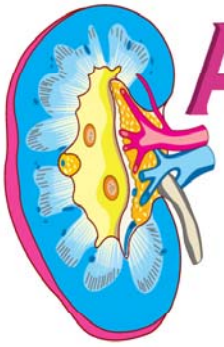


ADVANCE

Advances in Type 2 Diabetes Treatment: Novel Agents that Target the Kidney

Faculty

Lawrence Blonde, MD, FACP, FACE
(Activity Chair)
Director of the Ochsner Diabetes Clinical Research Unit
Associate Internal Medicine Residency Program Director
Ochsner Medical Center
New Orleans, LA

Dr. Lawrence Blonde reports that he has received research grant support (to Ochsner Medical Center) for his role as Investigator from Amgen Inc. and Eli Lilly and Company; research grant support (to Ochsner Medical Center) for his role as Investigator and consultant honoraria from Boehringer Ingelheim GmbH, F. Hoffman-La Roche Ltd, Johnson & Johnson Services, Inc., and sanofi-aventis U.S. LLC; research grant support (to Ochsner Medical Center) for his role as Investigator and consultant/speaker honoraria from Merck & Co., Inc. and Novo Nordisk A/S; consultant/speaker honoraria from AstraZeneca, Bristol-Myers Squibb, and Daiichi Sankyo Company, Limited; speaker honoraria from LifeScan, Inc.; consultant honoraria from GlaxoSmithKline plc, Halozyme Therapeutics, MannKind Corporation, Orexigen, and Veroscience; consultant honoraria and stock from his late spouse's estate from Amylin Pharmaceuticals, Inc.; and stock from his late spouse's estate from Pfizer, Inc.

Faculty

Jeffrey S. Freeman, DO, FACOI
Professor of Internal Medicine
Chairman, Division of Endocrinology and Metabolism
Philadelphia College of Osteopathic Medicine
Philadelphia, PA

Dr. Freeman indicated that he has nothing to disclose.

Faculty

Patricia J. Bonsignore, RN, MS, CDE
Diabetes Educator/Case Manager
Joslin Diabetes Center
Boston, MA

Ms. Bonsignore indicated that he has nothing to disclose.

What percent of your patients at currently at goal?

1. 0-25%
2. 26-50%
3. 51-75%
4. 76-100%

What prevents you MOST from prescribing agents in a new therapeutic class?

1. Cost
2. Lack of sufficient data
3. Lack of long-term (post-marketing surveillance) data
4. Unsure where they fit into treatment
5. Don't know enough about them

When do you typically begin to use new therapeutic agents?

1. At FDA approval
2. 3 months after FDA approval
3. 6 months after FDA approval
4. After my peers are comfortable using it
5. After checking with my attorney

Pre-test

Where is most of renally excreted glucose reabsorbed?

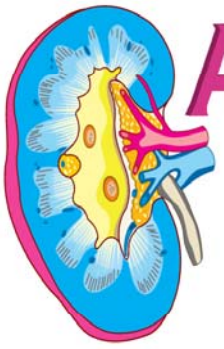
1. Proximal tubule***
2. Distal tubule
3. Collecting duct
4. Bladder

The primary mechanism of lowering glucose by SGLT2 drugs is:

1. Improving insulin sensitivity
2. Increasing insulin secretion
3. Preventing renal glucose reabsorption**
4. All of the above
5. None of the above

SGLT2 drugs have been shown to cause :

1. Electrolyte imbalances
2. Dehydration
3. Genital infections***
4. Severe hypoglycemia



ADVANCE

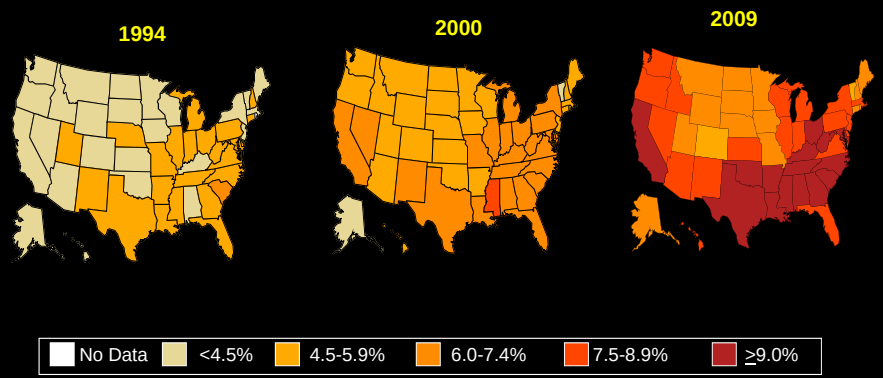
Advances in Type 2 Diabetes Treatment:
Novel Agents that Target the Kidney

Intro on DM Stats

- Diabetes affects 25.8 million people in the US (8.3% of the US population)
  - 18.8 million diagnosed, 7.0 million undiagnosed
- US residents ≥65 years: 10.9 million (26.9%)
- 215,000 people < 20
- 2005-2008: 35% of US adults >20 years had prediabetes
- 7th leading cause of death in the US

