Congresso Interassociativo
AMD-SID Regione Veneto

Gli SGLT inibitori: un possibile trattamento aggiuntivo nella cura del diabete di tipo 1?

Gian Paolo Fadini

Professore Associato di Endocrinologia

Dipartimento di Medicina, Università di Padova
Istituto Veneto di Medicina Molecolare

Il prof. Gian Paolo Fadini dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Abbott, AstraZeneca, Boehringer, Eli Lilly, MSD, NovoNordisk, Novartis, Sanofi

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

SGLT2i nel T1D?

Uso off-label

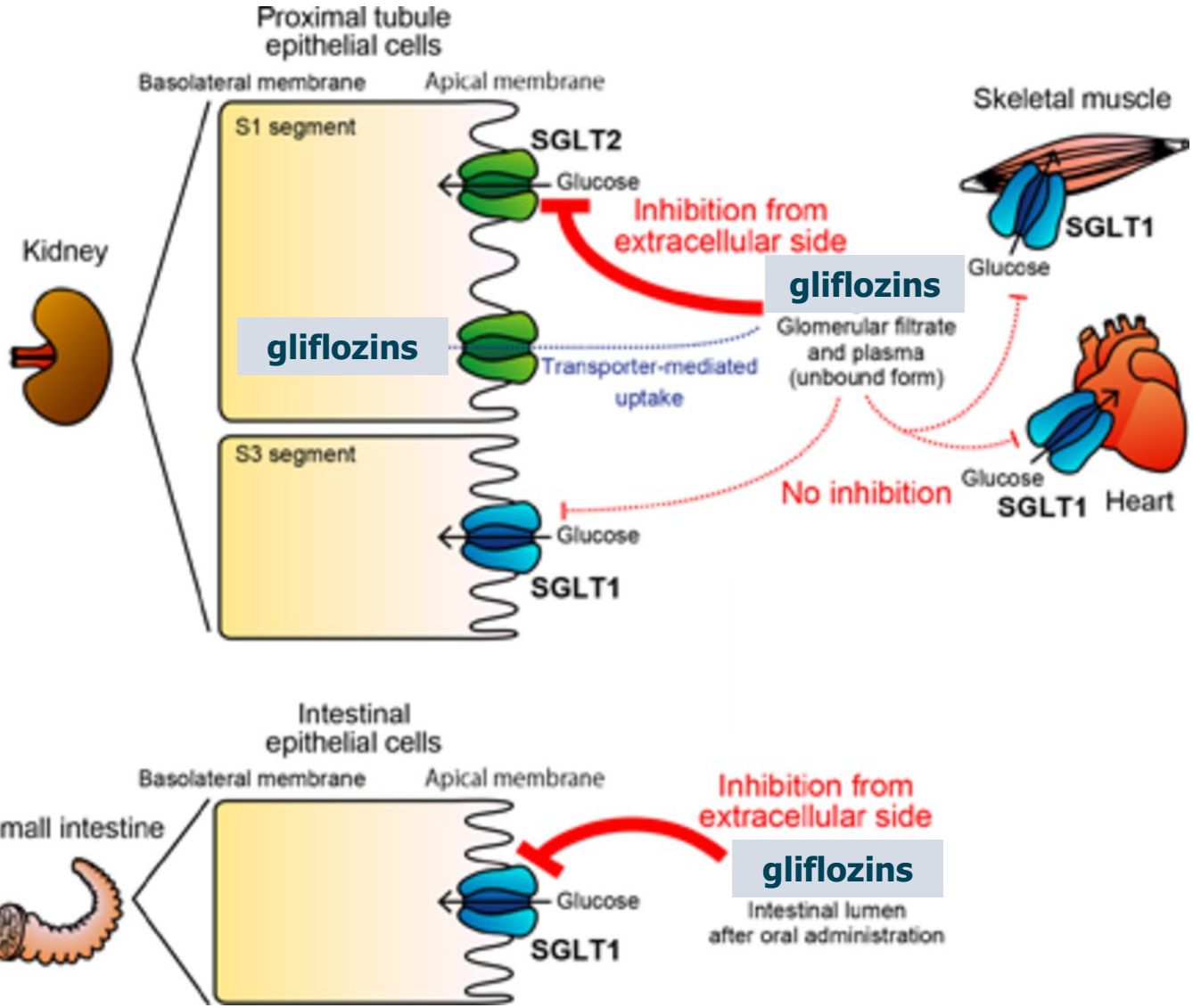
La legge permette un uso "diverso" del farmaco qualora il medico curante, sulla base delle ***evidenze documentate in letteratura*** *e* ***in mancanza di alternative terapeutiche migliori****, ritenga necessario somministrare un medicinale al di fuori delle indicazioni d'uso autorizzate.*
[…]
è necessario che il medico, oltre ad avvalersi del ***consenso informato*** *del paziente,* ***spieghi*** *il razionale della terapia, il rischio di possibili eventi avversi, e quali dati di efficacia sono effettivamente disponibili nell'uso off-label del farmaco che si intende somministrare.*

AIFA bollettino d'informazione sui farmaci.

SGLTs nel T1D?

Razionale

Glycosuria
Body weight
Blood pressure



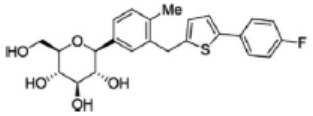
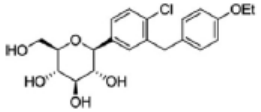
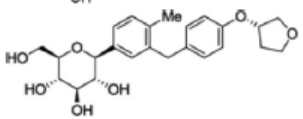
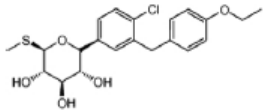
Peak glucose
GLP-1, PYY

SGLTs nel T1D?

