



SGLT2 inhibition: dapagliflozin

Dr. Chih Hao Chen Ku, FACE
Endocrinology Department, San Juan de Dios Hospital
Clinical Pharmacology and Toxicology Department,
University of Costa Rica

Disclosures

- Speaker: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk
- Clinical trials: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche

Case presentation

- 64 years old hispanic women diagnosed with T2DM in 2005
- Initially treated with SU+metformin until November 2007
- Switched to NPH+metformin
- November 2009: premix insulin bid + metformin
- 2011: Basal bolus + metformin

Case presentation

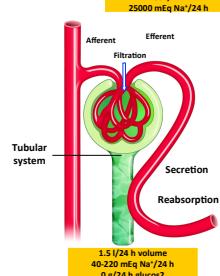
- Since 2011, her hba1c has been 10%, 10.8%, 8.9%, 8.6%, 8.9%, 8.9%, 8.7%
- September 2014: hba1c 8.3%
- Total daily dose of insulin: 144 units (1.6 u/kg)
- Current weight 90 kg
- What are the treatment choices?

Agenda

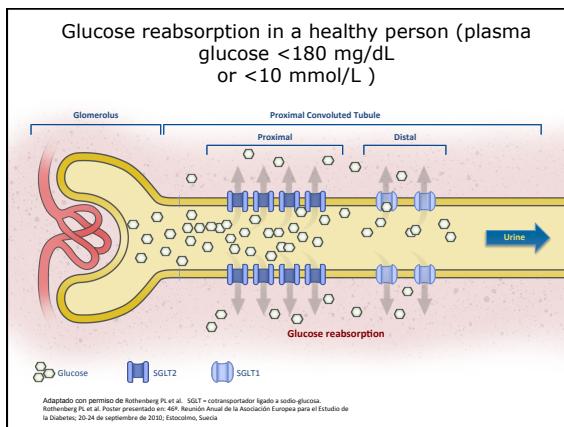
- Normal kidney glucose homeostasis
- SGLT-2 in diabetes mellitus
- SGLT2 inhibitors
 - Efficacy: focus on comparative efficacy (active control)
 - Safety

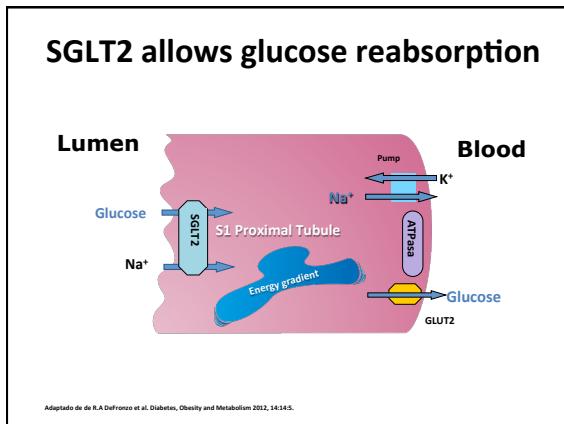
Glomerular filtration

- 125 ml de filtered/min (180 l/24 h)¹
 - Urinary output: 1.5 l/24 h
- 25000 mEq ofNa⁺ filtered
 - Urinary Na⁺ excretion: 40-220 mEq/24 h²
- Up to 180 g of glucose filtered/24 h³
 - Urinary glucose excretion = 0 in healthy individuals due to glucose reabsorption⁴



1. Abdulla M, et al. Endocr Pract. 2008;14:782-80. 2. Finkelstein EO. Yale J Biol Med. 1979; 52(3):271-87.
3. Kotzalidis P, et al. Cases Journal. 2009; 2:6813. 4. Wright EM, et al. J Intern Med. 2007;263:32-43.

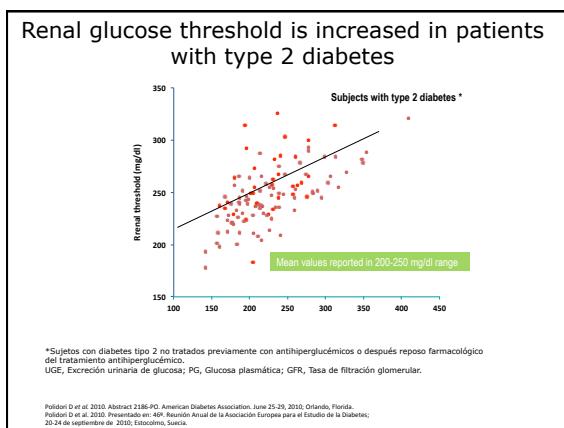
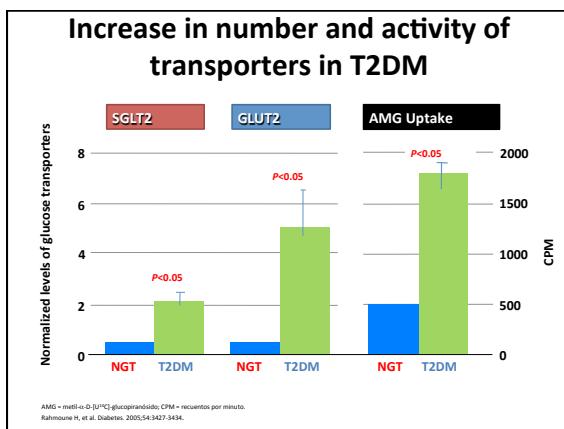




SGLT sodium glucose transporters

	SGLT1	SGLT2
Main expression sites	Kidney and gut	Kidney
Sugar specificity	Glucose or galactose	Glucose
Main role	Dietary intestinal absorption of glucose and galactose Renal glucose reabsorption	Renal glucose reabsorption

Modificado de Lee YJ et al. Kidney Int Suppl. 2007;72:S17-S35.



SGLTs Are Found Throughout the Body

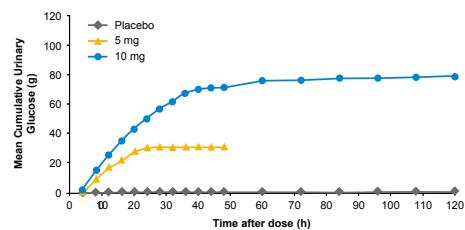
Transporter	Major site of action	Function	Disease Associated with Malfunction
SGLT1	Small intestine, heart, trachea and kidney	Co-transports sodium, glucose and galactose across the brush border of the intestine and proximal tubule of the kidney	Congenital glucose-galactose malabsorption syndrome
SGLT2	Kidney	Co-transports sodium and glucose in the S1 segment of the proximal tubule of the kidney	Familial renal glucosuria
SGLT3	Small intestine, uterus, lungs, thyroid and testis	Transports sodium (not glucose)	Unknown
SGLT4	Small intestine, kidney, liver, stomach and lung	Transports glucose and mannose	Unknown
SGLT5	Kidney	Unknown	Unknown
SGLT6	Spinal cord, kidney, brain, and small intestine	Transports myo-inositol and glucose	Unknown

Bays H. Curr Med Res Opin. 2009;25:671-681.

