NEW INSIGHTS IN DIABETES MELLITUS TYPE 2 TREATMENT

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Presenter Disclosures

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"No relationships to disclose"

GLYCEMIC CONTROL REDUCES MICROVASCULAR COMPLICATIONS

HbA_{1c}		DCCT (9.1%→7.4%)	UKPDS (7.9%→7.0%)
Risk Reduction	Retinopathy	63%	17-21%
	Nephropathy	54%	24-33%
	Neuropathy	60%	---

Macrovascular Complications with intensive glucose control

- *In DCCT, there was a nonsignificant reduction in macrovascular disease.*
- *In UKPDS, there was a nonsignificant reduction in MI and no improvement in all-cause mortality; except in a subgroup of obese patients on metformin which had significant risk reduction in MI, CV death and all-cause mortality.*

ACCORD STUDY

(Action to Control CV Risk in Diabetes)

- The reduction of HgbA1c from 8.1% to 6.4% in high CV risk diabetics led to a 22% increased rate of death from any cause and a 35% increase in rate of death from CV causes, although there was a decrease in the rate of nonfatal MI and no difference in stroke.
- There were significant higher rates of hypoglycemia, weight gain and fluid retention in the intensive group.

ADVANCE STUDY

(Action in Diabetes and Vascular Disease)

- *A reduction of HgbA1c from 7.5% to 6.5% led to no significant differences in rate of death from any cause or death from CV causes, despite achieving similar levels of glucose control as in the ACCORD study.*
- *Intensive control was associated with significant reduction in nephropathy.*

EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS STUDY (EDIC)

*NEJM 2005;353:2643-2653

- 11-year follow up study of the DCCT cohort
- Glycemic levels between the 2 original treatment groups approached each other during the initial 4-year follow up

SUSTAINED REDUCTION IN MICROVASCULAR COMPLICATIONS

mean $HgbA_{1C}$		DCCT (7.4% vs. 9.1%)	EDIC (8% vs. 8.2%)
Risk Reduction	Retinopathy	63%	76%
	Albuminuria	54%	86%
	Microalb	39%	53%
	Neuropathy	60%	51%
	any CV event		42%
	nonfatal MI, stroke or CV death		57%

10-YEAR FOLLOW UP OF UKPDS *NEJM 2008; 359:1577-1589

- ↓13% in all-cause mortality
- ↓15% in MI
- ↓24% in microvascular complications
- In the group on metformin, there was a ↓33% in MI and ↓27% in all cause mortality.
- Early glucose lowering does impact CV disease long term in diabetics.

PHARMACOTHERAPY IN DIABETES MELLITUS TYPE 2

ANTIDIABETIC AGENTS

Oral Agents

- *Sulfonylureas*
- *Metformin*
- *Thiazolidinediones*
- *Meglitinides*
- *α-glucosidase inhibitors*
- *DPP-IV inhibitors*

Injectable Agents

- *Insulin*
- *Incretins (GLP-1 analogs)*
- *Pramlintide*

SULFONYLUREAS

- *Increase insulin secretion.*
- *↓HgbA1c 1.5 - 2%.*
- *Ineffective when fasting glucose > 300*
- *Effect plateaus at ½ maximal dose.*
- *Significant risk of hypoglycemia and weight gain.*

SULFONYLUREAS: INDICATIONS

- As monotherapy or in combination with insulin and all available oral therapies, except the meglitinides.

METFORMIN ('GLUCOPHAGE')

- *Insulin sensitizer, mainly at liver.*
- *May be associated with slight weight loss or prevents weight gain caused by other hypoglycemic agents.*
- *↓HgbA1c 1.5 - 2%*
- *Decrease LDL chol and triglycerides.*
- *Mostly GI side effects; very rare metabolic acidosis.*

METFORMIN: INDICATIONS

- Approved as monotherapy or in combination with other oral agents.
- Recommended by ADA as preventive measure in prediabetics who are obese, hyperlipidemics or hypertensives.
- Avoid in renal or hepatic impairment.
- Avoid in alcoholics or heart failure.
- Hold prior to use of contrast agents or surgery.

