CONCERNS REGARDING SAFETY IN THE USE OF ORAL AND CERTAIN INJECTABLE THERAPIES FOR DIABETES MELLITUS5/28 17

DR. LUIS RAUL RUIZ RIVERA F.A.C.E.

luisra0451@yahoo.com SPED 2017

DISCLOSURES:

- NOTHING TO DISCLOSE FOR THIS LECTURE!!
- NO CONFLICT OF INTEREST

LB NEWS REGARDING ACTOS:

- FDA HAS ISSUED A BB WARNING FOR ACTOS[AGAIN] REGARDING BLADDER TUMORS.ALTHOUGHT THERE IS INSUFICIENT DATA TO DETERMINE WHETHER PIO IS A TUMOR PROMOTER OR NOT.IT SHOULD NOT BE USED IN PTE's WITH ACTIVE BLADDER CANCER,or HEMATURIA AND FAMILY HX OF BLADDER CANCER. THIS WAS OBTAINED FROM THE PROACTIVE TRIALS.

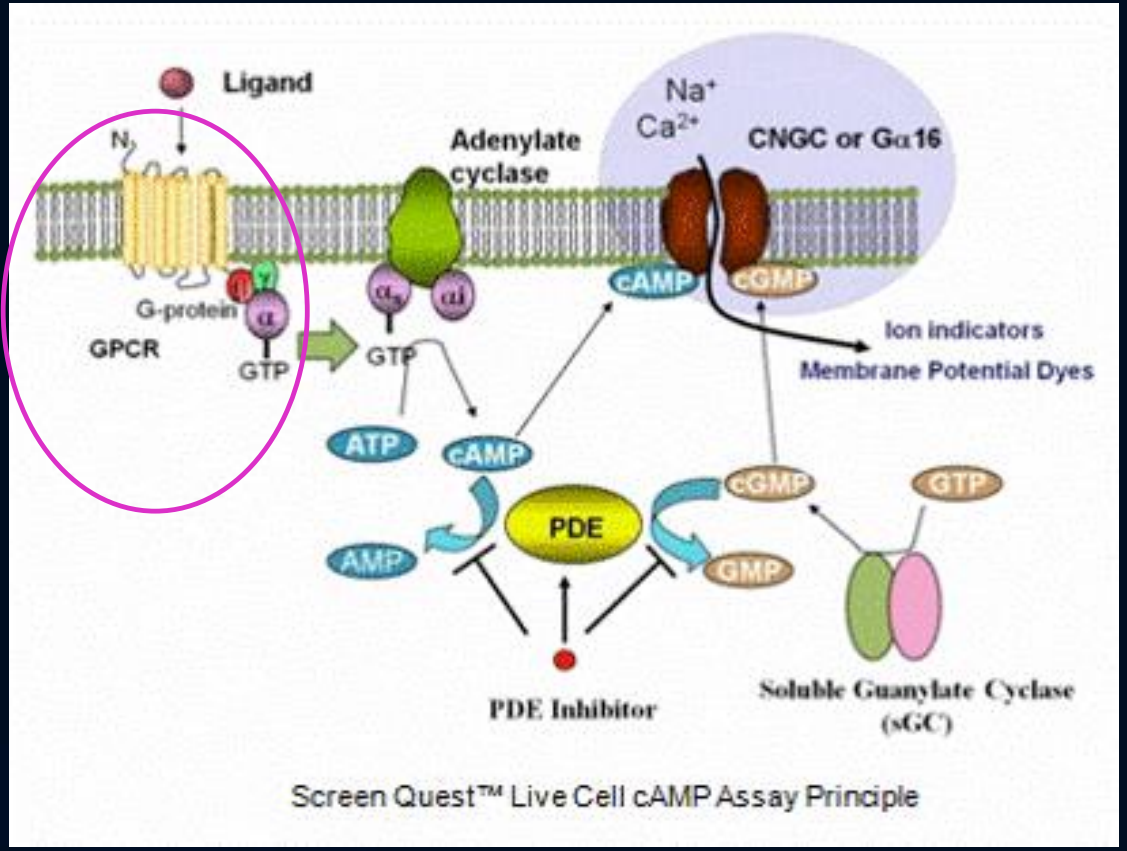
Controversies

- Pancreatic safety has become a subject of much debate concerning the incretins due to conflicting results from preclinical studies, AEs reporting, RCTs, and observational studies.
- Post-marketing reports of AP and PC in pts on incretin-based drugs surfaced since the first incretin medication was approved in 2005.
- A 2011 study of the FDA's database of AE's (FAERS) associated with sitagliptin and exenatide demonstrated a 6-fold increase in the OR for reported pancreatitis.
- OBVIOUSLY THE MAIN SAFETY CONCERN IN THESE TYPE OF TREATMENTS IS HYPOGLYCEMIA AVOIDANCE.

Diab,obes,Metab 2014;16:1041

Incretin Action in the Pancreas : Potential Promise, Possible Perils, and Pathological Pitfalls

- Recent studies have suggested that incretin Tx promote pancreatic inflammation as well as aberrant cell proliferation within the endocrine and exocrine pancreas
- To understand whether there are any potential adverse effects of GLP-1 RA in human pancreas the expression pattern of GLP-1 R may be imp.
- However, most studies measuring the GLP-IR may be invalid because most antisera used to detect GLP-1R expression are neither sensitive or specific.
- G protein coupled receptors are notorious for this problem.



Drucker Diabetes 2013 ;63:3316

Incretin-based Therapies and Inflammatory Markers

- 35.6% of subjects treated with DPP-4 I or GLP-1RA exhibited increases in plasma amylase and/or lipase .
- Notably, elevated levels of amylase/lipase also were observed, though less frequently, in diabetic subjects who didn't receive IBT.
- Further study needed to see if this reflects subclinical inflammation or dysregulated synthesis, secretion or clearance of these enzymes
- Available data indicates that iBT exert anti-inflammatory action in tissues ie exocrine and endocrine pancreas, as well as in circulating blood cells from diabetic subjects . Mechanisms mediating these actions remain poorly understood.