SGLT-2 inhibitors

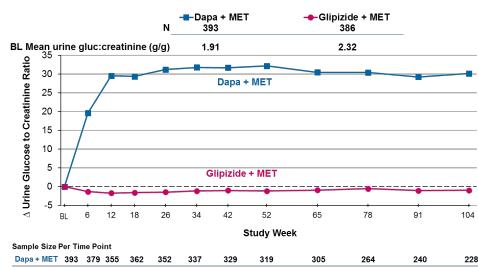
- Dapagliflozin: 5 mg and 10 mg
- Canagliflozin: 100 mg and 300 mg
- Empagliflozin: 10 mg and 25 mg
- Ertoglitazone
- Tofogliflozin

Dapagliflozin Induced Cumulative Urinary Glucose Excretion in Healthy Volunteers



Komoroski BJ, et al. Clin Pharmacol Ther. 2009;85:520–526.

Increase in Glucose Excretion Observed Over 2 Years



Repeated measures mixed model analysis.

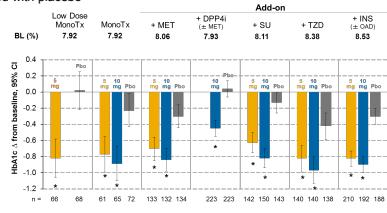
EMDAC Background document. Available at: <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologycarbohydratedrugsadvisorycommittee/ucm378079.pdf>

DAPAGLIFLOZIN EFFICACY AND SAFETY

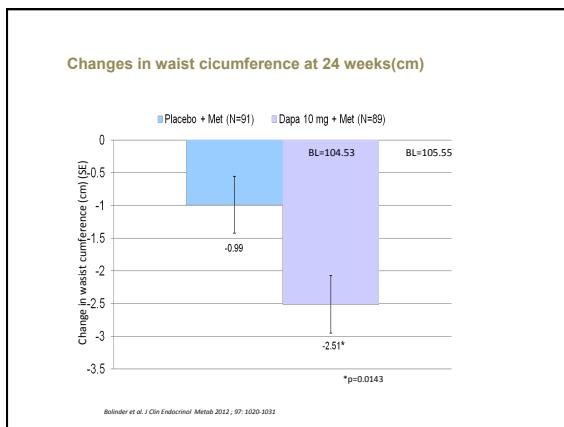
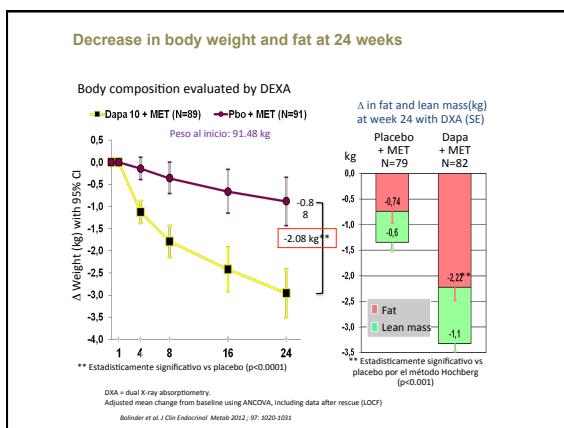
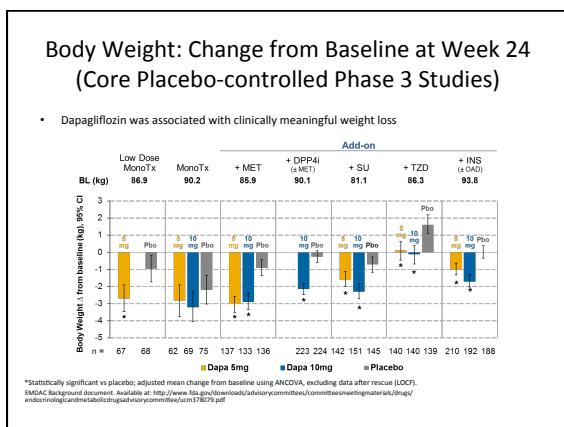
SHORT TERM DATA

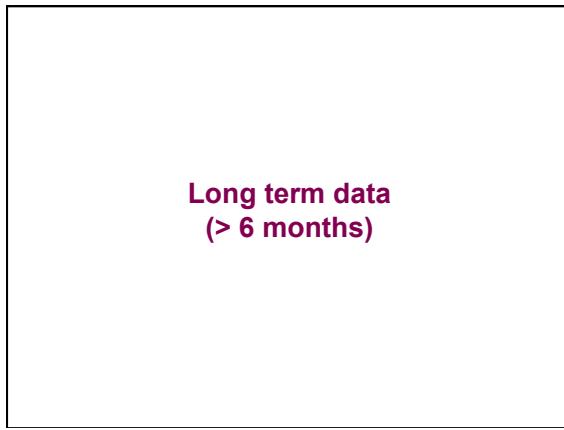
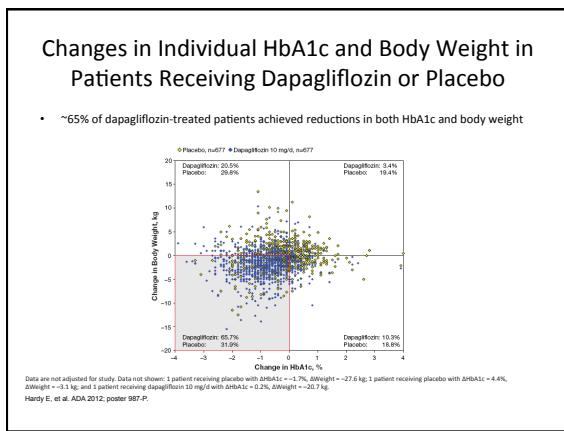
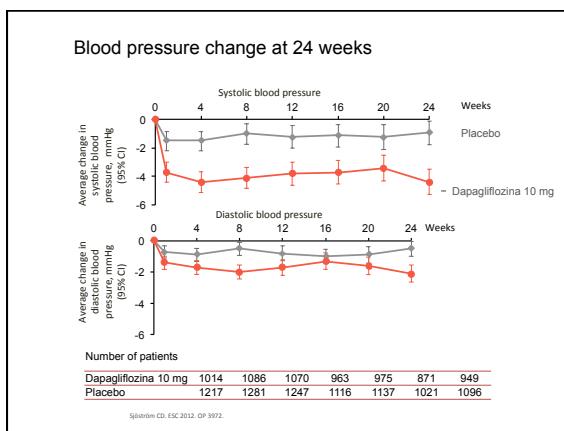
HbA1c: Change from Baseline at Week 24 (Core Placebo-controlled Phase 3 Studies)

- Dapagliflozin 5 and 10 mg results in significant reductions in HbA1c at week 24 compared with placebo