α-GLUCOSIDASE INHIBITORS

- *Inhibit carbohydrate-digesting enzymes.*
- *↓HgbA1c 0.7-1.0%*
- *Attenuates postprandial glucose excursions.*
- *Not a popular therapy due to significant GI side effects (flatulence, diarrhea).*
- *Approved as monotx and with SU.*
- *Available in US: acarbose (Precose) and miglitol (Glyset).*

MEGLITINIDES

- *Increase insulin secretion in the presence of glucose.*
- *Greater effect in postprandial glucose.*
- *↓HgbA1c 1.7-1.8%*
- *Cause weight gain (≈ 5-6 #)*
- *Caution in hepatic disease.*
- *Available in US: repaglinide (Prandin) and nateglinide (Starlix)*

MEGLITINIDES: INDICATIONS

- Similar to sulfonylureas but much shorter half-life.
- To be taken with meals in patients who need postprandial glucose control.
- Repaglinide can be used in severe renal impairment.

THIAZOLIDINEDIONES (TZD'S)

- *Increase insulin sensitivity in skeletal muscle.*
- *↓HgbA1c 1.0 – 1.4%*
- *Associated to weight gain, edema, anemia, increase in LDL chol and peripheral fractures in women.*
- *Beware of hepatotoxicity and CHF.*
- *Increase HDL and decrease triglycerides*

TZD's: INDICATIONS

- *Approved as monotherapy or in combination with sulfonylureas, metformin or insulin.*
- *Have been considered in prediabetes since slow the progression of β-cell loss.*

CONTROVERSIES WITH TZD'S

- *In 2007, meta-analysis reported an increased risk for MI with the use of rosiglitazone.*
- *This analysis had several limitations.*
- *An interim analysis of RECORD study shows no statistically significant increased risk of MI, cardiac death or all-cause mortality in patients taking rosi; but will be completed in 2009.*

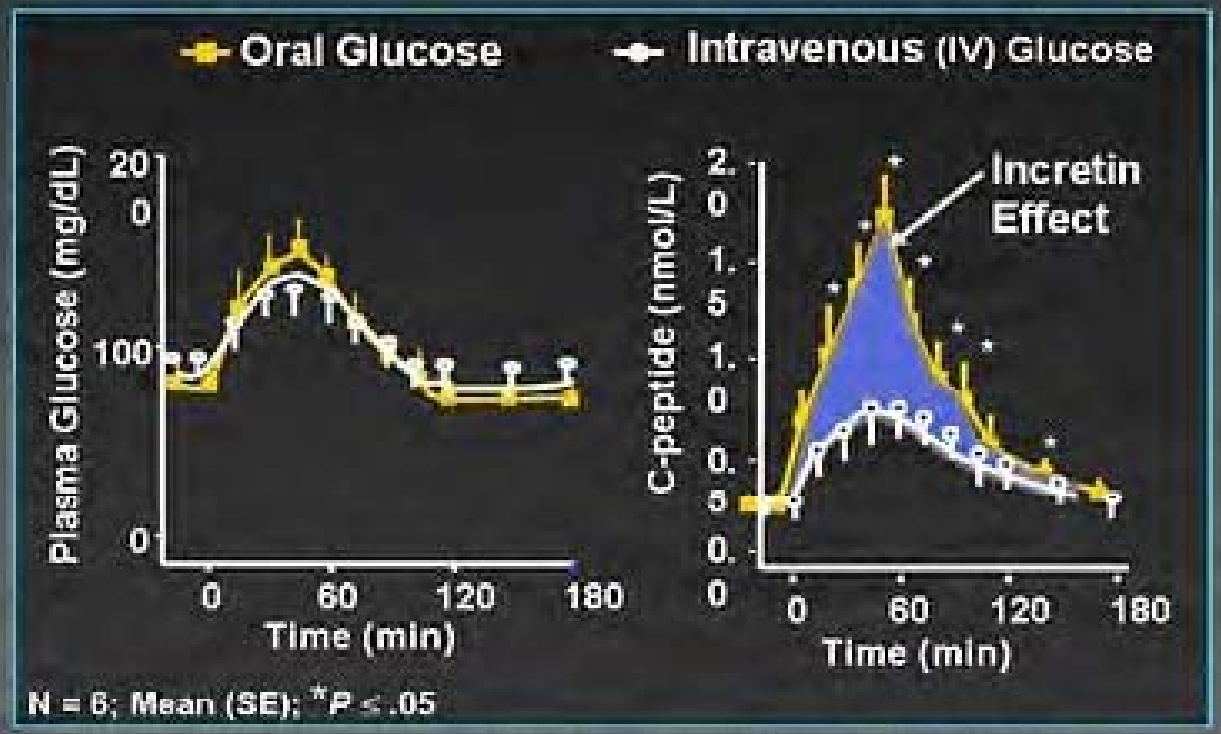
ADDITIONAL COMMENTS

- *This might not be a class effect and each TZD must be evaluated separately.*
- *The ProACTIVE study showed a significant effect on secondary outcomes (MI, stroke and death from any cause), although no significant benefit in terms of primary outcomes (coronary and peripheral vascular events) .*
- *No definitive resolution of controversy at present.*

