

# Typ 1 diabetes inte bara insulin/ Nyheter inom teknik

Prof Johan Jendle  
Örebro Universitet



# Utveckling av behandling vid typ 1 diabetes



Kommersiell  
produktion av  
insulin



Intensiv insulin  
behandling



Humant insulin  
godkänt



Pumps+CGM

Vad händer  
här näst?

1921

1923

1949

1980

1981

1982

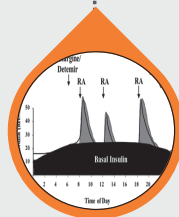
1993

2010

Insulin upptäcks  
beh av hundar  
med  
diabetes



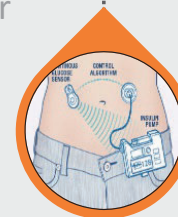
Standardiserad  
insulinspruta



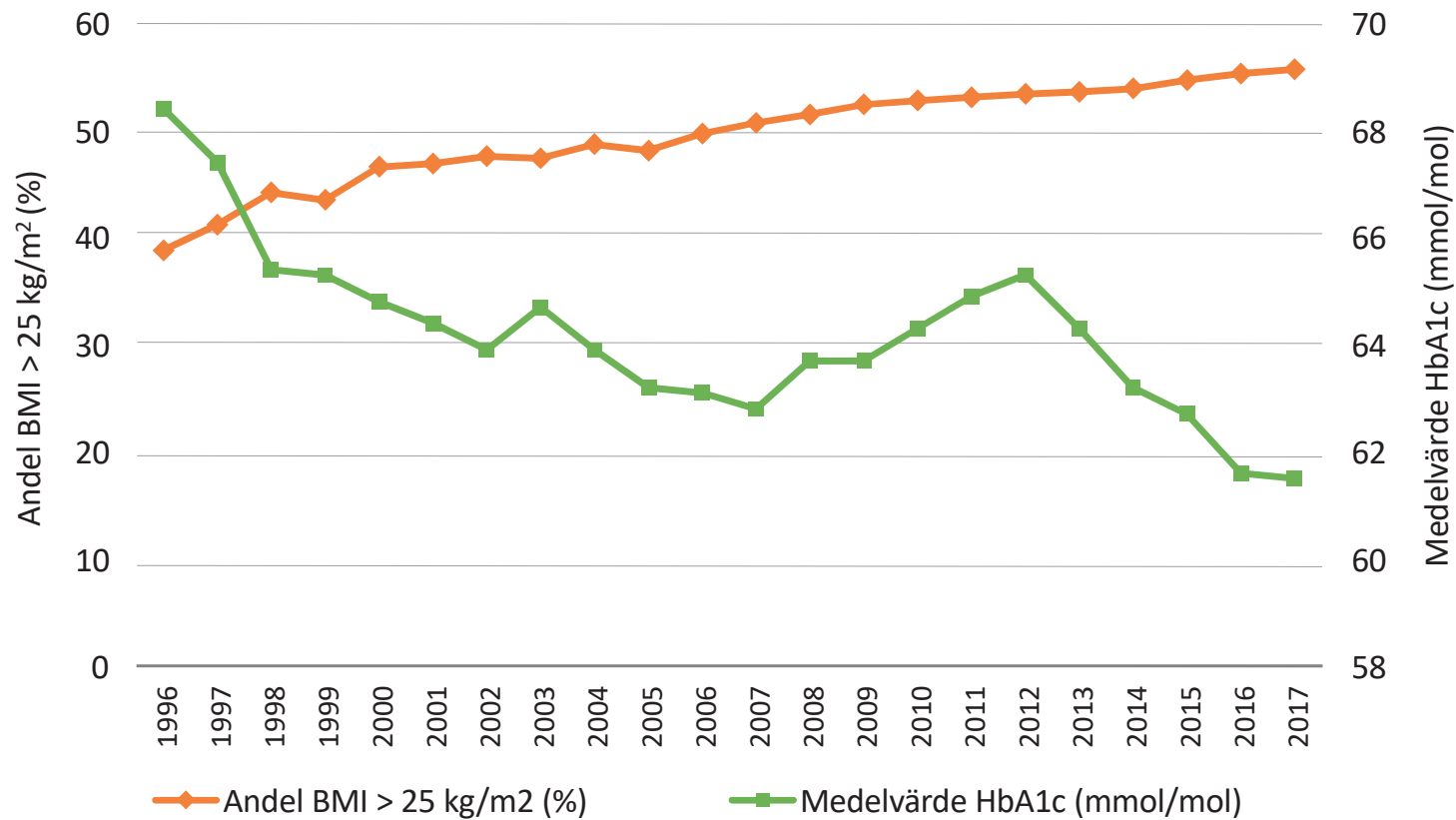
Glukosmätare  
för patienter



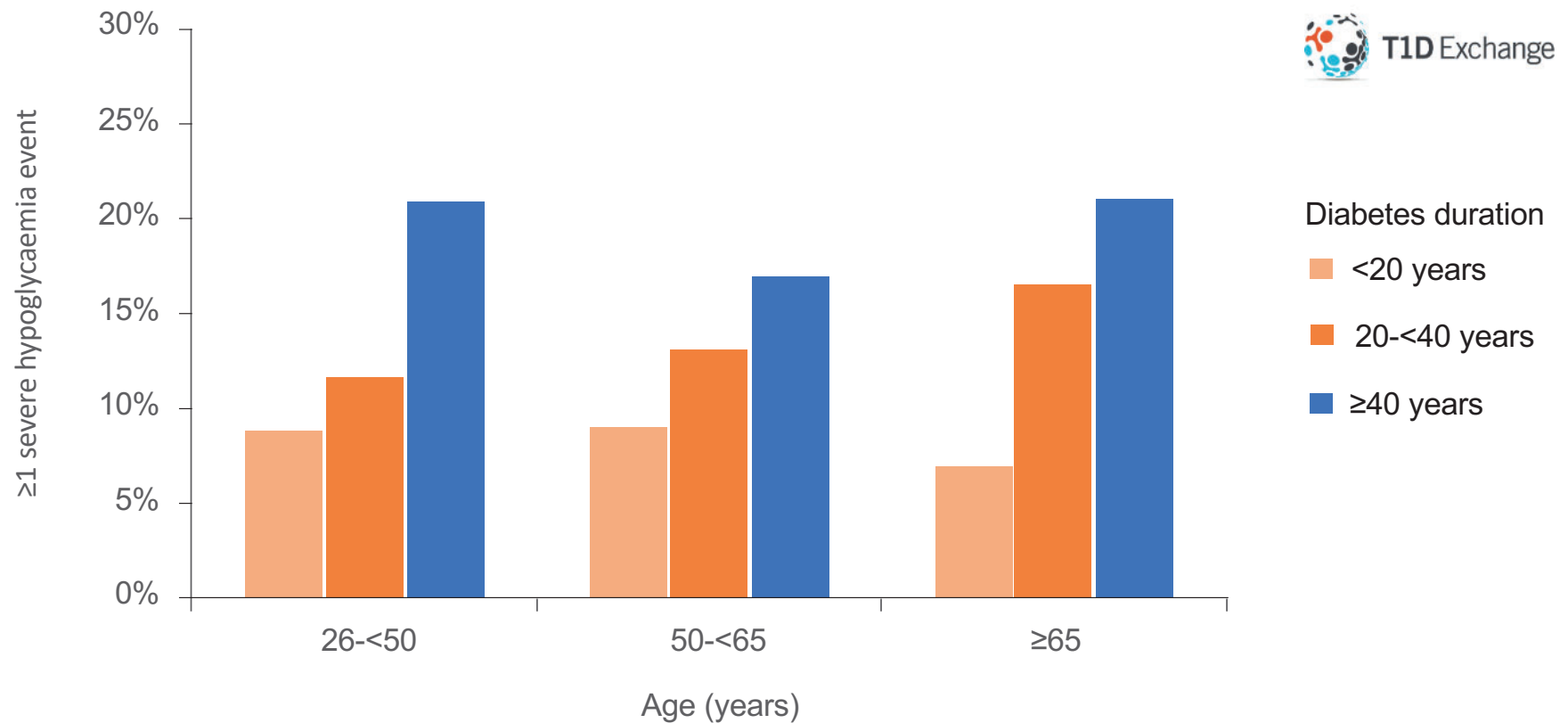
Studie som visar  
nyttan av god  
glukoskontroll



# Måluppfyllelse för behandling av typ 1 diabetes



# Andel typ 1 diabetes med allvarlig hypoglykemi relaterat ålder och diabetesduration



Weinstock RS, et al. J Clin Endocrinol Metab 2013;98:3411.