Razionale

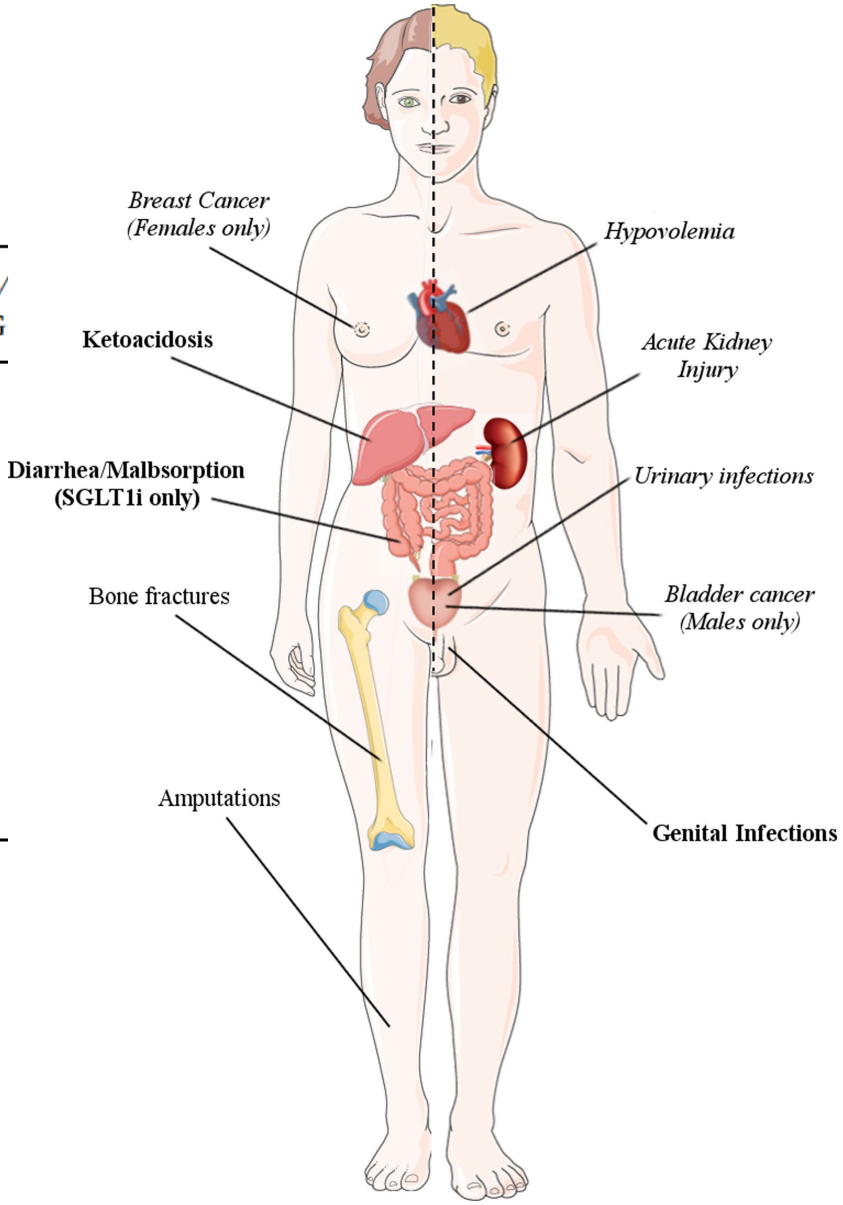
- Migliorare A1c
- Ridurre la variabilità
- Ridurre il fabbisogno insulinico
- Migliorare i fattori di rischio (peso, pressione)
- Ridurre il rischio renale
- Ridurre il rischio CV (HHF?)

Sodium glucose cotransporters inhibitors in type 1 diabetes

Molecule	Chemical structure	Transporter specificity	Tested dosages	$t_{1/2}$	Publications in T1D
Canagliflozin		SGLT2	100, 300 mg once/day	10–12 h	1 RCT 351 subjects [60]
Dapagliflozin		SGLT2	5, 10 mg once/day	13 h	1 RCT**, 1 case series, 82 subjects [58,59]
Empagliflozin		SGLT2	10, 25 mg once/day	10–12 h	1 cross over, 1 RCT; 115 subjects [55–57]
Sotagliflozin		SGLT1 SGLT2	400 mg once/day	24h	2 RCT, 1435 subjects [3,11]

Dellepiane et al. Pharm Res 2018

Molecule	Design/ duration	Add on	Placebo	N (groups)	Hb1AC	FBG/ MBG
Empagliflozin	RCT 4 wks	Insulin	yes	75 (4)	↓	↓
Empagliflozin	Cross Over 8wks	Insulin	no	40 (1)	↓	↓
Empagliflozin	Cross Over 8wks	Insulin	no	40 (1)	↓	
Sotagliflozin	RCT, 4wks	Insulin	yes	33 (2)	↓	↓
Sotagliflozin	RCT, 24wks	Insulin	yes	1402 (2)	↓	↓
Canagliflozin	RCT, 18wks	Insulin	yes	351 (3)	↓	↓

