Gli inibitori SGLT2: dalla farmacologia alla clinica

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DUALITY OF INTEREST DISCLOSURE

Dr Mannucci has received speaking and/or consulting fees from:

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SGLT-2 MOA

Tubular reabsorption of glucose
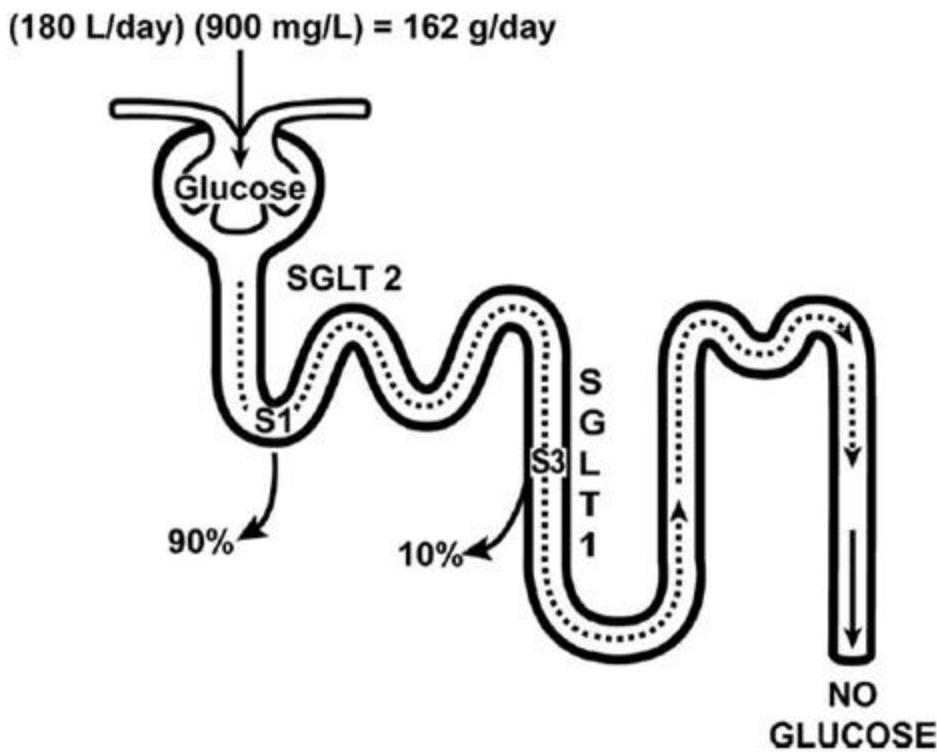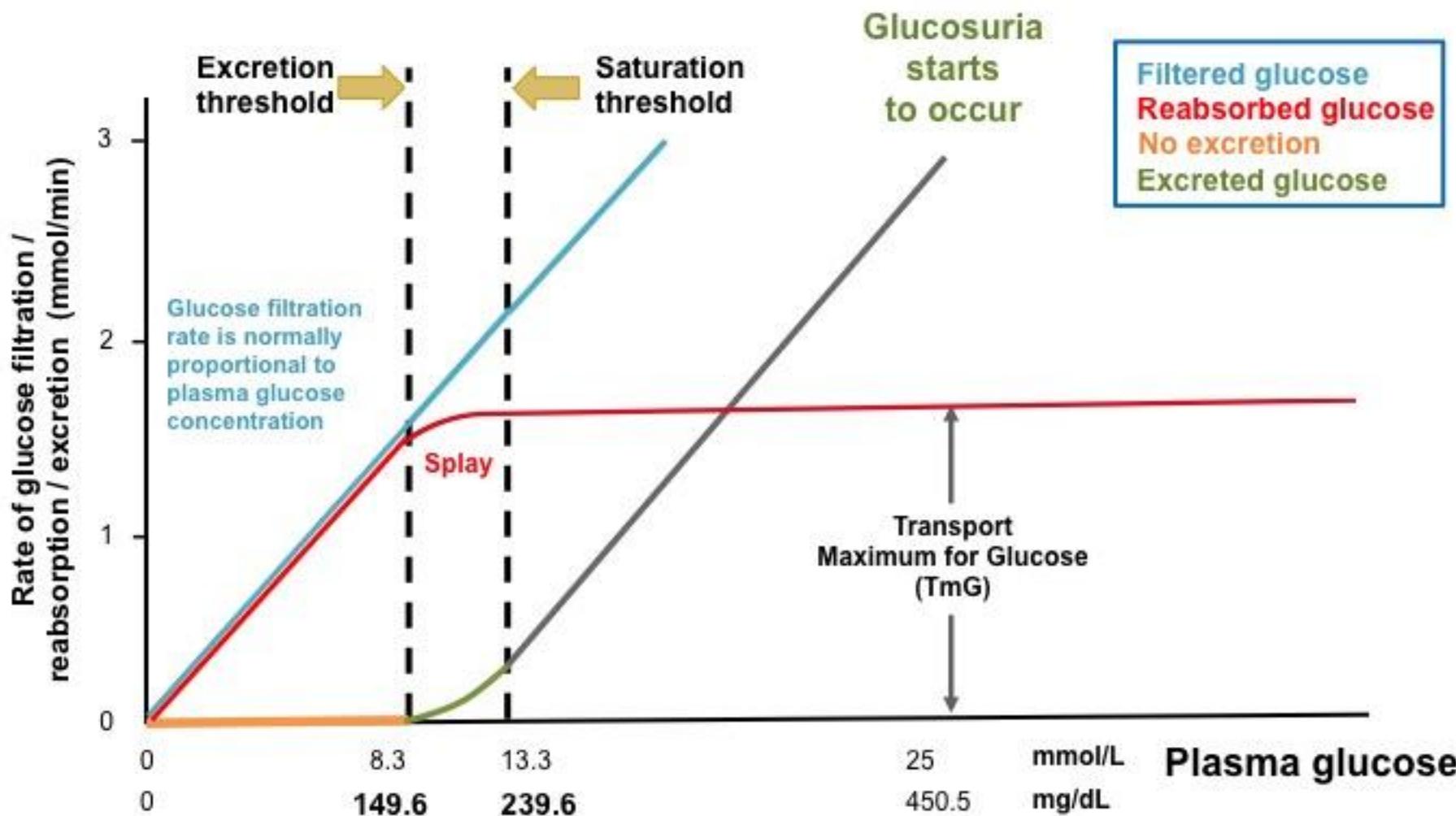
(180 L/day) (900 mg/L) = 162 g/day

Glucose

SGLT 2

S1

90%

S3

S
G
L
T
1

10%

NO GLUCOSE

Abdul-Ghani MA, *Endocrine Reviews* 2011; 35:515-531.

Renal glucose reabsorption

Adapted from Chao EC, et al. *Nat Rev Drug Discov* 2010;9:551-559; Marsenic O. *Am J Kidney Dis* 2009;53:875-883.