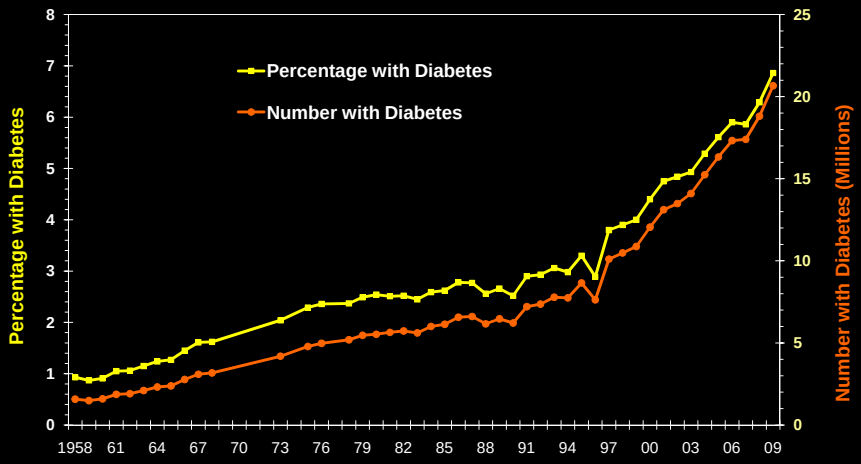
www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf

Percentage of U.S. Adults Who Had Diagnosed Diabetes



www.cdc.gov/diabetes/statistics

Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2009



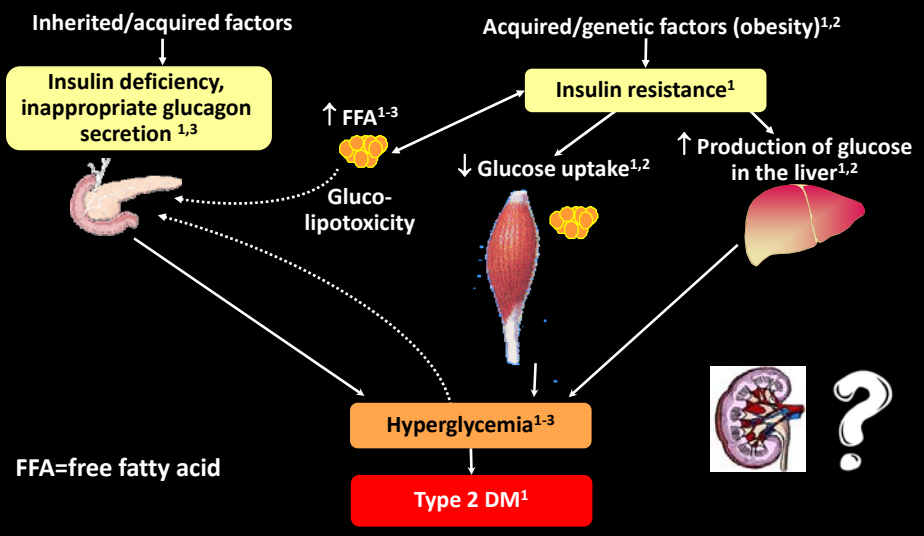
www.cdc.gov/diabetes/statistics

Cost of Diabetes

- Total (direct and indirect) estimated diabetes costs in the US in 2007 = $174 billion
  - *Medical expenses for people with diabetes are more than two times higher than for people without diabetes*
- A 50 year old with diabetes dies, on average, 6 years earlier that someone without diabetes

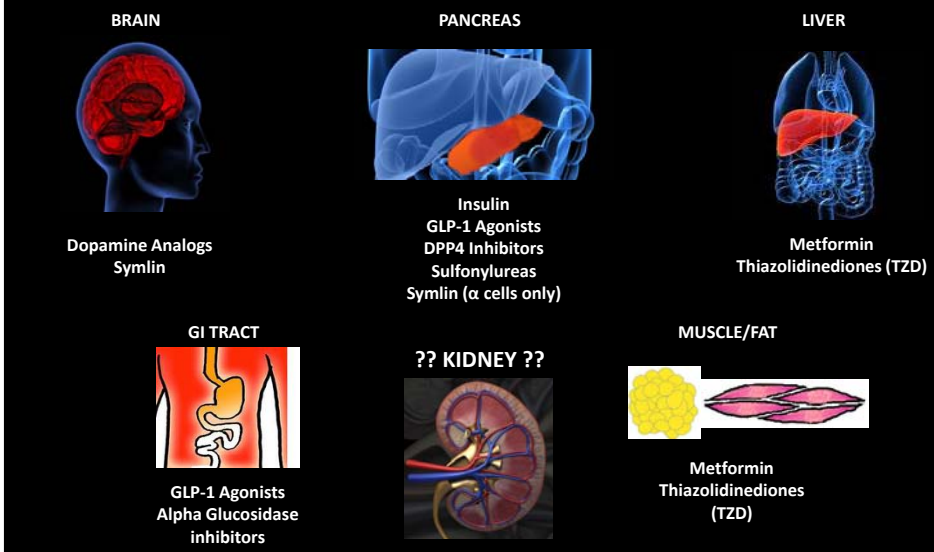
Emerging Risk Factors Collaboration. NEJM. 2011; www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf

Type 2 DM Pathophysiology



[1]Bergenstal RM, et al. *Endocrinology*. 2001; [2]DeFronzo RA. *Diabetes*. 1988; [3]Poitout V, et al. *Endocrinology*. 2002.