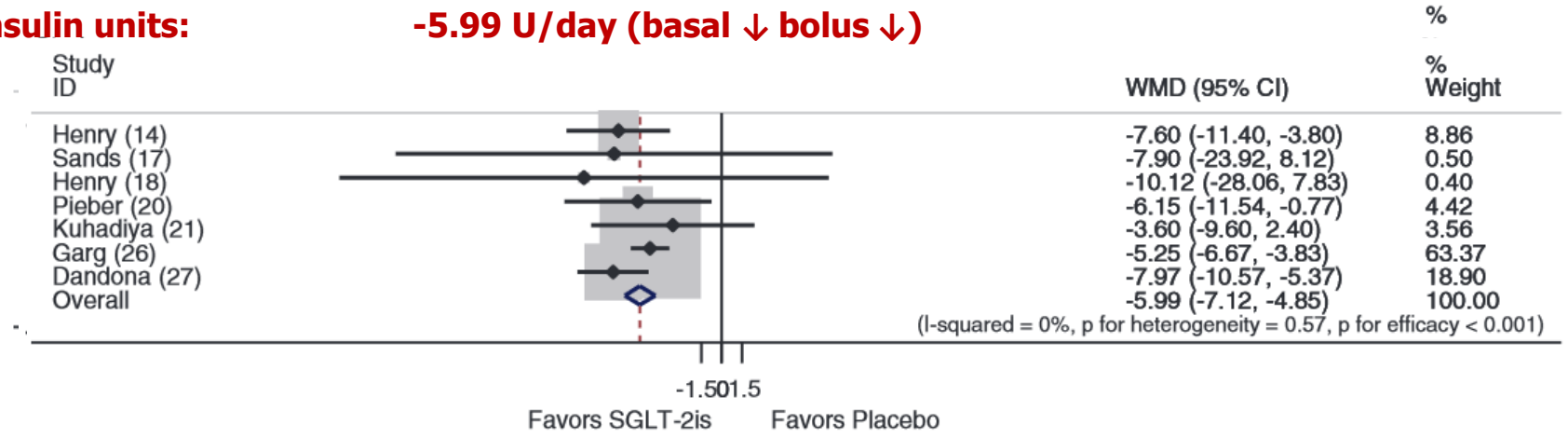


Dellepiane et al. Pharm Res 2018

SGLT2i nel T1D

Systematic review and meta-analysis of randomized controlled trials

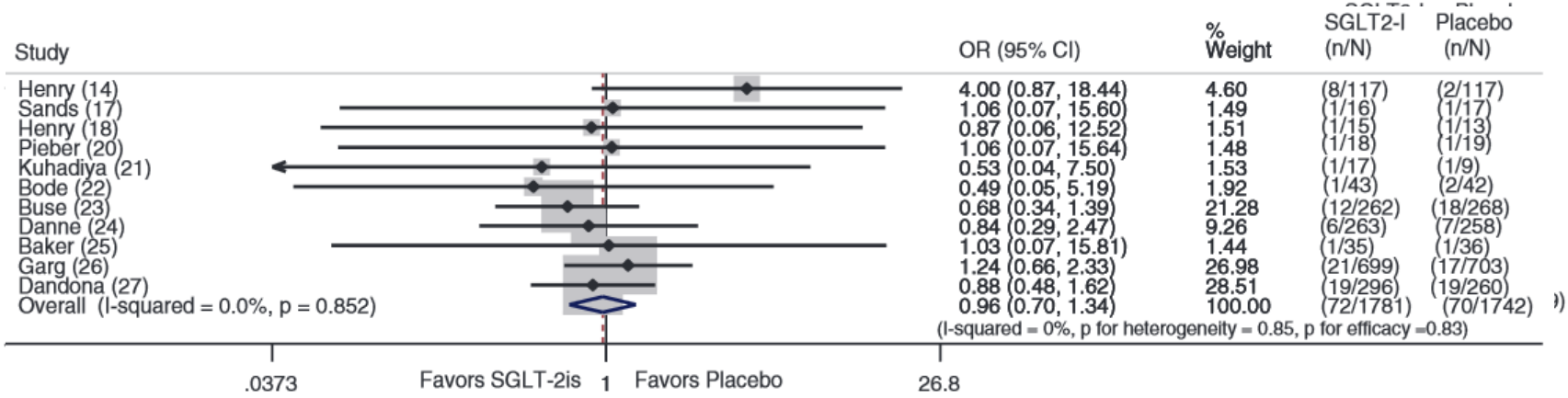
HbA1c pooled result: **-0.40%**
FPG pooled result: **-1.14 mmol/l**
Mean glucose: **-1.07 mmol/l**
Glucose variability: **SD↓ MAGE ↓**
Body weight: **-2.68 kg**
SBP: **-3.37 mmHg**
Insulin units: **-5.99 U/day (basal ↓ bolus ↓)**



Yamada et al. Diabetes Obes Metab 2018

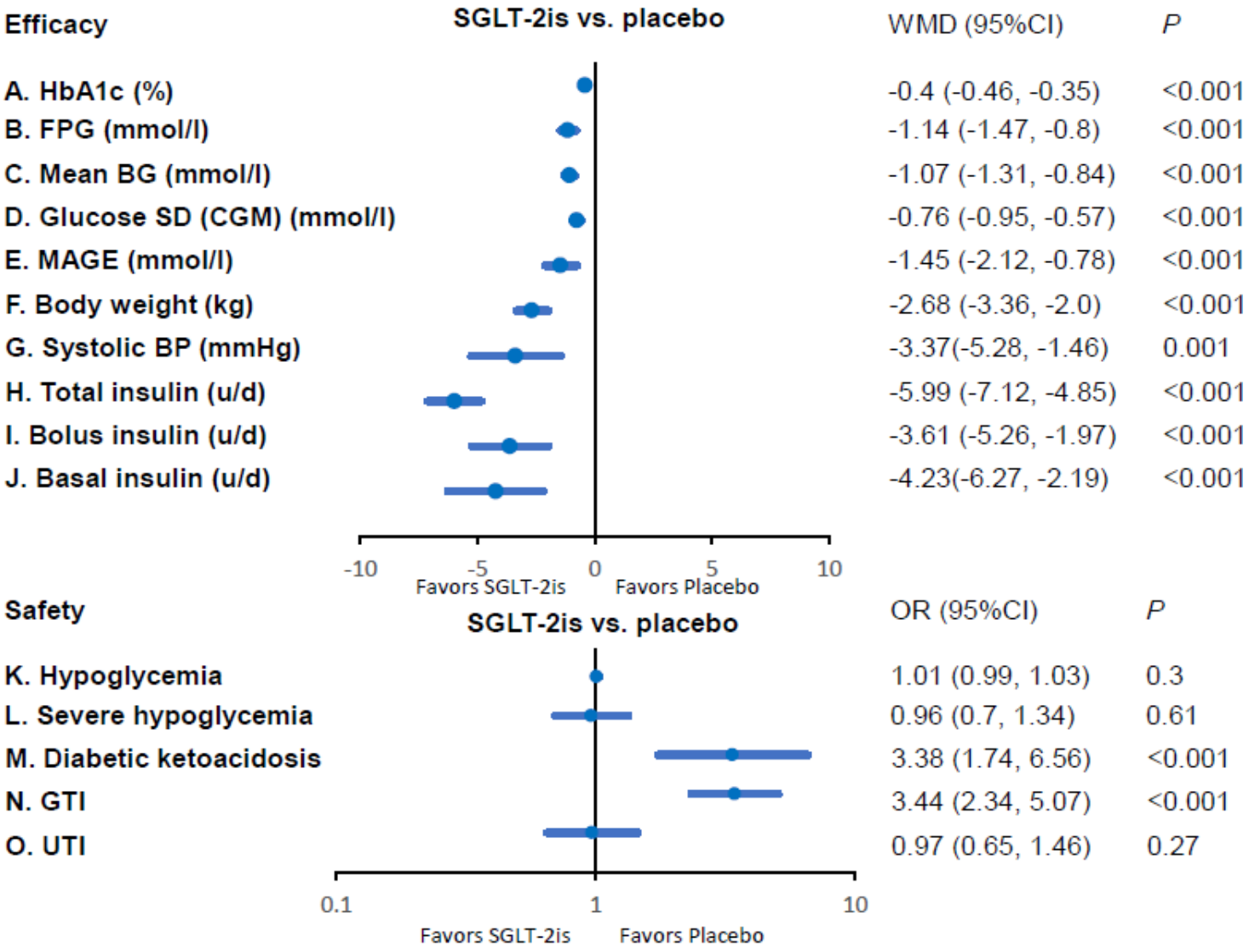
Systematic review and meta-analysis of randomized controlled trials