Renal glucose reabsorption
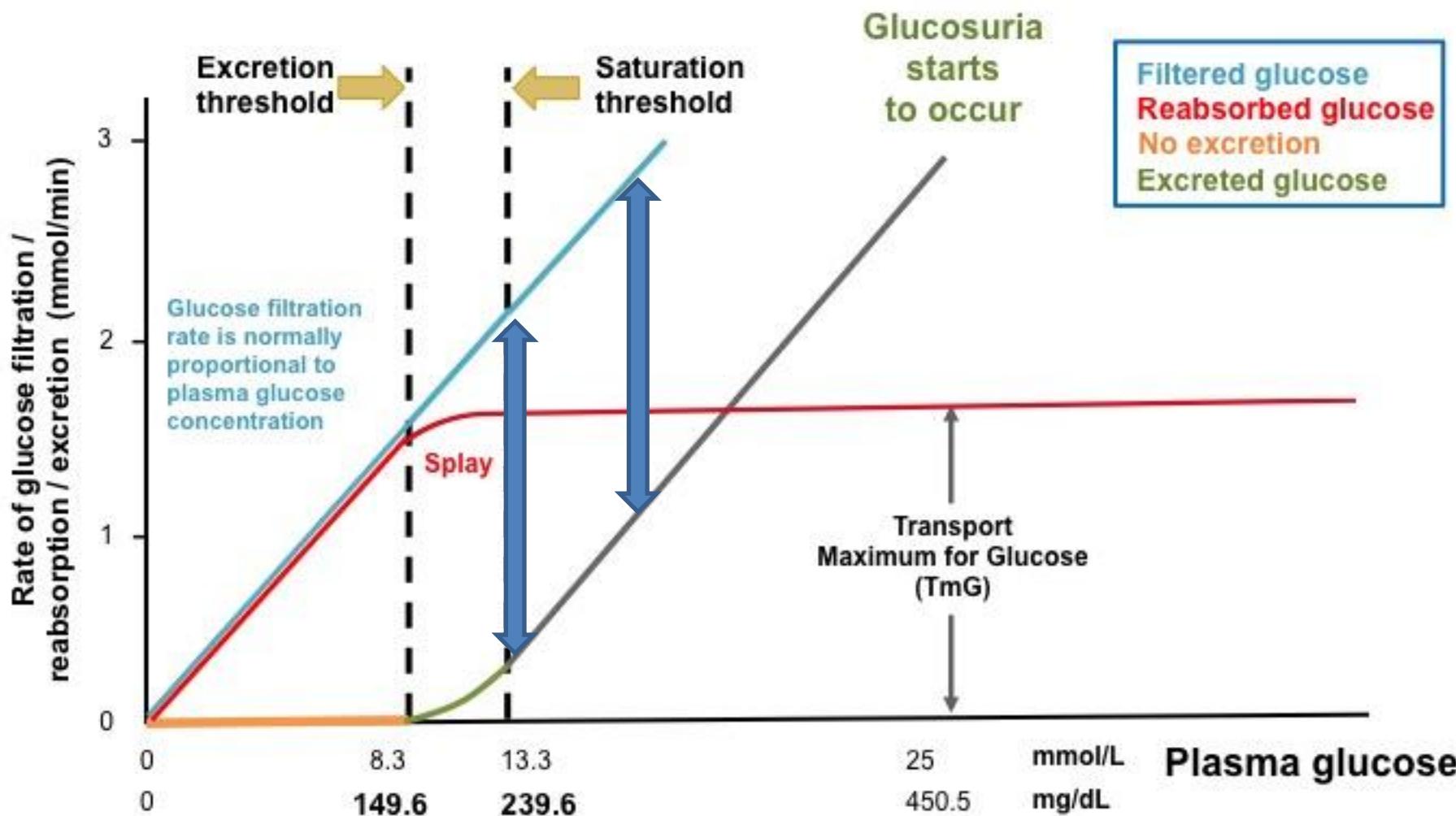
Adapted from Chao EC, et al. *Nat Rev Drug Discov* 2010;9:551-559; Marsenic O. *Am J Kidney Dis* 2009;53:875-883.

SGLT-2 inhibition

Effects on endogenous glucose production
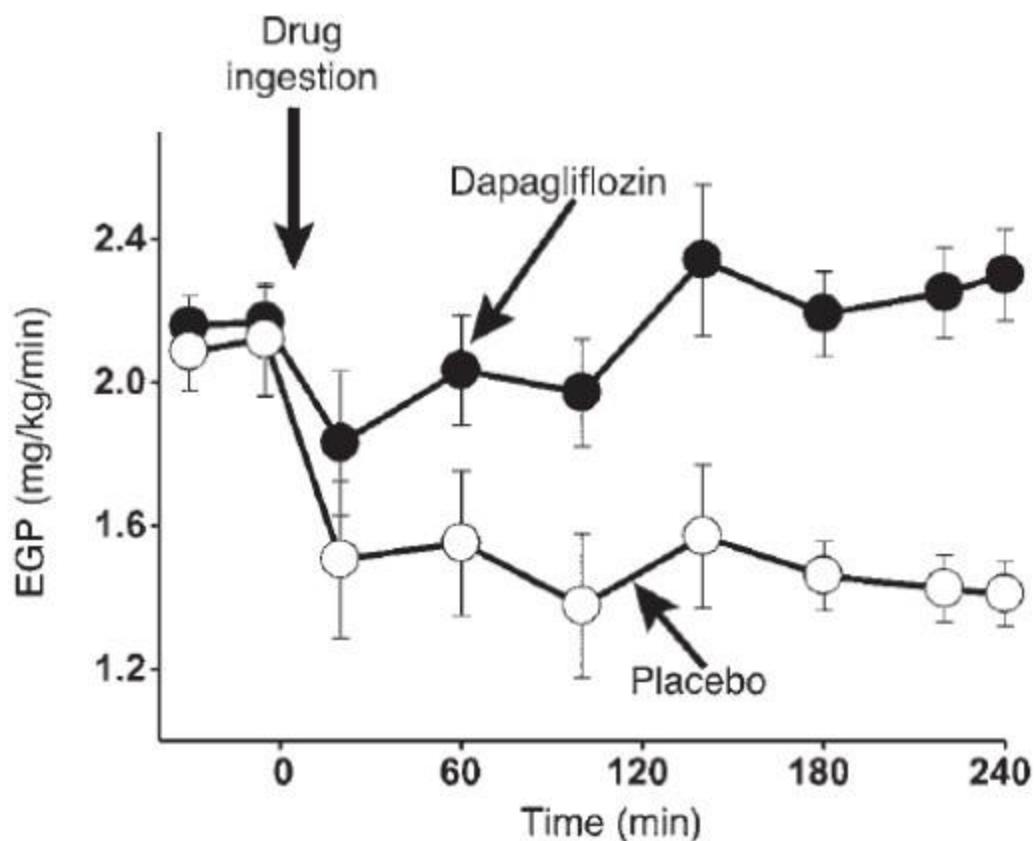
Merovci A et al, *J Clin Invest* 2014; 124:509.

Canagliflozin and β cell function

Insulin secretion rate vs placebo

Polidori D et al., *Diabetologia* 57: 891-901, 2014.
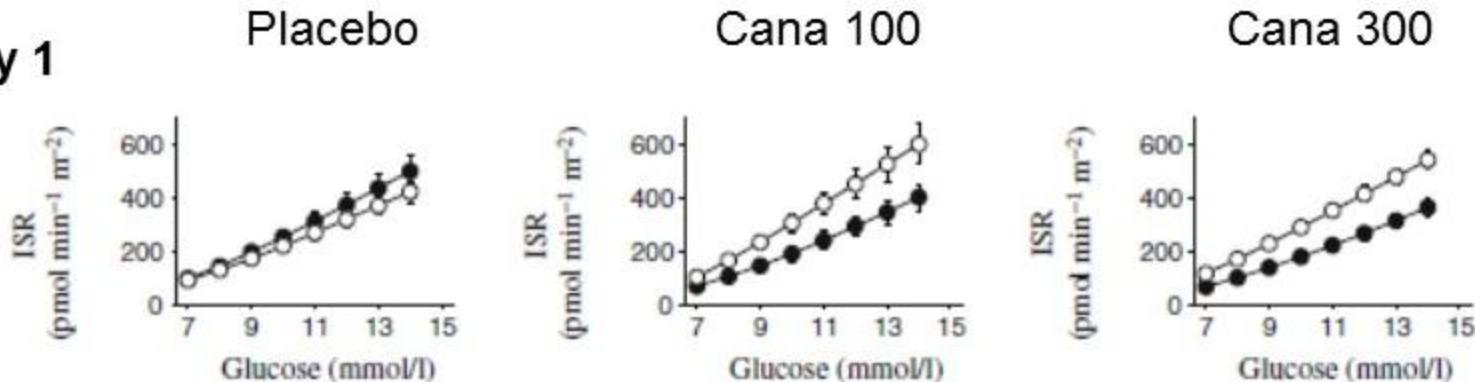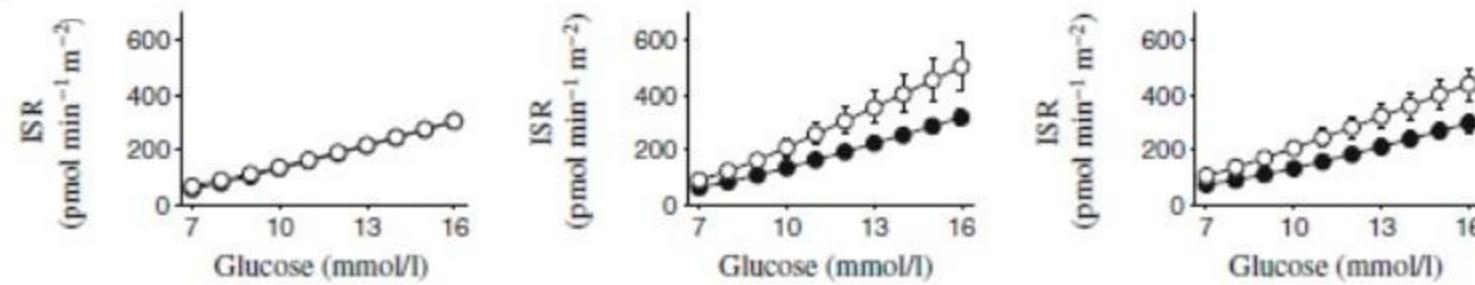
Canagliflozin vs placebo
Monotherapy