Current Therapeutic Targets



The Kidneys Play an Important Role in the Handling of Glucose

• Total glucose stored in body	~450 g
• Glucose utilization	~250 g/day
• Brain	~125 g/day
• Rest of body	~125 g/day
• Glucose in Western diet	~180 g/day
• Renal Glucose production (gluconeogenesis + glycogenolysis)	~70 g/day
• Renal glucose filtration and reabsorption	~180 g/day
• Urinary glucose	0 g

Wright EM, et al. *J Intern Med*. 2007.

Glomerular Filtration

125 mL of filtrate formed/min (180 L/24 h)

Urine output 1.5 L/24 h

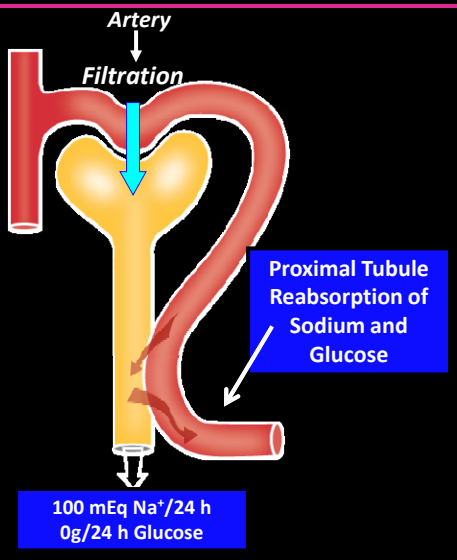
25,000 mEq of Na^+ filtered

Urine Na^+ excretion 100 mEq/L

180 g glucose filtered/24 h

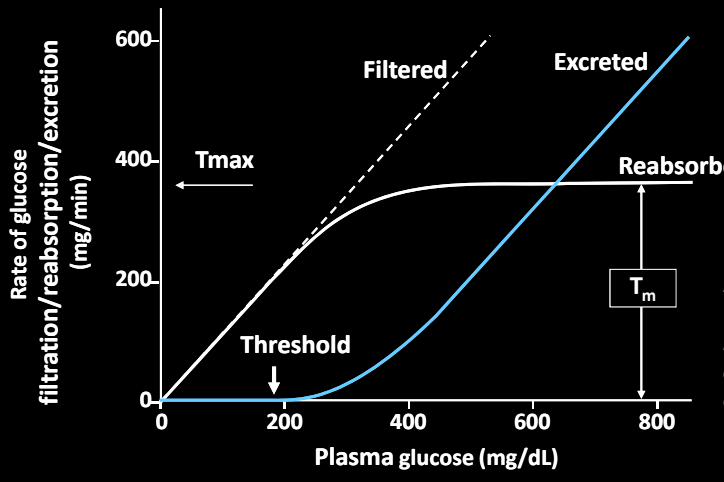
Urine glucose excretion= 0 g

Because ***reabsorption*** occurs



Mount DB, Yu ASL. In: Brenner BM, ed. *Brenner and Rector's The Kidney*; Abdul-Ghani M, DeFronzo R. *Endocr Pract*. 2008.

Renal Glucose Handling



Threshold, $Tm_{Glucose}$ represents the maximal resorptive capacity of the proximal tubule

Schematic representation of the typical titration curve for renal glucose reabsorption in man.

Adapted from Silverman M, Turner RJ. *Handbook of Physiology*. 1992.

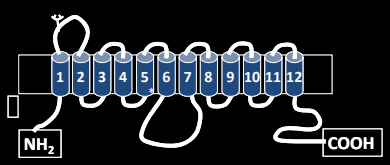
Two Families of Glucose Transporters

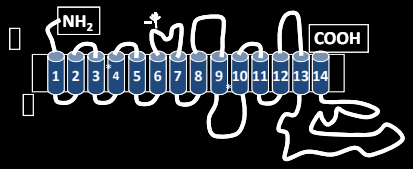
GLUT Family

- Facilitated glucose transporters
- Passive, downhill transport
- GLUT1 (widespread including the kidneys)
- GLUT2 (kidneys and pancreas)
- GLUT4 (muscle and adipose tissue)

SGLT Family

- Sodium coupled glucose cotransporter
- Active transport of glucose
- SGLT1 (brush border of small intestine)
- SGLT2 (proximal tubule)





Longo N, Elsas LJ. *Adv Pediatr*. 1998.

Sodium-Glucose Cotransporters

	SGLT1	SGLT2
Site	Mostly intestine with some kidney	Almost exclusively kidney
Sugar specificity	Glucose or galactose	Glucose
Affinity for glucose	High Km = 0.4 Mm	Low Km = 2 Mm
Capacity for glucose transport	Low	High
Role	Dietary glucose absorption Renal glucose reabsorption	Renal glucose reabsorption

Lee YJ, et al. *Kidney Int Suppl.* 2007.