DKA pooled result: **HR 3.38**
GTI pooled result: **HR 3.44 (for UTI: HR 0.97)**
Hypoglycemia: **HR 1.01**
Severe hypo: **HR 0.96**



Yamada et al. Diabetes Obes Metab 2018

Systematic review and meta-analysis of randomized controlled trials



Yamada et al. Diabetes Obes Metab 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes

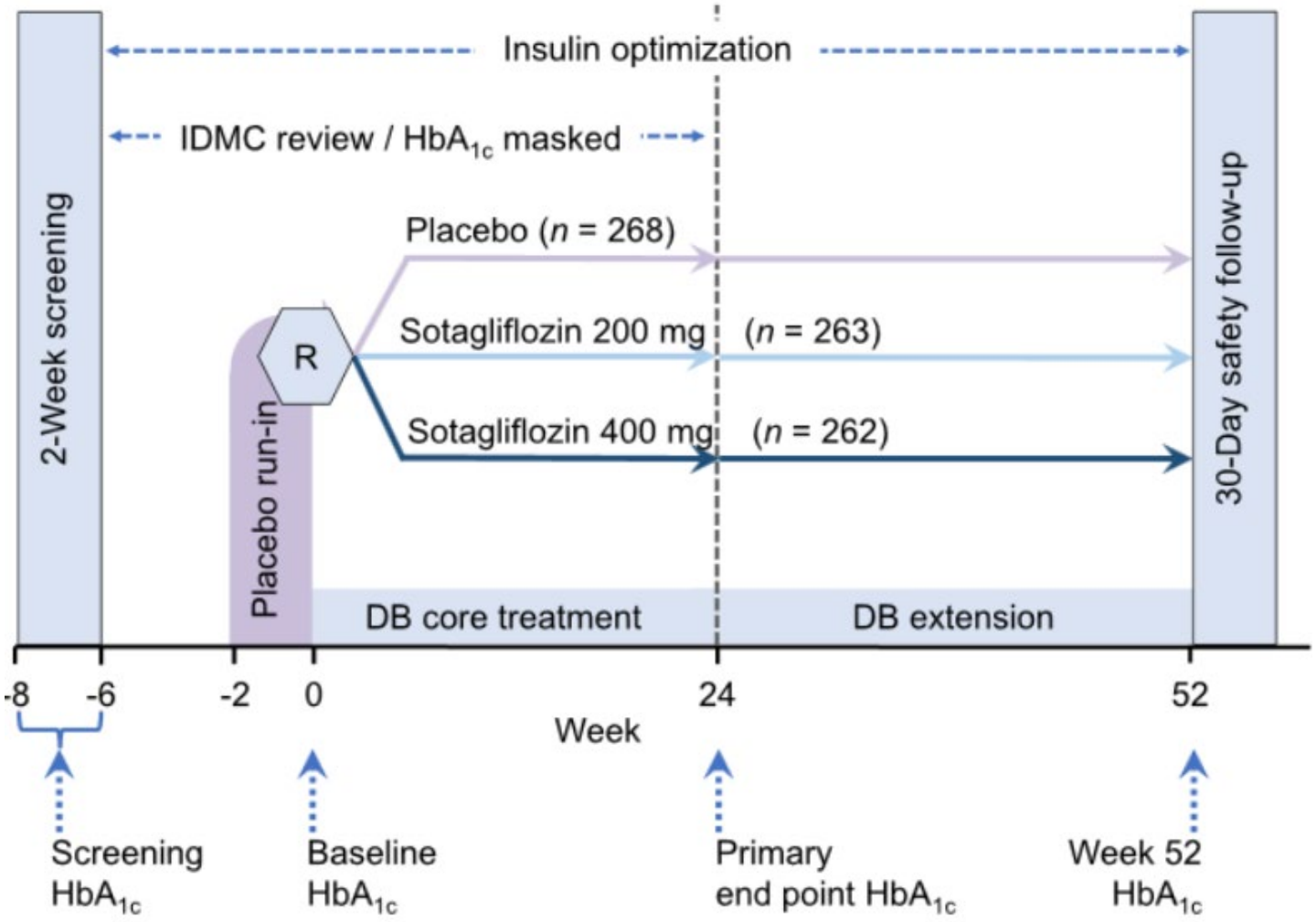
Satish K. Garg, M.D., Robert R. Henry, M.D., Phillip Banks, M.S., John B. Buse, M.D., Ph.D., Melanie J. Davies, M.D., Gregory R. Fulcher, M.D., Paolo Pozzilli, M.D., Diane Gesty-Palmer, M.D., Ph.D., Pablo Lapuerta, M.D., Rafael Simó, M.D., Ph.D., Thomas Danne, M.D., Darren K. McGuire, M.D., M.H.Sc., Jake A. Kushner, M.D., Anne Peters, M.D., and Paul Strumph, M.D.