Stenlof K, et al. *Diabetes Obes Metab* 15:372, 2013
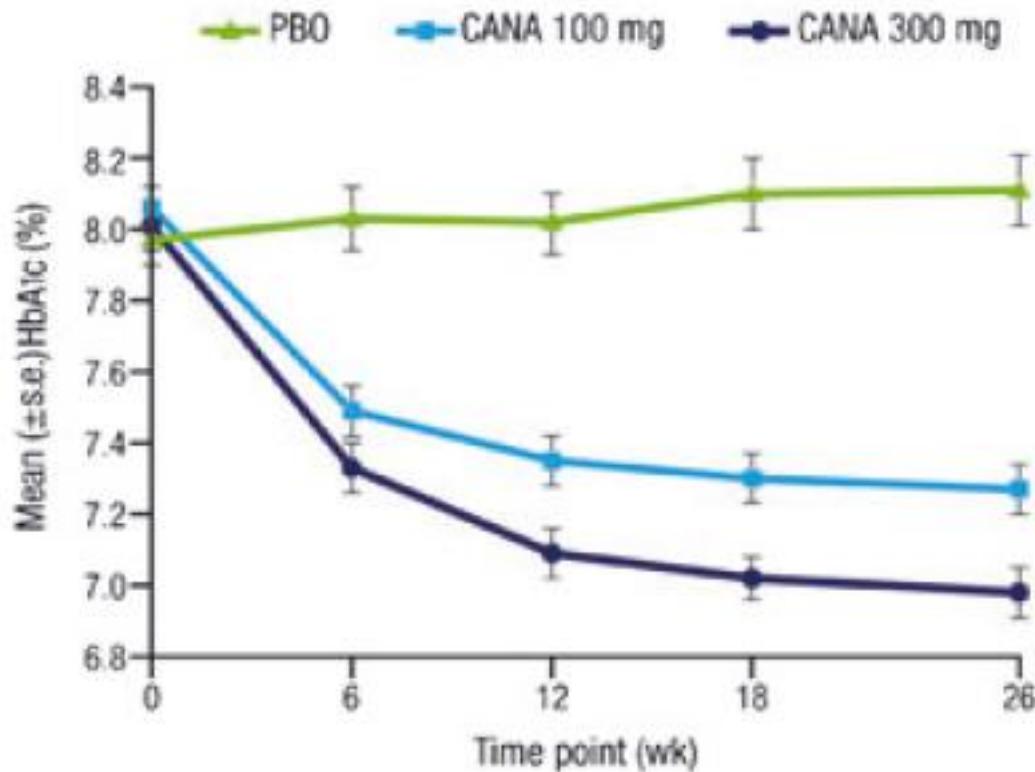
Dapagliflozin vs placebo

104-wk RCT, add-on to met
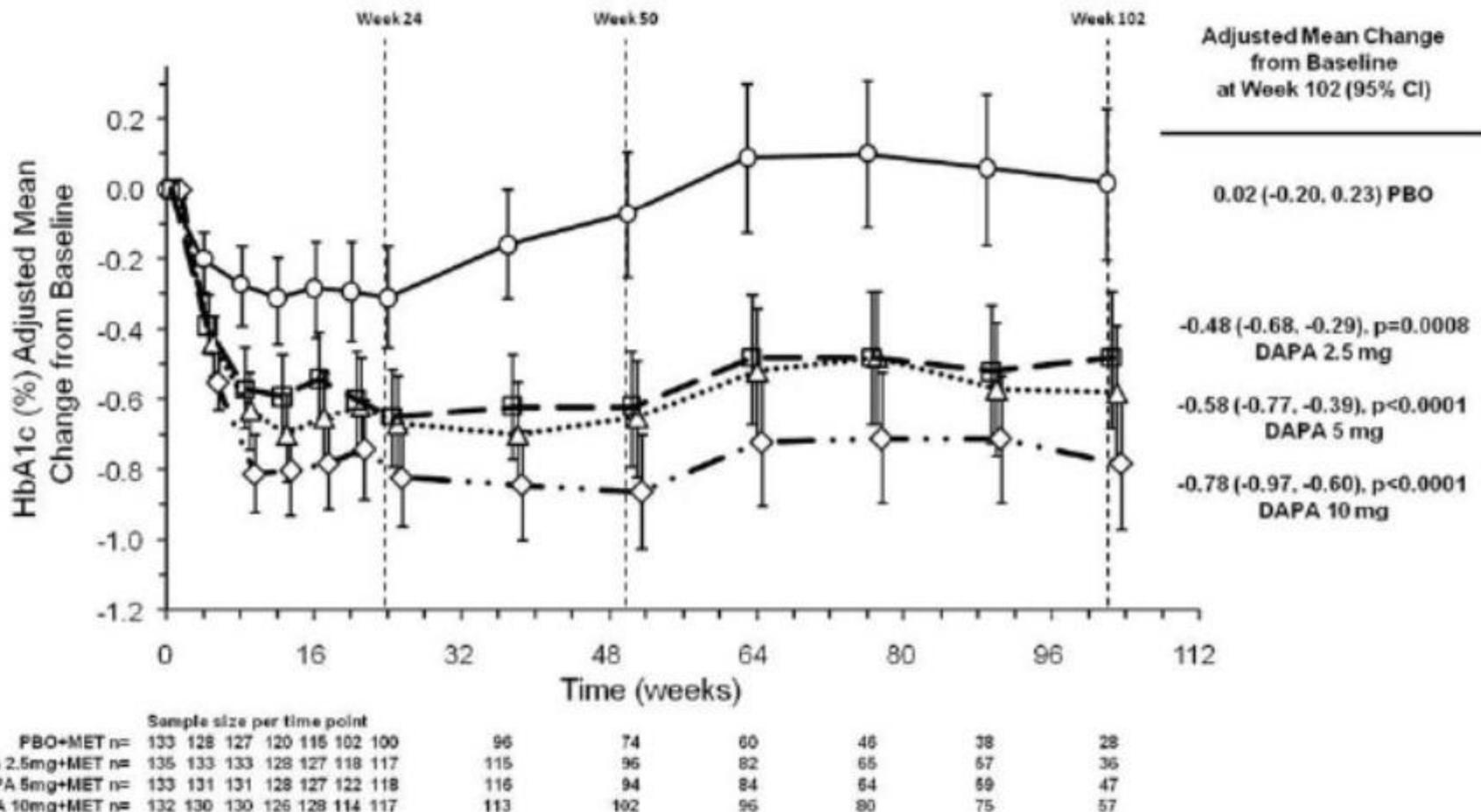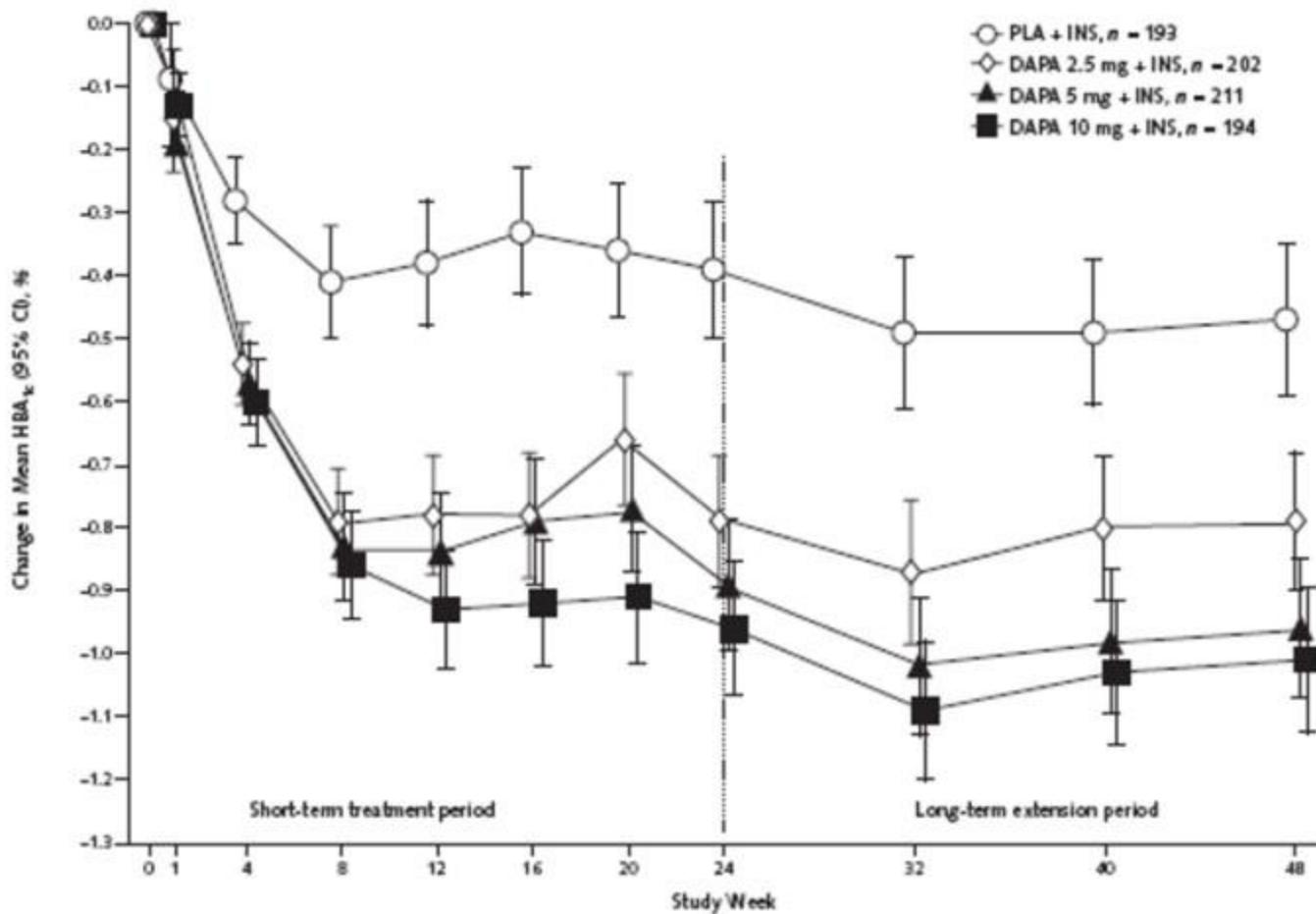
Bailey CJ et al., *BMC Med* 11:43, 2013