Incretin Therapy and Islet Pathology: A Time for Caution

- Increase in Beta-cell Mass
  - Due to differences in body size, age, sex ?
  - ↑ beta-cell mass not a result of an ↑ in b-cell replication
  - Imbalance in the types of diabetes ?
- Glugon-staining microadenomas 37.5%
  - Prevalence of pancreatic endocrine tumors is extremely low .005%
  - Even assuming a lower prevalence ,given the millions of patient-yrs. Exposure to these agents ..autopsy, biobsy clinical picture
- Post Gastric Bypass surgery
  - Pp GLP-1 levels are ↑> thaan 4-fold in the range of or > than those seen with DPP4 I
  - Hyperinsulinism due to ↑ GLP-1 stimulated insulin secretion : no evidence of inc. B-cell mass

Kahn Diabetes 2013;62:2178

Complexity of Biological association Between T2DM and Pancreatic Diseases

- Makes the evaluation challenging
- Unclear whether T2DM is a RF and/or a consequence of pancreatic disease.
- Consensus : risk of pancreatitis is increased in T2DM
  - 54-564/100,000 cases/100,000 pt. yrs vs 22-190/100,000 pt yrs in non diabetics
  - Meta-analysis of several observational studies estimates that T2DM patients have a 2-3-fold increased risk of AP
  - Mechanisms: many entangled factors: common RFs of obesity, hyper Tgs, the disease itself, comorbidities , and medications come into play .

Relationship between Pancreatic Cancer and DM

- Challenging due to cancer's long latency period
- Observational studies examining this possible association, must account for this latency period and exclude cases with PC with T2DM dx within a certain period before PC dx, ie 2 yrs.
- 15/19 studies published since 2003, which accounted for a latency period of at least 2 yrs., found a significantly ↑risk of PC in T2DM patients..
- Meta-analysis of 35 studies , T2DM patients were found to have a 2-fold increased risk of PC compared with non-diabetics, and 8o% in IGT
- Relationship may be due in part to shared RFs ie obesity, diet, and physical inactivity or may be directly linked to biological and hormonal characteristics of T2DM.found a significantly increased risk of PC in T2DM

Diab. Obes.Metab. 2014;16:1041

Effect of Incretin Therapy on Human Pancreata

Pancreata from JDRF Network for Pancreatic Organ Donors with Diabetes
34 brain-dead donors

Classified as

- Non diabetic
- T2D –on incretin therapy: 7 sitagliptin, 1 exenatide 25% females

7 of 8 were using 2 or > medications

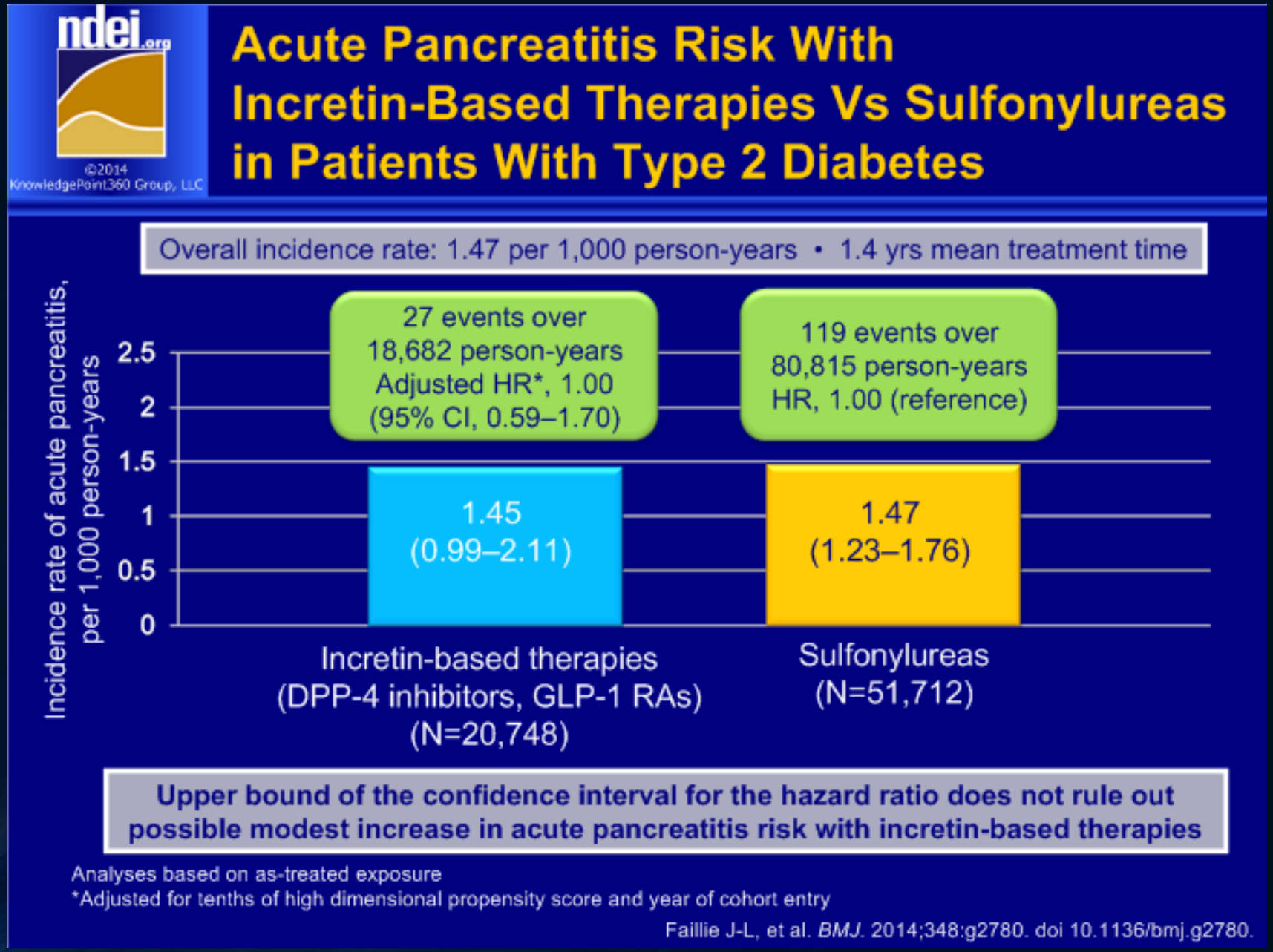
- T2D –not on incretin Therapy : 12 ; 7 on a single agent which for 4 was insulin

Results for T2D donors on incretin therapy:

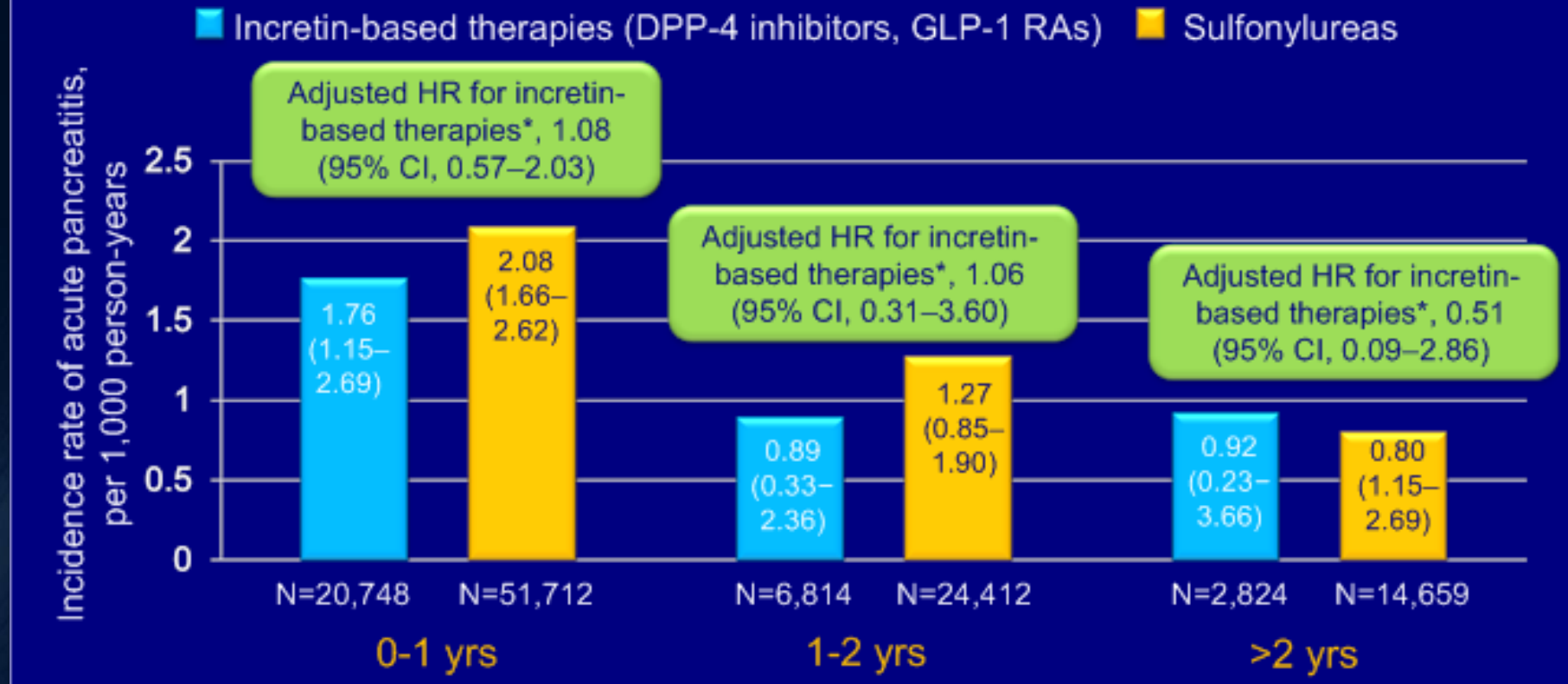
- Pancreatic mass increased (@ 40%) vs non-incretin therapy
- B cell mass ↑6-fold; 5-fold ↑ in # of alpha cells) Increased exocrine pancreas cell proliferation
- Dysplastic changes in the form of pancreatic intraepithelial neoplasia
- 3 subjects had glucagon producing microadenomas (37.5%)

Butler Diabetes 2013;62:2595

- UK Clinical Practice Research Datalink (CPRD) & Hospital Episode Statistics (HES)



Acute Pancreatitis Risk With Incretin-Based Therapies Vs Sulfonylureas in Patients With Type 2 Diabetes By Duration of Use



Upper bound of the confidence interval for the hazard ratio does not rule out possible modest increase in acute pancreatitis risk with incretin-based therapies

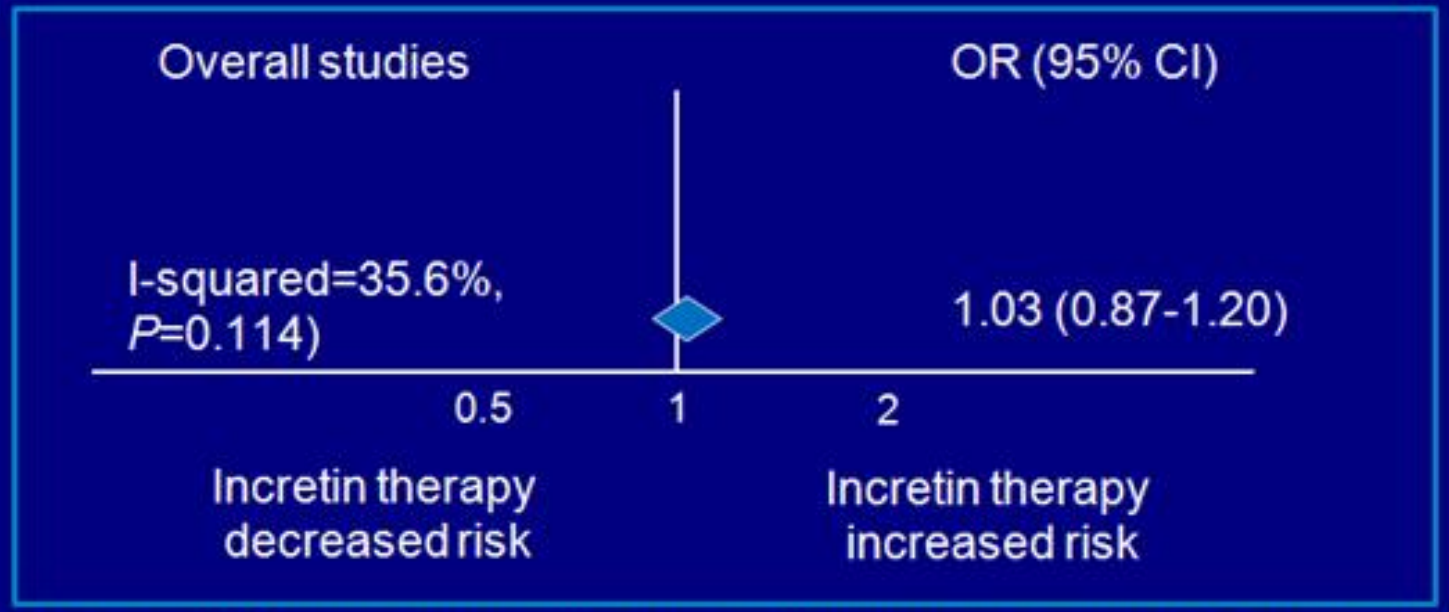
Analyses based on as-treated exposure

*Adjusted for tenths of high dimensional propensity score and year of cohort entry; HR 1.00 for sulfonylureas (reference)

Faillie J-L, et al. *BMJ*. 2014;348:g2780. doi 10.1136/bmj.g2780.