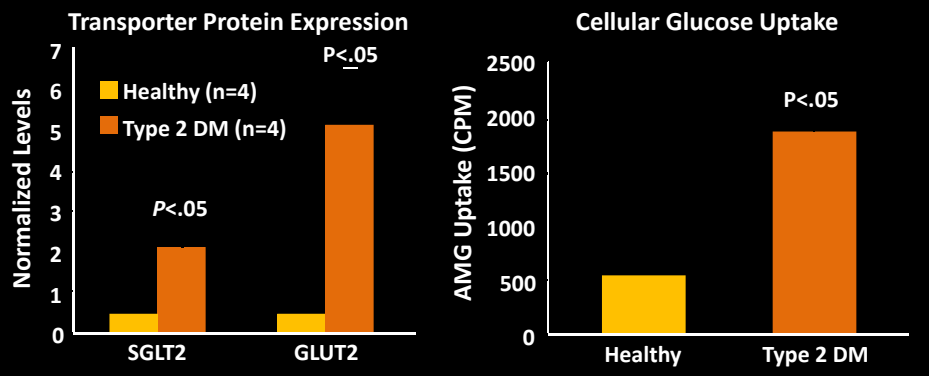
Altered Renal Glucose Control in Diabetes

- **Renal gluconeogenesis is increased in patients with Type 2 DM**
  - Renal contribution to hyperglycemia
  - 3-fold increase relative to patients without diabetes
- **Glucose reabsorption**
  - Increased SGLT2 expression and activity in renal epithelial cells from patients with diabetes vs. normoglycemic individuals

Marsenic O. *Am J Kidney Dis.* 2009; Bakris GL, et al. *Kidney Int.* 2009; Rahmoune H, et al. *Diabetes.* 2005.

Evidence for the Up-Regulation of SGLT2 and Renal Glucose Reabsorption in Type 2 Diabetes

Primary Cultured Proximal Tubule Epithelial Cells From Healthy Patients and Patients With Type 2 Diabetes



Uptake of alpha-methyl-glucose (AMG) is Na^+ dependent and is a measure of transport by SGLTs rather than GLUTs

Rahmoune H, et al. *Diabetes*. 2005.

Video animation- mechanism of action

Rationale for SGLT2 Inhibitors

- The SGLT2 is a glucose transporter responsible for 90% of glucose reabsorption
- Selective SGLT2 inhibitors could reduce blood glucose levels due to increased renal excretion of glucose
- Mutations in SGLT2 transporter linked to hereditary renal glycosuria, a benign condition in humans
- Selective SGLT2 inhibition would cause urine loss of the calories from glucose (200-300 kcal/day), also potentially leading to weight loss

Brooks AM, Thacker SM. *Ann Pharmacother.* 2009; Nair S, et al. *J Clin Endocrinol Metab*. 2010.

Effects of SGLT2 Inhibitors

Inhibition of renal tubular Na^+-glucose cotransporter

↓

Reversal of hyperglycemia

↓

Reversal of "glucotoxicity

↓

↑ Insulin sensitivity in muscle and liver
↓ Gluconeogenesis
↑ Improved beta cell function

Brooks AM, Thacker SM. *Ann Pharmacother.* 2009; Nair S, et al. *J Clin Endocrinol Metab*. 2010.

SGLT2 Inhibitors

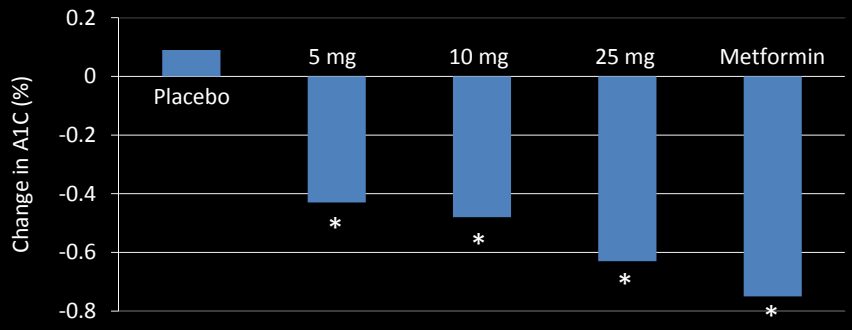
Early results provide proof of efficacy of SGLT2 inhibition in reducing both fasting and postprandial plasma glucose concentrations

Phase 3	Phase 2
BI-10773	ASP1941
Canagliflozin	ISIS 388626
Dapagliflozin	LX4211

Remogliflozin and Sergliflozin Discontinued

BI-10773: Change in A1C

Randomized, double-blind, 12 week trial comparing BI-10773 and open-label metformin*

