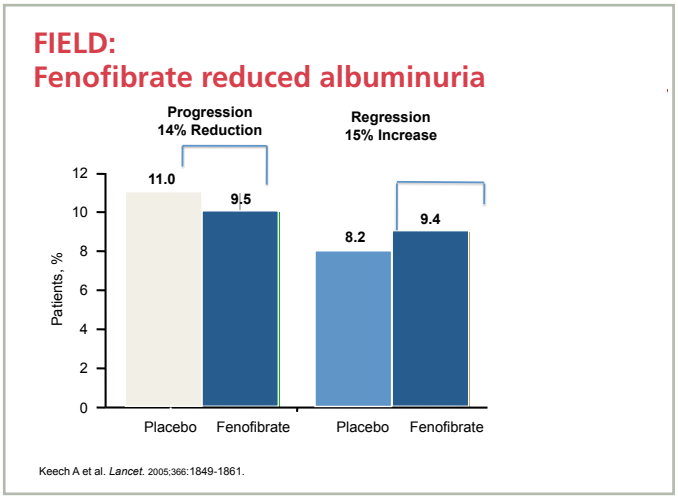


Although very promising, in each of these studies, the prandial insulin was not titrated aggressively enough to provide a perfect comparison and each was an open label study, with some potential impact of bias. The Endocrinologist audience generally concurred with the important caveat that therapy choice be individualized for each patient.

QUESTION 4 - statins and fibrates and the kidney - what is their impact on GFR and albuminuria in patients with or without CKD?

Dr. Weinstein addressed this key question, clarifying a recent misconception regarding fibrates and renal function. Initial interpretations of the serum creatinine levels in the course of the FIELD study had suggested a significant rise in serum creatinine and a decline in GFR, with fibrate use. However, we now understand that fibrates do not impair GFR (glomerular filtration as estimated by creatinine) but they actually reduce creatinine secretion, the other mechanism of creatinine clearance. The result is an artefactual increase in serum creatinine levels in patients assigned to fibrates. Inulin-based measures of GFR have since confirmed that there is no change in GFR when patients begin a fibrate. Fibrates are similar to cimetidine or trimethoprim in this phenomenon of creatinine rise but it is a non-pathological rise.

In fact, follow-up analyses of the FIELD data showed a remarkable stability in patients on fibrates, with a slower loss of renal function over time, than patients not treated with a fibrate. Dr. Goldenberg highlighted that this point was further reinforced in the FIELD and ACCORD washout studies suggesting that fenofibrate may be a nephroprotective agent. In fact, fenofibrate definitively slows progression of the albuminuria, much as it does in other microvascular diseases like retinopathy.



Statins and proteinuria have recently come under scrutiny again. Dr. Weinstein referenced two prior posters related to the rosuvastatin studies, PLANET 1 & 2, which showed increased proteinuria with statin therapy, found to be entirely related to tubular protein (2-microgolbulin) and therefore not suggestive of renal pathology.

Finally, in the area of statins and renal function – although a recent patient registry study suggested worsened renal function in patients using high-dose statins, meta-analysis of all the atorvastatin and all the rosuvastatin trials looking at renal function shows a minor improvement in GFR in patients randomized to statins versus placebo.

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