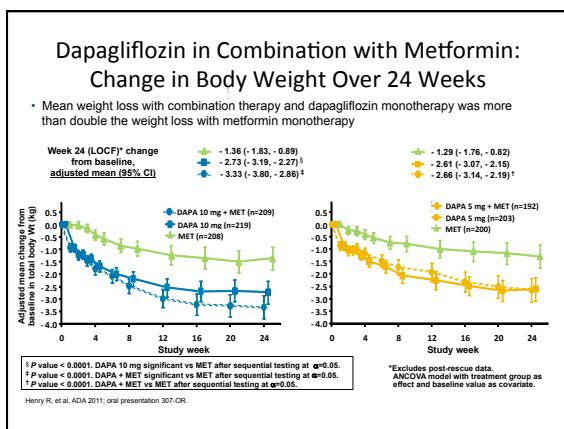
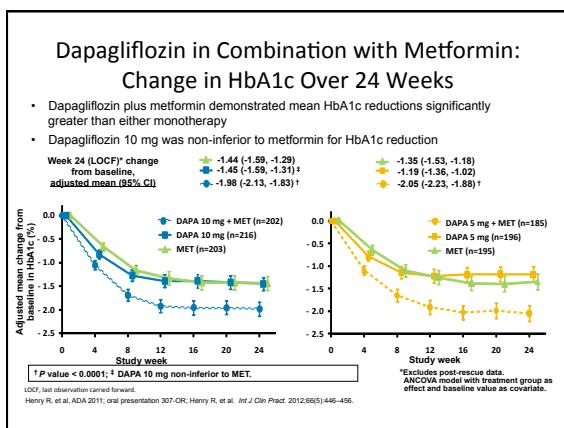


*Statistically significant vs placebo; adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF).
EMDAC Background document. Available at: <http://www.fda.gov/downloads/advisorycommittees/committees/meetings/committeesonmetabolicdrugsandvirologycommittee/ucm378079.pdf>





First line therapy: dapagliflozin vs metformin XR

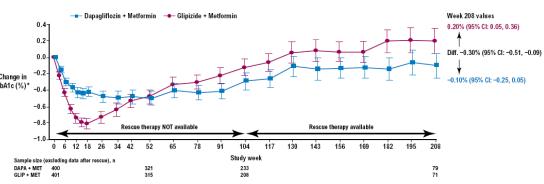


Second line treatment

DAPAGLIFLOZIN VS SU

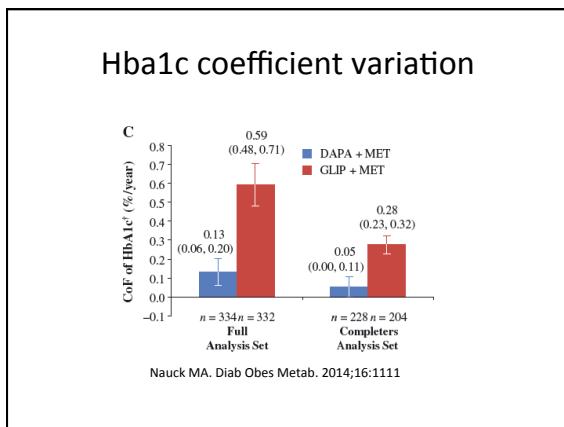
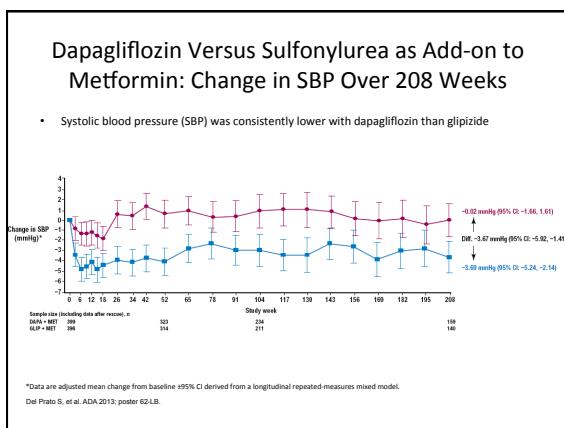
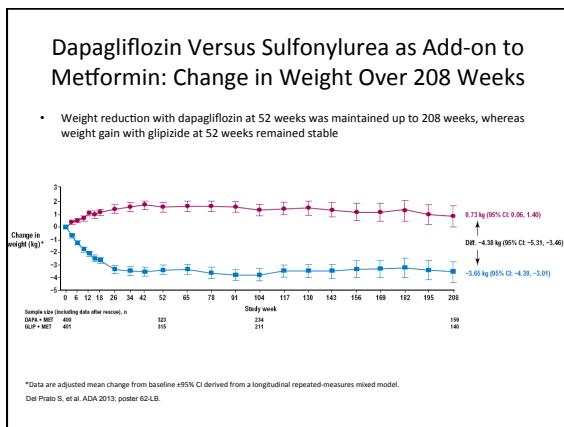
Dapagliflozin Versus Sulfonylurea as Add-on to Metformin: Change in HbA1c Over 208 Weeks

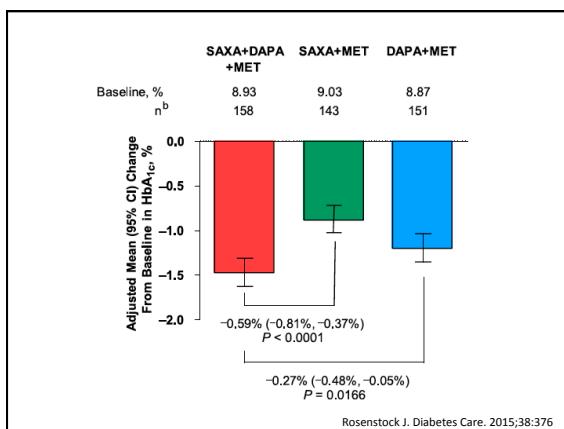
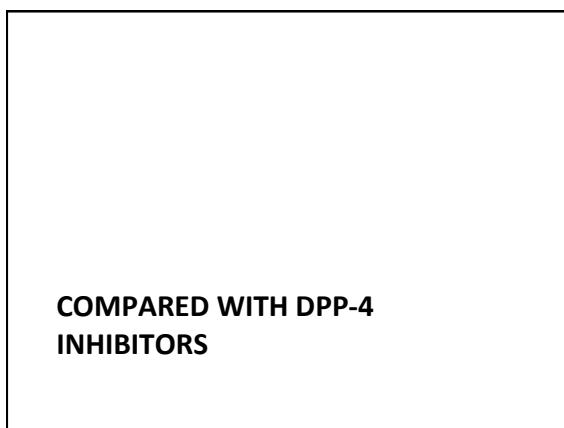
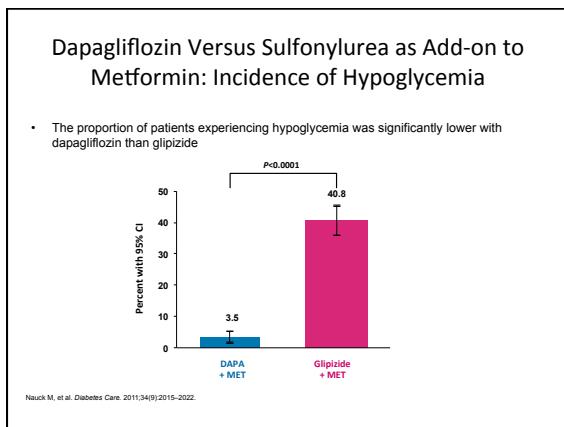
- **HbA_{1c} durability was better with dapagliflozin than glipizide**
 - The rise from 52–208 weeks was less compared with glipizide, giving a significant difference between treatments at 208 weeks