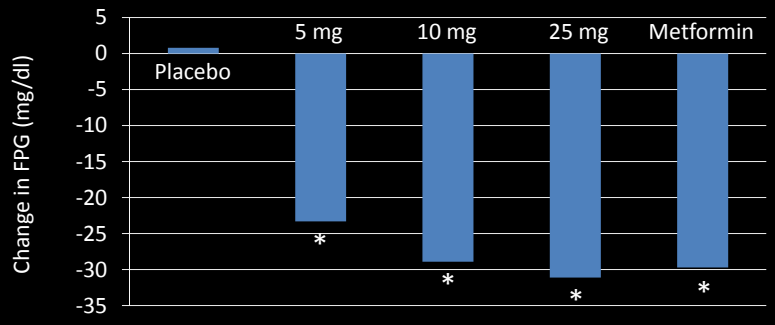


N = 408
Baseline A1C = 7.9%
*P<.001 vs. placebo
†500 mg BID for four weeks, then 1000 mg BID or the maximum tolerated dose

Ferrannini E, et al. Abstract 877. EASD 2010.

BI-10773: Change in FPG

Randomized, double-blind, 12 week trial comparing BI-10773 and open-label metformin*

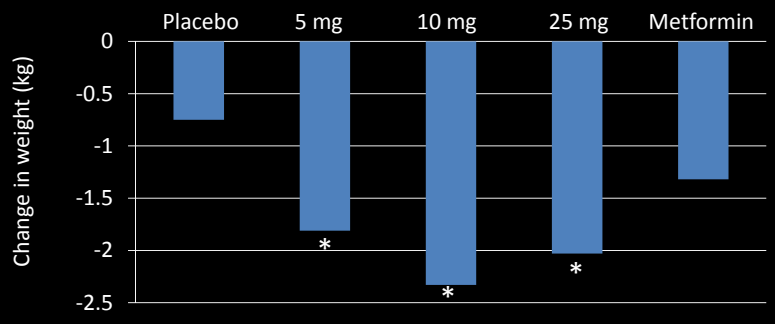


N = 408
*P<.001 vs. placebo
†500 mg BID for four weeks, then 1000 mg BID or the maximum tolerated dose

Ferrannini E, et al. Abstract 877. EASD 2010.

BI-10773: Change in Weight

Randomized, double-blind, 12 week trial comparing BI-10773 and open-label metformin*



N = 408
Baseline BMI = 29 kg/m^2
*P<.001 vs. placebo
†500 mg BID for four weeks, then 1000 mg BID or the maximum tolerated dose

Ferrannini E, et al. Abstract 877. EASD 2010.

BI-10773: Safety Considerations

Randomized, double-blind, 12 week trial comparing BI-10773 and open-label metformin (N = 408)

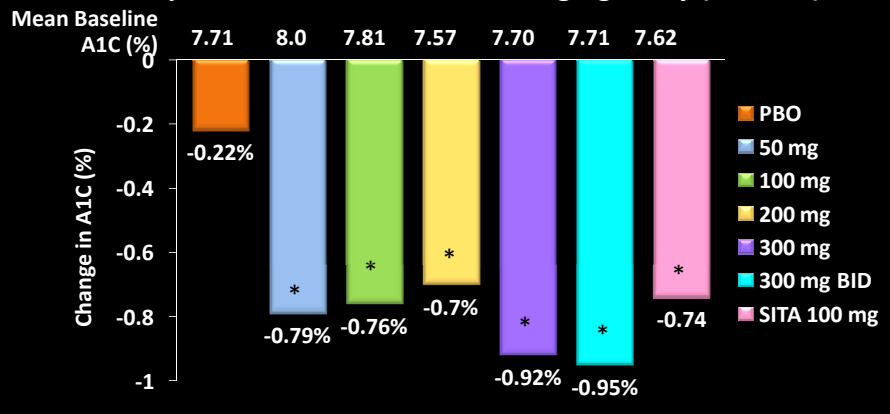
Side effects:

- Polyuria (3.3% vs. 0% in placebo), thirst (3.3% vs. 0% in placebo), and nasopharyngitis (2% vs. 1.2% in placebo) were the most frequently reported side effects
- UTI 1.2% vs. 1.2% in placebo and 1.3% in metformin

Ferrannini E, et al. Abstract 877. EASD 2010.

Canagliflozin: Change in A1C

Canagliflozin add-on to metformin, double-blind, placebo-controlled, dose-ranging study (Phase 2)



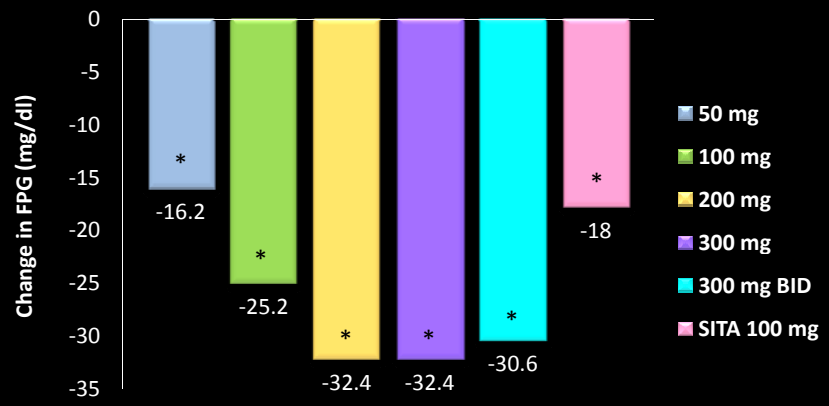
N = 451

*P<.001 vs. placebo calculated using LS means

Rosenstock J, et al. Abstract 77-OR. ADA 2010.