No Increased Acute Pancreatitis Risk With Incretins: Meta-Analysis

- Nine studies including 1,324,515 subjects
  - 219,228 subjects with diabetes exposed to incretin therapies
  - 1,105,287 subjects not exposed to incretin therapies



- Results do not suggest incretin-based therapy is associated with acute pancreatitis
  - Authors acknowledge limitations to databases used in meta-analysis

OR=odds ratio

Wang T, et al. *Diabetes Obes Metab*. 2015;17:32-41.

Odds of Hospitalization for Acute Pancreatitis

Pts on incretin therapy	Adjusted odds ratio	95% CI	P value
Current use within 30 days	2.24	1.36-3.69	.01
Recent use	2.01	1.37-3.18	.01
Any use	2.07	1.36-3.13	.01

When each class of drugs was analyzed separately rather than combining exenatide with sitagliptin, there was no increased risk

Singh JAMA 2013;173:534
Nauck Diab Care 2013;36:2126

Use of IBT and Other Antihyperglycemic Agents in Patients with AP

	Unadjusted OR	Adjusted OR
DPP4 I		
Ever use	1.38	1.04
Current use	0.98	0.78
Former use	2.02	1.44
New use	1.80	1.51
GLP-1 RA		
Ever use	1.35	0.82
Current use	1.46	0.84
Former use	1.05	0.74
New use	0.28	0.17
Other Antihy perglycemic		
Ever use	1.44	1.05
Current use	1.35	0.99
Former use	1.93	1.35
New use	2.20	1.64

LIRAGLUTIDE: LEADER TRIAL DIABETES CARE 5/1/17

- In LEADER, numerically fewer events of Acute Pancreatitis were observed in the LIRA group treated patients compared with placebo, LIRA increased serum amylase and lipase untill PLATEAUD and remained stable for the duration of the trial. These elevations in ASYMPTOMATIC pts were NOT predictive of Acute Pancreatitis.

Adjusted ORs for Hospitalization with AP According to Use of Non-incretin Antihyperglycemic drugs

Exposure	Pancreatitis cases N(%)	Population controls N(%)
Any non-incretin		
Ever use	1088 (8.46)	7853 (6.10)
Current use	860 (6.68)	6629 (5.15)
Former use	228 (1.77)	1224 (0.95)
New Use	85 (0.66)	400 (0.31)
Metformin		
Ever use	732 (5.69)	5475 (4.25)
Current use	499 (3.88)	4034 (3.13)
Former use	233 (1.81)	1441 (1.12)
New use	42 (0.33)	257 (0.20)
Sulfonylureas		
Ever use	546 (4.24)	3748 (2.91)
Current use	296 (2.30)	2202 (1.71)
Former use	250 (1.94)	1546 (1.20)
New Use	18 (0.14)	77 (0.06)
Insulin		
Ever use	355 (2.76)	2473 (1.92)
Current use	284 (2.21)	2082 (1.62)
Former use	71 (0.55)	391 (0.30)
New Use	29 (0.23)	60 (0.05)

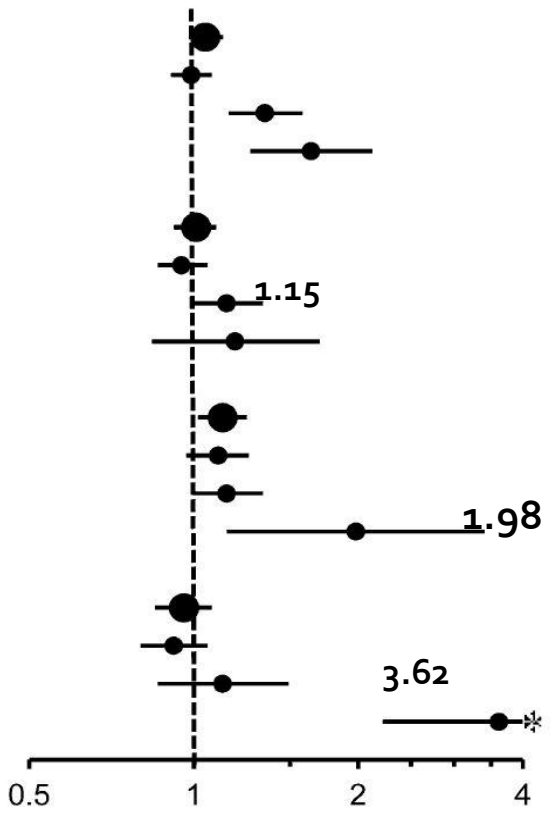


Figure 2—Adjusted ORs for hospitalization with acute pancreatitis according to use of non-incretin antihyperglycemic drugs. *Lower 95% confidence limit <0.5 or upper 95% confidence limit >4.

Diab Care 1/2015 Thomsen et al

TO ADD DAMAGE TO INJURY!

- RECENTLY PUBLISHED ON THE CARDIOLOGY JOURNAL
- SULFONYLUREAS USE IS ASSOCIATED WITH LARGER INFARCT SIZE IN PTS WITH DIABETES AND ST ELEVATION MYOCARDIAL INFARCTIONS.THE STUDY DEMOSTRATED A CAUSAL RELATIONSHIP BETWEEN SULFOS AND ADVERSE CARDIOVASCULAR EVENTS BY OBSERVING A SIGNIFICANT DIFFERENCE IN INFARCT SIZE AMONG TYPE 2 DIABETIC PTS PRESENTING WITH STEMI.CLINICIANS SHOULD CONSIDER THIS ASSOCIATION WHEN PRESCRIBING SULFOS TO TYPE 2 DIABETIC PTS.

Long-term Studies Examining the Safety of Incretin-based Therapies

Medications	Study name	comparator	# of subjects	Study start date	Estimated study end date
DPP4-inhibitors					
Linagliptin	EXAMINE	Glimepiride	6,000	10/2010	9/2018
sitagliptin	TECOS	Placebo	14,000	12/2008	12/2014
GLP-1 RAs					
Duraglutide	REWIND	Placebo	9,622	7/2011	4/2019
Exenatide	EXSCEL	"	9,500	6/2010	3/2017
Liraglutide	LEADER	"	9,340	8/2010	1/2016
lixisenatide	ELIXA	"	6,000	6/2010	5/2014

www. Clinical Trials.gov

Adverse Effects of GLP-1 Agonists and DPP-4 Inhibitors

	Nausea/vomiting	Diarrhea	Hypoglycemia	Pancreatitis
Alogliptin[5]			+	Rare
Linagliptin[6]			+	Rare
Sitagliptin[7,8]			+	Rare
Saxagliptin[9]		+/-	+	Rare

- In the first long-term clinical trials (EXAMINE, SAVOR, TECOS), there was no difference in the rate of pancreatitis between the active drug and placebo[10,]

BLACK BOX WARNING WAS PUT FOR CHF IN SAXA and ALOGLIPTIN.

