Il blocco del co-trasportatore sodio-glucosio come target della terapia anti-iperglicemica

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Disclosure

Grant di ricerca: Astra Zeneca

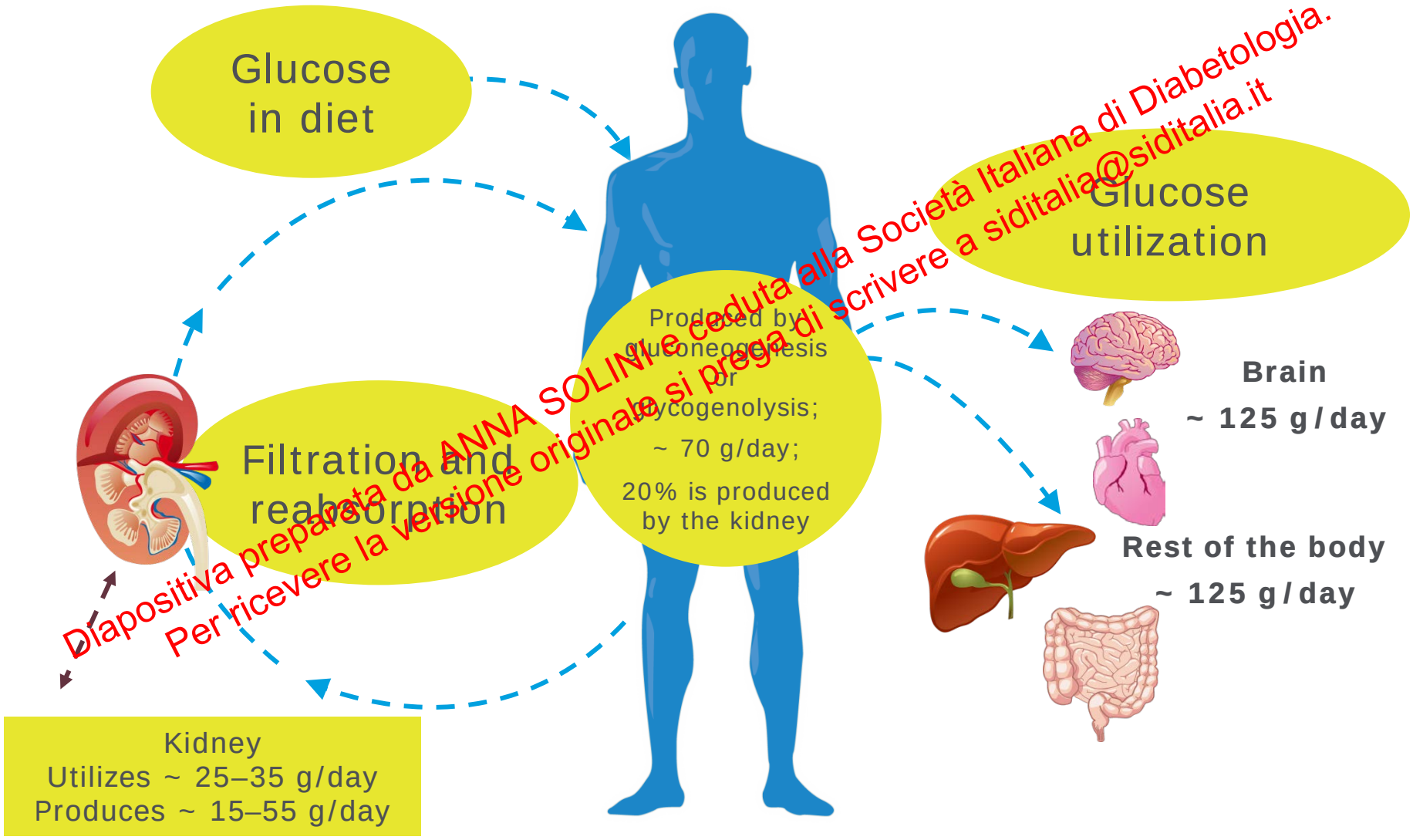
Advisory Board: Boehringer Ingelheim, MundiPharma, Sanofi

Lecturer: Boehringer Ingelheim, Lilly, Sanofi

Outline

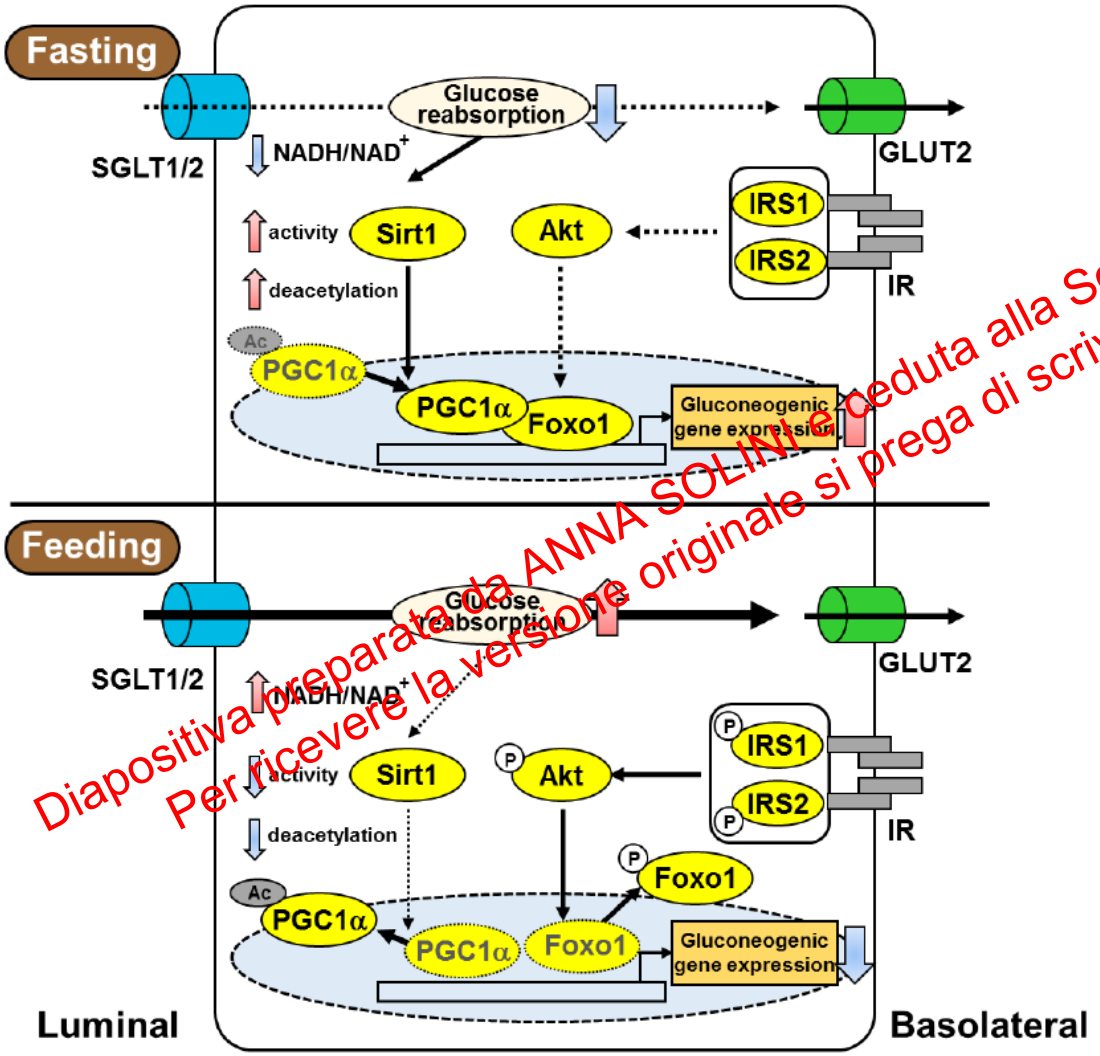
- Role of SGLT2 in regulating glucose metabolism
- Role of SGLT1
- PK and PD of different molecules
- Data on comparative efficacy

The kidney plays a significant role in glucose balance by reabsorbing ~ 180 g of glucose per day



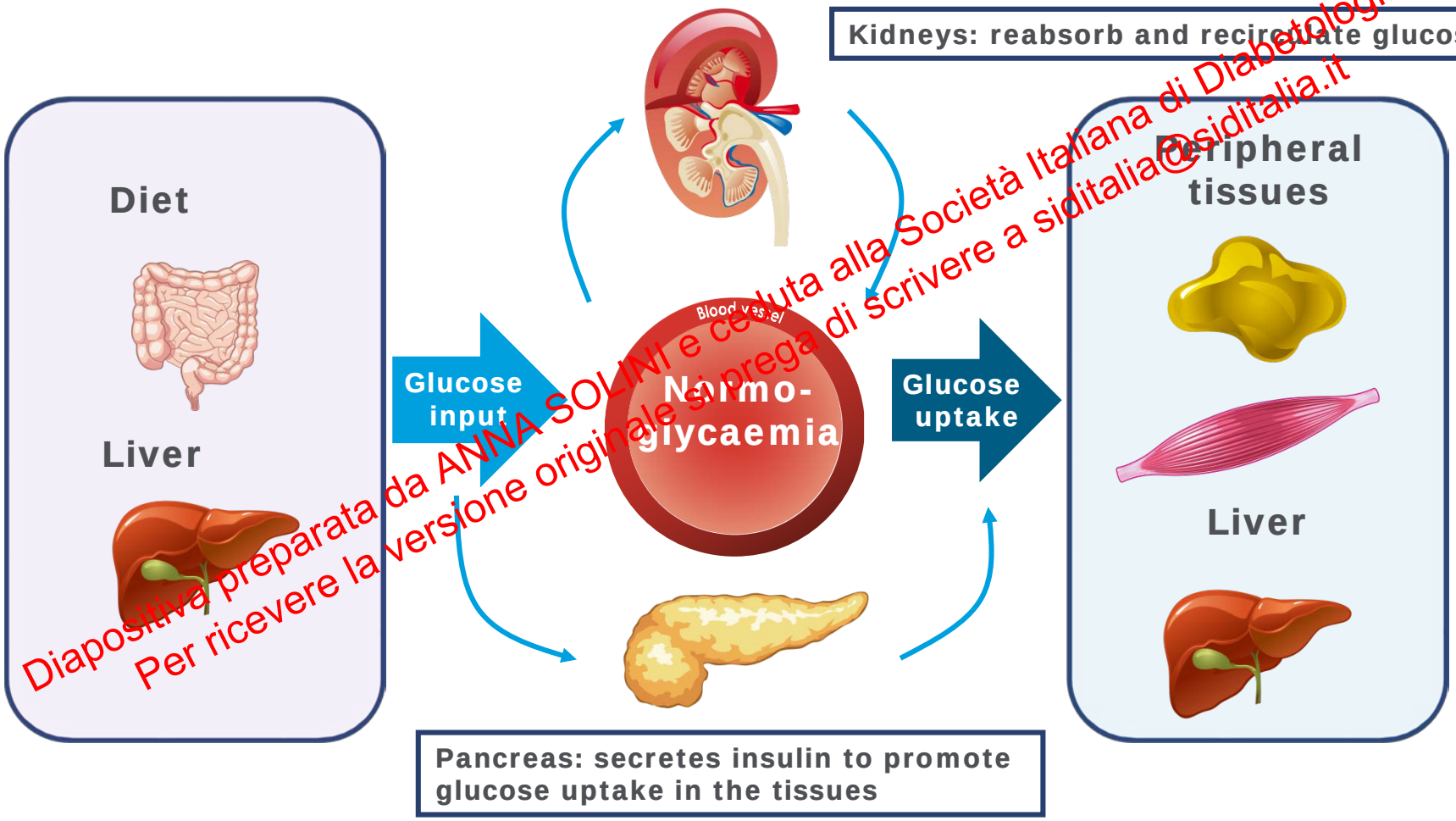
Gerich JE, Diabet Med. 2010;27:136-42
Wright EM, J Intern Med. 2007;261:32-43

Dual regulation of gluconeogenic gene expression by insulin and glucose in the renal proximal tubule