Canagliflozin: Change in FPG

Canagliflozin add-on to metformin, double-blind, placebo-controlled, dose-ranging study (Phase 2)

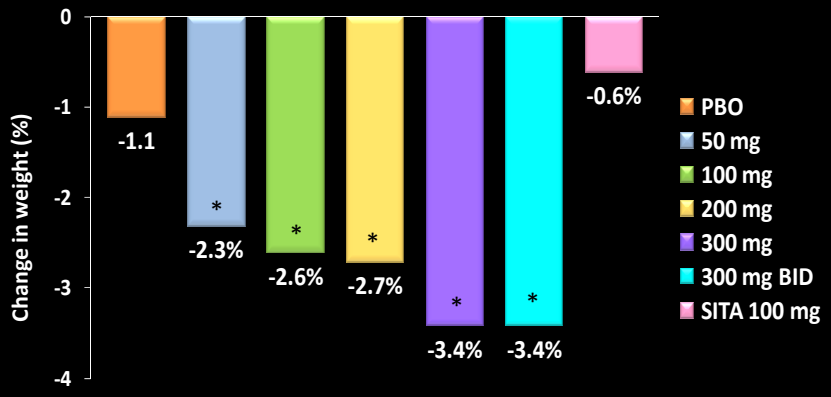


N = 451
Baseline FGP 162 mg/dl)
*P<.001 vs. placebo calculated using LS means

Rosenstock J, et al. Abstract 77-OR. ADA 2010.

Canagliflozin: Change in Weight

Canagliflozin add-on to metformin, double-blind, placebo-controlled, dose-ranging study (Phase 2)



N = 451
Baseline weight 87 kg
*P<.01 vs. placebo calculated using LS means

Rosenstock J, et al. Abstract 77-OR. ADA 2010.

Canagliflozin: Safety Considerations

Canagliflozin add-on to metformin, double-blind, placebo-controlled, dose-ranging study (Phase 2, N = 451)

Side effects:

- Mild-to-moiderate, transient
- Non dose-dependent increase in symptomatic genital infections: 3-8% in canagliflozin vs. 2% in placebo and 2% in sitagliptin
- UTI: 3-9% in canagliflozin (no dose-dependency) vs. 6% in placebo and 2% in sitagliptin
- Hypoglycemia: 0-6% in canagliflozin (no dose dependency) vs. 2% in placebo and 5% in sitagliptin

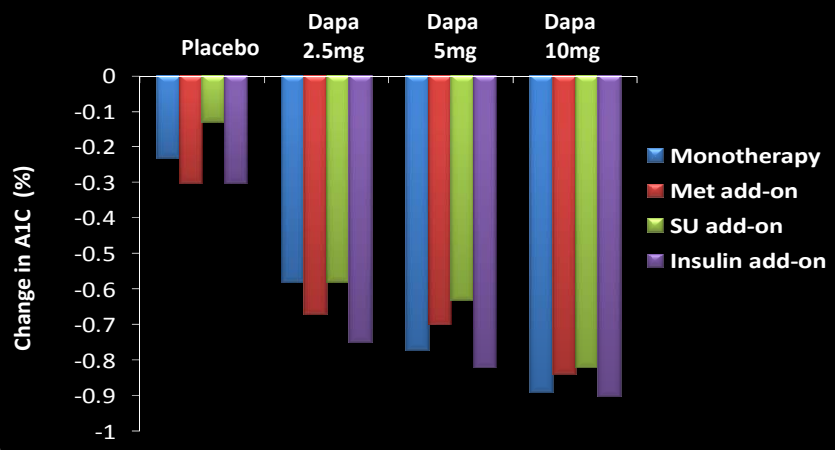
Rosenstock J, et al. Abstract 77-OR. ADA 2010.

Canagliflozin: More Safety Considerations

- **12-week, double-blind, placebo-controlled study in patients inadequately controlled on metformin[1]**
  - **There was slightly more systemic volvo candida infections, but none were serious and did not cause discontinuations of the medication**
- **Another study showed no increase in bacteriuria or UTIs in patients treated with canagliflozin was seen[2]**

[1]Nyirjesy P, et al. Abstract 0032-LB. ADA 2011; [2]Nicole L, et al. Abstract 0043-LB. ADA 2011.