1. Klonoff DC, et al. *Curr Med Res Opin.* 2008;24:275-286. 2. Kolterman OG, et al. *J Clin Endocrinol Metab.* 2003;88:3082-3089. 3. Garber A, et al. *Lancet.* 2009;373:473-481. 4. Exenatide QW Prescribing Information. 5. Alogliptin Prescribing Information. 6. Linagliptin Prescribing Information. 7. Hanefeld M, et al. *Curr Med Res Opin.* 2007;23:1329-1339. 8. Sitagliptin Prescribing Information. 9. Rosenstock J, et al. *Curr Med Res Opin.* 2009;25:2401-2411. 10. White WB, et al. *N Engl J Med*. 2013;369:1327-1335. 11. Scirica BM, et al. *N Engl J Med*. 2013 3;369:1317-1326.

FDA DRUG SAFETY COMUNICATION

- THE FDA WARNS THAT DPP4's INHIBITORS FOR DM TYPE 2 MAY CAUSE SEVERE AND DISABLING JONT PAIN. PTS SHOULD NOT STOP MEDS BUT CONTACT THEIR HCP's. SYMPTOMS APPEAR FROM DAY ONE TO YEARS AFTER THEY START THE MEDS. THIS SHOULD BE NOTIFIED TO THE FDA ADVERSE EVENTS REPORTING SYSTEM.

FDA and EMA Response

- Assertions concerning a causal association between incretin-based drugs and AP or PC are inconsistent with the current data
- Though the totality of the data that have been reviewed provides reassurance,
- The FDA and EMA have not reached a final conclusion at this time regarding such a causal relationship
- In a recent metaanalysis including TECOS, SAVOR- TIMI 53. LEADER and EXAMINE; there was no increased evidence of AP or PC!

NEJM 2014feb // DIABETES CARE

Key Takeaways

- Important to discuss therapy options with patient and use a personalized approach to therapy as per ADA 2o17 guidelines
- discuss benefits vs risk
- There are currently many long- term prospective , randomized studies and endeavors that will comparatively evaluate safety and efficacy of different diabetes therapy

ADVERSE EVENTS

OF SGLT 2”s and SAFETY CONCERNS

- Increased frequency of urinary tract and genital yeast infections.

►the latter particularly so in women and uncircumscised men

►appeared not to re-occur after initial treatment

►discontinuation for this adverse effect is rare

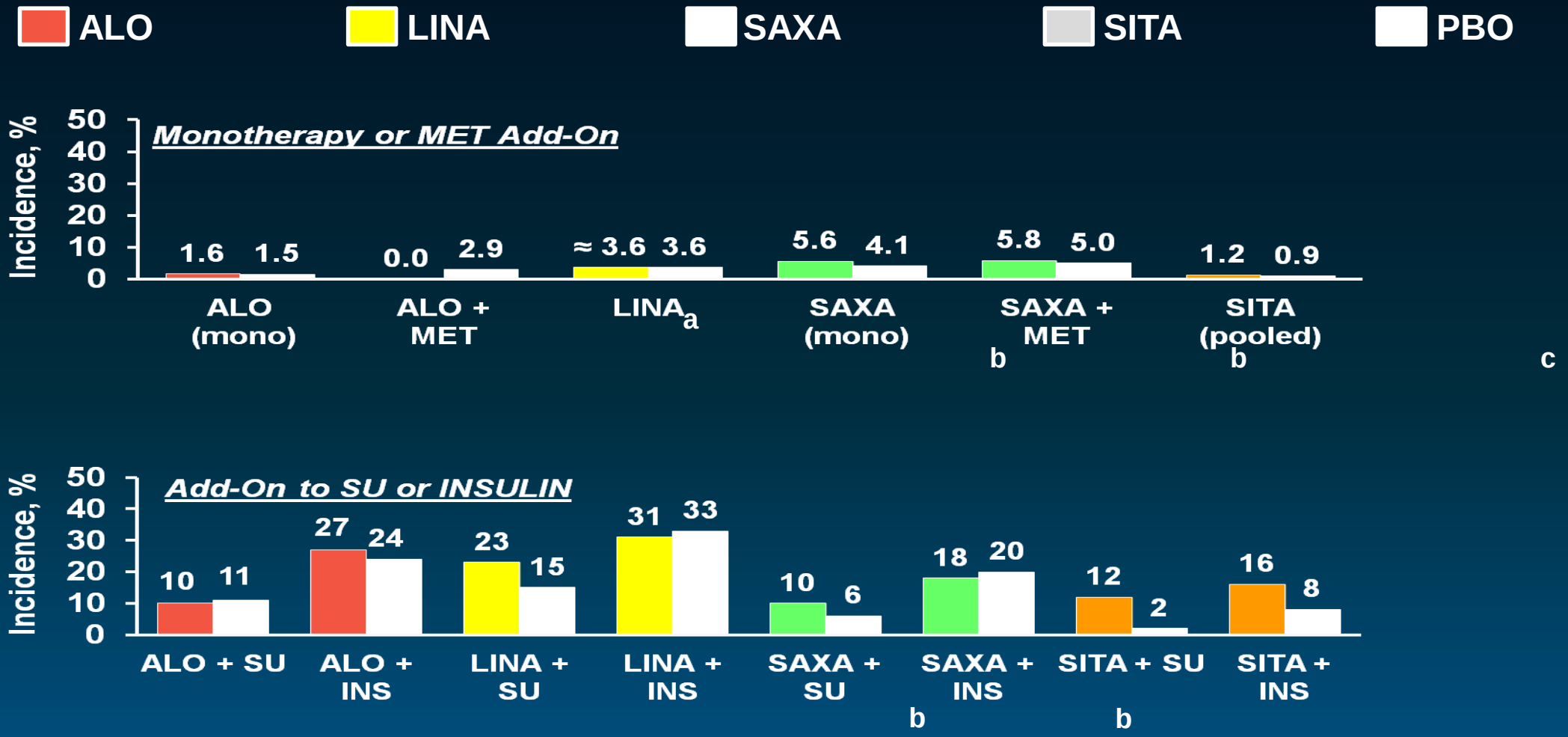
- Hypoglycemia occurred more frequently in clinical trials although it does not seem to be appreciable.