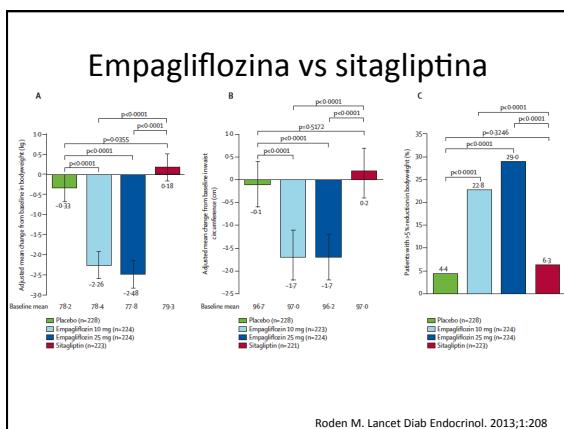
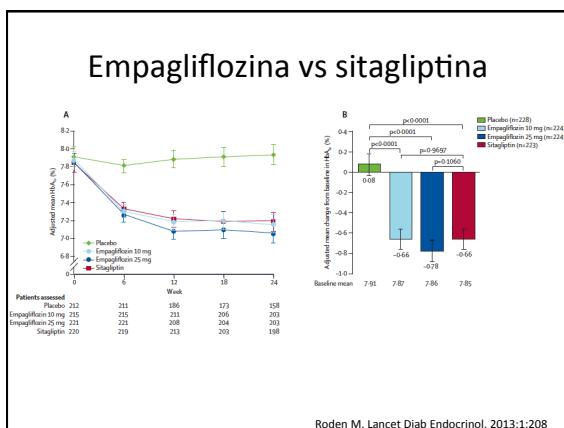
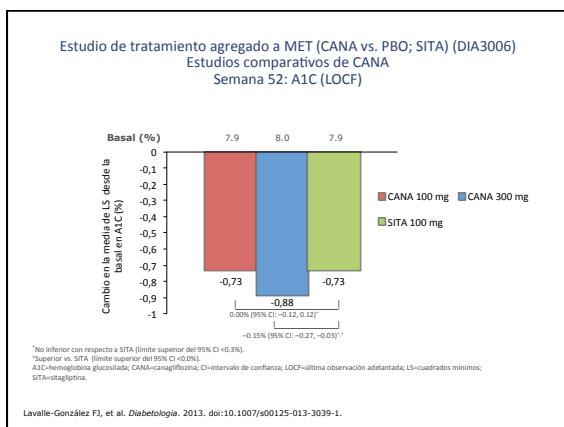


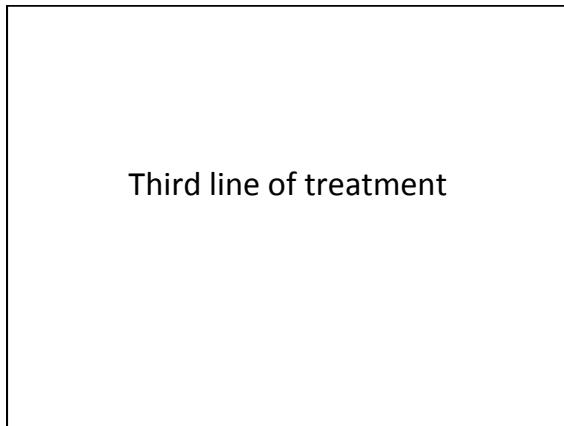
*Data are adjusted mean change from baseline \pm 95% CI derived from a longitudinal repeated-measures mixed model.

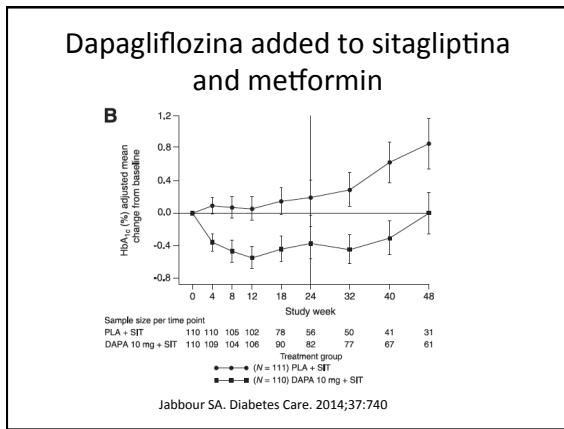
Del Prato S, et al. ADA 2013; poster 62-LB

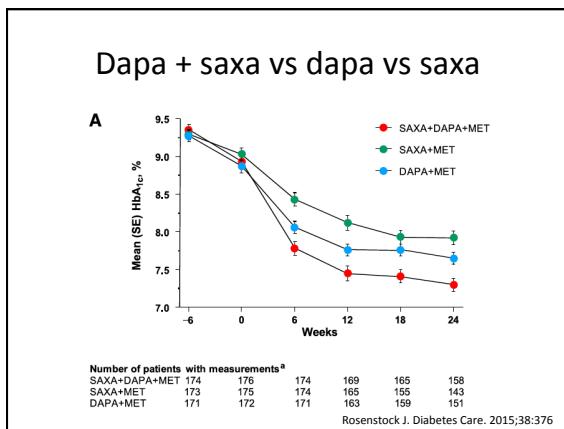


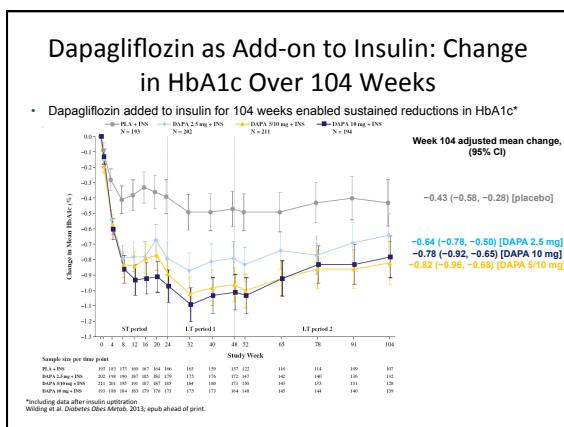
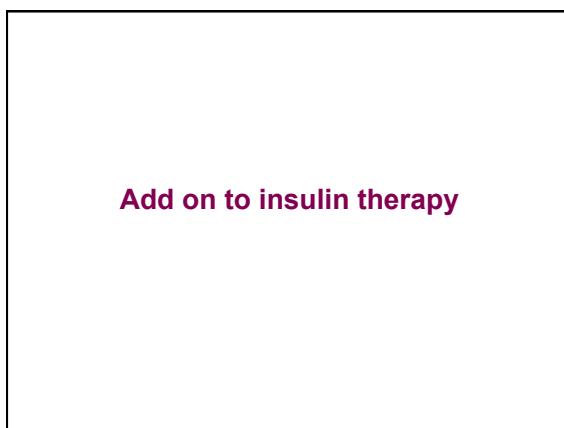
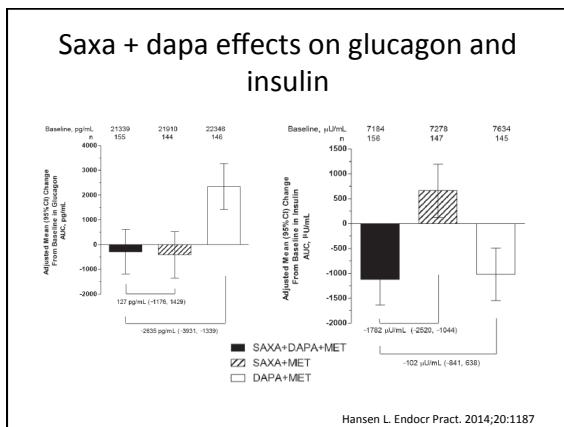