"the increased risk of ketoacidosis counterbalances the increased likelihood of achieving a glycated hemoglobin level of less than 7%"

(21/699 vs 4/703)

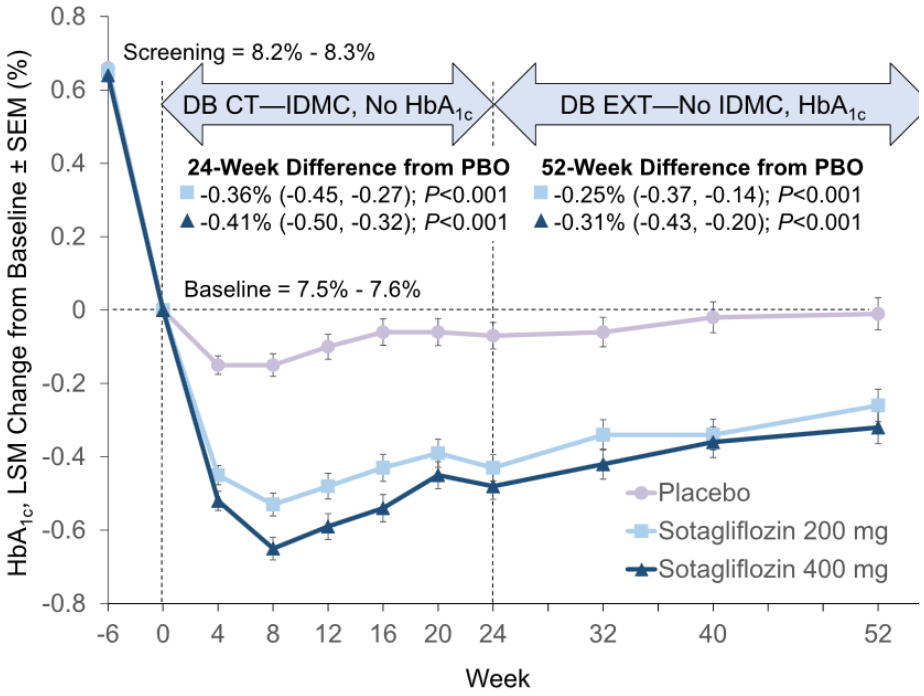
David M. Nathan, M.D.

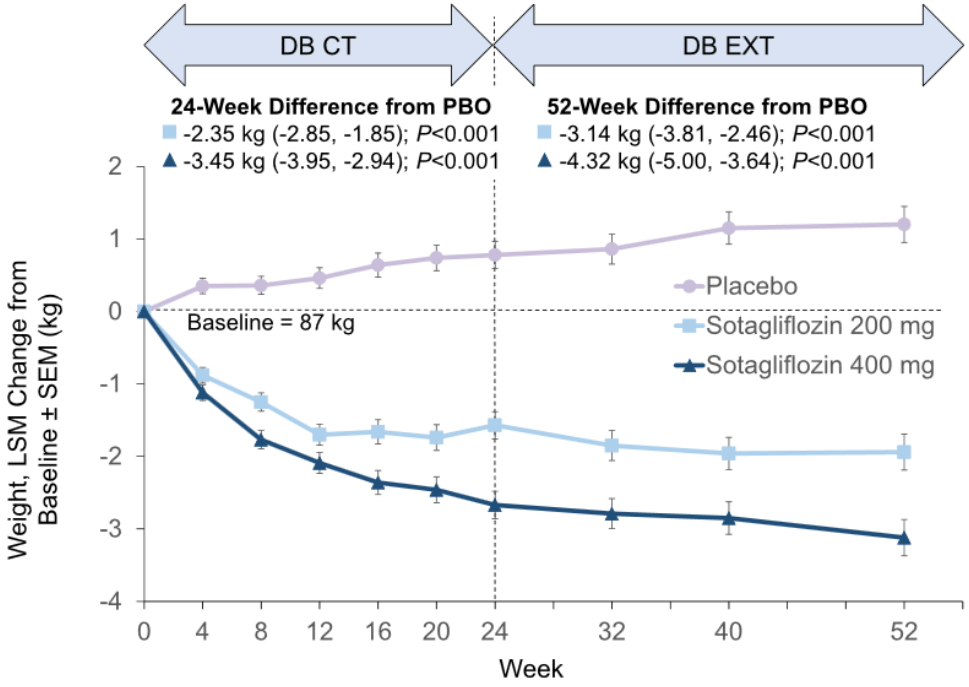
Sotagliflozin vs placebo, 52 week in T1D



Buse et al. Diabetes Care 2018

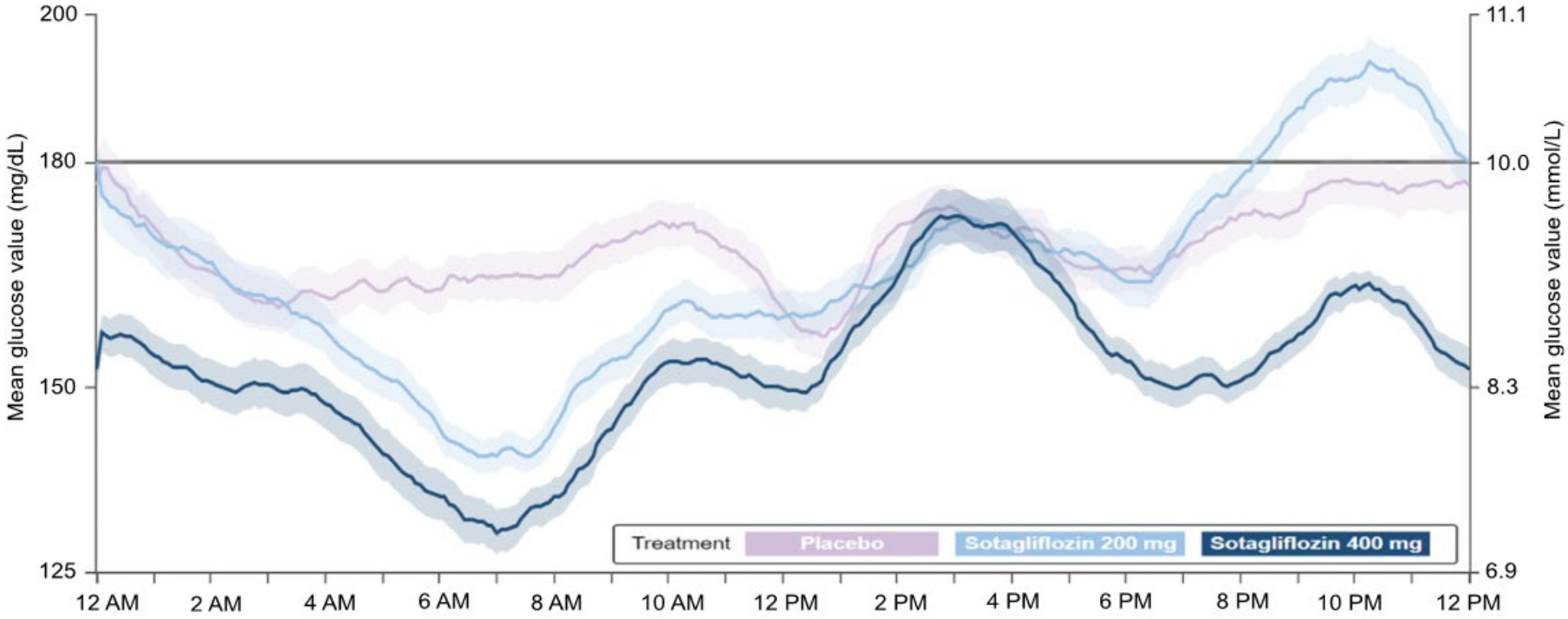
Sotagliflozin vs placebo, 52 week in T1D