UROSEPSIS and PIELONEPHRITIS

THE FDA HAS ISSUED A WARNING

SEVERAL CASES OF UROSEPSIS BEGINNING WITH UTI's THAT REQUIRED HOSPITALIZATIONS!

Overall Hypoglycemia Incidence Increases When DPP-4 Inhibitors Are Added to Sulfonylurea or Insulin Regimens



[a] Incidence with LINA monotherapy or MET add-on was similar to that in PBO-treated patients; 3.6% of PBO patients reported hypoglycemia.
[b] SAXA (5.0 mg).
[c] SITA monotherapy, MET add-on, and PIO add-on trials.

US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

Perspectives on SGLT2 Inhibition

Advantages

- Improved glycemic control
- Weight loss
- Low risk of hypoglycemia
- Blood pressure lowering
- Reduce cardiovascular events and mortality

Concerns

- Polyuria
- Electrolyte disturbances
- Urinary tract infections
- Fungal genital infections
- DKA
- Bone fractures

Euglycemic DKA in T2DM

Case #	8	9	10
Age/Dur	58/2	64/6	39/9
Gender	M	F	M
BMI	26.5	32.8	40
A1C	9.8	7.8	6.6
Contributors	Surgery 1 week prior	Surgery 12 hours prior	Surgery 5 days prior
Cana Dose	300	300	300
Insulin Dose Reduction?	N/A	N/A	N/A
BG	150	169	108 - 162
Bicarb	10	5	4
Anion Gap	17	19	Arterial pH = 7.06 AG ~20

All had strongly positive urine ketones with positive serum ketones. Negative anti-GAD abs/+ Cpeptide.

Peters AL et al Diabetes Care 2015;38:1687-1693

Precipitating Factors

- In all subjects with DKA, possible precipitating factors that could have caused or contributed to the event were present,
  - Infections (pneumonia, influenza, bronchitis, infection of infusion site of insulin pump)
  - Insufficient insulin dosing (pump failure, lack of compliance with insulin treatment)

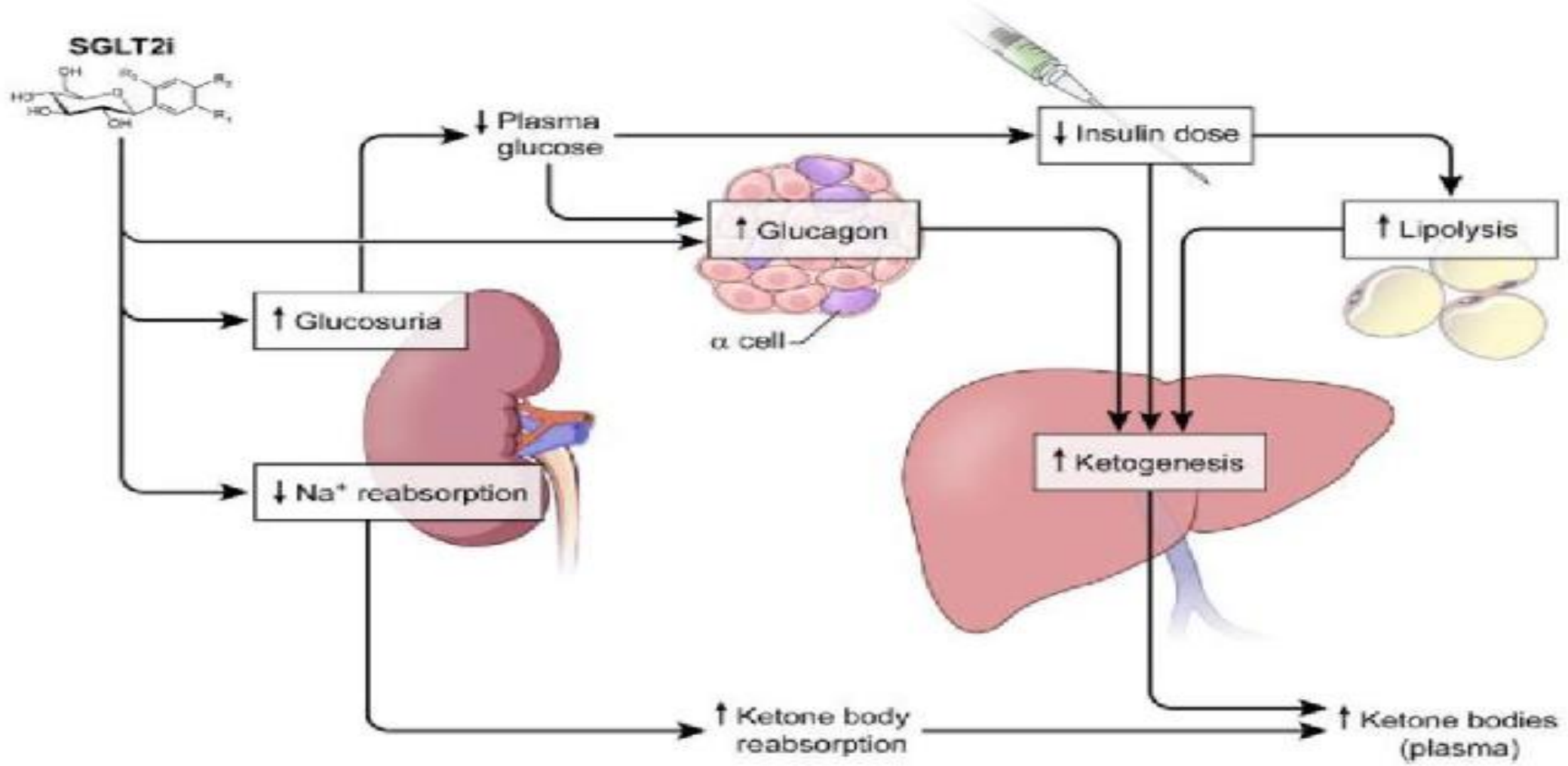
A. Peters. Personal Communication. Manuscript under review.

Mechanism(s) for Increased Risk of DKA

1. Increase in insulin-independent urinary glucose excretion may result in adherent under dosing of insulin
2. There is an increase in glucagon secretion associated with SGLT2 inhibition, which could cause a decrease in the insulin to glucagon ratio, which in turn would promote ketogenesis.

Bonner C et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med 2015;21:512-517

SGLT2-I and risk of ketoacidosis in T1D: Potential Mechanisms



Taylor et al. J Clin Endocrinol & Metabol 2015

HOW DKA DEVELOPS??