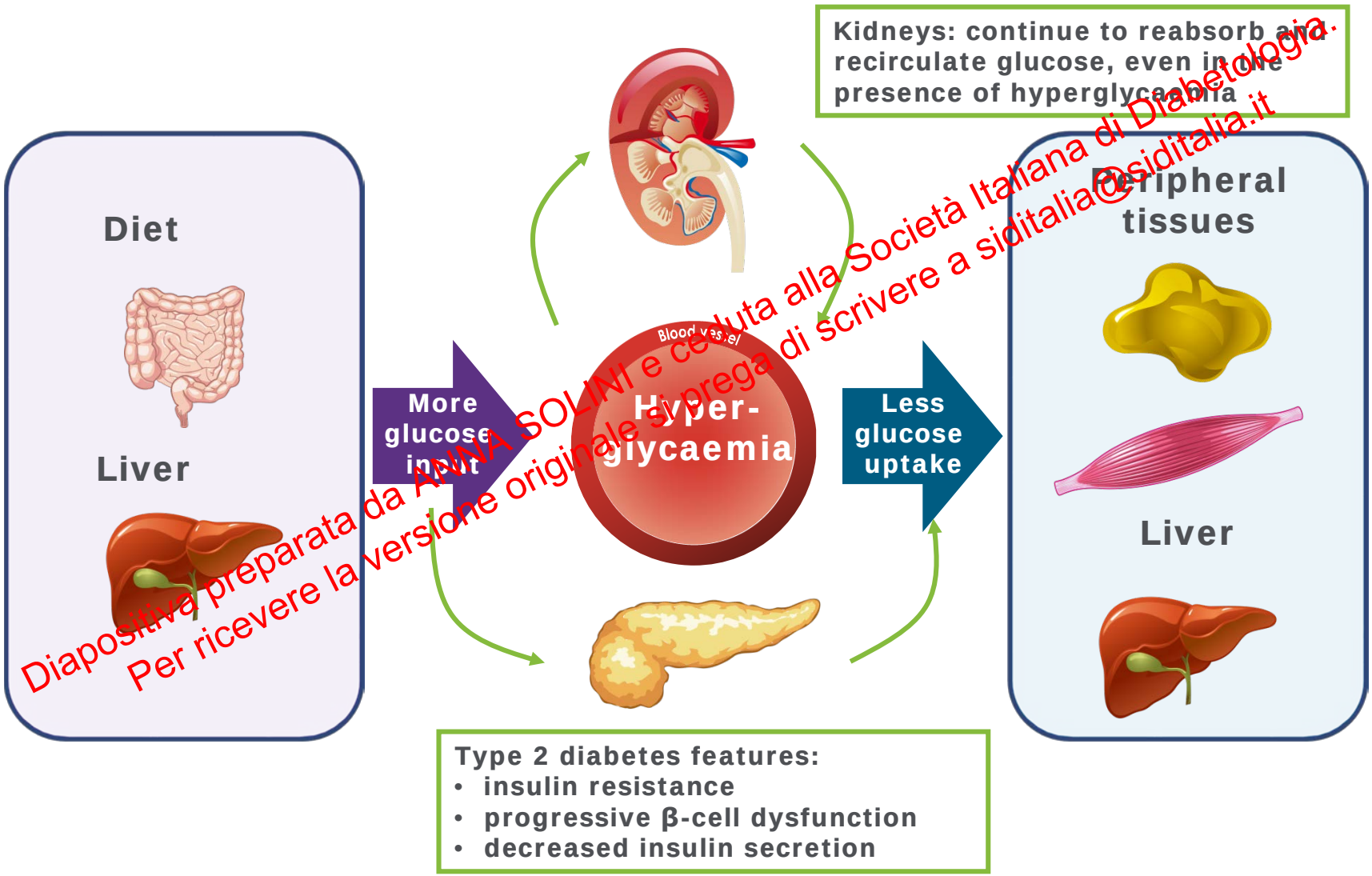
Sasaki M, Diabetes. 2017;66:2339-50

In the non-diabetic state, glucose input and uptake are well balanced



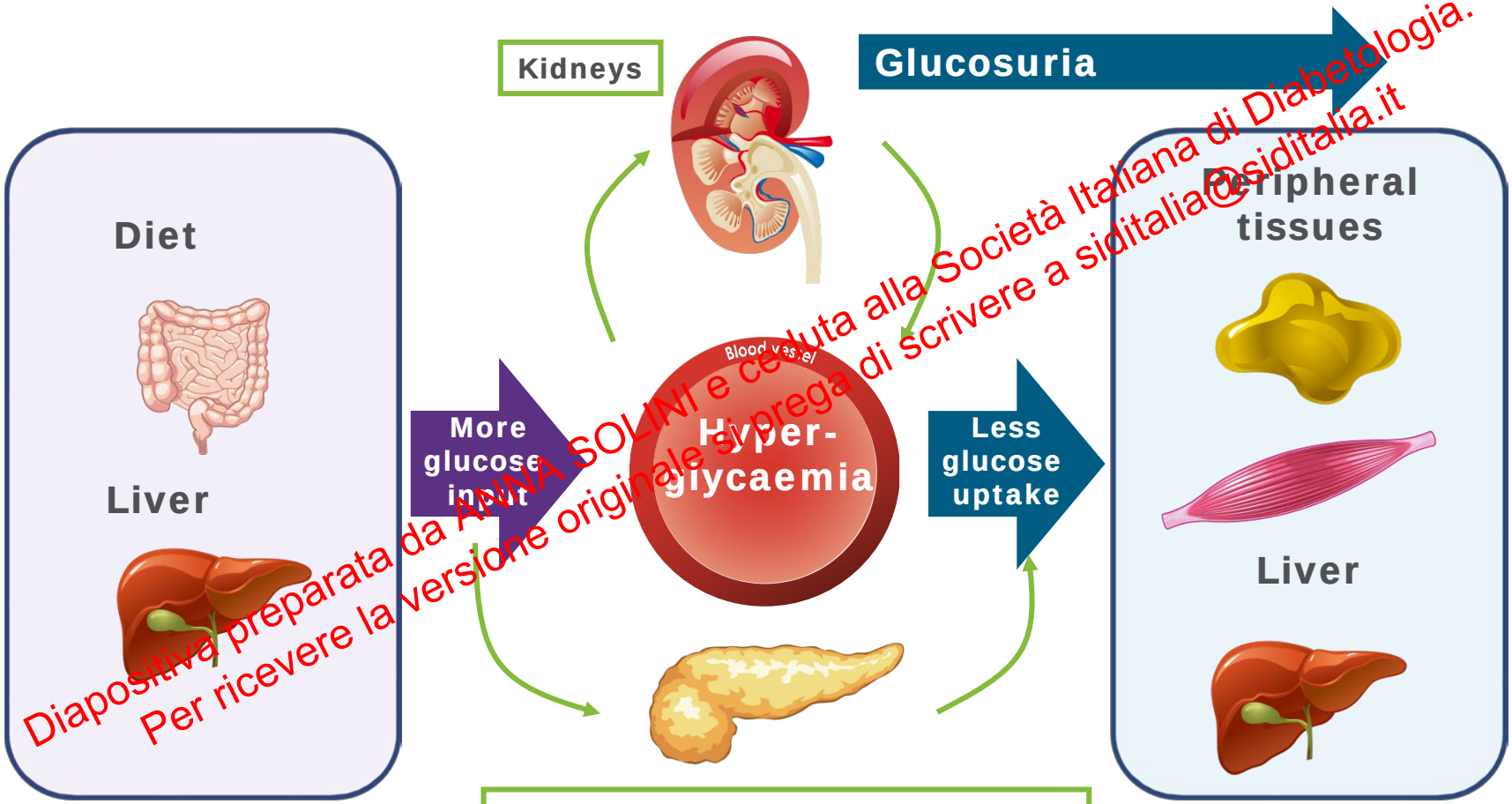
Guyton AC, Textbook of Medical Physiology. 7th ed. Philadelphia, PA: WB Saunders Company; 1986
DeFronzo RA, Diabetes. 2009;58:773-95

In type 2 diabetes, glucose input and uptake are imbalanced



DeFronzo RA, Diabetes. 2009;58:773-95
DeFronzo RA, Med Clin North Am. 2004;88:787-835

The kidneys provide an insulin-independent pathway for glucose removal

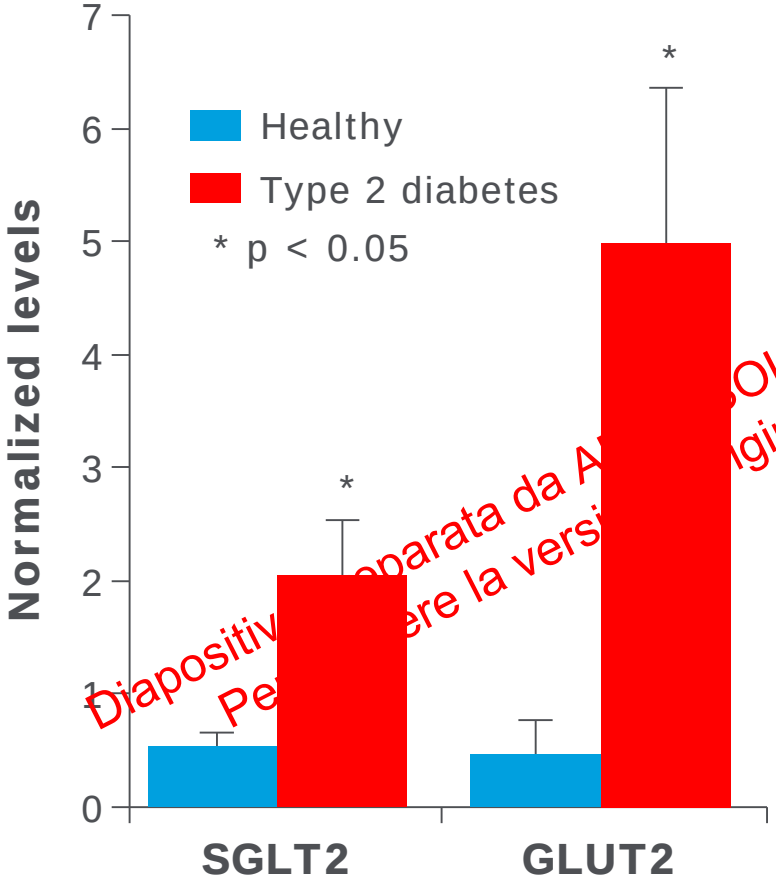


Glucose uptake is reduced due to:
- **insulin resistance**
- **progressive β-cell dysfunction**
- **decreased insulin secretion**

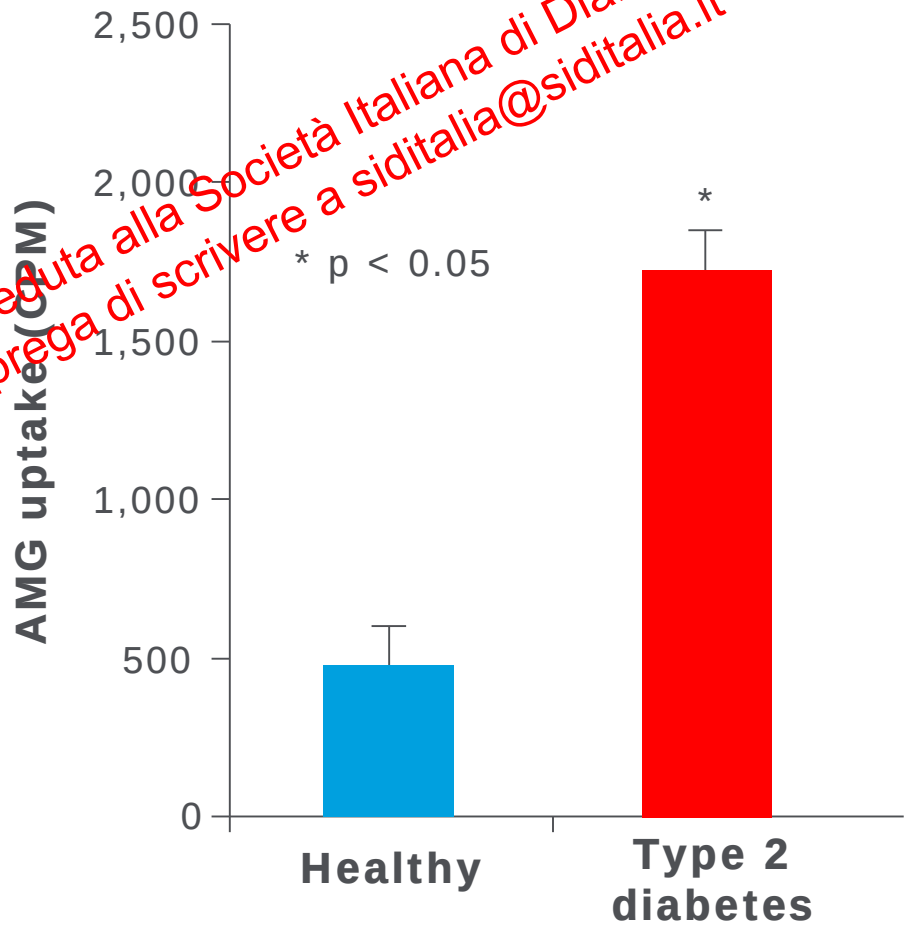
DeFronzo RA, Diabetes. 2009;58:773-95
DeFronzo RA, Med Clin North Am. 2004;88:787-835

In type 2 diabetes, SGLT2 upregulation and increase in glucose reabsorption occur

Transporter protein expression



Glucose uptake into tubular epithelial cells[a]

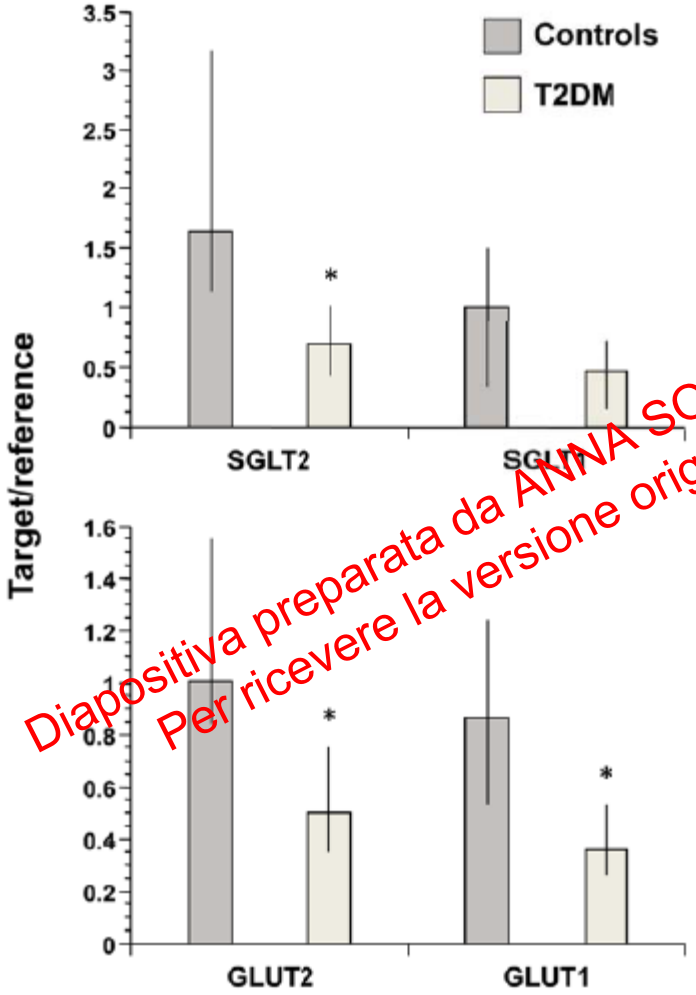


[a] From human exfoliated proximal tubular epithelial cells.
AMG, alpha-methyl glucoside; CPM, counts per minute.