Buse et al. Diabetes Care 2018

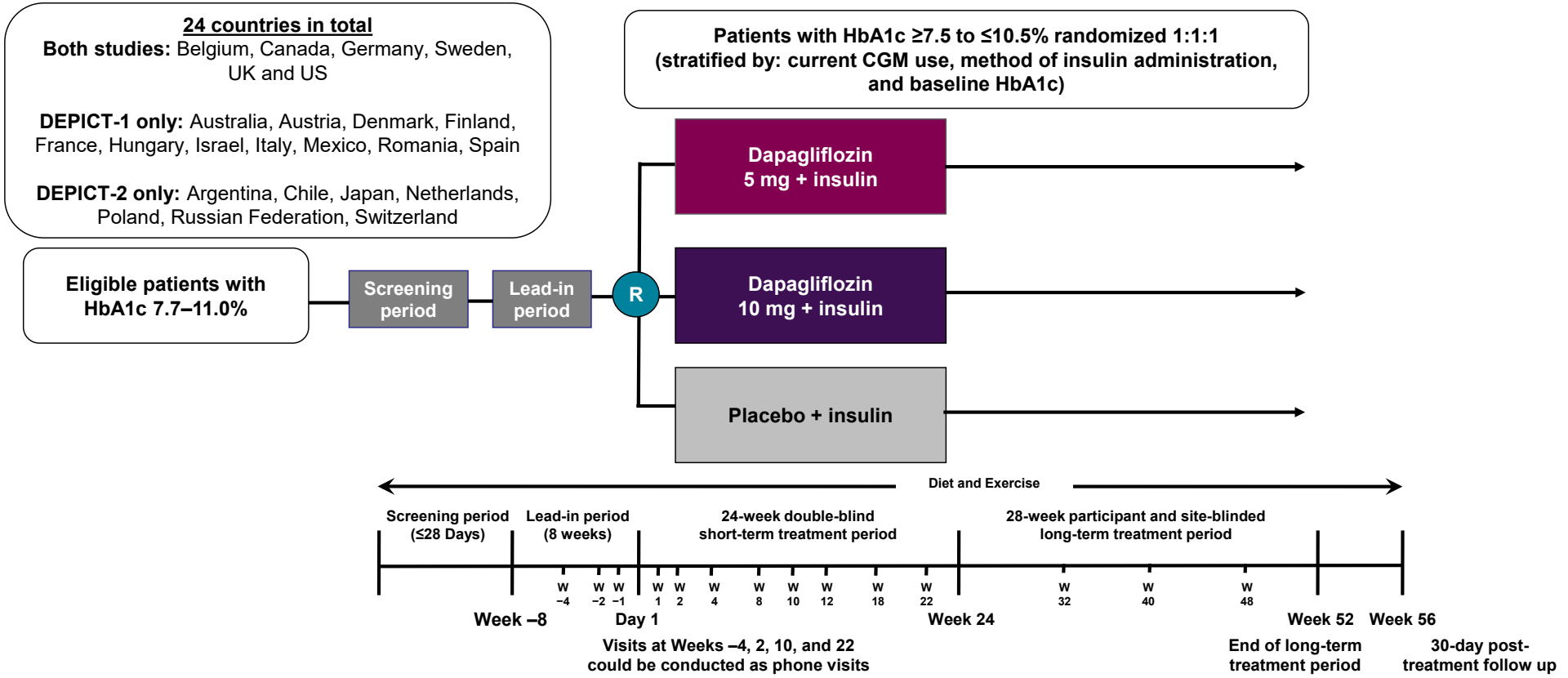
Sotagliflozin vs placebo, 52 week in T1D