- DUE TO THE DECREASE IN EXTRACELULAR BLOOD GLUCOSE IT WILL CAUSE AN INTRACELULAR LACK OF SUBSTRATE FOR THE KREBS CYCLE PRODUCING ACETYL CO A TO PRODUCE MORE ACETOACETATE FOR ENERGY EXPENDITURE, CAUSING AN INCREASE IN KETOSIS. ALSO THE IMBALANCE BETWEEN INSULIN TO GLUCAGON RATIO WILL PRODUCE HEPATIC KETOGENESIS,VIA AUGMENTATION OF FFA’s!

Conclusions

- Increased risk of DKA in patients with T1D treated with SGLT2-inhibitors.
- Use of SGLT-2 inhibitors is off-label in individuals with T1DM other than in clinical trials.
- If an SGLT-2 inhibitor is used in an individual with T1DM -
  - ketone monitoring
  -- Watch for hyper and euglycemic DKA
- DKA may also occur in patients with T2D treated with SGLT2-inhibitors

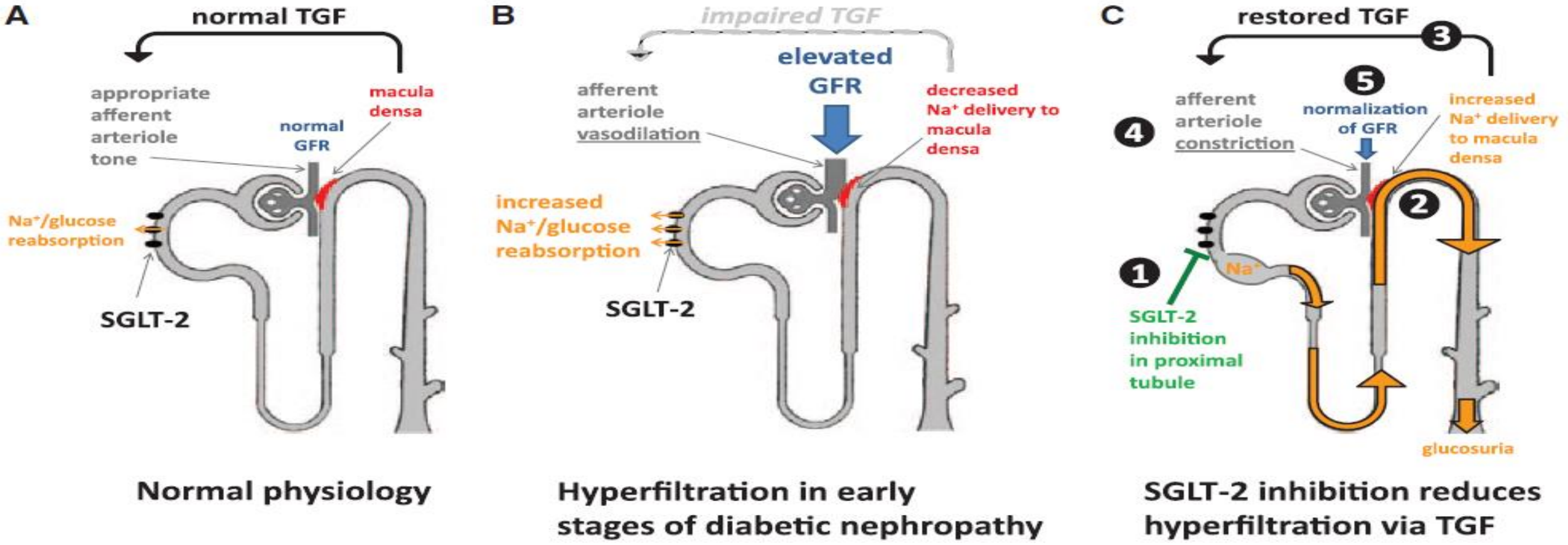


Figure 1. Postulated tubuloglomerular feedback (TGF) mechanisms in normal physiology, early stages of diabetic nephropathy, and after sodium-glucose cotransporter (SGLT) 2 inhibition. **A,** Under physiological conditions, TGF signaling maintains stable glomerular filtration rate (GFR) by modulation of preglomerular arteriole tone. In cases of conditional increases in GFR, the macula densa within the juxta-glomerular apparatus senses an increase in distal tubular sodium delivery and adjusts GFR via TGF accordingly. **B,** Under chronic hyperglycemic conditions (diabetes mellitus), increased proximal SGLT2-mediated reabsorption of sodium (Na^+) and glucose impairs this feedback mechanism. Thus, despite increased GFR the macula densa is exposed to lowered sodium concentrations. This impairment of TGF signaling likely leads to inadequate arteriole tone and increased renal perfusion. **C,** SGLT2 inhibition with empagliflozin treatment blocks proximal tubule glucose and sodium reabsorption, which leads to increased sodium delivery to the macula densa. This condition restores TGF via appropriate modulation of arteriolar tone (eg, afferent vasoconstriction), which in turn reduces renal plasma flow and hyperfiltration.

ACUTE RENAL FAILURE

- It is well known that the use of SGLT’2 produce an increase in creatinine and decrease in GFR, so they have to be used with caution in pts with declining GFR or documented lower GFR <3o.
- Recently the FDA has added a black box warning to CANA and DAPAGLIFOXIN regarding fatal cases of Acute Renal Failure, needing Dyalisis and cases of ESRD’s

LATE BREAKING NEWS:DAMAGE TO INJURY

- THE FDA ISSUES NEW WARNING FOR CANAGLIFOXIN:BEFORE STARTING CANA CONSIDER FACTORS POSSIBLY PREDISPOSING TO AMPUTATIONS, INCLUDING HX OF PRIOR AMPUTATIONS, PVD, NEUROPATHY AND DIABETES FOOT ULCERS.CLOSELY MONITOR PTS FOR SIGNS AND SYMPTOMS OF THESE FACTORS AND DISCONTINUE CANA IF COMPLICATIONS OCCURS.REPORT ADVERSE EVENTS TO THE FDA MED WATCH. THIS IS BASED ON FINAL DATA FROM THE CANVAS AND CANVAS RENAL DATA REGARDING THE DOUBLING OF LEG AND FOOT AMPUTATIONS;TOES AND TRANSMETATARSAL BUT ALSO BKA AND AKA.Postulated mechanism is decrease in blood flow as the HCTZ's or a CLASS EFFECT??