NEW THERAPIES IN DIABETES

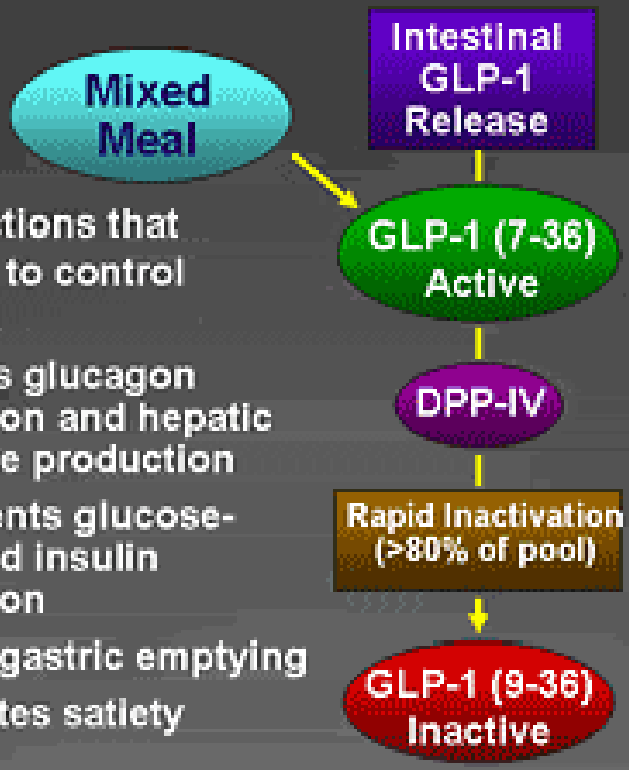
INCRETINS

The Incretin Effect in Healthy Subjects



Data from Nauck MA, et al. *J Clin Endocrinol Metab.* 1986;63:492-498.

Release and Action of GLP-1



GLP-1 actions that combine to control glycemia

- Inhibits glucagon secretion and hepatic glucose production
- Augments glucose-induced insulin secretion
- Slows gastric emptying
- Promotes satiety

Additional characteristics of GLP-1-based therapies:

- Restores beta cell function
- Increases insulin biosynthesis
- Promotes beta cell differentiation

Drucker DJ. *Diabetes Care.* 2003;26:2929-2940.

NATURAL INCRETIN

Exendin-4

A Salivary Gland Hormone
in the Gila Monster

Heloderma suspectum

BYETTA

- *Synthetic form of exendin-4.*
- *Injected subcutaneously within one hour prior to breakfast and dinner.*
- *↓HgbA1c 1.3%*
- *Causes a significant weight reduction.*
- *Promotes β-cell neogenesis in rodents.*
- *Most common side effect is nauseas and vomiting, but tends to disappear with time.*

BYETTA: INDICATIONS

- For type 2 diabetics unable to achieve glucose control on a sulfonylurea, metformin or a combination of both.
- Not a substitute for insulin.
- Not recommended for severe renal insufficiency (CrCl< 30ml/min/1.73m^2).
- Contraindicated in gastroparesis.

Postmarketing Precaution with Byetta

- *Several cases of hemorrhagic or necrotizing pancreatitis have been reported which might be related to Byetta use.*
- *Has been added to the precaution section of safety labeling.*
- *Should be discontinued in persistent abdominal pain, especially accompanied by vomiting.*

DPP-IV INHIBITORS: SITAGLIPTIN (JANUVIA)

- *oral incretin that increases postprandial GLP-1*
- *inhibits postprandial glucagon*
- *weight neutral or some weight loss*
- *β-cell preservation*
- *mild risk of nauseas and hypoglycemia*
- *may be associated with higher risk of nasopharyngitis, UTI, headache and serious allergic reactions*