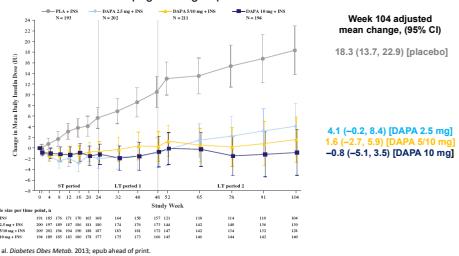






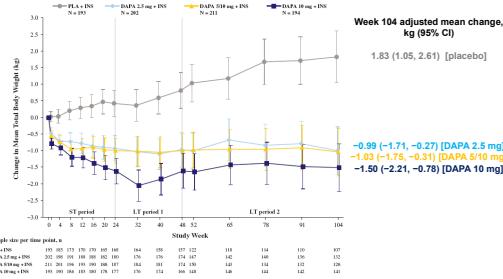
Dapagliflozin as Add-on to Insulin: Change in Daily Insulin Dose Over 104 Weeks

- Insulin requirement increased progressively in the placebo group but remained stable over 104 weeks in the dapagliflozin groups



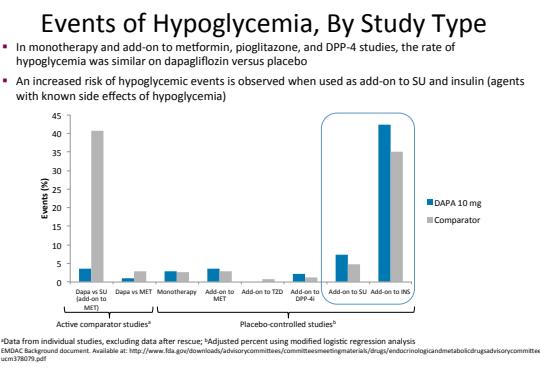
Dapagliflozin as Add-on to Insulin: Change in Body Weight Over 104 Weeks

- Dapagliflozin added to insulin for 104 weeks enabled sustained reductions in body weight*



ADVERSE EVENTS

Hypoglycemia



GENITAL AND URINARY INFECTIONS

Events of Urinary Tract Infections

- A small increase in events of UTIs was reported with dapagliflozin versus placebo
 - Events of UTIs were more common in females than males
 - Most events were mild or moderate in intensity
 - Pyelonephritis was rare and balanced between treatment groups (0.1% dapagliflozin vs 0.2% control)

	Placebo-controlled pool (short-term)		Placebo-controlled pool (short- plus long-term)	
	DAPA 10 mg	PBO	DAPA 10 mg	PBO
Events of UTI, n (%)	N=2360 110 (4.7)	N=2295 81 (3.5)	N=2026 174 (8.6)	N=1956 121 (6.2)
Females, n (%)	N=1003 85 (8.5)	N=952 64 (6.7)	N=852 121 (14.2)	N=799 86 (10.8)
Males, n (%)	N=1357 25 (1.8)	N=1343 17 (1.3)	N=1174 53 (4.5)	N=1157 35 (3.0)

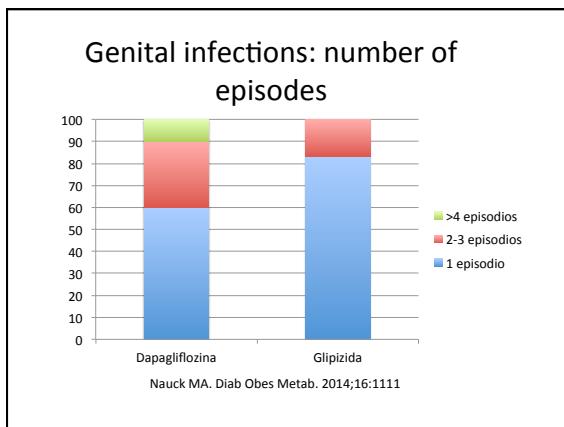
EMDAC Background document. Available at: <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologandmetabolic/usadvisorycommittee/ucm178079.pdf>

Events of Genital Infections

- Genital infections were reported more frequently with dapagliflozin versus placebo
 - Events of genital infections were more common in females than males
 - Most frequently reported genital infections: vulvovaginal mycotic infection, balanitis and vaginal infections

	Placebo-controlled pool (short-term)		Placebo-controlled pool (short- plus long-term)	
	DAPA 10 mg	PBO	DAPA 10 mg	PBO
Genital infection, n (%)	N=2360 130 (5.5)	N=2295 14 (0.6)	N=2026 156 (7.7)	N=1956 19 (1.0)
Females, n (%)	N=1003 84 (8.4)	N=952 11 (1.2)	N=852 98 (11.5)	N=799 15 (1.9)
Males, n (%)	N=1357 46 (3.4)	N=1343 3 (0.2)	N=1174 58 (4.9)	N=1157 4 (0.3)

EMDAC Background document. Available at: <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologandmetabolic/usadvisorycommittee/ucm178079.pdf>



Canagliflozina – Urinary and genital infections

Incidence of urinary and genital infections (DS1)

	Placebo	Canagliflozina 100 mg	Canagliflozina 300 mg
Genital infections – Men	0.6%	4.2%	3.7%
Genital Infections - Women	3.2%	10.4%	11.4%
Urinary infection	4.0%	5.9%	4.3%

- Keon H. Canagliflozin: Clinical Efficacy and Safety. FDA Slides for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting January 15, 2013. <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologyandMetabolicDrugsAdvisoryCommittee/slides30523.htm> Accessed April 2, 2014.
- FDA Briefing Information for the January 15, 2013 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologyandMetabolicDrugsAdvisoryCommittee/slides30523.htm> Accessed April 2, 2014.

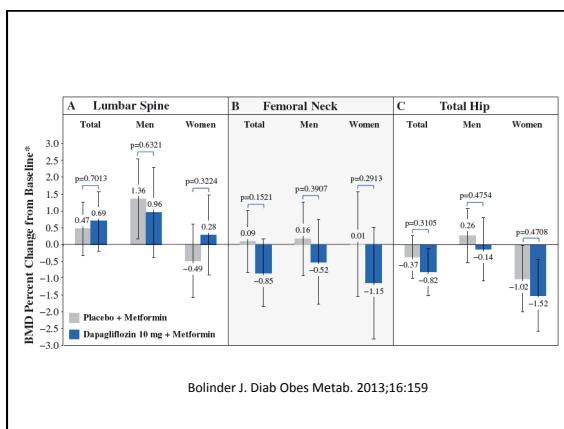
Empagliflozina – Genital and Urinary Infections

Incidence of Urinary and Genital Infections

	Placebo	Empagliflozina 10 mg	Empagliflozina 25 mg
Genital infections – Men	0.4%	3.1%	1.6%
Genital Infections - Women	1.5%	5.4%	6.4%
Urinary infections	7.6%	9.3%	7.6%

Jardiance Prescribing Information, 2014
EFFICACY AND SAFETY OF SGLT2 INHIBITORS Riser Taylor and Harris PHARMACOTHERAPY Volume **, Number **, 2013