Buse et al. Diabetes Care 2018

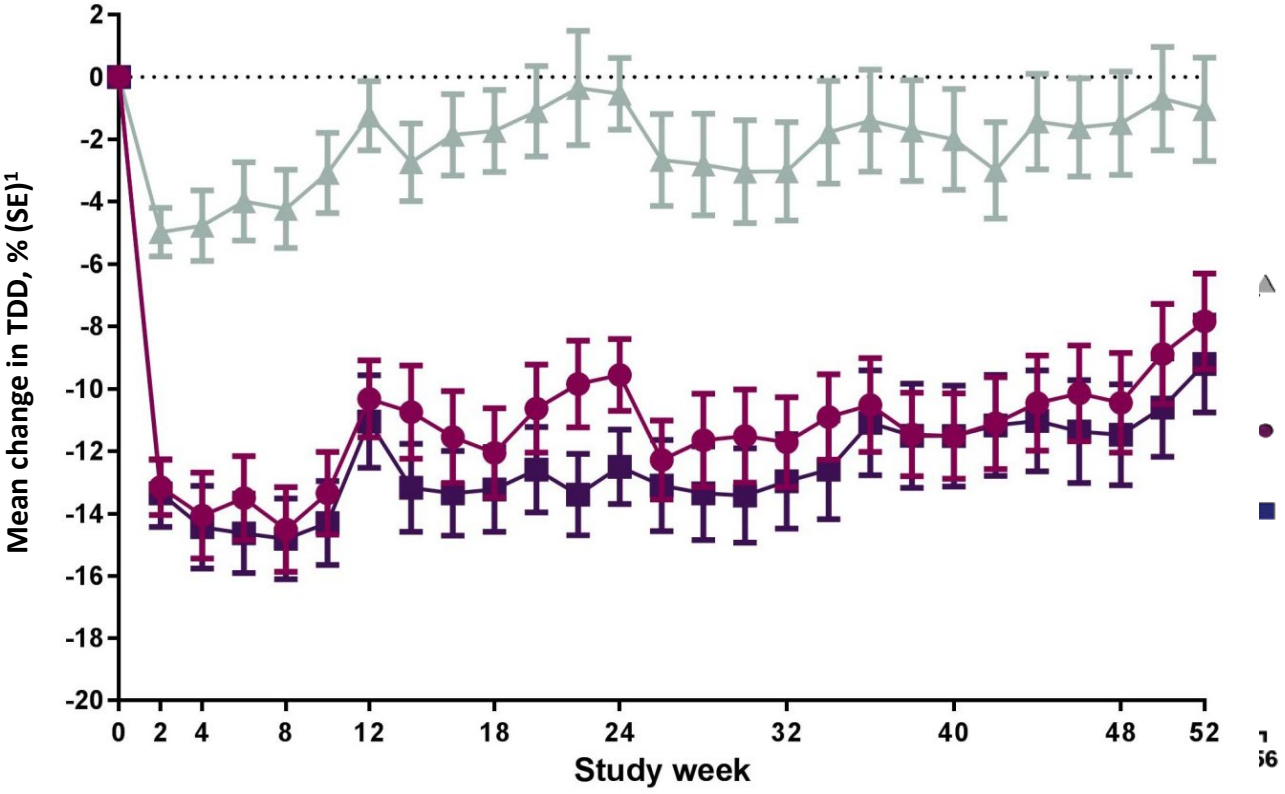
Dapagliflozin vs placebo in T1D
DEPICT-1

DEPICT Study Design



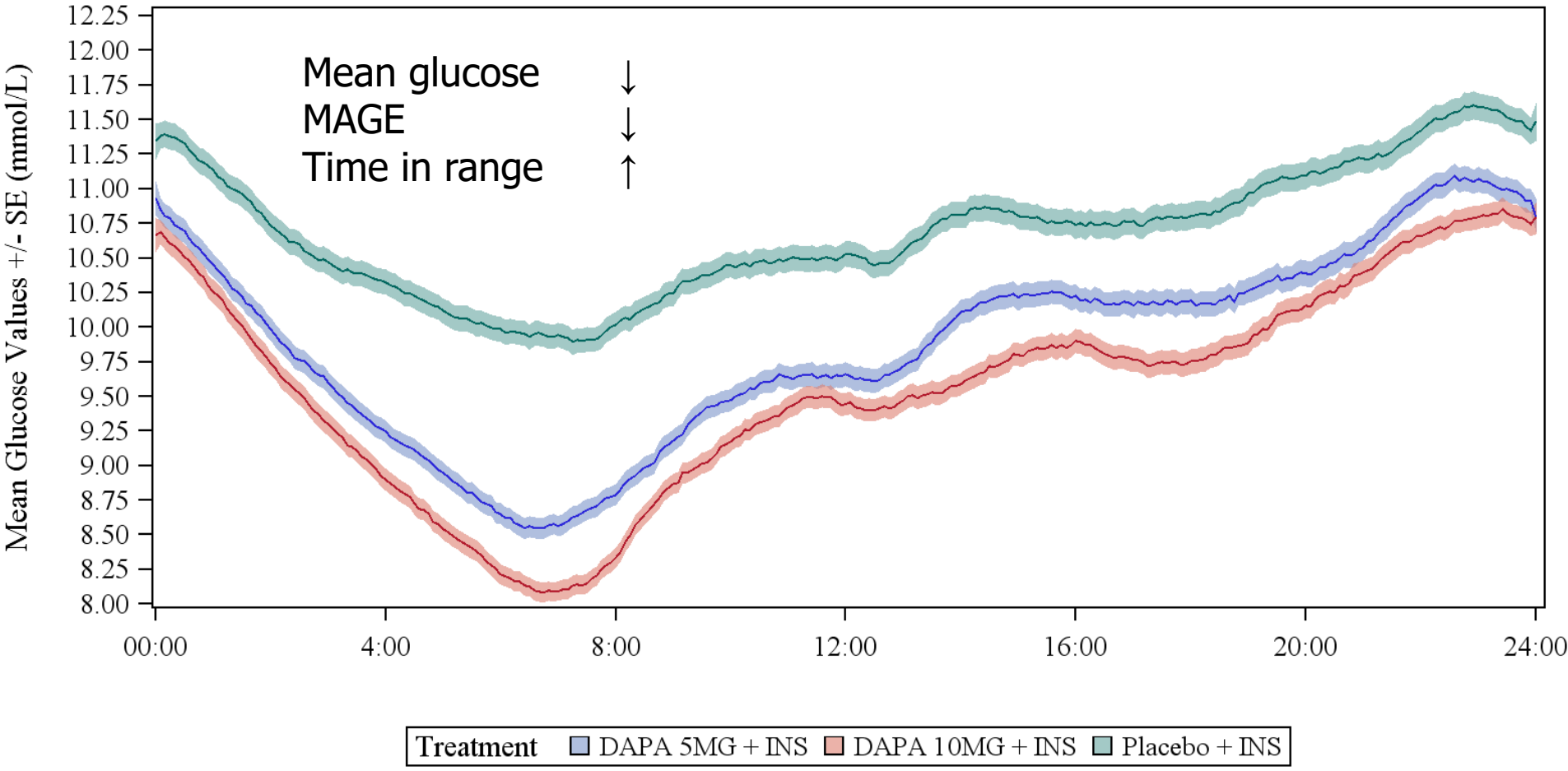
Dapagliflozin vs placebo in T1D

DEPICT-1



Patients per timepoint											
DAPA 5 mg + INS	258	256	251	246	240	237	237	232	231	229	225
DAPA 10 mg + INS	258	253	254	249	244	245	231	232	228	228	229
PBO + INS	258	257	257	246	236	231	225	222	218	219	213