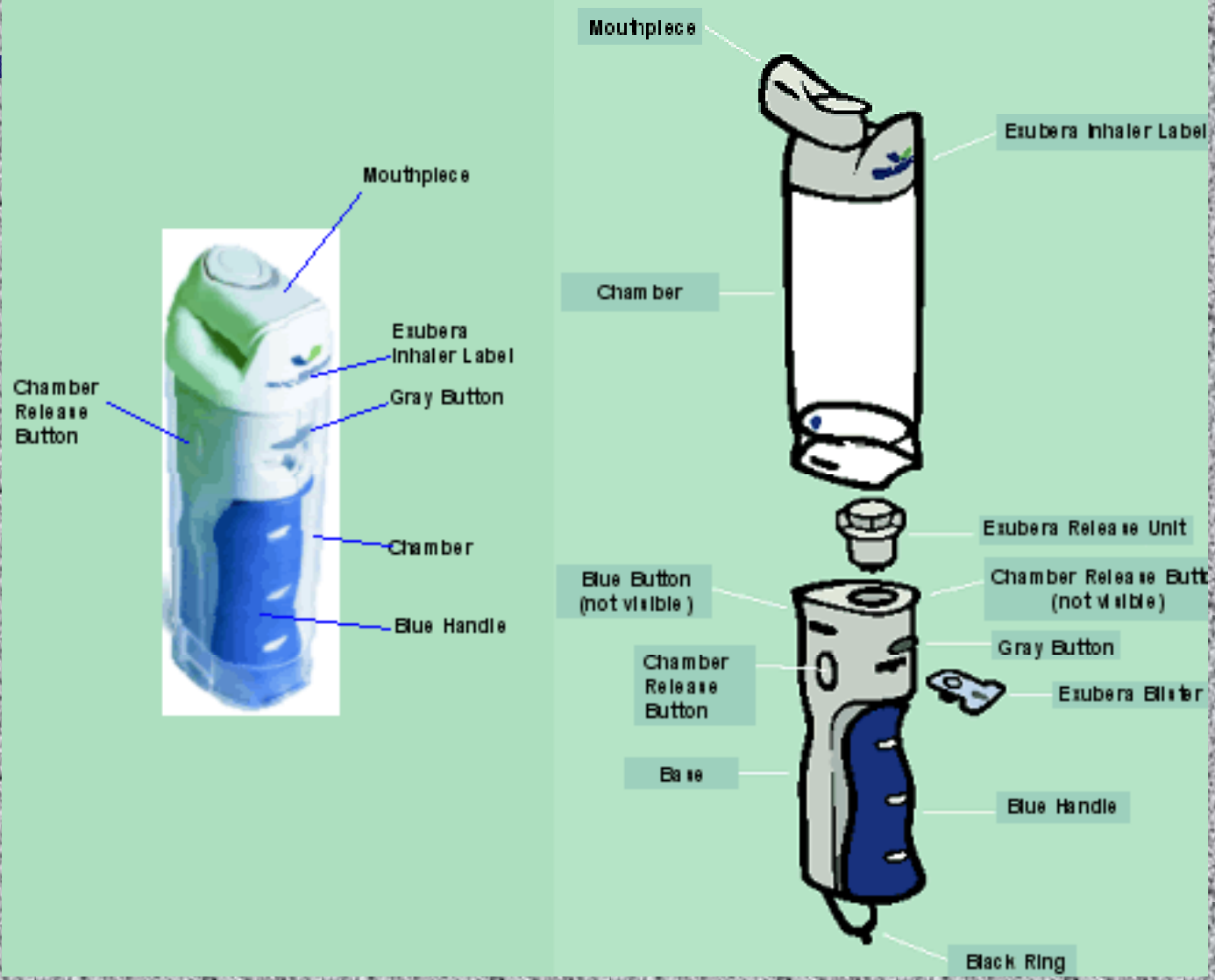
DPP-IV INHIBITORS: INDICATIONS

- *Can be initiating treatment as monotherapy or in combination with metformin (Janumet) or TZD.*
- *Start Januvia 100mg once daily with or without food. If CrCl 30-50, start 50mg daily. If CrCl < 30, start 25mg daily.*
- *Or Janumet 50/500mg twice a day with meals and increase to 50/1000mg bid.*

EXUBERA

- *First inhaled insulin.*
- *Short-acting insulin given 0-10mins before meals.*
- *Must have spirometry with FEV_1 >70% prior to initiating therapy.*
- *Causes decrease in pulmonary function and is contraindicated in smokers and asthmatics.*
- *Production has been discontinued.*