Perspectives on SGLT2 Inhibition

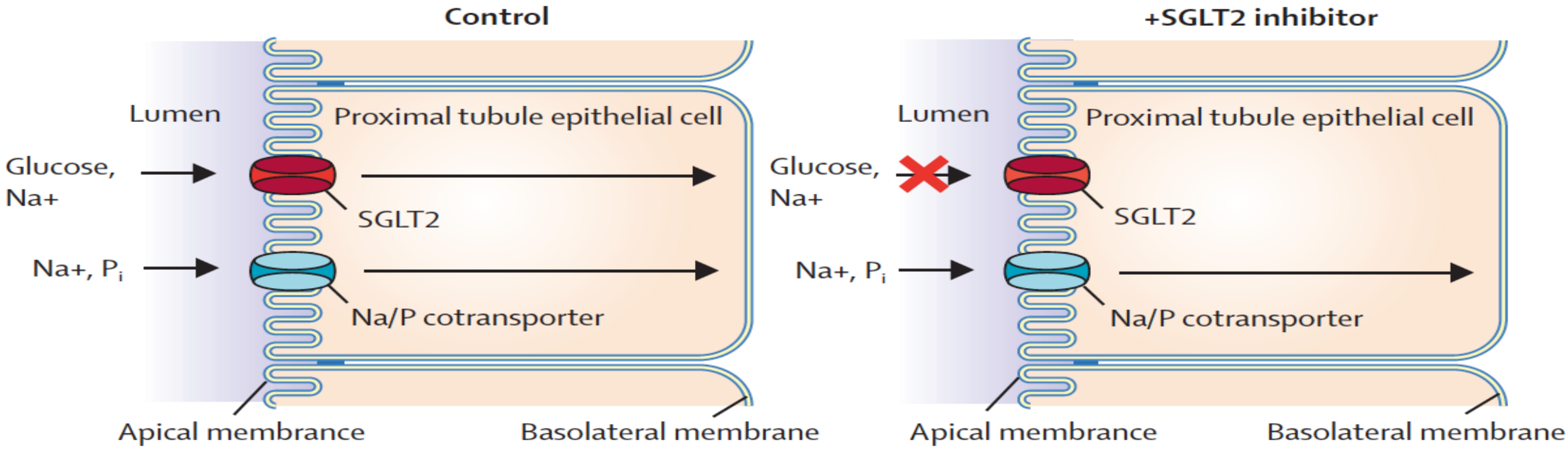
Advantages

- Improved glycemic control
- Weight loss
- Low risk of hypoglycemia
- Blood pressure lowering
- Reduce cardiovascular events and mortality

Concerns

- Polyuria
- Electrolyte disturbances
- Urinary tract infections
- Fungal genital infections
- DKA
- Bone fractures

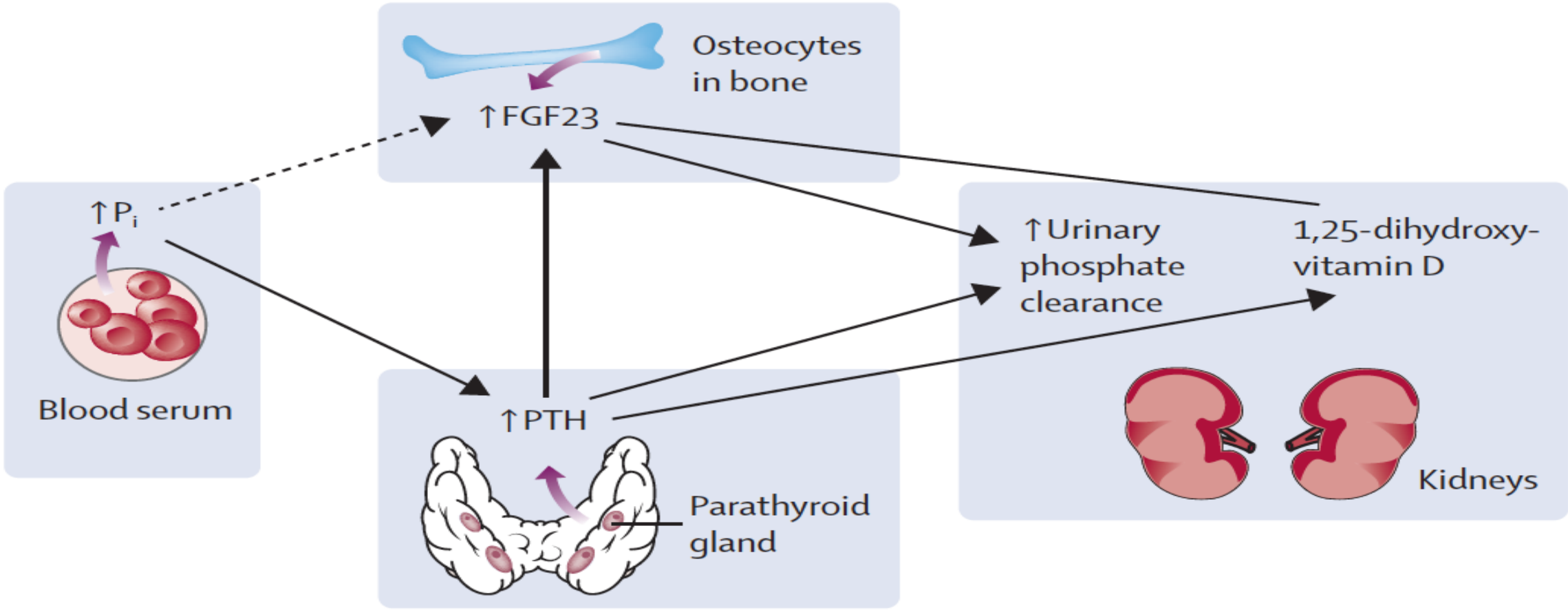
SGLT2-I and Osteopenia- Potential Mechanisms



SGLT2 inhibitors reduce Na^+ transport, which increases availability of Na^+ to drive co-transport of phosphate and Na^+

Taylor S. Lancet Endocrinology, January 2015

SGLT2-I and Osteopenia- Potential Mechanisms



Taylor S. Lancet Endocrinology, January 2015

Conclusions

- SGLT2 inhibitors have been reported to increase the frequency of treatment-emergent bone fractures.
- The increase in fractures may be mediated by falls (Watts et al 2015).
- There are plausible pathophysiological mechanisms
- with potential to mediate adverse effects on bone (Taylor 2015).

FOOD FOR THOUGHT!

- **DO NOT LET OURSELVES GET OVERWHELMED BY THE ADVERSE NEWS and THE MEDIA! Or……. LAWYERS!**
- **MUST WEIGHT RISKS vs BENEFITS and INDIVIDUALIZE EACH PATIENT AS PER ADA-AACE 2017 GUIDELINES. DR. LUIS RAUL RUIZ-RIVERA**

Preguntas ?

Gracias

por su atención

Dr. Luis Raul Ruiz Rivera

F.A.C.E.