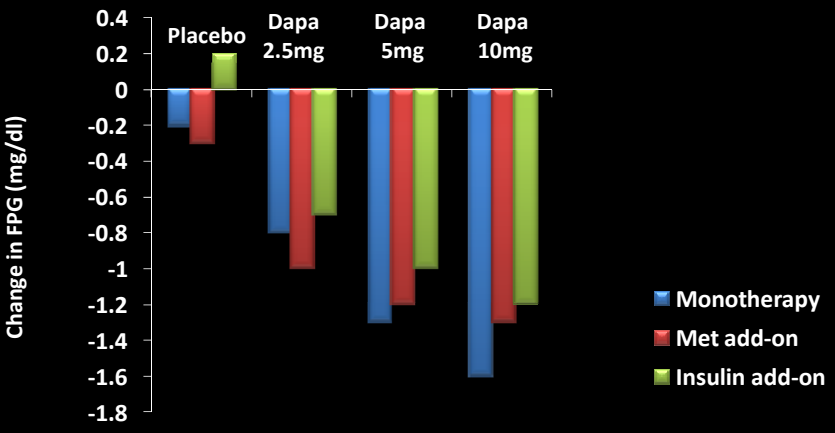
Dapagliflozin Phase 3 Studies: Change in A1C



Baseline-
Monotherapy (N=591): 8.6%
Met add-on (N=546): 8%
SU add-on (N=597): 8.1%
Insulin add-on (N=808): 8.5%

Wilding JPH, et al. Abstract 871. EASD 2010;
Strojek K, et al. Abstract 870. EASD 2010;
Ferrannini E, et al. *Diabetes Care*. 2010; Bailey CJ, et al. *Lancet*. 2010.

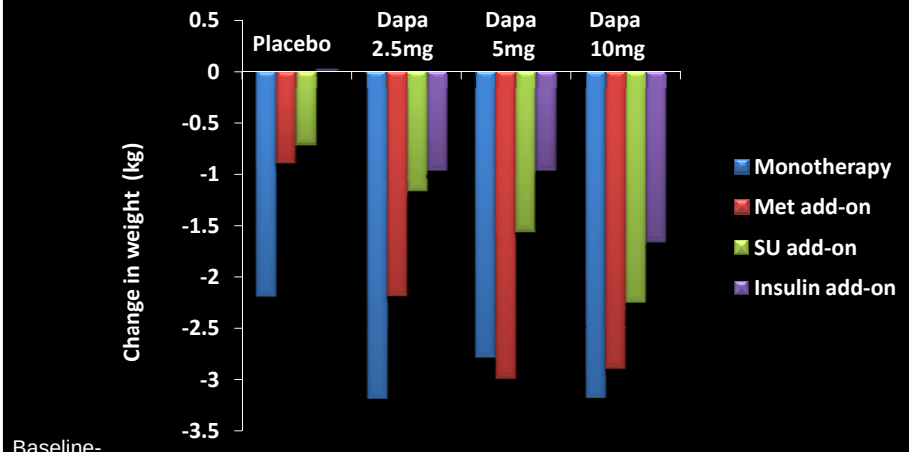
Dapagliflozin Phase 3 Studies: Change in FPG



Baseline-
Monotherapy (N=591): 179 mg/dl
Met add-on (N=546): 163.9 mg/dl
Insulin add-on (N=808): 178 mg/dl

Wilding JPH, et al. Abstract 871. EASD 2010;
Ferrannini E, et al. *Diabetes Care*. 2010; Bailey CJ, et al. *Lancet*. 2010.

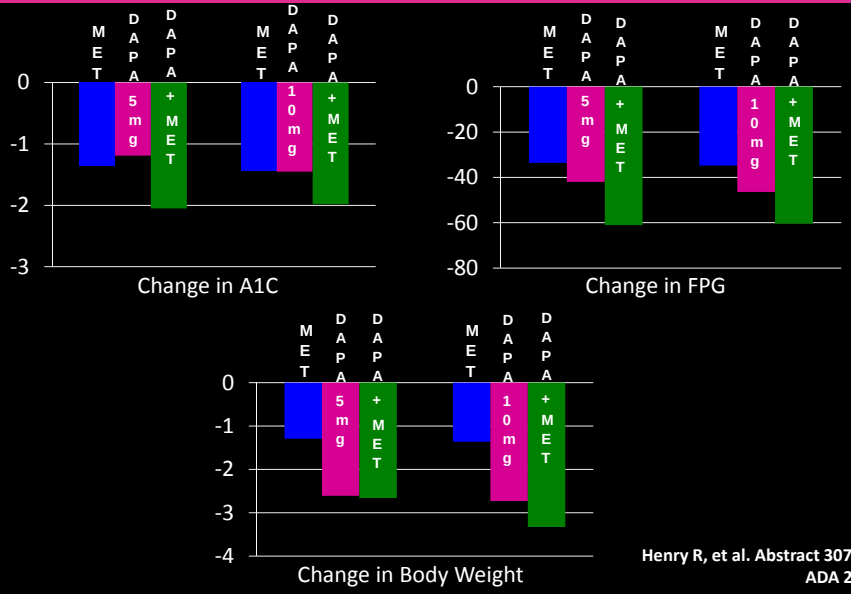
Dapagliflozin Phase 3 Studies: Change in Weight



Baseline-
Monotherapy (N=591): 89.7 kg
Met add-on (N=546): 85.9 kg
SU add-on (N=597): 81.1 kg
Insulin add-on (N=808): 94 kg

Wilding JPH, et al. Abstract 871. EASD 2010;
Strojek K, et al. Abstract 870. EASD 2010;
Ferrannini E, et al. *Diabetes Care*. 2010; Bailey CJ, et al. *Lancet*. 2010.