Dapagliflozin vs placebo

RCT add-on to insulin

Wilding P et al., *Ann Intern Med* 2012; 156:405-415

Canagliflozin vs placebo

RCT, add-on to Insulin, 28 d

C   300 MG BID

Legend:
- ●— Baseline (day -1)
- ○— Canagliflozin (day 1)
- ▼— Canagliflozin (day 27)

Y-axis: Plasma Glucose Concentration (mmol/l)
X-axis: Time (Hours)

Devineni et al. *Diabetes Obes Metab* 14:539-45, 2012
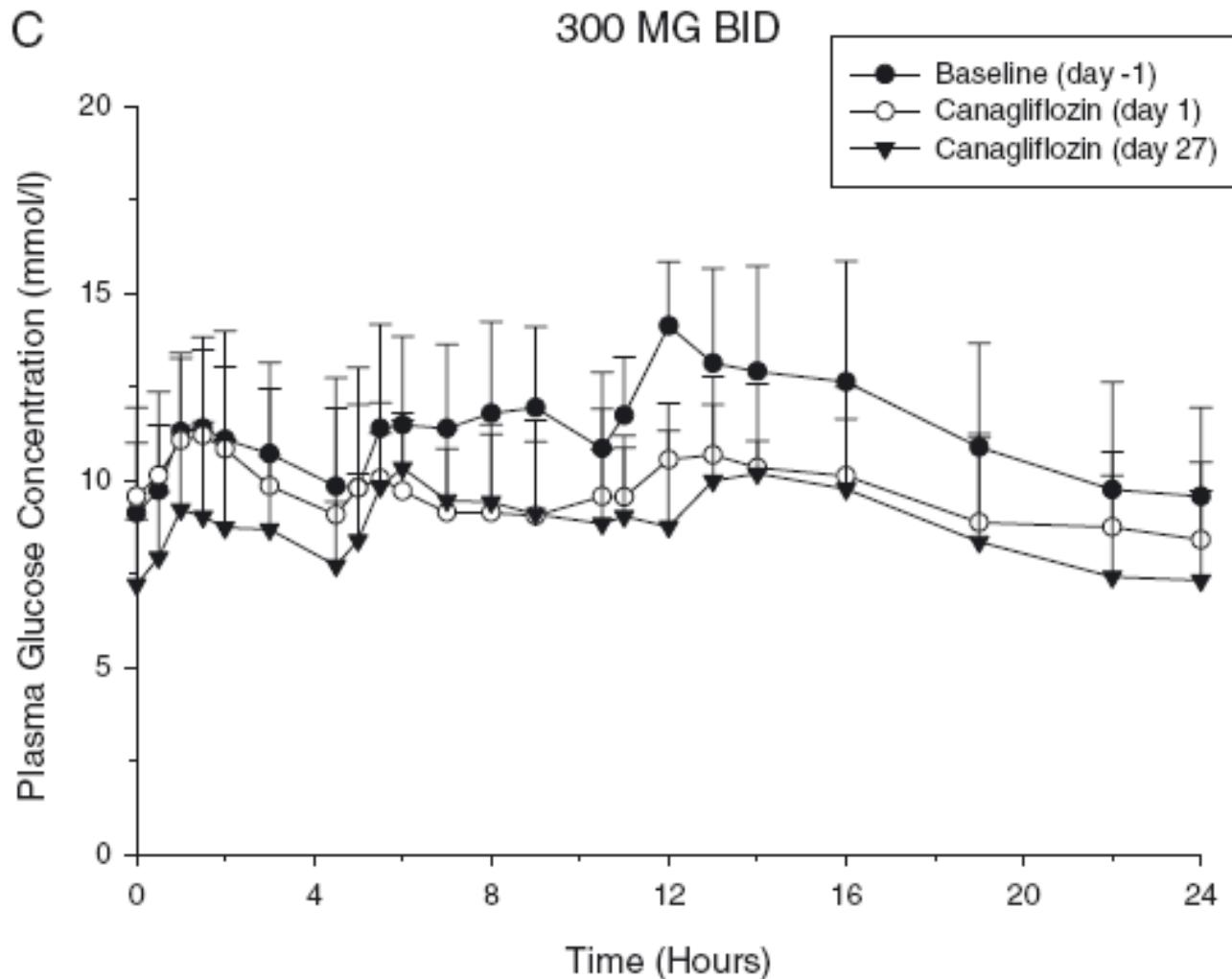
Canagliflozin vs placebo

