## SGLT2 Inhibitors in the Treatment

## of Type 2 Diabetes Mellitus

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SGLT2 in glucose homeostasis

- Clinical Outcome of SGLT2 inhibitors
  - Clinical efficacy
  - Safety issues
- Why aren't SGLT2 inhibitors more potent?
  - Up-regulation of glucose reabsorption by SGLT1
  - Effect on endogenous glucose production

## **SGLT Family & Inhibitors**

 SGLT member	Substrate	Distribution in human tissue
SGLTI	Glucose,	Intestine, trachea, kidney, heart,
	galactose	brain, testis, prostate
SGLT2	Glucose	Kidney, brain, liver, thyroid,
		muscle, heart
SGLT3	Glucose	Intestine, testis, uterus, lung,
		brain, thyroid
SGLT4	Glucose,	Intestine, kidney, liver, brain,
	mannose	lung, trachea, uterus, pancreas
SGLT5	Glucose,	Kidney
	galactose	
SGLT6	D-chiro-	Brain, kidney, intestine
	inositol	



Canagliflozin

Dapagliflozin

Drug Design, Development and Therapy 2014:8 1335–1380

Empegliflozin

C-glucosides

### **Renal Tubular Reabsorption of Glucose**



Diabetes Metab J 2014;38:261-273

#### Renal Glucose Handling before & after Sodium-Glucose Cotransporter 2 (SGLT2) Inhibition



### **Reabsorption of Glucose & SGLT2 Inhibition**



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## **Clinical Efficacy: HbA1c & FPG**



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## **Clinical Efficacy: BP & Body Weight**



### **Efficacy in Asian Population**





### **Effects in Korean Population**



Lee MK et al: DRCP 2013

### Safety Issues: Hypoglycemia



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### **Genital & Urinary Tract Infections**



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### Safety issue: Overview

- Hypoglycemia: rare, except add-on to insulin or insulin secretagogues
- Genital infections: increased especially in women and those with Hx of genital infections, generally mild to moderate
- Urinary tract infection: ?mild increase
- Volume depletion: mild, elderly and those on loop diuretics
- Renal function: small initial decrease  $\rightarrow$  return to baseline
- Fractures, Hepatic safety: no signals
- Malignancy: ?bladder cancer signal with dapagliflozin
- Cardiovascular: small increase in LDL, no signal of CV harm

#### Why aren't SGLT2 inhibitors more potent?

PERSPECTIVES IN DIABETES

## Why Do SGLT2 Inhibitors Inhibit Only 30–50% of Renal Glucose Reabsorption in Humans?

Jiwen (Jim) Liu,<sup>1</sup> TaeWeon Lee,<sup>2</sup> and Ralph A. DeFronzo<sup>3</sup>

Diabetes 61:2199-2204, 2012

PERSPECTIVES IN DIABETES

#### Novel Hypothesis to Explain Why SGLT2 Inhibitors Inhibit Only 30–50% of Filtered Glucose Load in Humans

Muhammad A. Abdul-Ghani, Ralph A. DeFronzo, and Luke Norton

Diabetes 62:3324-3328, 2013

# Hypothesis: SGLT1 compensation for increased distal tubular glucose delivery



#### Diabetes 62:3324-3328, 2013

#### Why aren't SGLT2 inhibitors more potent? (1) Incomplete reduction of glucose reabsorption

- SGLT2 reabsorbs 80-90% of the 160-180g glucose filtered daily
- But SGLT2 inhibitors induce a maximum of 50-80g glycosuria
- Hypothesis
  - SGLT1 compensation for increased distal tubular glucose delivery
  - Incomplete exposure of renal SGLT2
  - Possible presence of other SGLT/GLUTs
- Unanswered question
  - Is there a therapeutic role for **dual inhibition of SGLT2/1**?

#### Why aren't SGLT2 inhibitors more potent? (2) Increased endogenous glucose production



Related Commentary, page 485 🛛 Clinical medicine

#### Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients

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J Clin Invest. 2013;124(2):499-508.

## Dapagliflozin improves muscle insulin sensitivity, but enhances endogenous glucose production.



## Blunted suppression of endogenous glucose production by increased glucagon secretion



A 4h hyperinsulinemic euglycemic clamp with 3<sup>-3</sup>H-glucose

(continuous insulin infusion for 240min)

## Increased glucagon/insulin ratio during chronic administration of dapagliflozin



J Clin Invest. 2014;124(2):509-514.

## Acute and chronic administration of empagliflozin increases endogenous glucose production.



J Clin Invest. 2013;124(2):499-508.

## Acute and chronic administration of empagliflozin increases GLP-1 secretion and decreases FFA.



J Clin Invest. 2013;124(2):499-508.

## Hormonal & Glucose Flux Responses to SGLT2 inhibition

- Despite lowering FPG, glucosuria produced by inhibition of SGLT2 stimulated a compensatory increase in EGP.
- ↑Glucagon, ↓Insulin → Blunted suppression of endogenous glucose production → Attenuation of the reduction in fasting and prandial glycemia
- Greater β-cell sensitivity (↑GLP-1, ↓glucose toxicity) is insufficient to reverse these changes.
- Unanswered questions
  - Would combined incretin therapy + SGLT2 inhibition reverse these?

## Summary

- SGLT2 inhibitors show glucose lowering effects in monotherapy and add-on with metformin, insulin, SU, DPP-4I, or TZDs.
- Body weight reduction and BP-lowering effects were also demonstrated.
- SGLT2 inhibitors could preserve beta-cell function and improve insulin sensitivity, and increased endogenous glucose production & glucagon secretion.
- SGLT2 inhibitors are well tolerated, but increased risks of genital infections and UTIs and rise in LDL-cholesterol level were reported.