Dapagliflozin, Metformin XR, or Both as Initial Therapy



Henry R, et al. Abstract 307-OR.
ADA 2011.

Dapagliflozin: Effect on BP and Lipids

Systolic Blood Pressure
- Placebo: -0.2
- Dapa 2.5mg: -2.1
- Dapa 5mg: -4.3
- Dapa 10mg: -5.1

Diastolic Blood Pressure
- Placebo: -0.1
- Dapa 2.5mg: -1.8
- Dapa 5mg: -2.5
- Dapa 10mg: -1.8

HDL
- Placebo: +0.4
- Dapa 2.5mg: +1.8
- Dapa 5mg: +3.3
- Dapa 10mg: +4.4

Triglycerides
- Placebo: +2.1
- Dapa 2.5mg: -2.4
- Dapa 5mg: -6.2
- Dapa 10mg: -6.2

Bailey CJ, et al. *Lancet*. 2010.

Dapagliflozin: Safety Considerations

Based on all trials (Monotherapy, metformin add-on, sulfonylurea add-on, and insulin add-on)

Side effects:
- Hypoglycemia: 0-7.9% in dapagliflozin vs. 2.7-4.8% in placebo[2-4]
- UTI*: 3.9-13.2% in dapagliflozin vs. 4-6.2% in placebo[1-3]
- Genital infections*: 3.9-12.9% in dapagliflozin vs. 0.7-5% in placebo[1-4]

* Most occurred during the first 24 weeks, were generally mild, and responded to routine management

[1]Wilding JPH, et al. Abstract 871. EASD 2010;
[2]Strojek K, et al. Abstract 870. EASD 2010;
[3]Ferrannini E, et al. *Diabetes Care*. 2010; [4]Bailey CJ, et al. *Lancet*. 2010.

Dapagliflozin: Sulfonylurea Comparator Study

Randomized, double-blind, parallel-group, multicenter trial comparing dapagliflozin to glipizide as add-on to meformin

Results

- Average A1C 7.72%
- Change in A1C: -0.52% for dapagliflozin vs. -0.52% for glipizide
- Weight change: -3.2kg for dapagliflozin vs. +1.4 kg for glipizide
- Hypoglycemic episodes: 3.5% for dapagliflozin vs. 40.8% with glipizide
- Significant reductions diastolic and systolic blood pressure and improvement in HDL with dapagliflozin vs. glipizide (p<.0001)
- Side effects:
  - UTI: 10.8% with dapagliflozin vs. 6.4% with glipizide (actively solicited)
  - Genital infection: 12.3% with dapagliflozin vs. 2.7% with glipizide (actively solicited)

Nauck M, et al. Abstract 241. EASD 2010.

Dapagliflozin as Add-on to Insulin Therapy: Summary and Conclusions

- **Add-on to insulin in patients poorly controlled with insulin**
  - Sustained effectiveness and stable tolerability
  - Less likely to D/C or require insulin up-titration due to poor glycemic control versus placebo
  - Increased frequency of weight loss and reduced frequency of peripheral edema over time
  - Adverse events and discontinuations were balanced across groups
  - Actively solicited signs and symptoms suggestive of urinary tract (UTI) and genital infections (GI) were higher with dapagliflozin vs. placebo
    - Most reported in the first 24 weeks, were of mild/moderate intensity ,and responded to standard treatment

Strojek K, et al. Abstract 870. EASD 2009; Bailey CJ, et al. *Lancet*. 2010.

SGLT2 Safety Considerations

- Urinary tract/genital infections
- Intravascular volume depletion (osmotic diuresis)
- Electrolyte imbalance (Na^+, K^+, Ca^{++}, PO_4)
- Nephrotoxicity (AGEs)
- Nocturia
- Drug-drug interactions

SGLT2 Inhibitors: Summary

- In treatment-naive patients with newly-diagnosed Type 2 DM, SGLT2 inhibitors resulted in:
  - Clinically meaningful decreases in A1C and fasting plasma glucose with a near absence of hypoglycemia
- In process

Post-test

Where is most of renally excreted glucose reabsorbed?

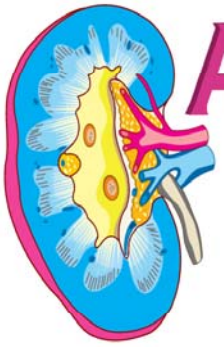
1. Proximal tubule***
2. Distal tubule
3. Collecting duct
4. Bladder

The primary mechanism of lowering glucose by SGLT2 drugs is:

1. Improving insulin sensitivity
2. Increasing insulin secretion
3. Preventing renal glucose reabsorption**
4. All of the above
5. None of the above

SGLT2 drugs have been shown to cause :

1. Electrolyte imbalances
2. Dehydration
3. Genital infections***
4. Severe hypoglycemia



ADVANCE

Advances in Type 2 Diabetes Treatment:
Novel Agents that Target the Kidney