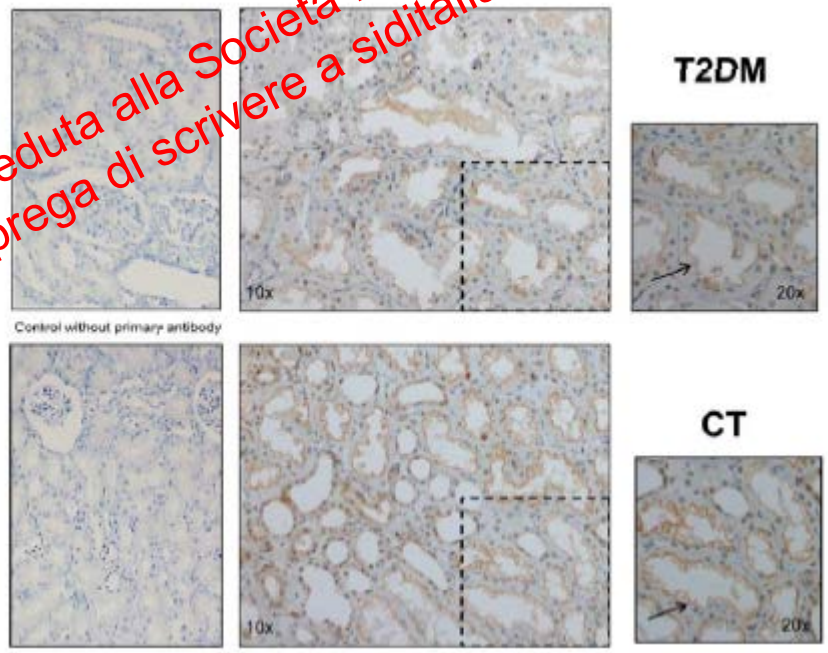
Rahmoune H, Diabetes. 2005;54:3427-34

SGLT1 and SGLT2 renal expression in diabetes

Renal specimens from 19 T2DM and 20 CT



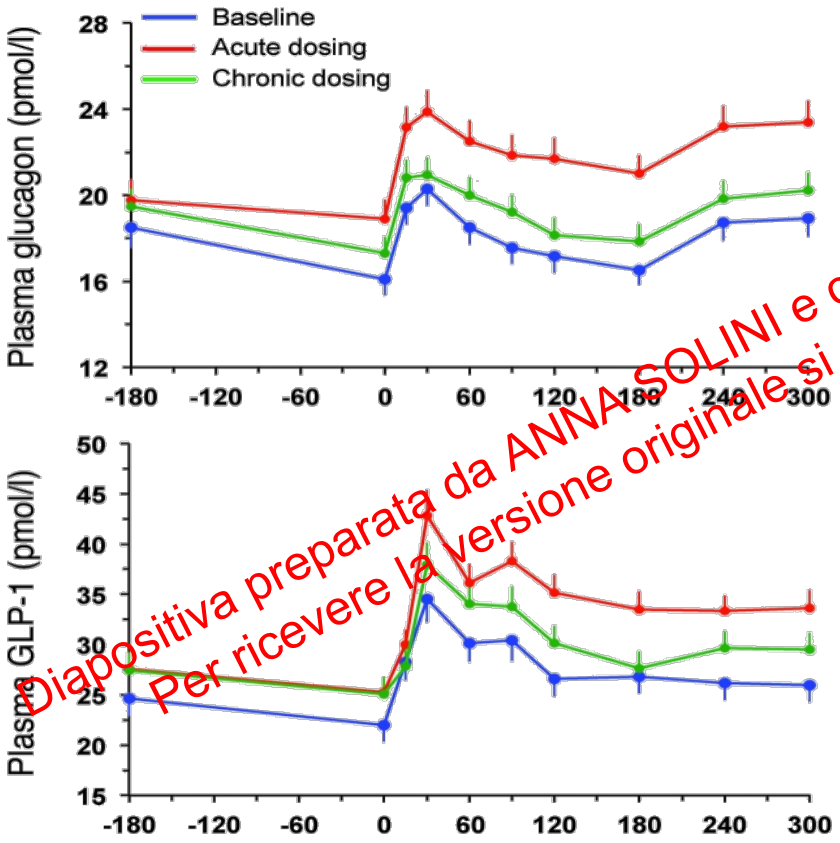
SGLT2 protein

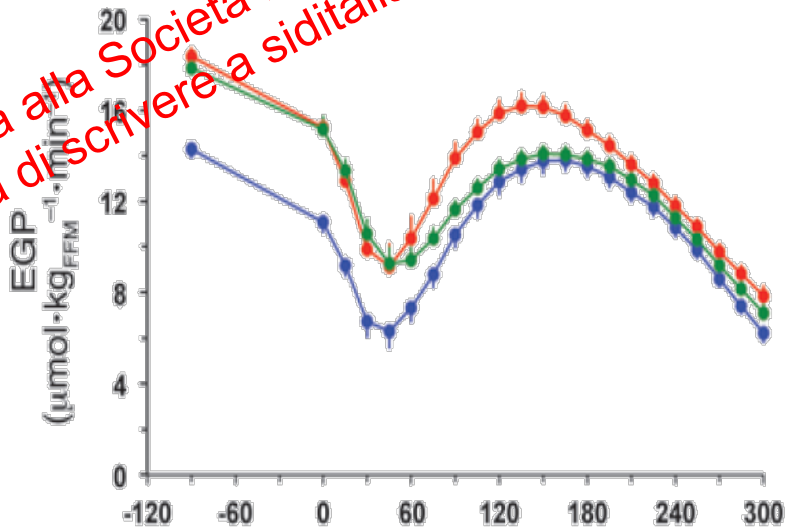


Solini A, Diabetes Obes Metab. 2017;19:1289-94

SGLT2 inhibitors: adjunctive metabolic effects

Empagliflozin





Ferrannini E, J Clin Invest. 2014;124:499-508

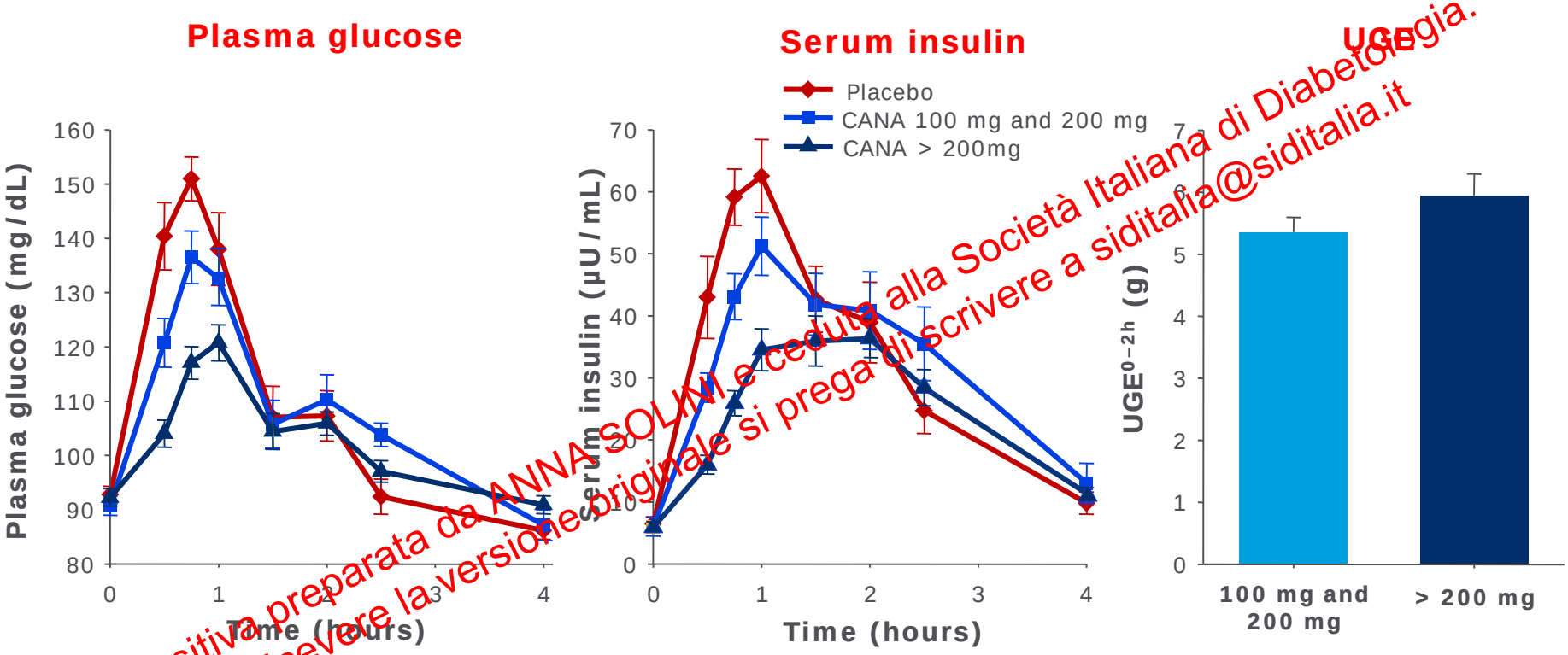
Outline

- Role of SGLT2 in regulating glucose metabolism
- Role of SGLT1
- PK and PD of different molecules
- Data on comparative efficacy

Selectivity of SGLT2 inhibitors vs SGLT1

Compound	IC50 (nM)		pIC50 (mean)	
	SGLT2	SGLT1	SGLT2	SGLT1
Empagliflozin	3.1	8,300	8.50±0.02	5.08±0.03
Dapagliflozin	1.2	1,400	8.94±0.06	5.86±0.07
Canagliflozin	2.7	710	8.56±0.02	6.15±0.06
Ipragliflozin	5.3	3,000	8.27±0.04	5.53±0.02
Tofogliflozin	6.4	12,000	8.18±0.12	4.92±0.09

NAP1001: CANA doses > 200 mg reduced PPG and insulin more than explained by UGE



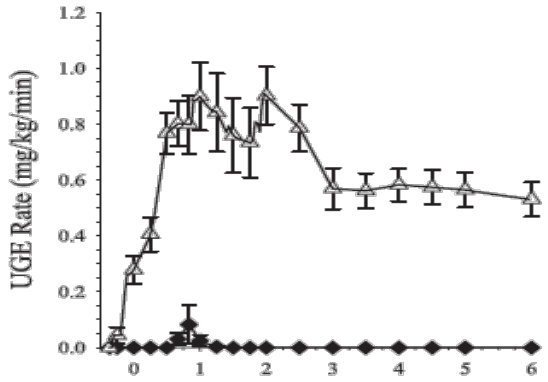
Reductions in glucose and insulin were observed only in first meal after dosing

Hypothesis: higher doses of CANA transiently inhibit intestinal SGLT1 during drug absorption

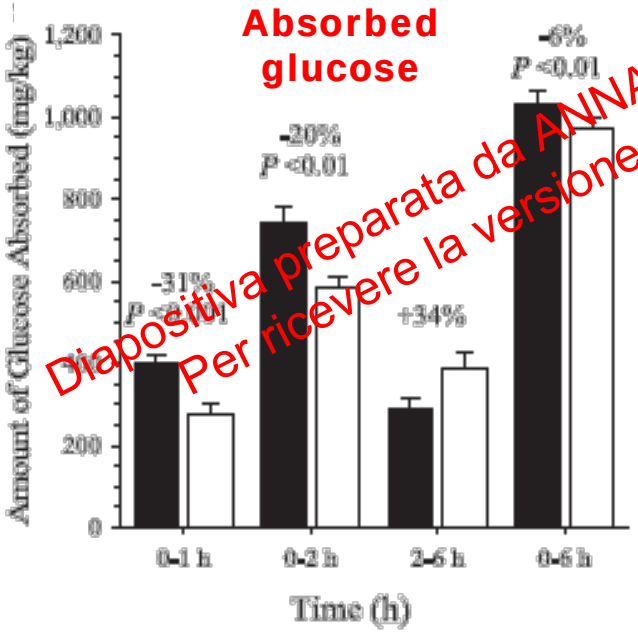
Sha S, Diabetes Obes Metab. 2011;13:669-72