BONE SAFETY



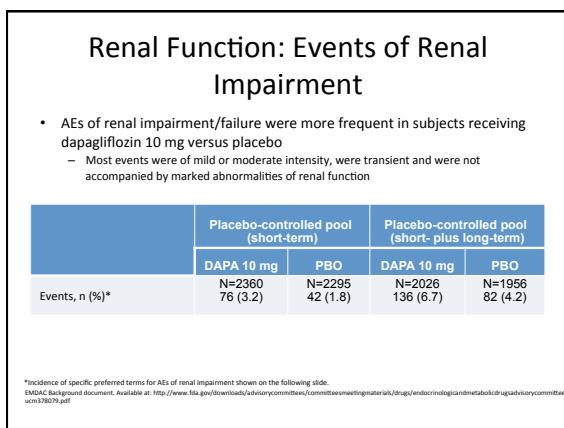
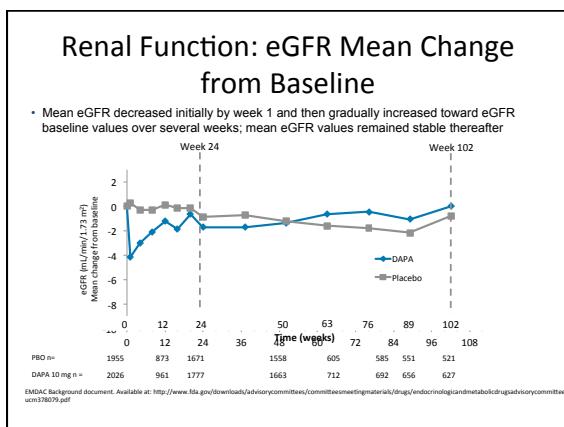
Events of Fracture

- The proportions of patients with fractures were small and balanced for dapagliflozin versus placebo

	Placebo-controlled pool (short-term)		Placebo-controlled pool (short- plus long-term)	
	DAPA 10 mg	PBO	DAPA 10 mg	PBO
Events, n (%)	N=2360 8 (0.3)	N=2295 17 (0.7)	N=2026 23 (1.1)	N=1956 32 (1.6)

EMEAAC Background document. Available at: <http://www.ema.europa.eu/ema/-/sites/default/files/documents/ePAR/medicinal-products-for-human-use/antidiabetics/dapagliflozin/000378D09.pdf>.

RENAL FUNCTION



Empagliflozina – Changes in creatinine and eGFR

Combined data from 4 24 week placebo controlled studies

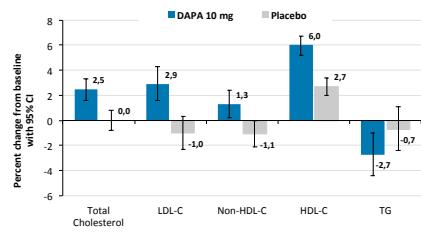
Creatinine (mg/dL)	Basal Value	Change at 12 weeks	Change at 24 weeks
Placebo (N=825)	0.84	0.00	0.00
Empagliflozina 10 mg (N=830)	0.85	0.02	0.01
Empagliflozina 25 mg (N=822)	0.85	0.01	0.01
eGFR (mL/min/1.73m ²)			
Placebo (N=825)	87.3	-0.3	-0.3
Empagliflozina 10 mg (N=830)	87.1	-1.3	-0.6
Empagliflozina 25 mg (N=822)	87.8	-1.4	-1.4

1. Jardiance Prescribing Information, 2014

CHANGES IN LIPID PROFILE

Laboratory Data: Lipids

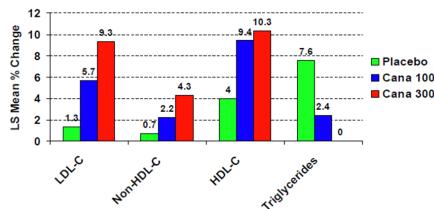
- Small mean changes from baseline in fasting lipid levels were observed with dapagliflozin 10 mg after 24 weeks of treatment



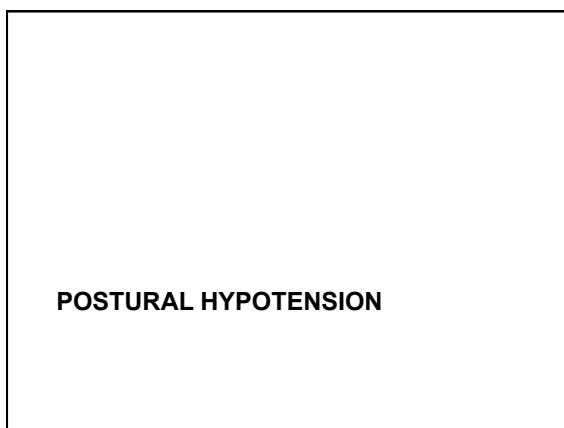
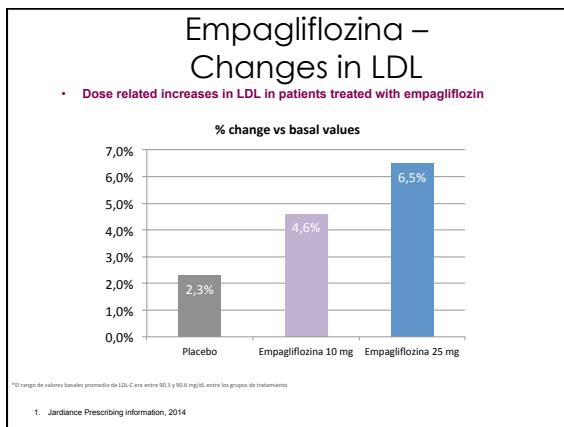
EMDAG slide presentation. Available at: <http://www.fda.gov/brownbag/advisorycommittee/committeeonmetabolicdrugsandmetabolism/advisorycommitteeucm379659.pdf>

Canagliflozin: Changes in lipid profile

Dataset from placebo controlled studies
Percentaje change from basal values to week 26



Can = Canagliflozin; GM = Geometric mean; HDL-C = High-density lipoprotein cholesterol; LS = Least squares ; Non-HDL-C = Cholesterol Non-HDL; TG= Triglycerides
1. Kevin H. Canagliflozin: Clinical Efficacy and Safety. FDA Slides for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting January 10, 2013. <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologyandMetabolicDrugsAdvisoryCommittee/ucm35223.htm> Accessed April 2, 2014.
2. William T Cefalu. Lancet 2013



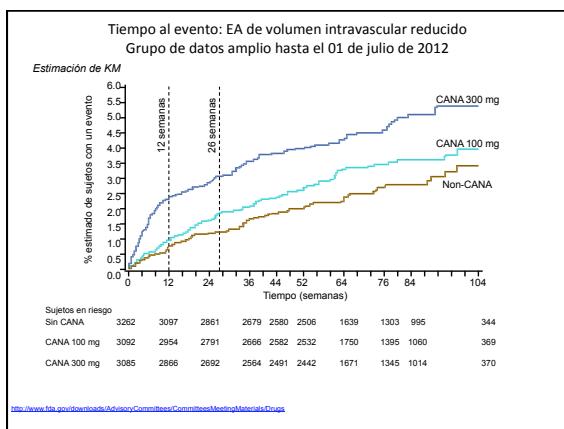
Events of Volume Depletion

- Events of volume depletion (hypotension/hypovolemia/dehydration) were infrequent but more common in patients treated with dapagliflozin than placebo
 - Most events were mild or moderate in intensity
 - In the short-term and short- plus long-term placebo-controlled pool, most events were "hypotension" in the dapagliflozin 10-mg (0.6% and 0.9%) and placebo (0.2% and 0.3%) groups, respectively