RCT, add-on to Insulin, 28 d

Parameter	Mean (s.d.)		
	Placebo (n = 7)*	Canagliflozin 100 mg QD (n = 10)	Canagliflozin 300 mg BID (n = 10)
Baseline 24-h PG (mmol/l)	9.82 (2.19)	9.30 (1.67)	11.29 (1.62)
Δ 24-h PG (mmol/l)	0.07 (2.09)	−1.64 (1.47)	−2.46 (1.51)
Baseline FPG (mmol/l)	8.14 (2.38)	9.03 (1.49)	9.55 (2.38)
ΔFPG (mmol/l)	0.48 (2.29)	−2.11 (1.26)	−2.35 (1.59)
Baseline HbA1c (%)	7.99 (0.52)	8.38 (0.88)	8.42 (1.02)
ΔHbA1c (%)	−0.19 (0.49)	−0.73 (0.50)	−0.92 (0.66)
Baseline UGE (g/day)	11.30 (15.88)	5.21 (9.89)	27.50 (38.48)
ΔUGE (g/day)	−3.2 (15.64)	71.9 (33.85)	129.2 (65.89)
Baseline 24-h RT_G (mmol/l)	12.70 (1.64)‡	12.40 (1.77)	12.35 (0.85)
Δ24-h RT_G (mmol/l)	0.62 (1.19)‡	−6.62 (1.59)	−8.94 (0.66)
Baseline body weight (kg)	97.97 (14.01)	108.80 (23.33)	94.41 (15.73)
Δbody weight (kg)	0.03 (0.61)	−0.73 (0.89)	−1.19 (1.40)

Devineni et al. *Diabetes Obes Metab* 14:539-45, 2012

Effect of SGLT2 inhibitors

Meta-analysis of available RCTs

Predictors of placebo-substracted HbA1c variation from baseline

Parameter	unit	% A1c difference for each unit
Age (lower)	years	0.06 [0.05;0.07]
Duration of diabetes (lower)	years	0.05 [0.04;0.06]
Baseline A1c (higher)	%	-0.37 [-0.46;-0.27]
Baseline FPG (higher)	mmol/l	-0.34 [-0.42;-0.27]
Baseline BMI (higher)	Kg/m^2	-0.28 [-0.37;-0.19]

Monami M, Nardini C, Mannucci E. *Diabetes Obes Metab* 2013

Canagliflozin vs sitagliptin

RCT add-on to metformin and SU
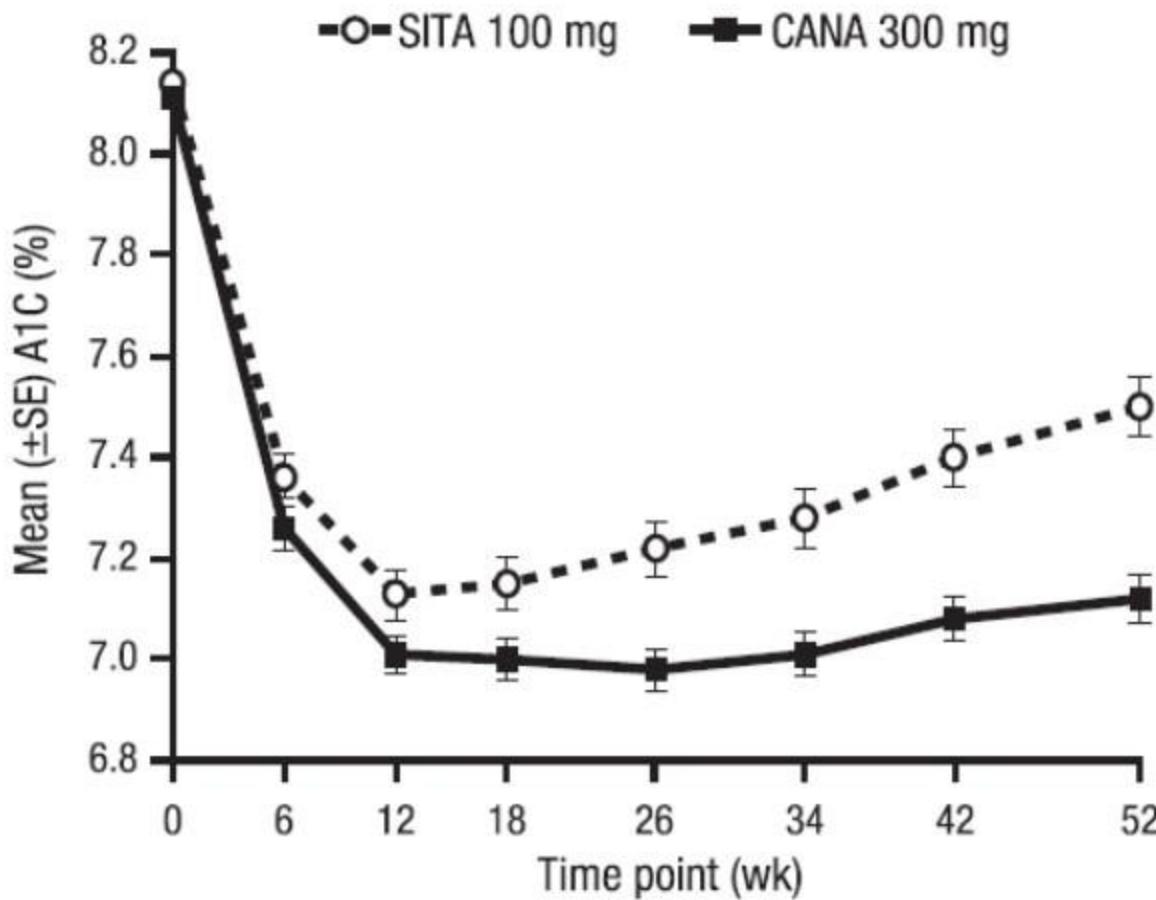
Schernthaner G et al., *Diabetes Care* 36: 2508-2515, 2013

Canagliflozin vs glimepiride
Add-omn to metformin (CANTATA-SU)
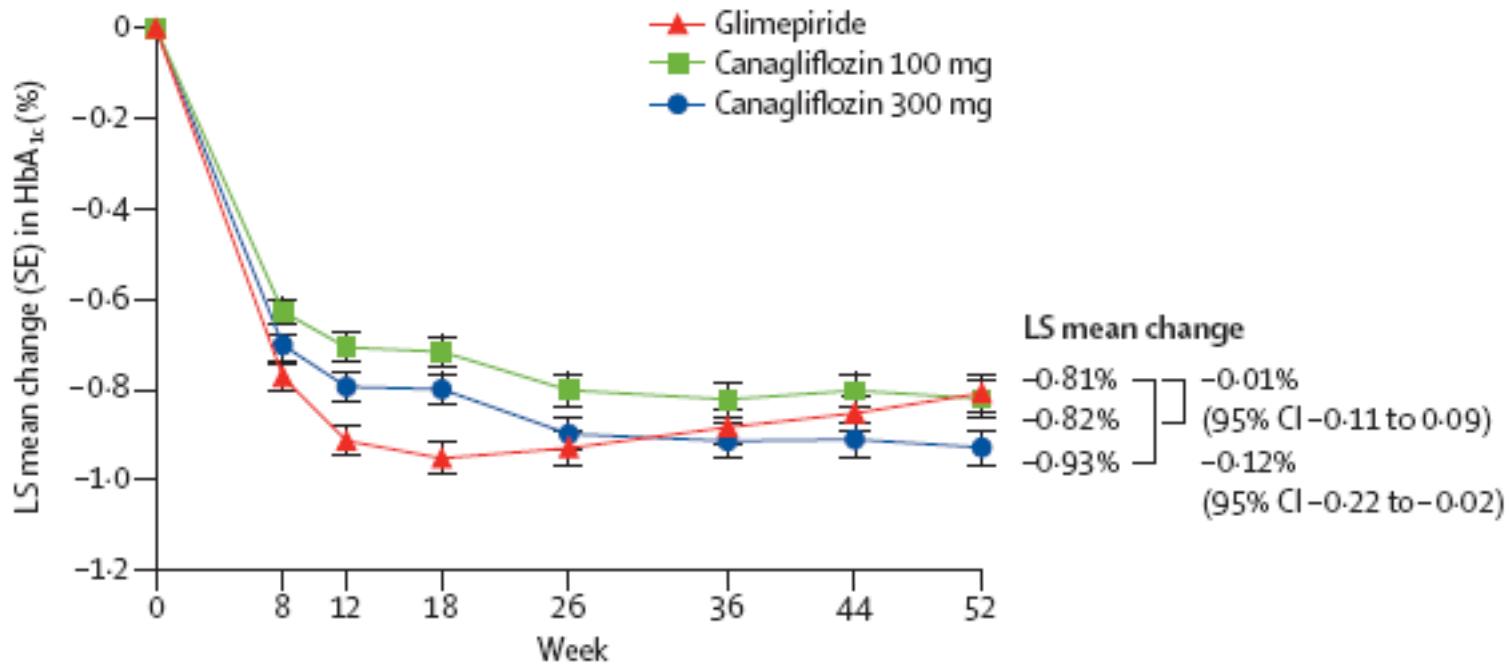
Cefalu WT, et al. *Lancet* 382:941-50, 2013