Canagliflozin and gut glucose absorption

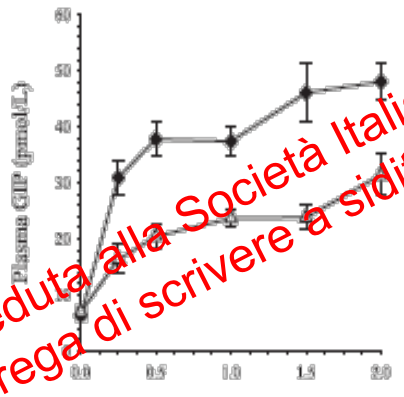
Excreted glucose



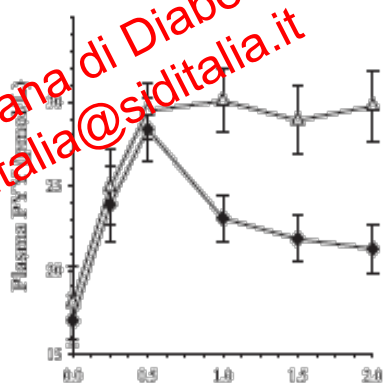
Absorbed glucose



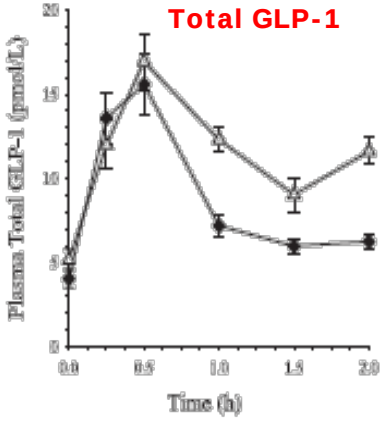
GIP



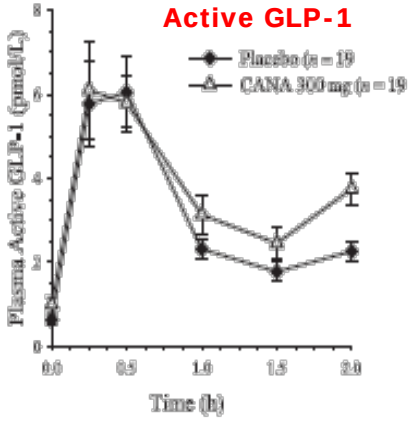
PYY



Total GLP-1



Active GLP-1



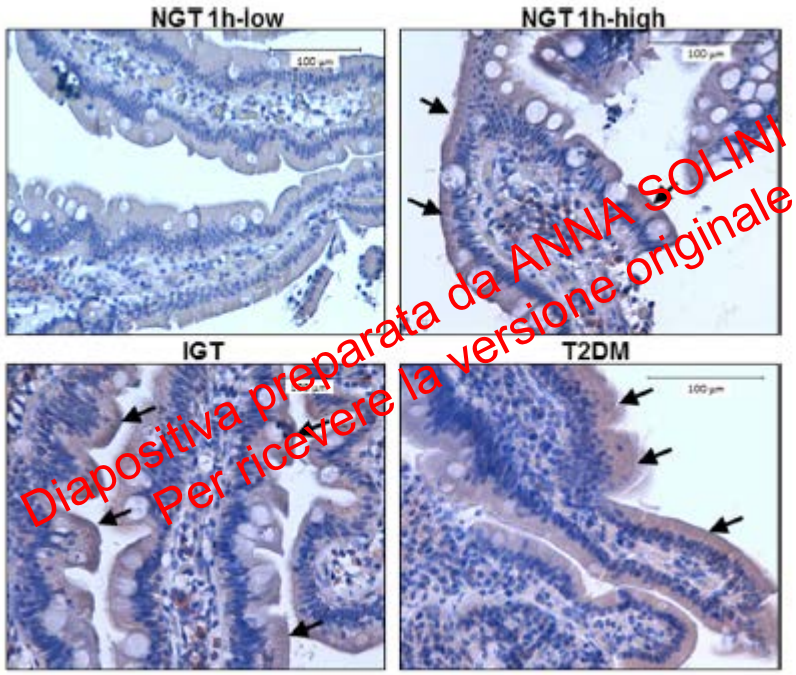
ΔAUC insulin

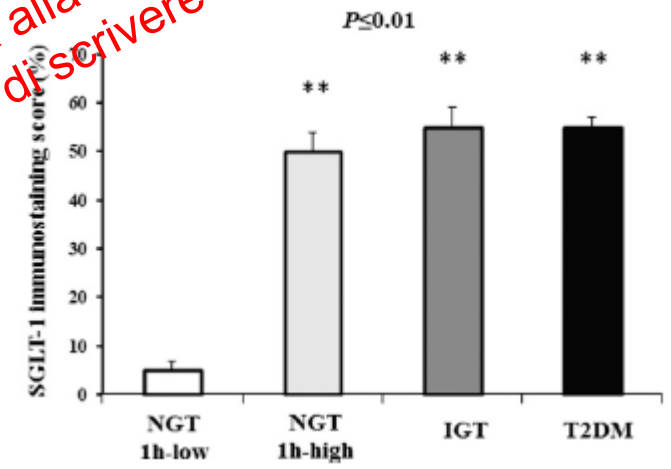
0-1 h: -43%; 0-2 h: -43%; 0-6 h: -33%
following canagliflozin administration

Polidori D, Diabetes Care. 2013;36:2154-61

Duodenal SGLT1 expression in subjects with different degrees of glucose tolerance

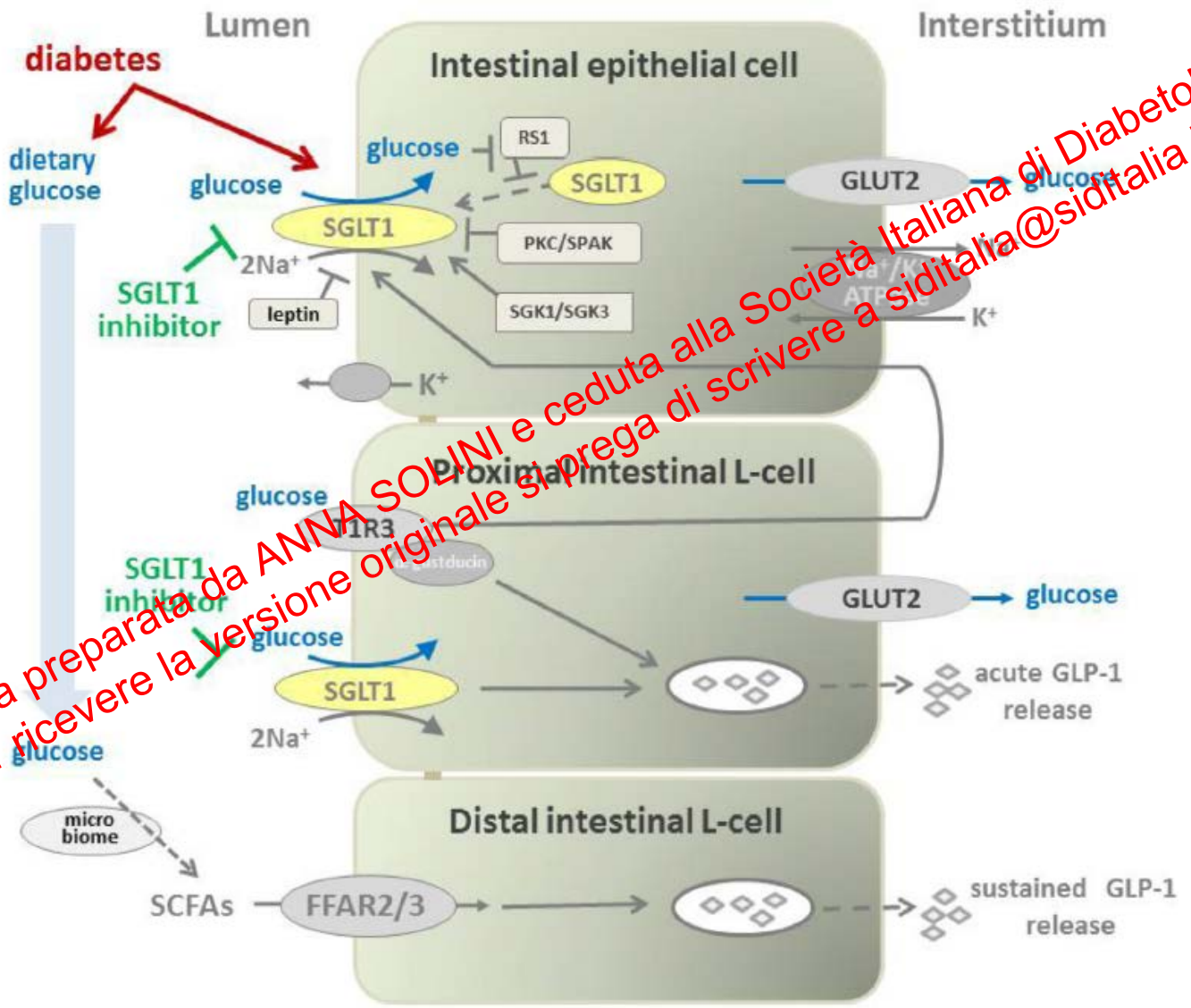
Duodenal SGLT1 in NGT 1h-low, NGT 1h-high, IGT and T2DM





Fiorentino TV, J Clin Endocrinol Metab. 2017;102:3979-89

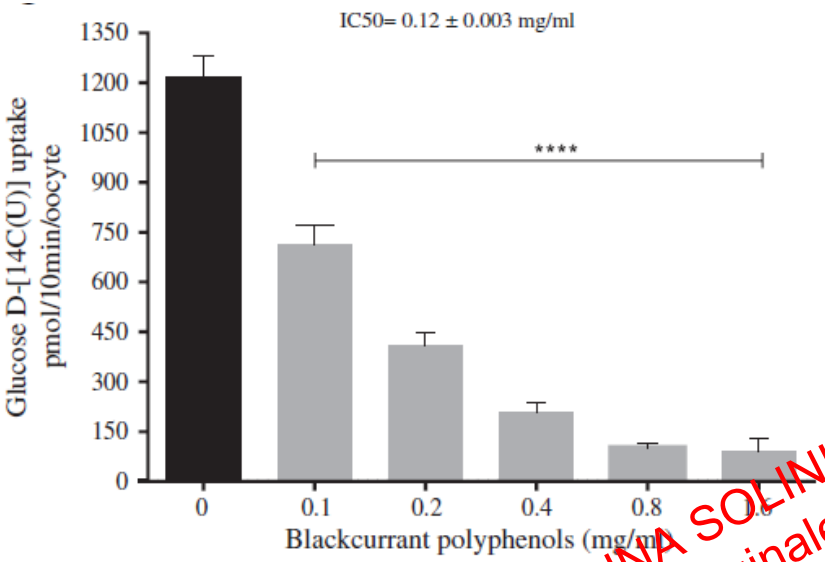
SGLT1 inhibition reduces intestinal glucose absorption and enhances GLP-1 release from the distal intestine



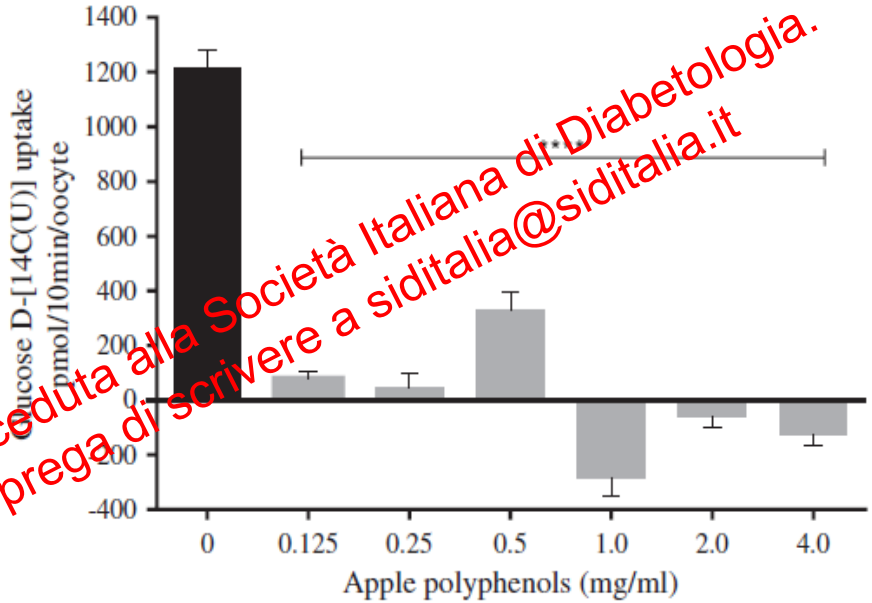
Song P, Expert Opin Ther Targets. 2016;20: 1109-25

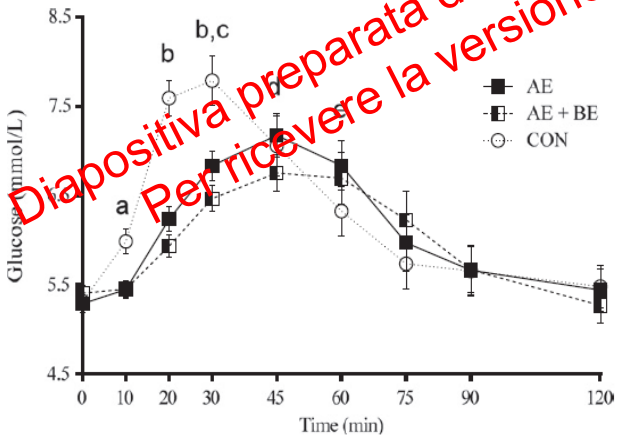
SGLT1 as interesting target of polyphenol-rich food