EXUBERA DEVICE



PRAMLINTIDE ('SYMLIN')

- *synthetic analogue of the β-cell hormone amilyn (cosecreted with insulin)*
- *inhibits postprandial increase in glucagon*
- *decreases A1c 0.5-0.7%*
- *delays gastric emptying*
- *promotes satiety, decreasing caloric intake and causing weight loss (3-4 lbs)*

SYMLIN: INDICATIONS

- *As an adjunct therapy for type 1 or type2 diabetics on regular or rapid-acting insulin that have not achieved glucose control.*
- *Administered subcutaneously 15 mins before meals when eating at least 30gms of carbs.*
- *Must be given in a separate syringe from insulin and injected at least 2 inches apart, cannot be mixed.*

SYMLIN: DOSING

- *In Type 2 diabetics, start with 60µg before meals and increase to 120µg if 3 days with no nauseas.*
- *In Type 1 diabetics, start with 15µg before meals and increase to 45 and then 60µg every 3 days if no nauseas.*
- *Stored in fridge before use and either in refrigerator or at room temp after use, for up to 30 days.*

SYMLIN: ADVERSE EVENTS

- *Infrequent mild to moderate nauseas that dissipates over time (usually after first 4 weeks).*
- *Minimal risk of hypoglycemia which would occur within 3 hours of injection (reduce 25-50% of short-acting insulin).*
- *Contraindicated in gastroparesis.*
- *May interfere with absorption of oral drugs (take 1hr pre or 2hrs post-Symlin)*

INSULIN ANALOGS

Insulin Analogs

Short Acting

lispro (Humalog de Lilly)

aspart (Novolog de Novo)

glulisine (Apidra de Aventis)

Long Acting

glargine (Lantus de Aventis)

detemir (Levemir de Novo)

Short-Acting Insulins

Type	Onset	Peak	Duration
Regular	30-60min	2-4hr	5-8hr
Lispro	0-15min	0.5-1.5hr	3-5hr
Aspart	0-15min	1-3hr	3-5hr
Glulisine	0-15min	0.5-1.5hr	3-5hr

- The analogs are associated to less hypoglycemic episodes and provide more flexibility to mealtime than Regular insulin.

Long-Acting Insulins

Type	Onset	Peak	Duration
NPH	2-4hr	4-8hr	10-16hr
Glargine	1-2hr	none	24hr
Detemir*	1-2hr	none	12-20hr

* Could require twice daily dosage, but is associated to less weight gain and less hypoglycemic episodes than NPH.

Analog Insulin Mix

- *Humalog mix 75/25 (lispro with and without protamine)*
- *Humalog mix 50/50*
- *Novolog mix 70/30 (aspart with and without protamine)*

GUIDELINES FOR DIABETES MANAGEMENT

AACE Guidelines for untreated diabetics

- HgbA1c

  6%-7%

  7%-8%

- Treatment

  oral monotherapy (metformin, glitazones, secretagoges, DPP-IV inh or α-glucosidase inh)

  2 oral agents

AACE Guidelines for untreated diabetics

- HgbA1c

  8%-10%

  >10%

- Treatment

  high dose oral combination or basal insulin/ premixed insulin

  High dose oral combo and basal/bolus or premixed insulin

PATIENTS PREVIOUSLY TREATED WITH ORAL AGENTS

HgbA1c	Treatment
6.5%-8.5% despite oral combo	add exenatide to oral therapy or add a third oral agent
6.5%-8.5% despite intensified oral combo	add insulin

PATIENTS PREVIOUSLY TREATED WITH ORAL AGENTS

- HgbA1c

  >8.5%

  despite oral combination therapy and insulin

- Treatment

  Intensify basal/bolus insulin or add pramlintide to insulin therapy

BASAL INSULIN REGIME

- *Start long-acting insulin at 0.2 U/kg hs as basal insulin and continue oral therapy.*
- *Monitor fasting glucose and give correction bolus to reach appropriate dose.*

TREAT-TO-TARGET PROTOCOL

7-day average FBS	Correction dose
< 70	- 2
70-100	0
101-120	+ 2
121-140	+ 4
141-180	+ 6
>180	+ 8

Insulin Mix (Humalog75/25, Novolog70/30): Starting Patients

- Patients New to Insulin
  - Twice daily:
    - At breakfast: Start with 10 units
    - At evening meal: Start with 10 units
  - Once daily:
    - At evening meal: Start with 10 units