Canagliflozin vs glimepiride
Add-omn to metformin (CANTATA-SU)

Cefalu WT, et al. *Lancet* 382:941-50, 2013
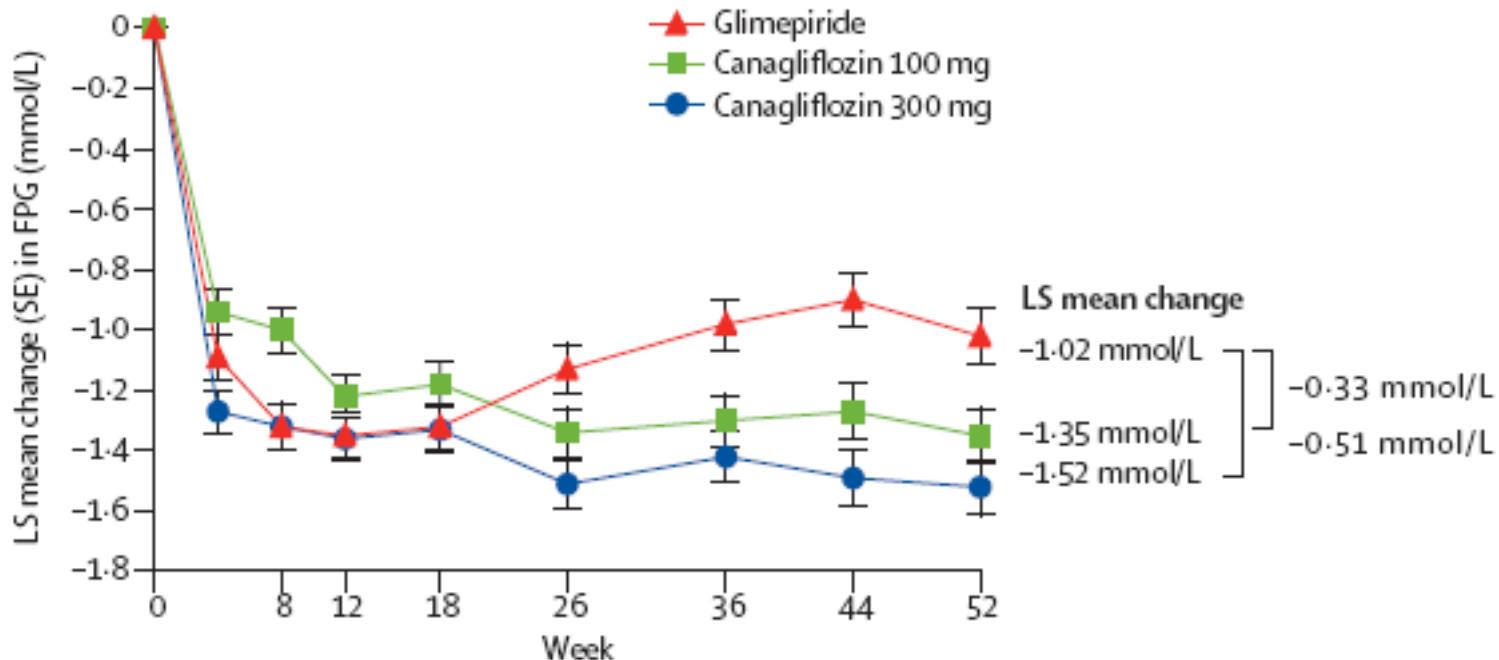
Effect of SGLT2 inhibitors

Meta-analysis of available RCTs

Total hypoglycemia
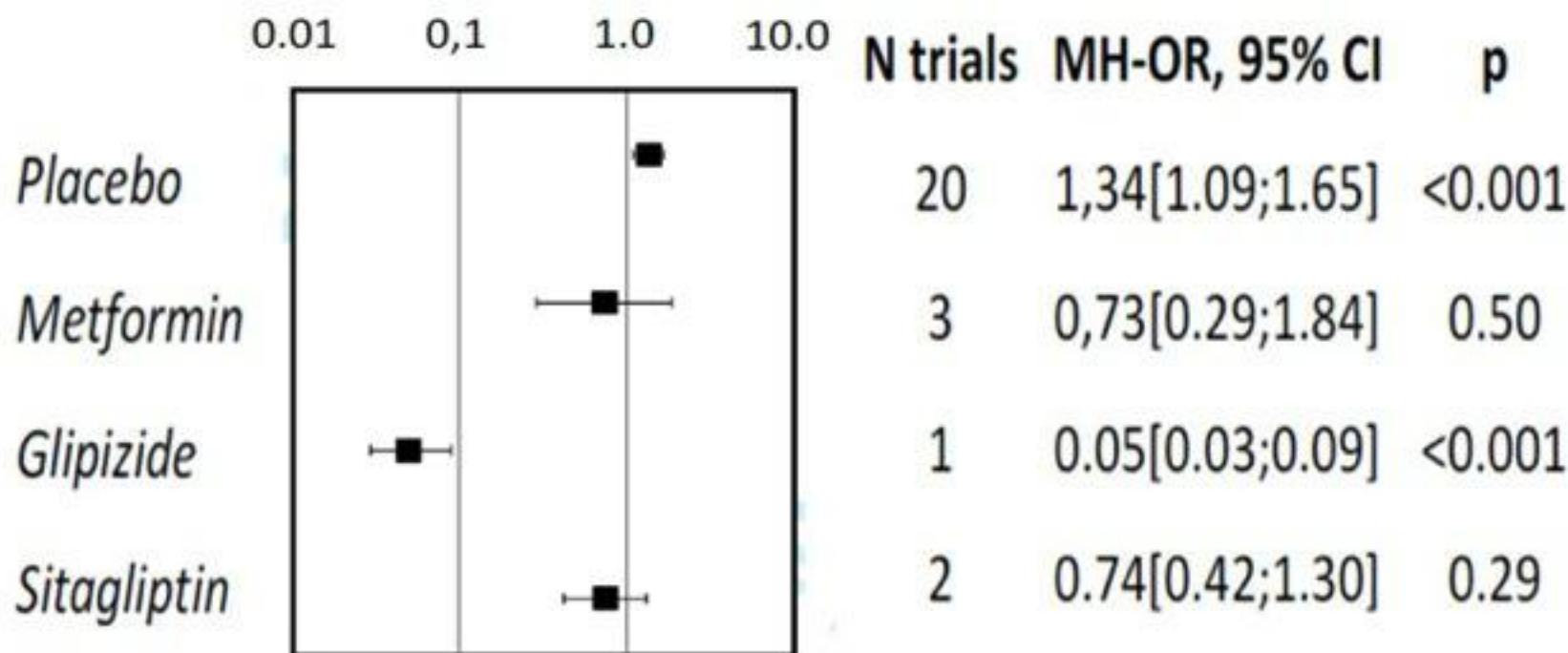
	0.01	0,1	1.0	10.0	N trials	MH-OR, 95% CI	p
Placebo					20	1,34[1.09;1.65]	<0.001
Metformin					3	0,73[0.29;1.84]	0.50
Glipizide					1	0.05[0.03;0.09]	<0.001
Sitagliptin					2	0.74[0.42;1.30]	0.29