GLUT-mediated glucose transport



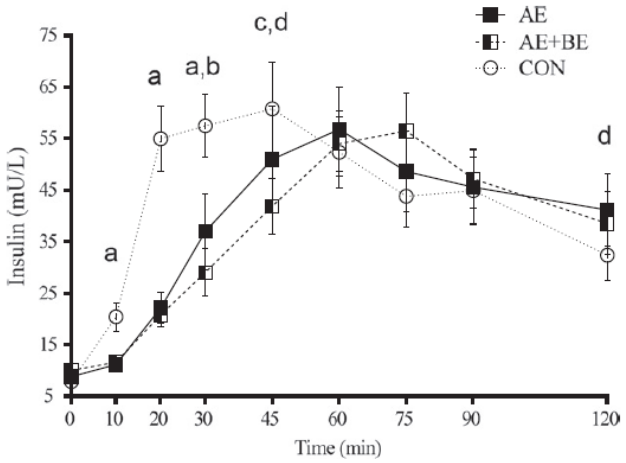
SGLT1-mediated glucose transport





Glucose

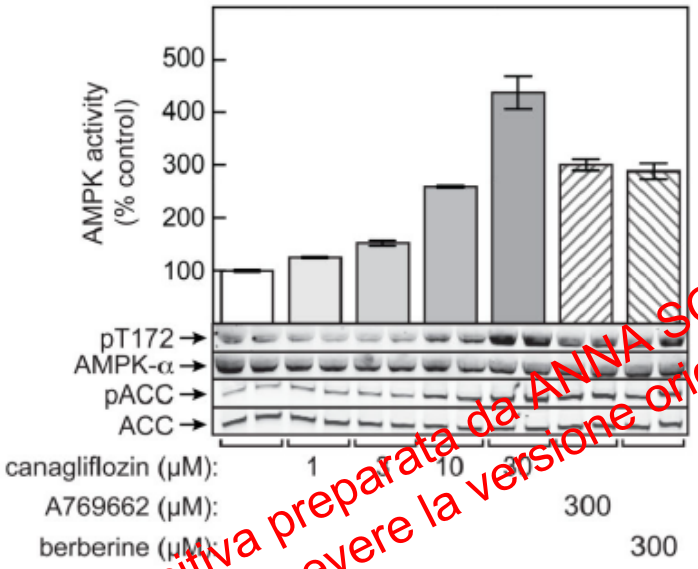
Insulin



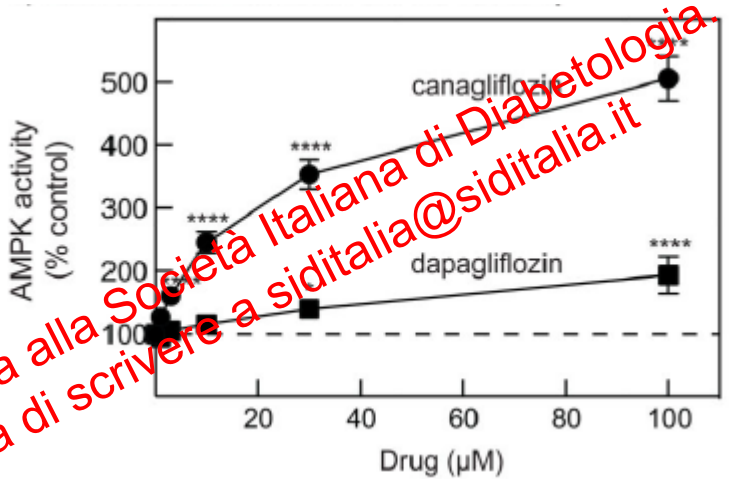
Castro-Acosta ML, J Nutr Biochem. 2017;49:53-62

Canagliflozin activates AMPK

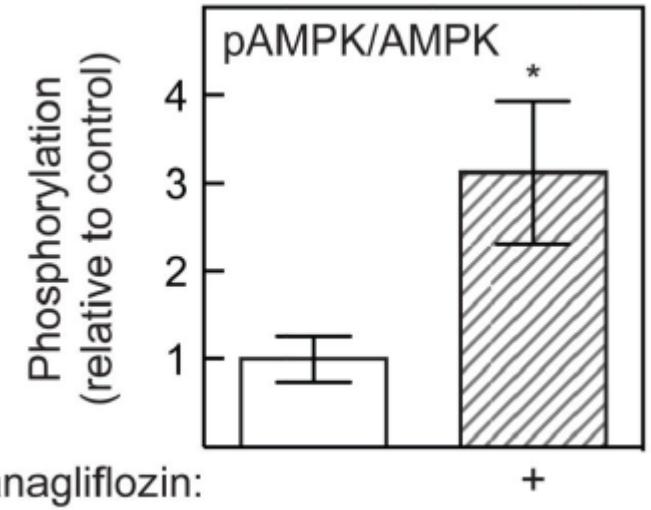
Activation of AMPK by canagliflozin



Effect of SGLT2 inhib on AMPK activity



AMPK phosphorylation in the liver



Hawley SA, Diabetes. 2016;65:2784-94

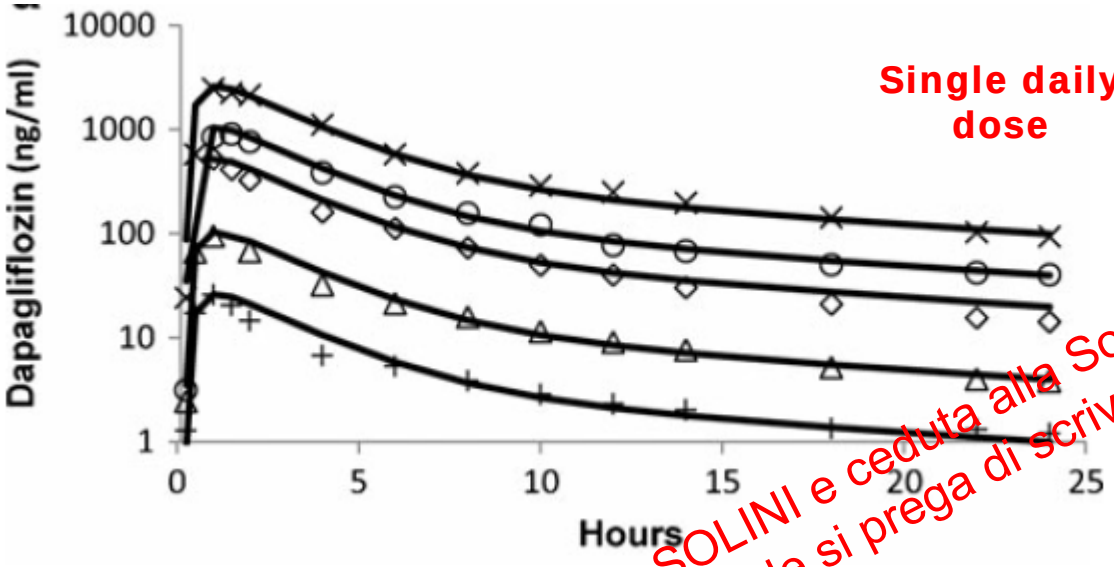
Outline

- Role of SGLT2 in regulating glucose metabolism
- Role of SGLT1
- PK and PD of different molecules
- Data on comparative efficacy

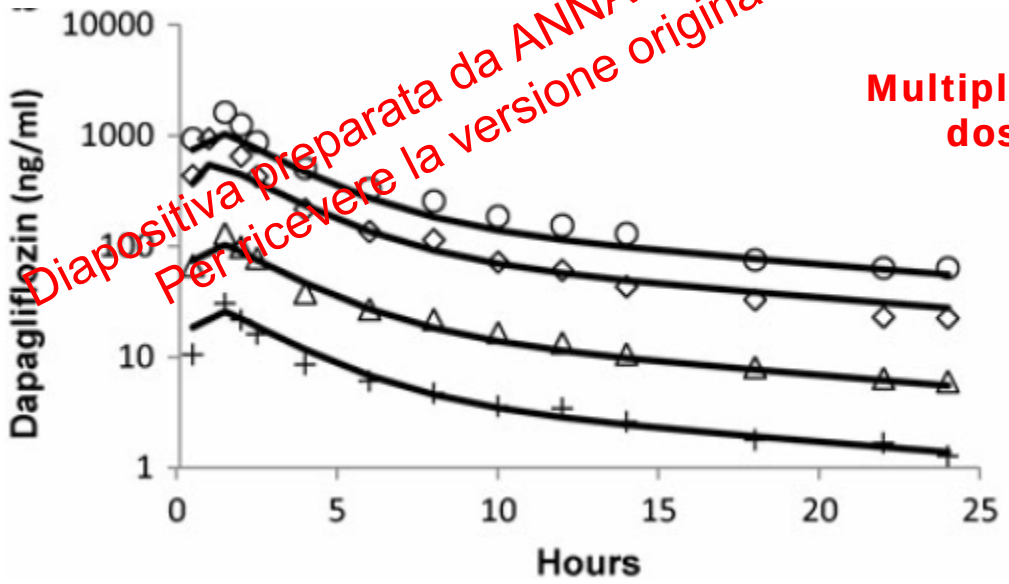
Main pharmacokinetic characteristics of dapagliflozin, canagliflozin and empagliflozin

Parameter	Dapa	Cana	Empa
Dose (single; mg)	5/10	100/300	10/25
Oral bioavailability (%)	78	≈65	NA
t_{max} (h)	1–2	1–2	1–2
C_{max} (ng/ml)	94/158	1,069/2,939	202/227[a]
AUC (ng·h/ml)	324/628	6,871/20,972	786/1725[a]
Plasma protein binding (%)	91	99	NA
Elimination $t_{½}$ (h)	12.2/12.9	10.6/13.1	13.1/10.2
V_{ss} (IV administration; L)	118	119	NA
Mean systemic clearance (IV administration; ml/min)	207	192	NA
Renal clearance (ml/min)	≈5	≈1–2	≈40
Metabolism	Extensive glucuronidation to inactive conjugates	*O*-glucuronidation to M7 (major metabolite) and M5 (minor metabolite)	ADME not yet reported
Elimination	75 % in urine (parent drug and inactive metabolites) and 21 % in faeces	Biliary excretion (60 %) and urine (32 %) <1 % unchanged in urine	11–19 % unchanged in urine
Main metabolizing enzyme	UGT1A9 (kidney and liver)	UGT1A9 (M7) and UGT1B4 (M5)	ADME not yet reported
CYP metabolism (substrate/ inhibitor/inducer)	No	Minimal (7 % CYP3A4) Weak inhibition of CYP2B6, CYP2C8, CYP2C9, and CYP3A4	ADME not yet reported
P-gp substrate	Weak	Weak inhibitor	ADME not yet reported
OAT3 substrate	Main inactive metabolite dapagliflozin 3-*O*-glucuronide		
Dose proportionality	Yes (0.1–500 mg)	Yes (50–300 mg)	Yes (0.5–800 mg)
Time-dependency (repeated doses)	No	No	No