Dapagliflozin vs placebo in T1D
DEPICT-1



Dapagliflozin vs placebo in T1D
DEPICT-1

	Over 24 weeks[1]			Over 52 weeks[2]		
	DAPA 5 mg + INS (N=277)	DAPA 10 mg + INS (N=296)	PBO + INS (N=260)	DAPA 5 mg + INS (N=277)	DAPA 10 mg + INS (N=296)	PBO + INS (N=260)
Patients with event sent for DKA adjudication, n (%)	16 (6)	19 (6)	6 (2)	24 (9)	28 (9)	9 (3)
Events of definite DKA, n	4	5	3	12	10	5
Patients with definite DKA, n (%)	4 (1)	5 (2)	3 (1)	11 (4)	10 (3)	5 (2)
IR/100 patient-years	3.29	3.78	2.64	4.76	3.67	2.15
Severity of events, n						
Mild	2	1	1	5	2	3
Moderate	1	3	1	3	6	1
Severe	1	1	1	4	2	1
Number of events of euglycemic DKA, n	0	2	0	NA	NA	NA
Primary cause of definite events, n						
Insulin pump failure	2	1	1	3	2	2
Missed insulin dose	1	3	1	4	4	1
Not identified	1	0	0	3	2	0
Other	0	1	1	2	2	2

SGLT2i in T1D

Why the risk of DKA varies across studies?

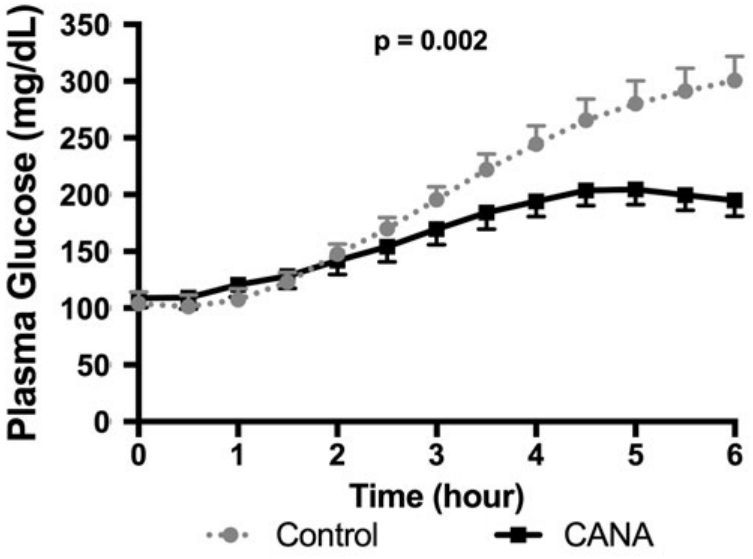
1) Random variations
2) SGLT1/2i or selective SGLT2i
3) Trial design

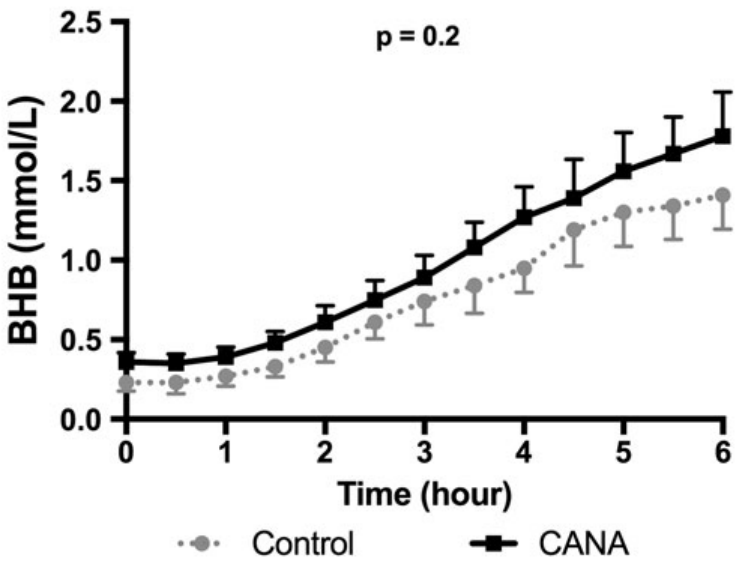
Dapagliflozin vs placebo in T1D
DEPICT-1

- Patients were provided with a combined home blood glucose and ketone meter
- Advised to measure glucose four times daily and ketones whenever glucose concentrations were consistently raised.
- Risk of ketoacidosis was reviewed at face-to-face visits every 2 weeks.
- Very simple rule that insulin doses should be reduced by no more than 20%

Pump suspension during SGLT2i

Stop pump at 3am (with PG <150 mg/dl and BHB <0,6 mmol/l)
→ check YSI and BHB every 30 min
→ up to 6h (9am) or until PG>350 mg/dl or BHB >2,5 mmol/l.





Patel et al. Diabetes Technol Ther 2017

SGLT2i in T1D

How to minimize DKA risk

- Patient selection
- Instruct the patients on «euglycemic» DKA
- Avoid excess insulin dose reduction (especially basal)
- Limit alcohol intake
- Sick days rule
- Monitor BHB
- Repeat at each visit!

SGLT2i in T1D

Conclusions

- **Patient selection**: overweight/obese, high insulin doses; well educated.
- Carefully **instruct the patient**
- **Keep only if effective**
- **Rechallenge** at each visit