	Placebo-controlled pool (short-term)		Placebo-controlled pool (short- plus long-term)	
	DAPA 10 mg	PBO	DAPA 10 mg	PBO
Events, n (%)	N=2360 27 (1.1)	N=2295 17 (0.7)	N=2026 38 (1.9)	N=1956 27 (1.4)

- In the all phase 2b and 3 pool, serious AEs of volume depletion were infrequent and occurred in 6 (0.1%) patients treated with dapagliflozin and 8 (0.2%) patients treated with control

EMDAC Background document. Available at: <http://www.fda.gov/downloads/advisorycommittees/committeesmeetings/materials/drug/endocrinologymetabolicdrugsadvisorycommittee/ucm378679.pdf>

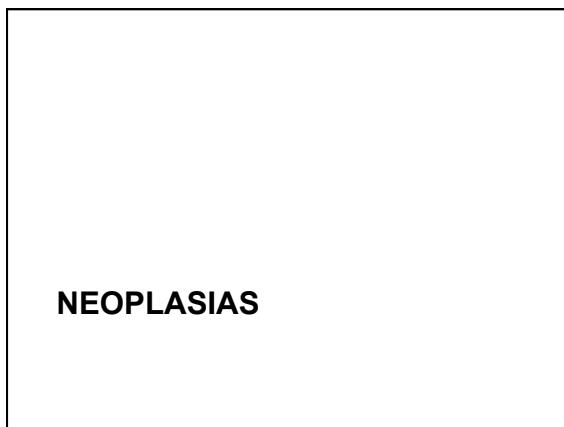
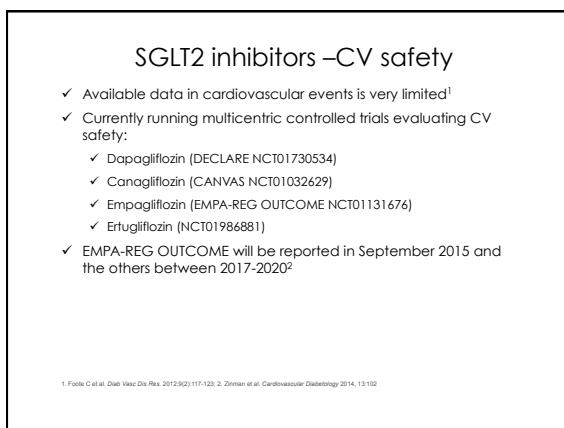
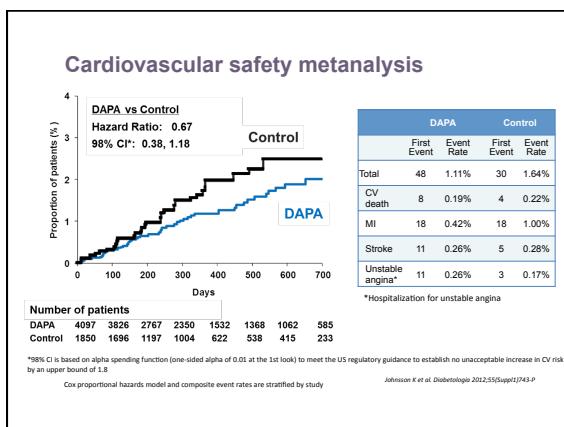


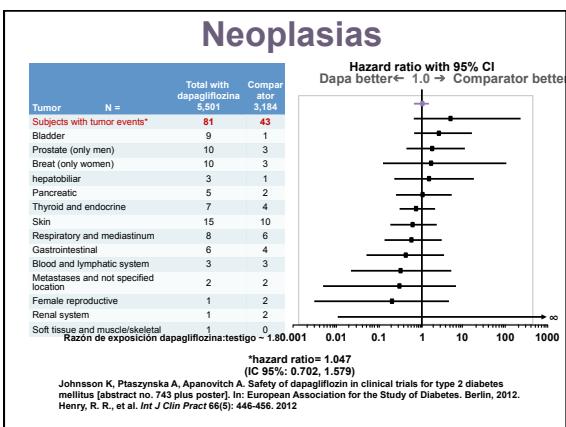
Risk factors: AEs of postural hypotension
Grupo de datos amplio del período principal

eGFR (mL/min/ 1.73m ²)	Without CANA % (n/N)	CANA 100 mg % (n/N)	CANA 300 mg % (n/N)
<60	2.8 (12/436)	5.0 (19/382)	8.1 (33/405)
60 a <90	1.5 (26/1788)	2.4 (40/1686)	2.9 (48/1680)
≥90	1.2 (12/1035)	1.3 (13/1021)	2.4 (24/999)
Age (years)			
<75	1.5 (46/3107)	2.2 (64/2929)	3.1 (90/2913)
≥75	2.6 (4/155)	4.9 (8/163)	8.7 (15/172)
Use of loop diuretics			
No	1.2 (37/3006)	2.3 (65/2876)	2.9 (83/2835)
Yes	5.1 (13/256)	3.2 (7/216)	8.8 (22/250)
Age <75, no loop diuretics and eGFR ≥60 mL/min/1.73m ²	1.1 (29/2604)	1.8 (45/2491)	2.2 (54/2434)

<http://www.fda.gov/industry/AdvisoryCommittees/CommitteesMeetingMaterials/Drops>

WHAT IS THE OVERALL
CARDIOVASCULAR SAFETY PROFILE?





Canagliflozin and cancer

Canagliflozin	N	Subjects with events (%)	Rate per 1000 patient-year
Bladder Cancer			
Canagliflozin 100 mg	3139	2 (0.06)	0.44
Canagliflozin 300 mg	3506	3 (0.09)	0.63
All canagliflozin	6645	5 (0.07)	
All noncanagliflozin	3640	4 (0.11)	0.84
Breast Cancer			
Canagliflozin 100 mg	1313	5 (0.38)	2.61
Canagliflozin 300 mg	1514	7 (0.46)	3.39
All canagliflozin	2827	12 (0.42)	
All noncanagliflozin	1501	6 (0.4)	3.05

Source: reference [14], data obtained from 8 phase 3 clinical trials, data cutoff date: Nov 15, 2012.
Lin HW. *Int J Endocrinol*. 2014

EUGLYCEMIC DKA

Euglycemic DKA

- Almost 5% of T1DM have reported a DKA episode in the last year
 - Reported by FDA on May 15th, 2015
 - Euglycemic DKA is rare but perhaps it is unrecognized and underreported
 - euDKA:
 - Partial treatment of DKA
 - Food restriction
 - Alcohol intake
 - Inhibition of gluconeogenesis

Peters AL. Diabetes Care. Online June 15th.

FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

[05-15-2015]

Safety Announcement

The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. We are continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for this class of drugs, called sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Do not stop or change your diabetes medicines without first talking to your prescriber. Health care professionals should evaluate for the presence of acidosis, including ketocacidosis, in patients experiencing these signs or symptoms; discontinue SGLT2 inhibitors if acidosis is confirmed; and take appropriate measures to correct the acidosis and monitor sugar levels.

EndoDrChen.com

Data Summary

FDA searched the FDA Adverse Event Reporting System (FAERS) database from March 2013 (approval of the first drug in the class) through June 6, 2014, and identified 20 cases of diabetic ketoacidosis (DKA), ketoacidosis, or ketosis reported with the sodium-glucose cotransporter-2 (SGLT2) inhibitors. Type 2 diabetes mellitus was noted as the indication in most of the cases, type 1 diabetes mellitus was noted in a few cases, and some cases did not specify the indication.

In all cases, a diagnosis of DKA or ketoacidosis was made by a health care professional, and hospitalization of the patients was required to treat the episode. A temporal association with SGLT2 inhibitor initiation was noted in all cases. The median time to onset of symptoms following initiation of drug therapy was 2 weeks (range = 1 to 175 days). DKA case presentations were atypical in that glucose levels were only mildly elevated at less than 200 mg/dL. In some reports, while patients with type 1 diabetes who have DKA typically have glucose levels greater than 250 mg/dL. In addition, DKA is not typically observed in patients with type 2 diabetes.

In most cases, a high anion gap metabolic acidosis accompanied by elevated blood or urine ketones was reported. Potential DKA-triggering factors that were identified in some cases included acute illness or recent significant changes such as infection, uresepsis, trauma, reduced caloric or fluid intake, and reduced insulin doses. Potential factors, other than hypovolemia, contributing to the development of a high anion gap metabolic acidosis identified in the cases included hypovolemia, acute renal impairment, hypoxemia, reduced oral intake, and a history of alcohol use. Half of cases did not identify a triggering factor for DKA.

We are continuing to investigate this safety issue. Additional reports of DKA continue to be submitted to us, and we will determine whether changes are needed in the labeling for this class of drugs.

EndoDrChen.com

Table 1 – Clinical Characteristics of euDKA Cases									
Case patient	1	2	3	4	5	6	7	8	9
Age (years)	40	58	27	28	31	55	26	39	64
Sex	Female	Male	Female	Female	Female	Female	Female	Female	Female
T1/T2	T1	T2	T1	T1	T1	T1	T1	T1	T2
HbA1c (%)	6.03	NA	CDR	CDR	CDR	CDR	CDR	CDR	NA
Duration years	17	2	25	6	15	18	13	26.1	8
BMI (kg/m ²)	26.5	26.5	24.3	25.9	33.2	22.0	22.0	26.1	32.8
Prior A1c (%) (mean/med)	11.4 (10.1, 11)	9.8 (8.8, 10)	7.8 (6.1, 7)	8.0 (6.8, 9)	7.0 (5.3, 8)	7.2 (5.5, 21)	6.6 (4.6, 8)	7.7 (5.4, 10)	7.8 (6.2, 8)
Current insulin dose (mg)	100	100	100	300	200	300	150	300	200
Potential contributors	URI	Surgery	1	URI, alcohol	Alcohol	Exercise, alcohol	Exercise	GI	None
Insulin dose reduction	Yes	N/A	Yes	No	Yes	Yes	Unknown	No	No
Just prior to euDKA	Yes	N/A	Yes	No	Yes	Yes	Unknown	No	No
Presenting plasma glucose (mmol/L)	220 (12.2)	150 (8.3)	150 (8.3)	96 (5.3)	224 (12.4)	158 (8.8)	—125 (—6.9)	203 (11.3)	190 (10.6)
pH	6.9	7.12	6.89				7.15 ^a		
Base excess	9						26 ^b		
Bicarbonate (mmol/L)	6	10	6	11	18	15	5	9	13 and then 5
Anion gap (mmol/L)	25	17	35	22	18	26	21	24	16 and then 19
Ketones*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (serum and urine)
Where treated	ICU	ICU	ICU	Outpt.	ICU	Inpt.	Outpt.	ICU	ICU

CSL: continuous subcutaneous insulin infusion; GI, gastrointestinal; Inpt., inpatient; N/A, not available; Outpt., outpatient. *Urine ketones were strongly positive in all cases.

Peters AL. Diabetes Care. Online June 15th.

Common features

- Did not recognize DKA because blood glucose was not that high
- Instead of increasing insulin dose, it was decreased or unchanged
- Medical care providers did not recognize the entity either
- Mostly T1DM and in 2 T2DM in postoperative setting

Peters AL. Diabetes Care. Online June 15th.

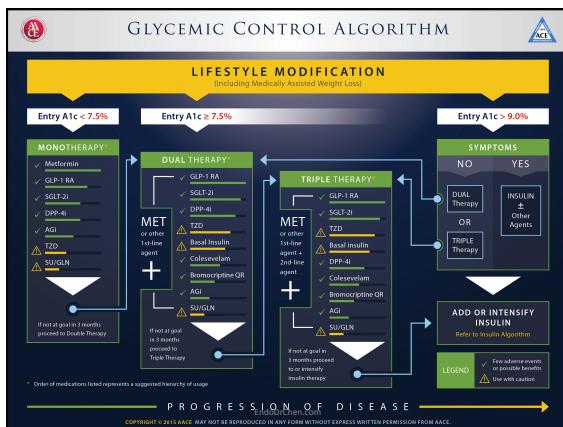
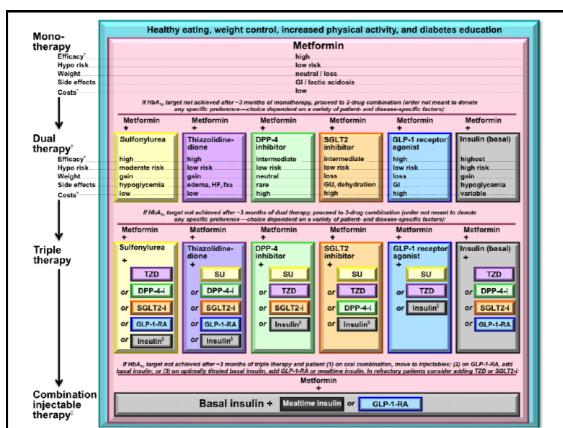
Pathophysiology

- Increased renal clearance of glucose may lead to deceptively low blood glucose levels
- Reduced insulin dose
- Ketosis
- SGLT-2 inhibitors may increase glucagon levels
 - Negative fluid and sodium balance
 - Hypovolemia drives elevation in cortisol, glucagon, epinephrine which further increases insulin resistance, lipolysis and ketogenesis

Peters AL. Diabetes Care. Online June 15th.

Case presentation

- Started dapagliflozin 10 mg per day on November 2014
- Current hba1c 7.8%
- Total daily insulin dose: 128 units (was 144)
- Current weight 89 kg (was 90 kg)



Take home messages

- Kidney plays a very important role in glucose homeostasis
- SGLT-2 inhibition provides sustained glucose reduction with weight loss and decrease in blood pressure
- Main adverse events related to urogenital infections and increase in LDL
- Extremely careful with off label use in T1DM and euDKA