Mean dapagliflozin pharmacokinetics in healthy subjects



Single daily dose



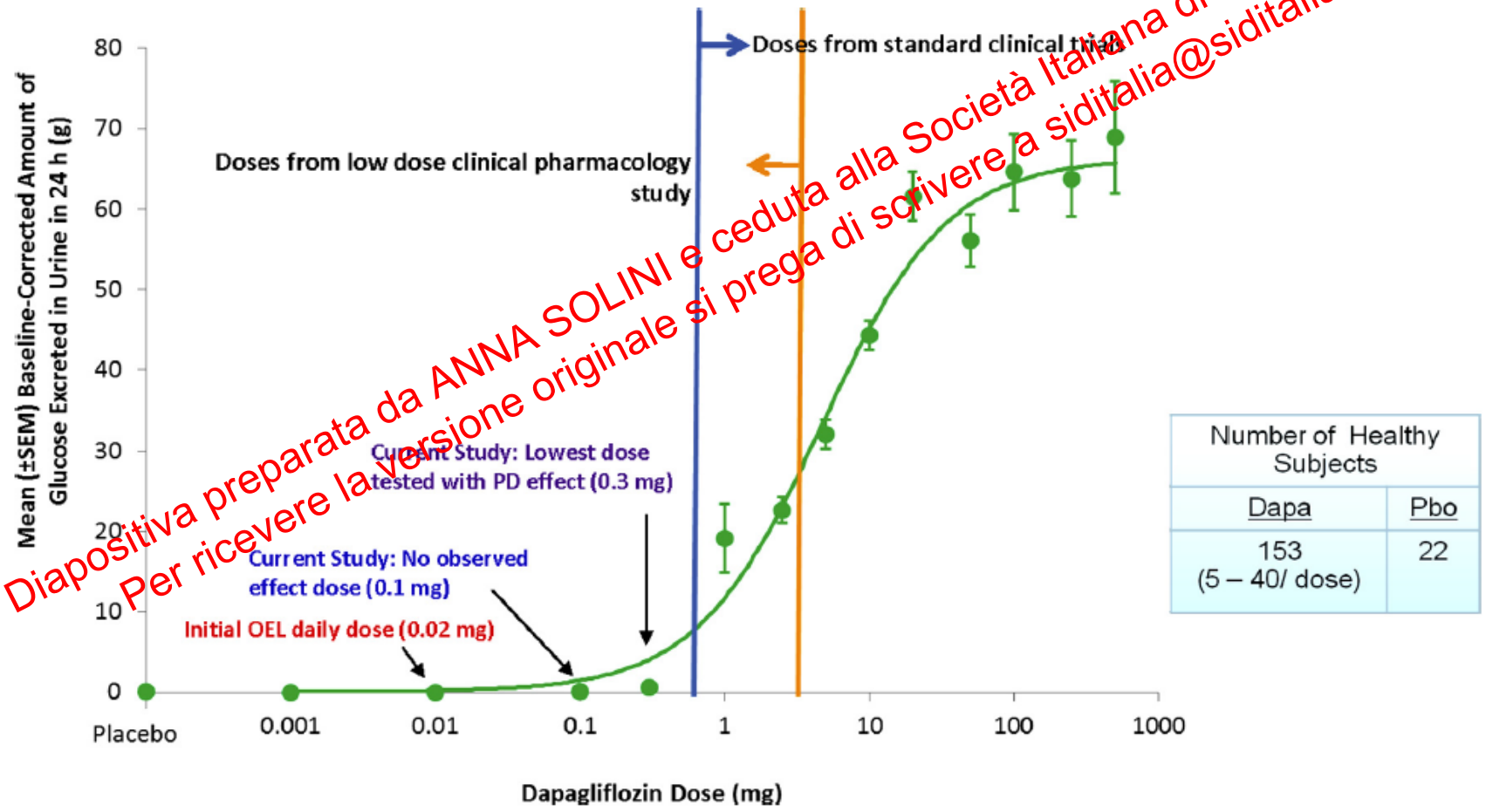
Multiple daily doses

+	2.5 mg
Δ	10 mg
◊	50 mg
O	100 mg
X	250 mg

Komoroski B, Clin Pharmacol Ther. 2009;85:520-26

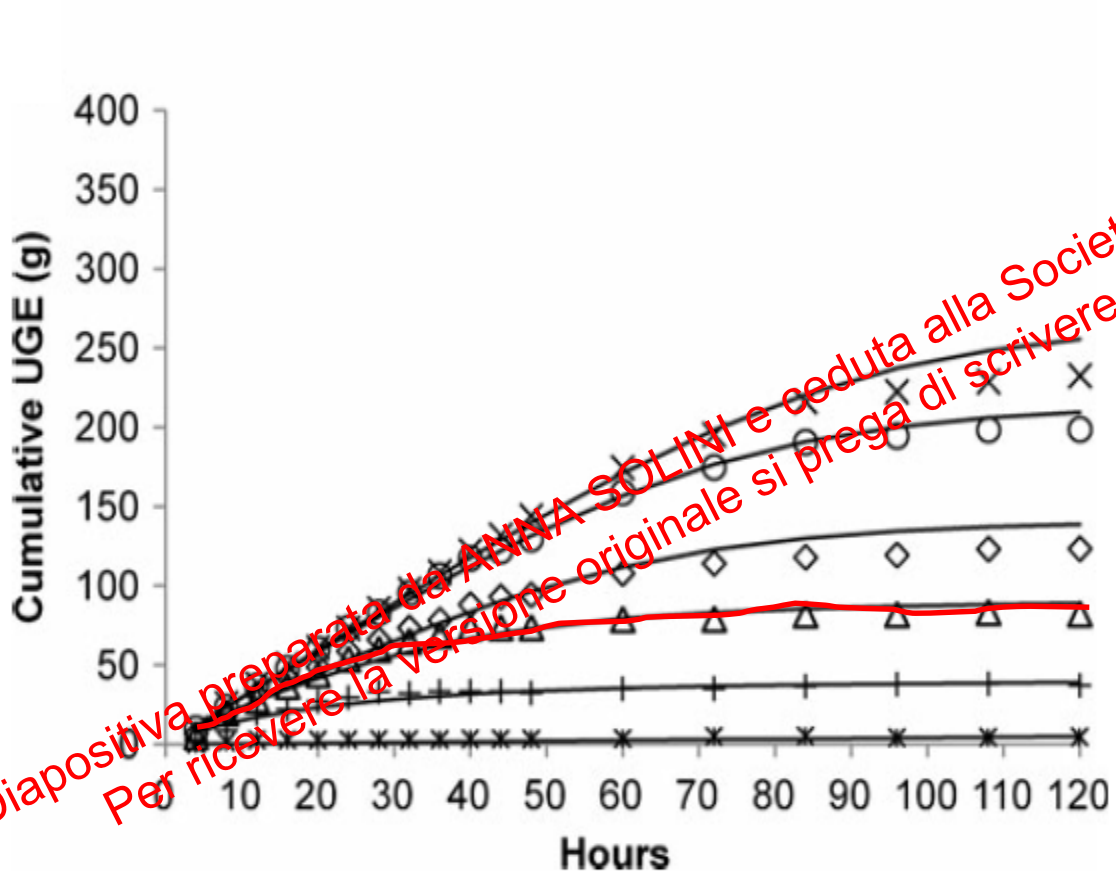
Dose response of UGE after single oral dose of dapagliflozin

E_{max} (90% CI) for 24 h glucose in healthy subjects: 66 g (60, 73 g)



Gould JC, Regul Toxicol Pharmacol. 2013;67:89-97

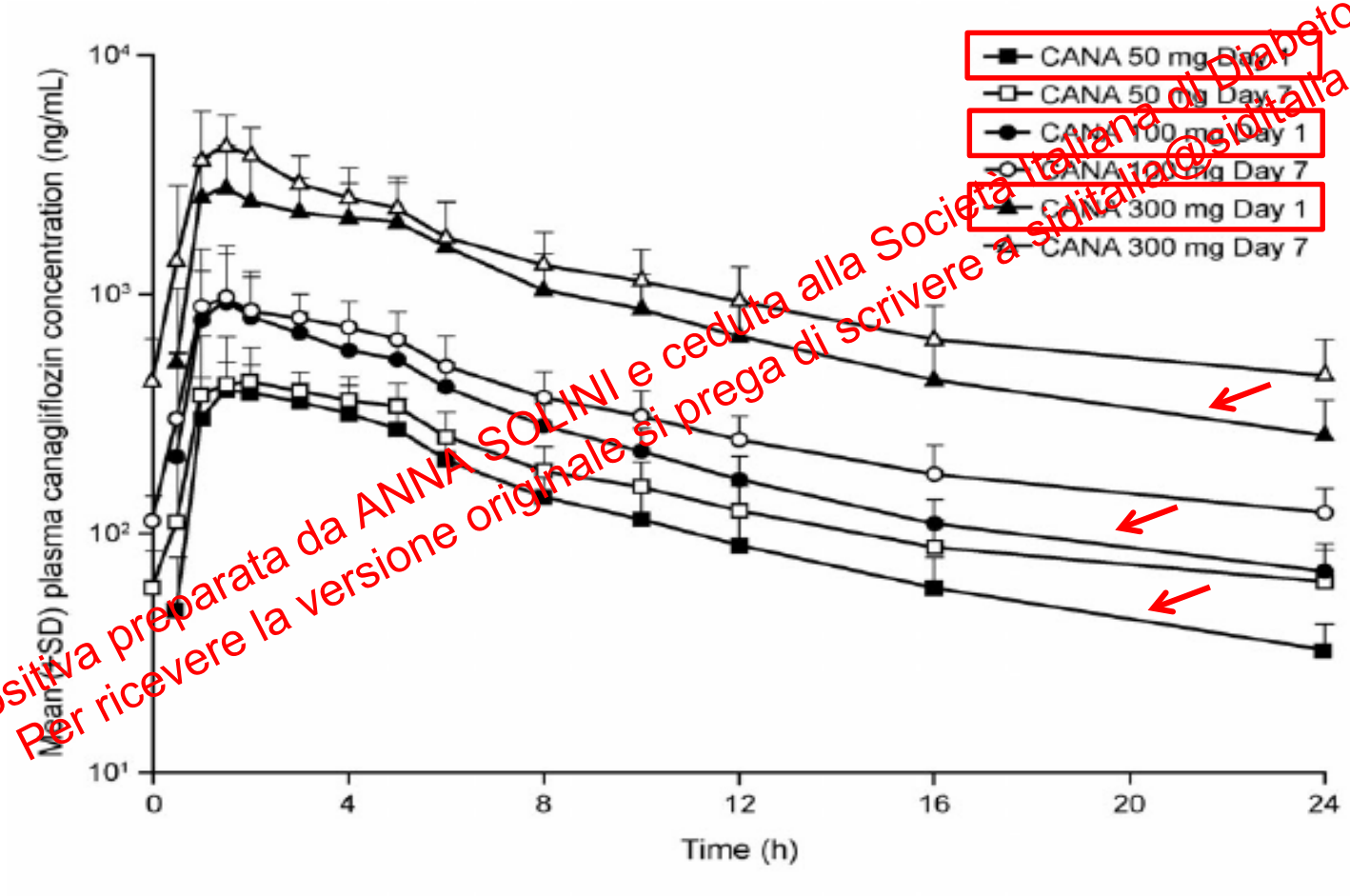
Mean UGE after a single dapagliflozin dose in healthy subjects



* 0
\+ **2.5 mg**
Δ 10 mg
◊ 50 mg
O 100 mg
X 250 mg

Maurer TS, AAPS J. 2011;13:576-84

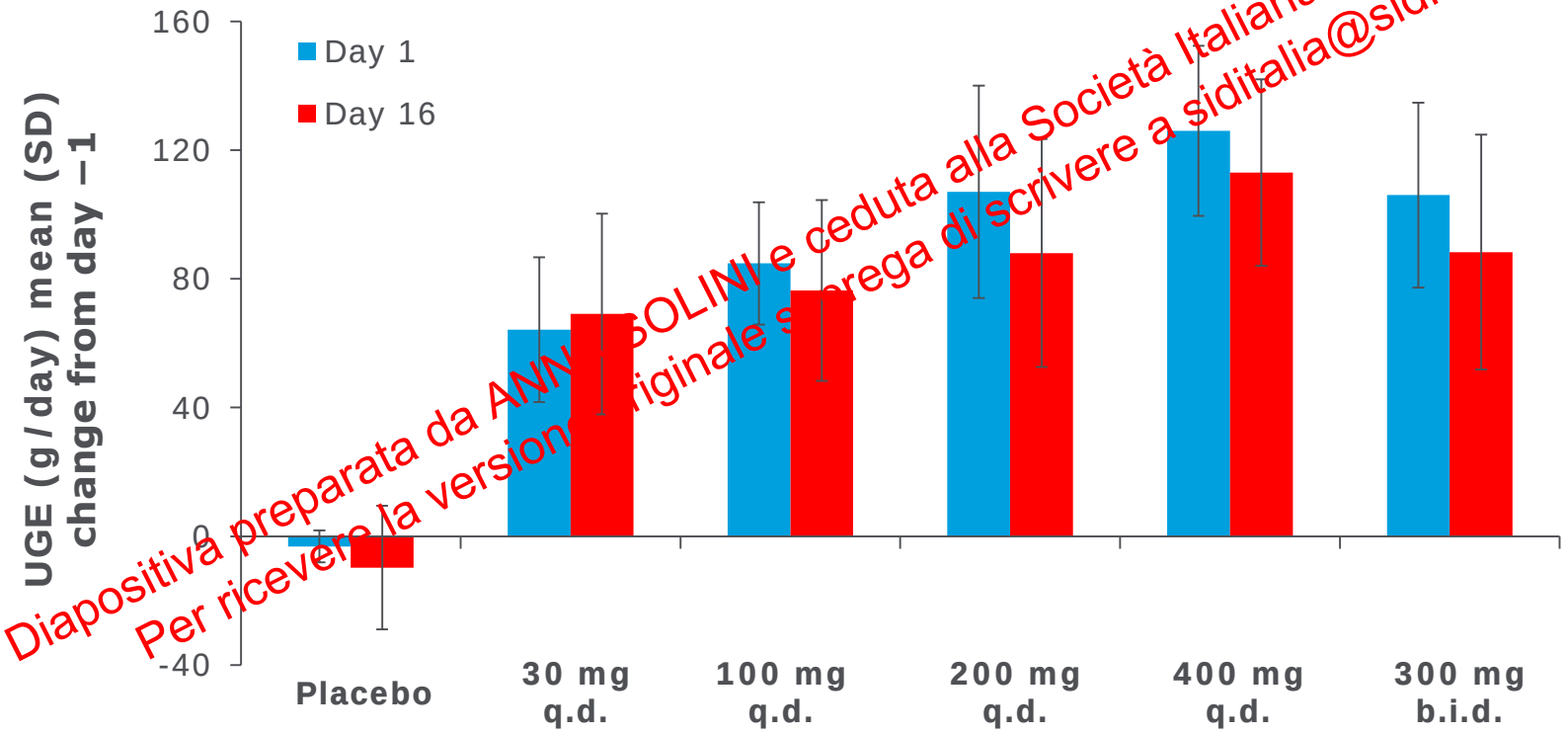
Mean canagliflozin plasma concentrations in T2DM patients



Devineni D, J Clin Pharmacol. 2013;53:601-10

NAP1002: 24-hour UGE: CANA single and multiple ascending doses in subjects with type 2 diabetes

Change from baseline 24-hour UGE after single dose (day 1) and multiple-dose treatments (day 16)



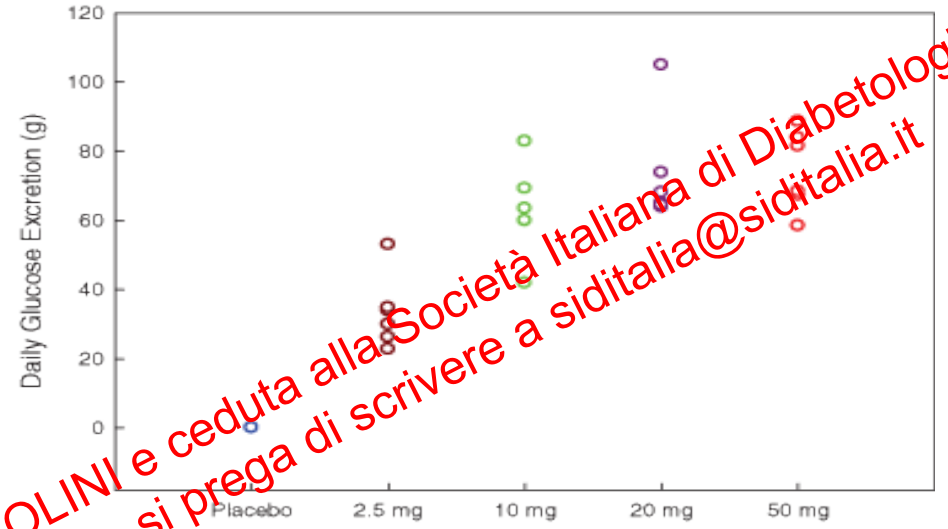
CANA increased UGE in a dose-dependent manner up to 400 mg q.d.