Monami M, Nardini C, Mannucci E. *Diabetes Obes Metab* 2013

Effect of SGLT2 inhibitors

Meta-analysis of available RCTs

Effect on BMI (vs. placebo)
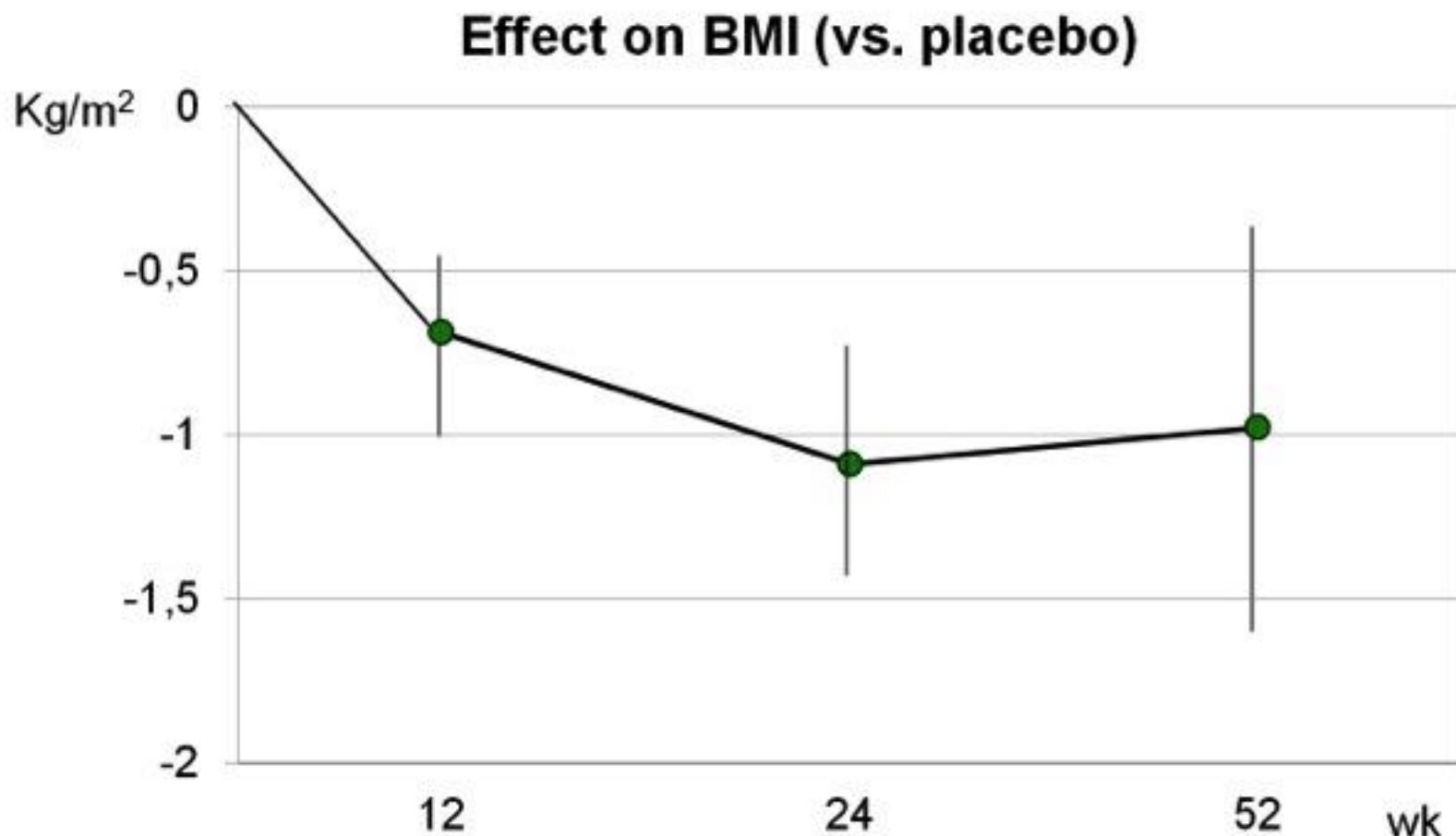
Monami M, Nardini C, Mannucci E. *Diabetes Obes Metab* 2013

Empagliflozin and CV risk

## Effect on blood pressure– Pooled phase III trials

Patients with uncontrolled BP

All patients (controlled or uncontrolled BP)

Hach T, et al. *Diabetes*. 2013;(Suppl 1) (P69-LB).
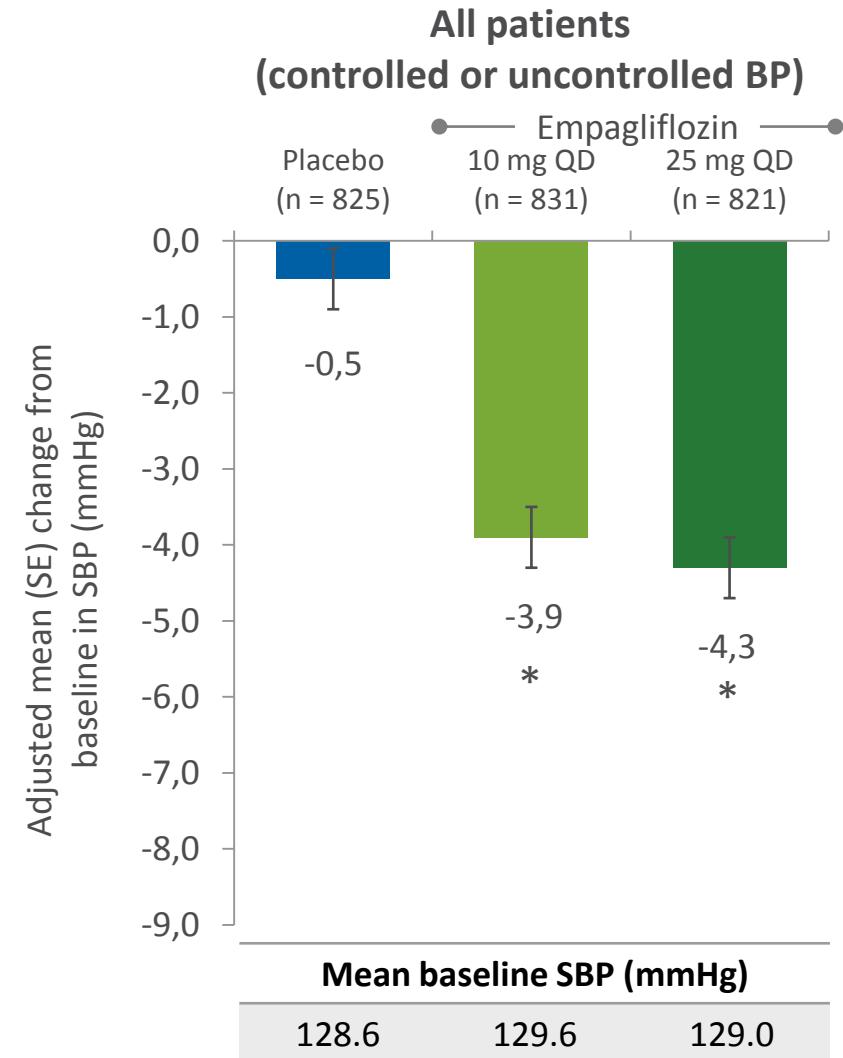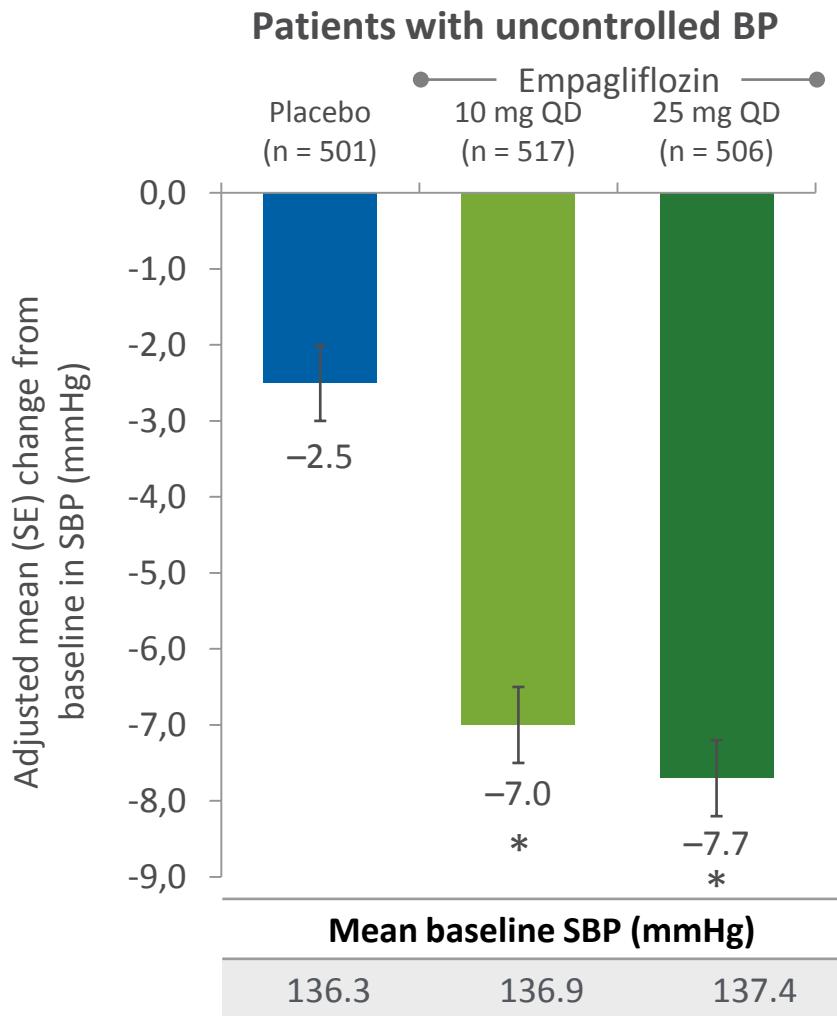
Canagliflozin and MACE