BASAL/BOLUS REGIME

- Determine TDD (= 0.5 U/kg)
- TDD is then divided into ½ as basal insulin and ½ as bolus insulin
- 50% TDD is BASAL (TDD X 0.5 U/kg)
  - - Given at bedtime
- 50% TDD is BOLUS (TDD X 0.5 U/kg)
  - - Divided between breakfast, lunch, supper, and snacks

COMING ATTRACTIONS

GLP-1 ANALOGS

- *Byetta-LAR (once a week)*

  -appears to achieve better HgbA1c control (↓1.9%), less nauseas and similar weight loss

  -approval for this summer halted due to concerns about comparability of new production facility with original facility producing the prototype

GLP-1 ANALOGS

- *Liraglutide (one injection daily)*
  - *↓HgbA1c 1.6% and may also have useful effects on endothelial dysfunction*
  - *FDA approval still pending until concerns about relation to C-cell tumors on rodents is clarified*

DPP-4 INHIBITORS

- *Vildagliptin (Galvus)*

  - concerns regarding adverse skin reactions and renal impairment in earlier animal trials have been raised during FDA review, halting its approval

- *Saxagliptin (Onglyza)*

  - FDA review postponed until July 30 due to requirement of more stringent clinical trials to assess cardiac risk.

NOVEL TREATMENTS FOR DIABETES

SGLT-2 (Na+/glucose-linked transporter) Inhibitors

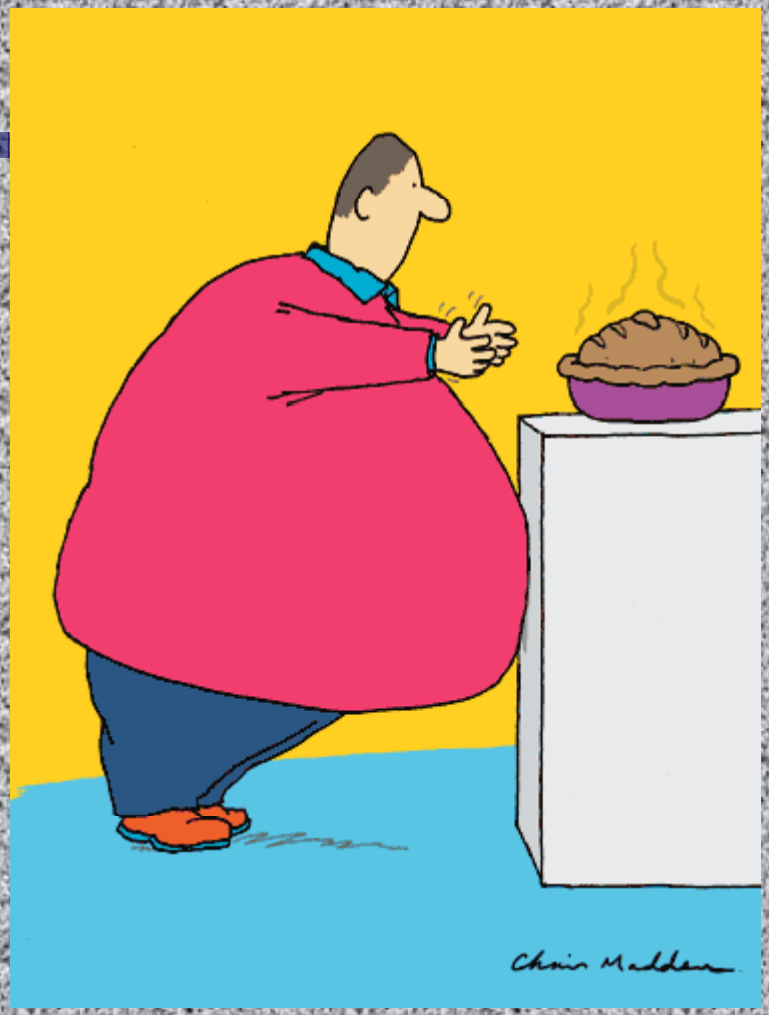
- *Dapagliflozin*

  - increases urine glucose excretion

  - may be associated to weight loss of ≈5-7# due to 200-300 calories lost in urine daily

  - urine infections or electrolyte abnormalities have not been seen

  -currently in Phase 3 trials


Chris Madden