q.d., once daily

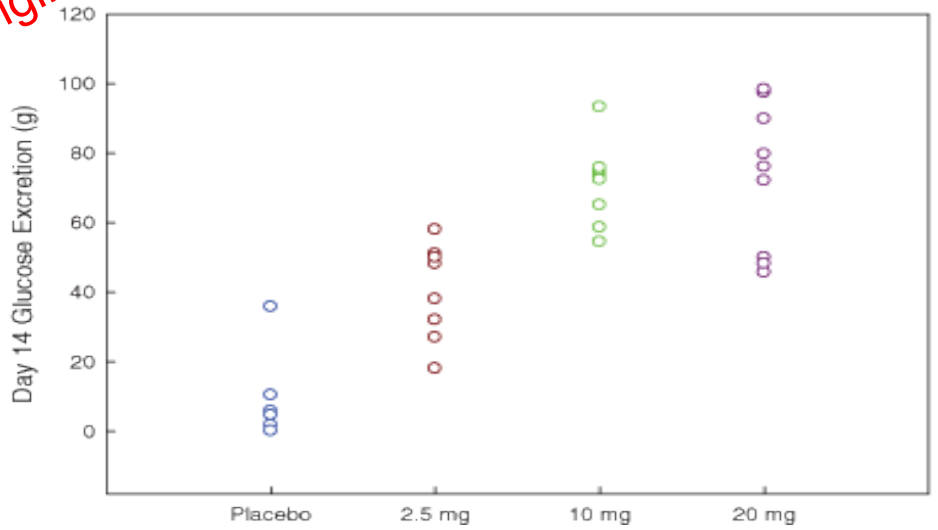
Sha S, et al. Poster presented at ADA 2010; abstract 76-OR

24-h UGE after various doses of dapagliflozin

Single-dose ascending, healthy controls

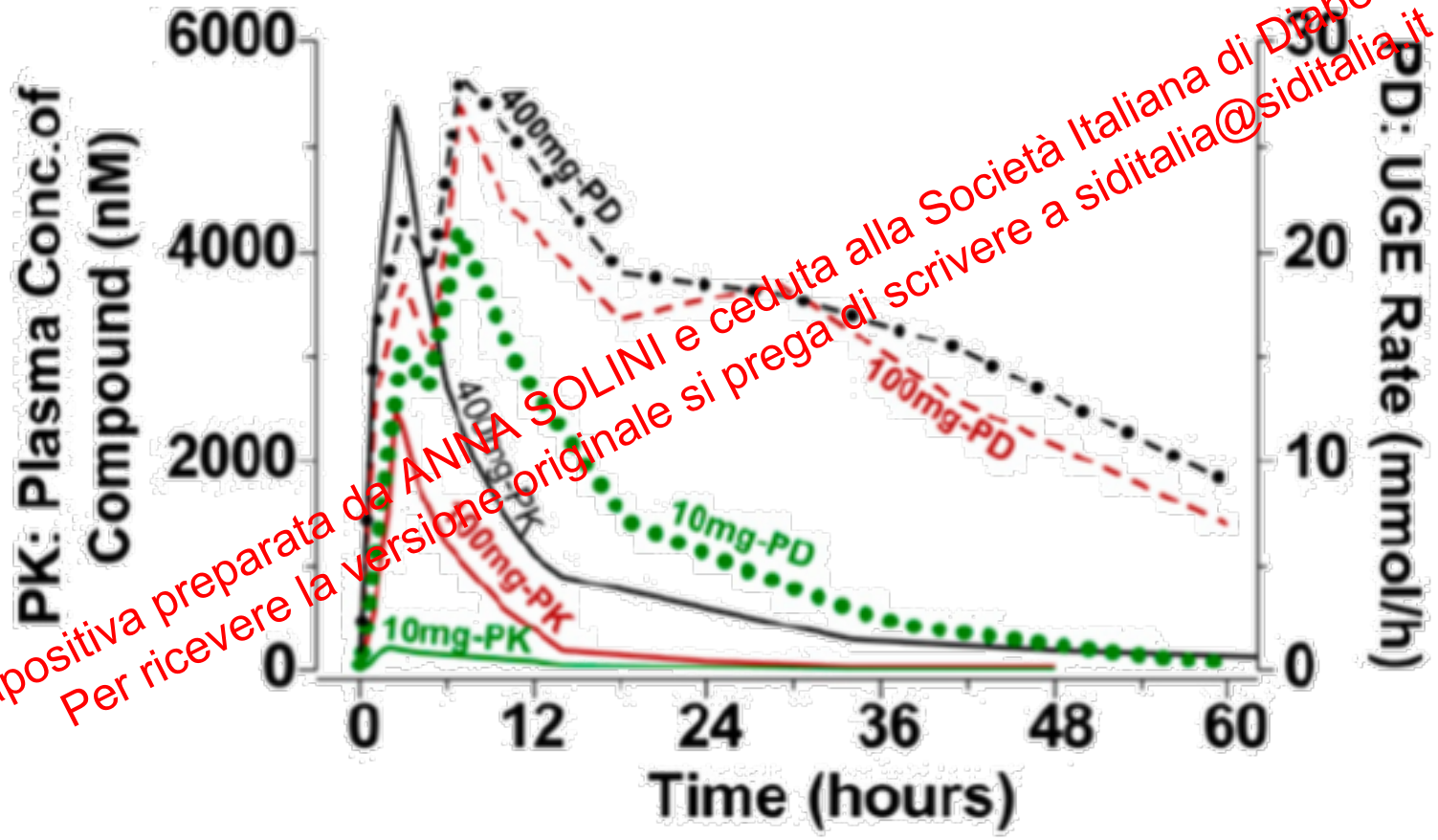


Multiple-dose ascending, T2DM



Kasichayanula S, Diabetes Obes Metab. 2011;13:357-65

Desincronization between plasma concentration and effect



Solid lines plasma concentration-time profiles
Dotted or dashed lines UGE rate-time profiles

Liu J, Diabetes. 2012;61:2199-204

Outline

- Role of SGLT2 in regulating glucose metabolism
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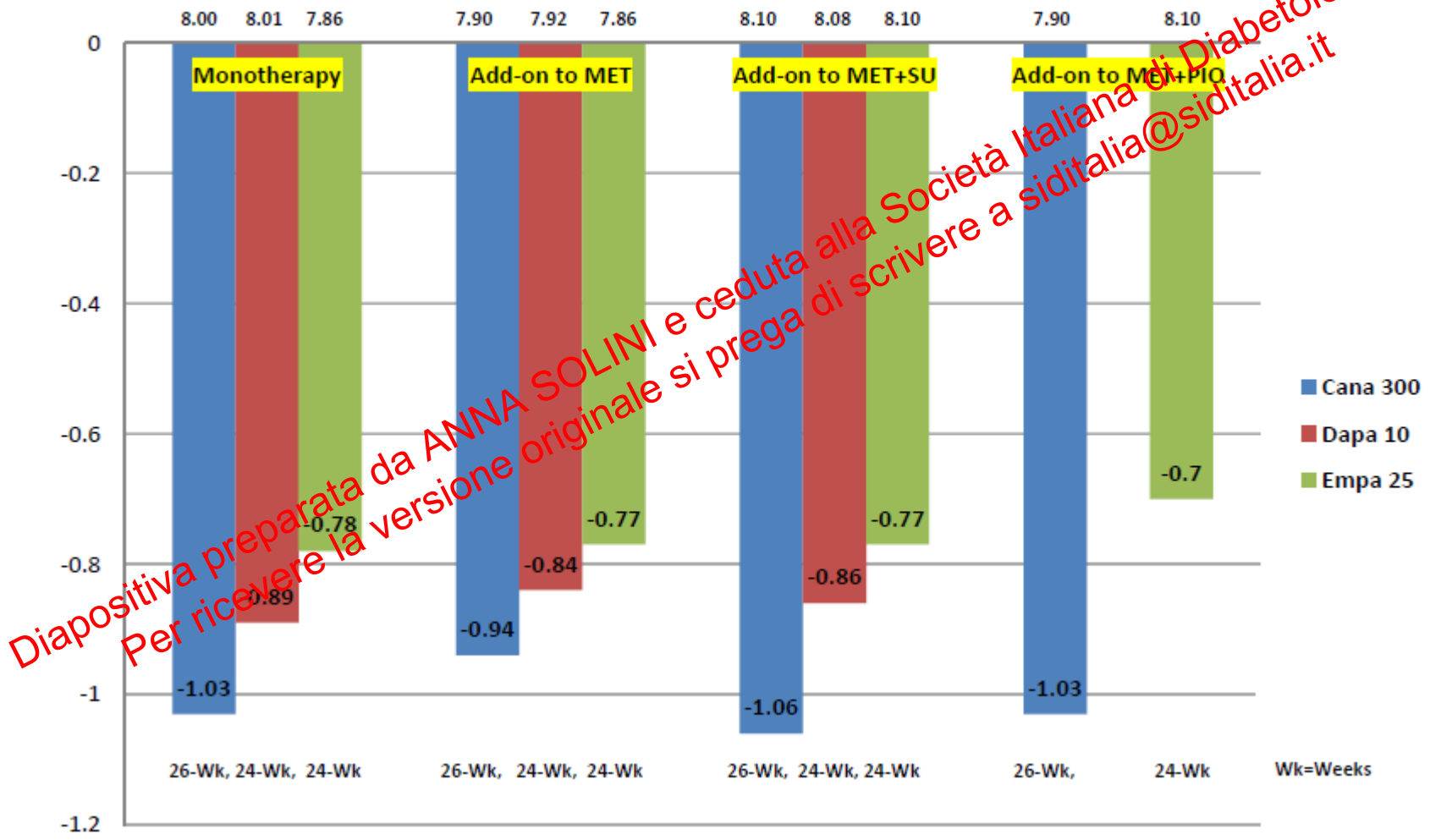
Comparative efficacy of different agents on HbA1c: a network meta-analysis

Agent vs. Placebo	Change in HbA1c, % WMD (95% CI)
Canagliflozin	−0.70 (−0.88 to −0.52)
Dulaglutide	−0.97 (−1.13 to −0.81)
Empagliflozin	−0.55 (−0.73 to −0.37)
Exenatide	−0.58 (−0.74 to −0.41)
Glibenclamide	−1.17 (−1.33 to −1.00)
Glimepiride	−0.98 (−1.2 to −0.76)
Linagliptin	−0.57 (−0.92 to −0.22)
Liraglutide	−1.00 (−1.24 to −0.76)
Sitagliptin	−0.77 (−0.92, −0.61)
Taspoglutide	−0.87 (−1.04, −0.70)

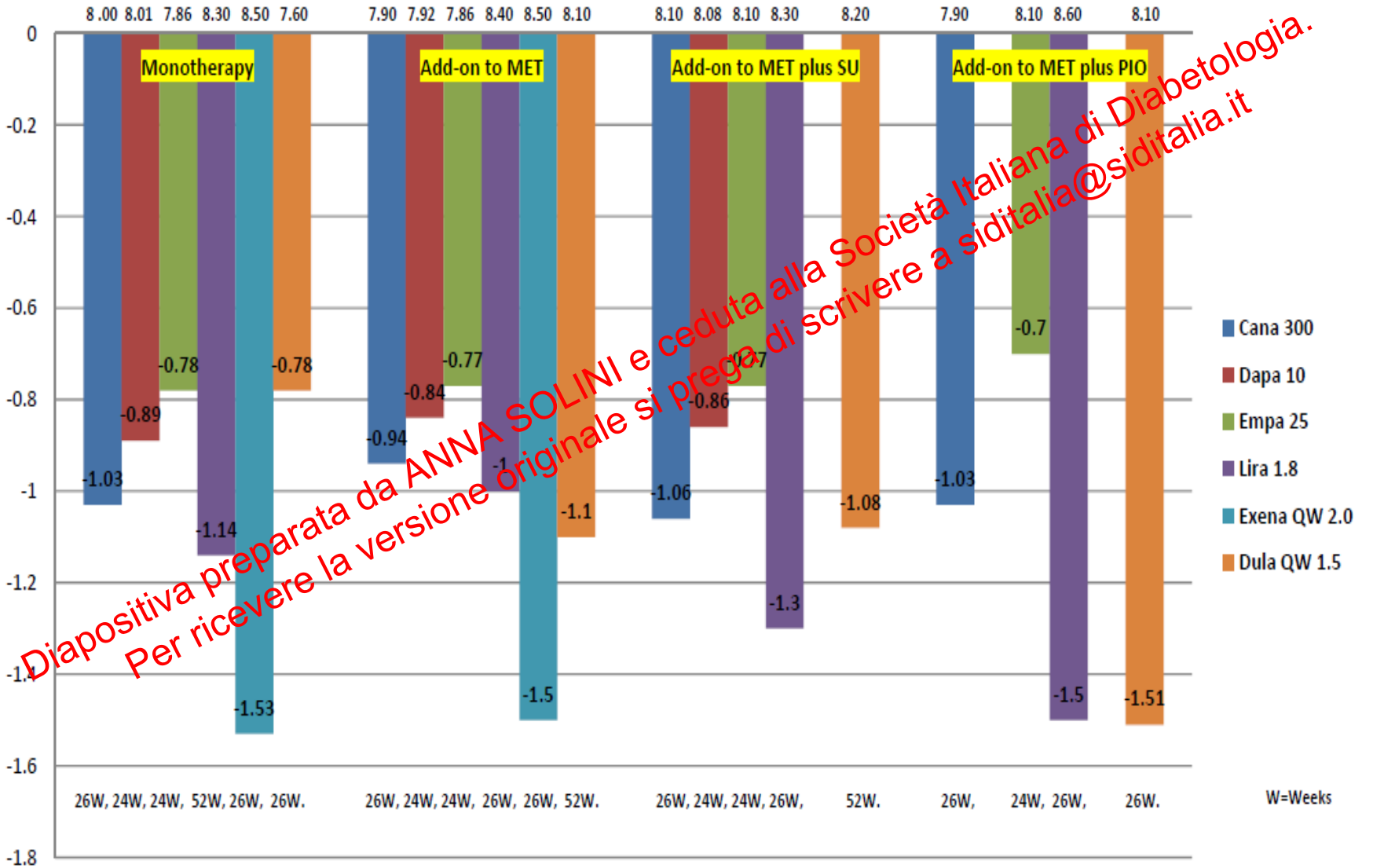
Saulsberry WJ, Int J Clin Pract. 2015;69:1221-35