EMA Public Assessment Report

Table 21: MACE Events for CANVAS Subjects and Selected Non-CANVAS Subjects (mITT)

JNJ-28431754 Phase 2/3 Studies (results through 31 Jan 2012)

	Control k/N (%)	CANA 100 mg k/N (%)	CANA 300 mg k/N (%)	CANA Pooled k/N (%)	Hazard Ratio (95% CI)[a]
CANVAS	38/1441(2.6)	46/1445(3.2)	40/1441(2.8)	86/2886(3.0)	1.11 (0.76,1.63)
Non-CANVAS(with CV risk similar to CANVAS)[b,c]	10/643(1.6)	7/580(1.2)	4/549(0.7)	11/1129(1.0)	0.61 (0.26,1.44)
Overall CV high risk population (CANVAS + non-CANVAS)[d]	48/2084(2.3)	53/2025(2.6)	44/1990(2.2)	97/4015(2.4)	**1.01** (0.71,1.43)
Non-CANVAS(without high CV risk)	5/1243(0.4)	2/1131(0.2)	5/1159(0.4)	7/2290(0.3)	**0.73** (0.23,2.29)

SGLT2i and 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)

Empagliflozin safety

Genital infections – Pooled phase III trials

With/without history of chronic/recurrent genital infection

- Placebo (n = 825)
- Empagliflozin 10 mg QD (n = 830)
- Empagliflozin 25 mg QD (n = 822)

Y-axis: Patients with events consistent with genital infection (%)

All patients with events:
- 0,7
- 4,2
- 3,6

With history of chronic/recurrent genital infection:
- 14,3
- 50,0
- 23,1

Without history of chronic/recurrent genital infection:
- 0,6
- 4,0
- 3,3
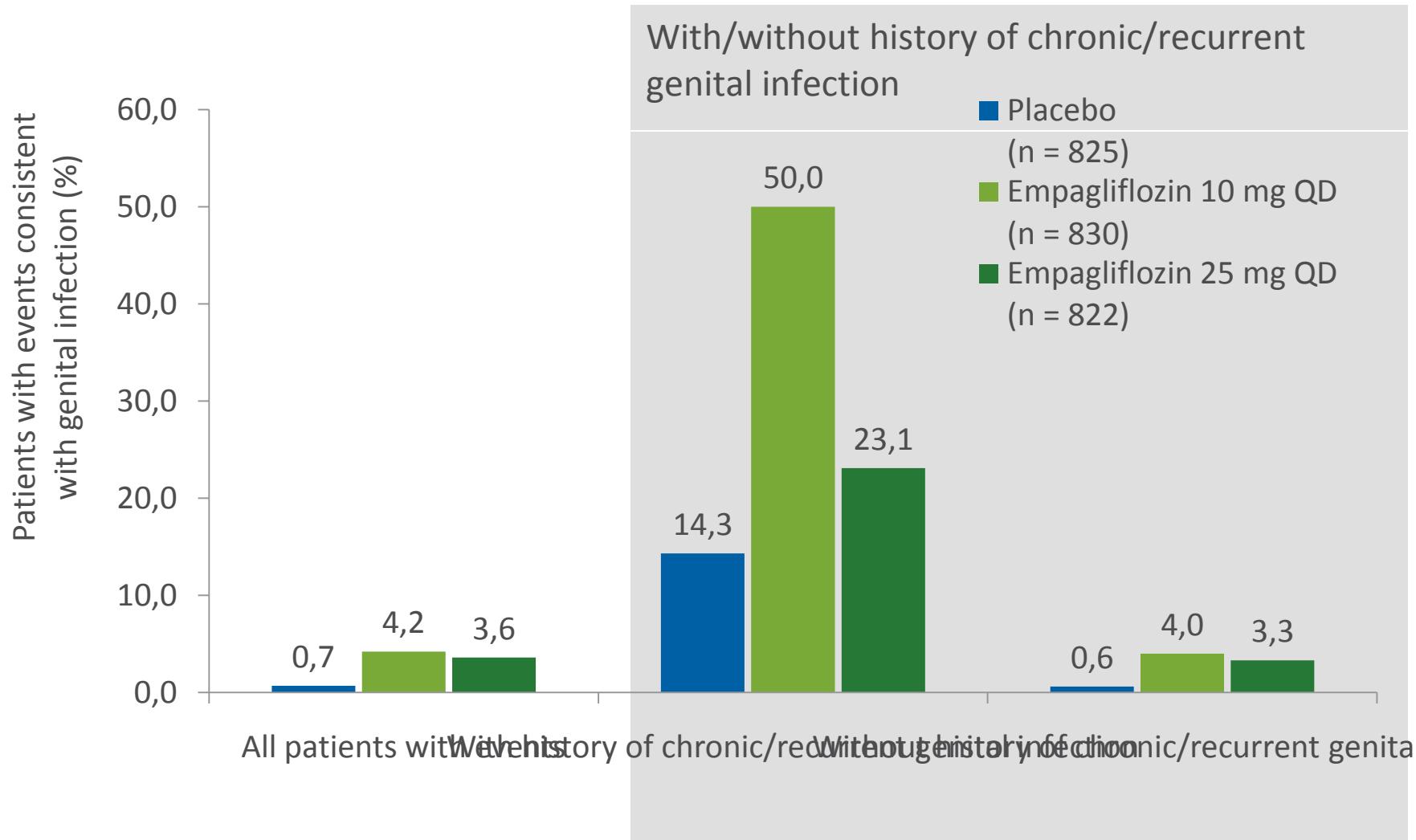
Kim G, et al. *Diabetes*. 2013;(Suppl 1) (P74-LB).

Renal function and efficacy

eGFR category	Treatment group	Number of subjects	Difference vs placebo (Dapa-Placebo) with 95% CI	Difference vs placebo	95% CI
≥30 - <60*	Placebo	101			
	DAPA 2.5 mg	71		-0.23	(-0.50, 0.05)
	DAPA 5 mg	102		-0.23	(-0.47, 0.02)
	DAPA 10 mg	85		-0.39	(-0.65, -0.14)
≥60 - <90*	Placebo	688			
	DAPA 2.5 mg	387		-0.47	(-0.58, -0.35)
	DAPA 5 mg	545		-0.54	(-0.65, -0.44)
	DAPA 10 mg	562		-0.54	(-0.64, -0.44)
≥90*	Placebo	443			
	DAPA 2.5 mg	227		-0.49	(-0.63, -0.34)
	DAPA 5 mg	353		-0.57	(-0.70, -0.45)
	DAPA 10 mg	395		-0.69	(-0.81, -0.57)

-2   -1.5   -1   -0.5   0   0.5

DAPA better   Placebo better

* mL/min/1.73 m^2

DAPA should not be used in patients with moderate to severe renal impairment (eGFR < 45 [MDRD] or CrCl < 60 [Cockroft-Gault])

Indications of SGLT2i

Monotherapy

Failure to metformin

Failure to dual oral therapy
(Met + SU, Met + Pio, Met + DPP4i)

Add-on to basal insulin

Add-on to basal-bolus insulin