HbA1c lowering with highest approved dose of SGLT2 inhibitors



Singh AR, Exp Rev Clin Pharmacol. 2017;10:633-47

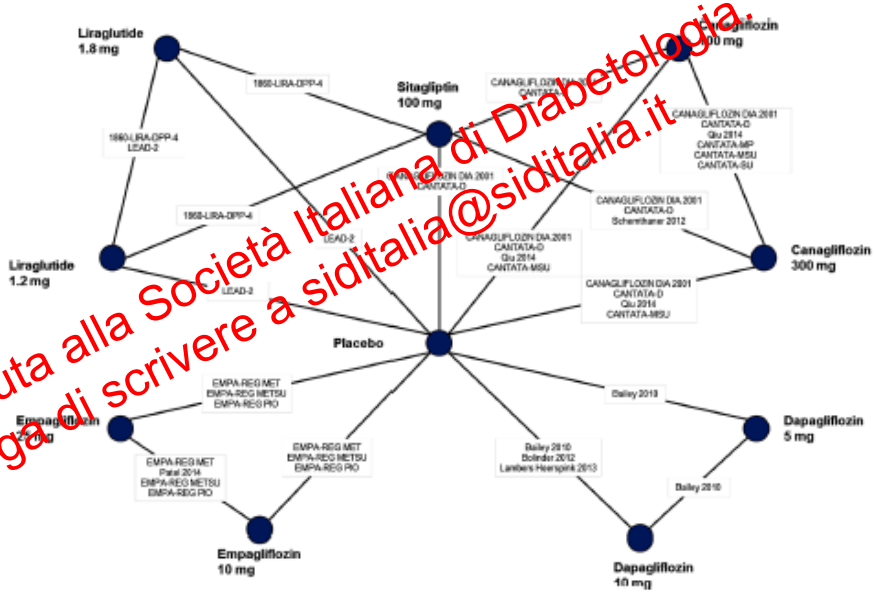
HbA1c lowering with highest approved dose of SGLT2 inhibitors and long-acting GLP-1 analogues



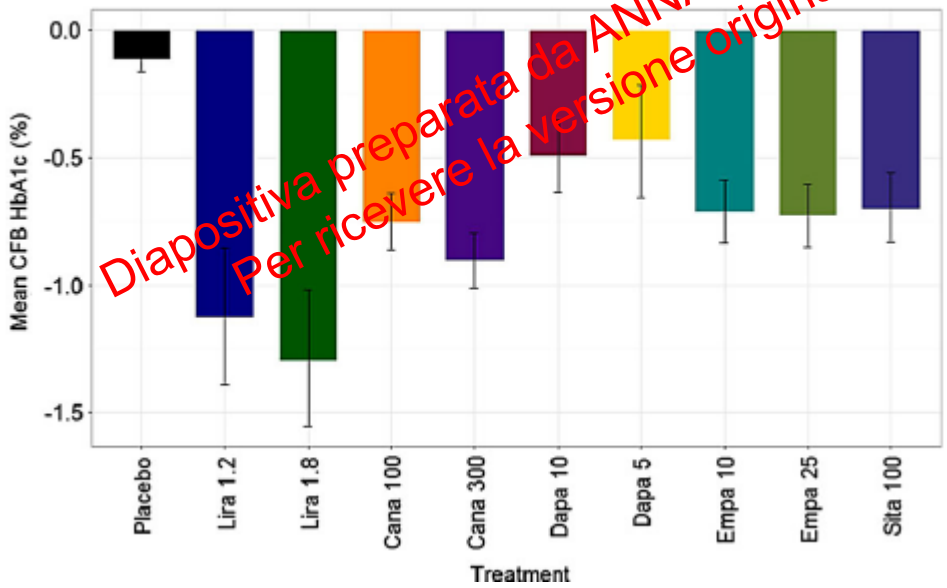
Singh AR, Exp Rev Clin Pharmacol. 2017;10:633-47

Liraglutide *vs* SGLT2 inhibitors: a network meta-analysis

Overall network of evidence (16 trial)



No difference in weight loss and risk of hypoglycemia



Modelled outcomes in change from baseline in HbA1c (%) in metformin-experienced T2DM patients

Lorenzi M, Diabetes Ther. 2017;8:85-99

Liraglutide *vs* SGLT2 inhibitors: a network meta-analysis

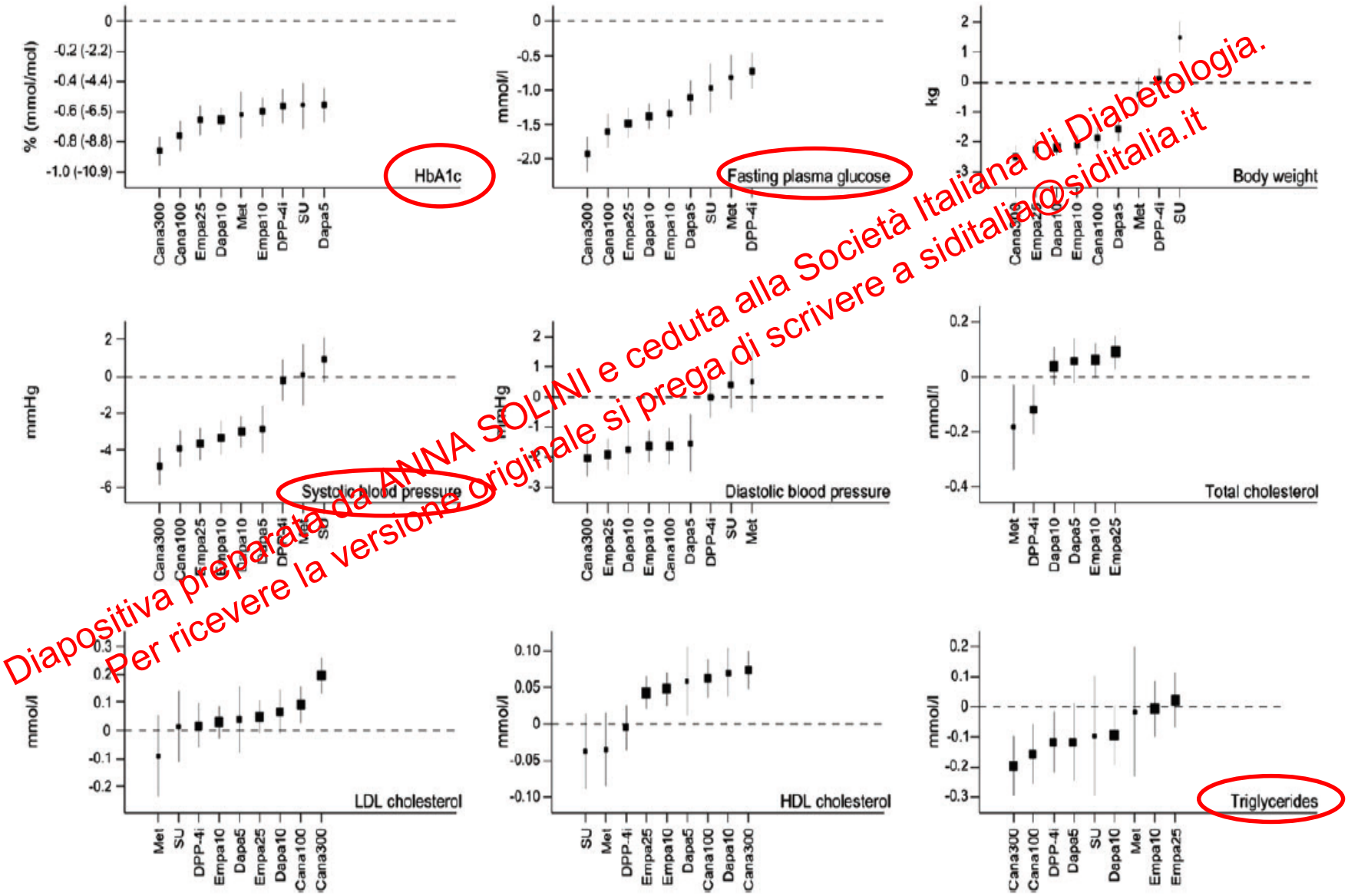
Change from baseline in HbA1c between treatments (%)

Placebo	**1.02 (0.73, 1.28)**	**1.18 (0.89, 1.45)**	**0.64 (0.51, 0.76)**	**0.79 (0.67, 0.91)**	**0.37 (0.23, 0.53)**	**0.31 (0.09, 0.55)**	**0.59 (0.41, 0.72)**	**0.60 (0.49, 0.74)**	**0.58 (0.44, 0.73)**
-1.02 (-1.28, -0.73)	**Liraglutide 1.2 mg**	0.17 (-0.02, 0.35)	**-0.37 (-0.67, -0.08)**	-0.23 (-0.51, 0.07)	**-0.64 (-0.94, -0.32)**	**-0.70 (-1.05, -0.33)**	**-0.42 (-0.72, -0.11)**	**-0.41 (-0.71, -0.09)**	**-0.43 (-0.73, -0.12)**
-1.18 (-1.45, -0.89)	-0.17 (-0.35, 0.02)	**Liraglutide 1.8 mg**	**-0.54 (-0.84, -0.24)**	**-0.39 (-0.69, -0.09)**	**-0.81 (-1.11, -0.48)**	**-0.87 (-1.21, -0.49)**	**-0.59 (-0.88, -0.27)**	**-0.57 (-0.87, -0.25)**	**-0.60 (-0.90, -0.28)**
-0.64 (-0.76, -0.51)	**0.37 (0.08, 0.67)**	**0.54 (0.24, 0.84)**	**Canagliflozin 100 mg**	**0.15 (0.06, 0.24)**	**-0.27 (-0.45, -0.07)**	**-0.32 (-0.58, -0.06)**	-0.04 (-0.22, 0.13)	-0.03 (-0.20, 0.15)	-0.05 (-0.18, 0.07)
-0.79 (-0.91, -0.67)	0.23 (-0.07, 0.51)	**0.39 (0.09, 0.69)**	**-0.15 (-0.24, -0.06)**	**Canagliflozin 300 mg**	**-0.42 (-0.60, -0.22)**	**-0.47 (-0.72, -0.21)**	**-0.19 (-0.37, -0.02)**	**-0.18 (-0.35, -0.00)**	**-0.20 (-0.33, -0.09)**
-0.37 (-0.53, -0.23)	**0.64 (0.32, 0.94)**	**0.81 (0.48, 1.11)**	**0.27 (0.07, 0.48)**	**0.42 (0.22, 0.60)**	**Dapagliflozin 10 mg**	-0.06 (-0.28, 0.17)	**0.22 (0.02, 0.41)**	**0.24 (0.04, 0.42)**	0.21 (-0.00, 0.41)
-0.31 (-0.55, -0.09)	**0.70 (0.33, 1.05)**	**0.87 (0.49, 1.21)**	**0.32 (0.06, 0.58)**	**0.47 (0.21, 0.72)**	0.06 (-0.17, 0.28)	**Dapagliflozin 5 mg**	**0.28 (0.02, 0.54)**	**0.30 (0.04, 0.55)**	0.27 (-0.01, 0.53)
-0.59 (-0.72, -0.47)	**0.42 (0.11, 0.72)**	**0.59 (0.27, 0.88)**	0.04 (-0.13, 0.22)	**0.19 (0.02, 0.37)**	**-0.22 (-0.41, -0.02)**	**-0.28 (-0.54, -0.02)**	**Empagliflozin 10 mg**	0.02 (-0.10, 0.13)	-0.01 (-0.21, 0.18)
-0.60 (-0.74, -0.49)	**0.41 (0.09, 0.71)**	**0.57 (0.25, 0.87)**	0.03 (-0.15, 0.20)	**0.18 (0.00, 0.35)**	**-0.24 (-0.42, -0.04)**	**-0.30 (-0.55, -0.04)**	-0.02 (-0.13, 0.10)	**Empagliflozin 25 mg**	-0.03 (-0.22, 0.16)
-0.58 (-0.73, -0.44)	**0.43 (0.12, 0.73)**	**0.60 (0.28, 0.90)**	0.05 (-0.07, 0.18)	**0.20 (0.09, 0.33)**	-0.21 (-0.41, 0.00)	-0.27 (-0.53, 0.01)	0.01 (-0.18, 0.21)	0.03 (-0.16, 0.22)	**Sitagliptin 100 mg**

Each cell represents the comparison (mean difference and 95% CrI) of the row treatment versus the column treatment. All values in bold are statistically significant at the 0.05 significance level. DIC 72.36, deviance 41.53, SD 0.06

Lorenzi M, Diabetes Ther. 2017;8:85-99

Comparative efficacy of oral agents on cardiometabolic outcomes vs placebo (n=23,997)



Zaccardi F, Diabetes Obes Metab. 2016; 18:783-94

Conclusive remarks

- ✓ Multiple, mainly favorable metabolic effects of SGLT2 inhibitors.
- ✓ Quickly absorbed, reaching the Cmax approximately 2 hrs after the administration. Plasma levels are dose-dependent. Consider the desincronization between plasma concentration and effect.
- ✓ Interesting effects of a mild SGLT1 inhibition are emerging.
- ✓ Less SGLT2 selectivity translates into a small, albeit clinically relevant, increased potency