# Potential för SGLT-2 hämmare vid typ 1 diabetes?

## Påvisad effekt hos patienter med typ 2 diabetes



↓ HbA1c



↓ Kroppsvikt



↓ Blodtryck



↓ CV död (forxiga, jardiance)



↓ HF sjukhusinläggning

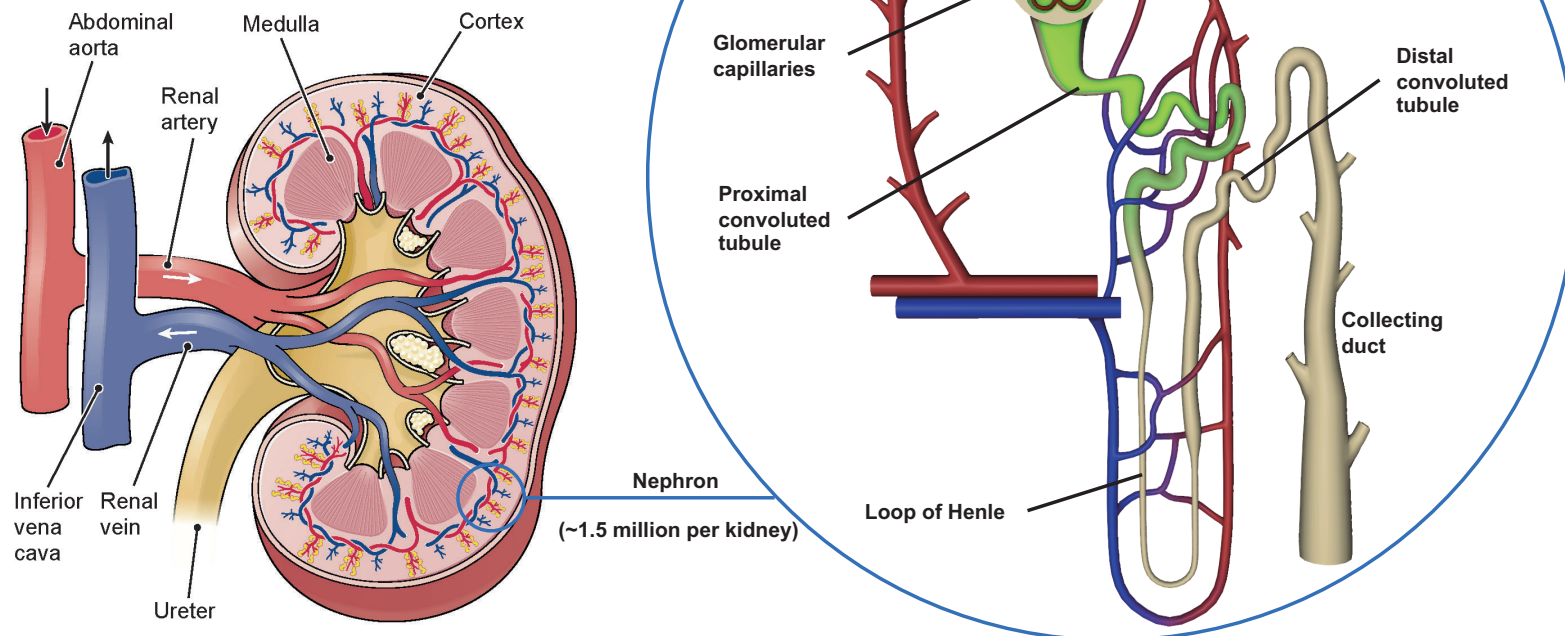


↓ Njurfunktions  
nedsättning

## Potential vid typ 1 diabetes?

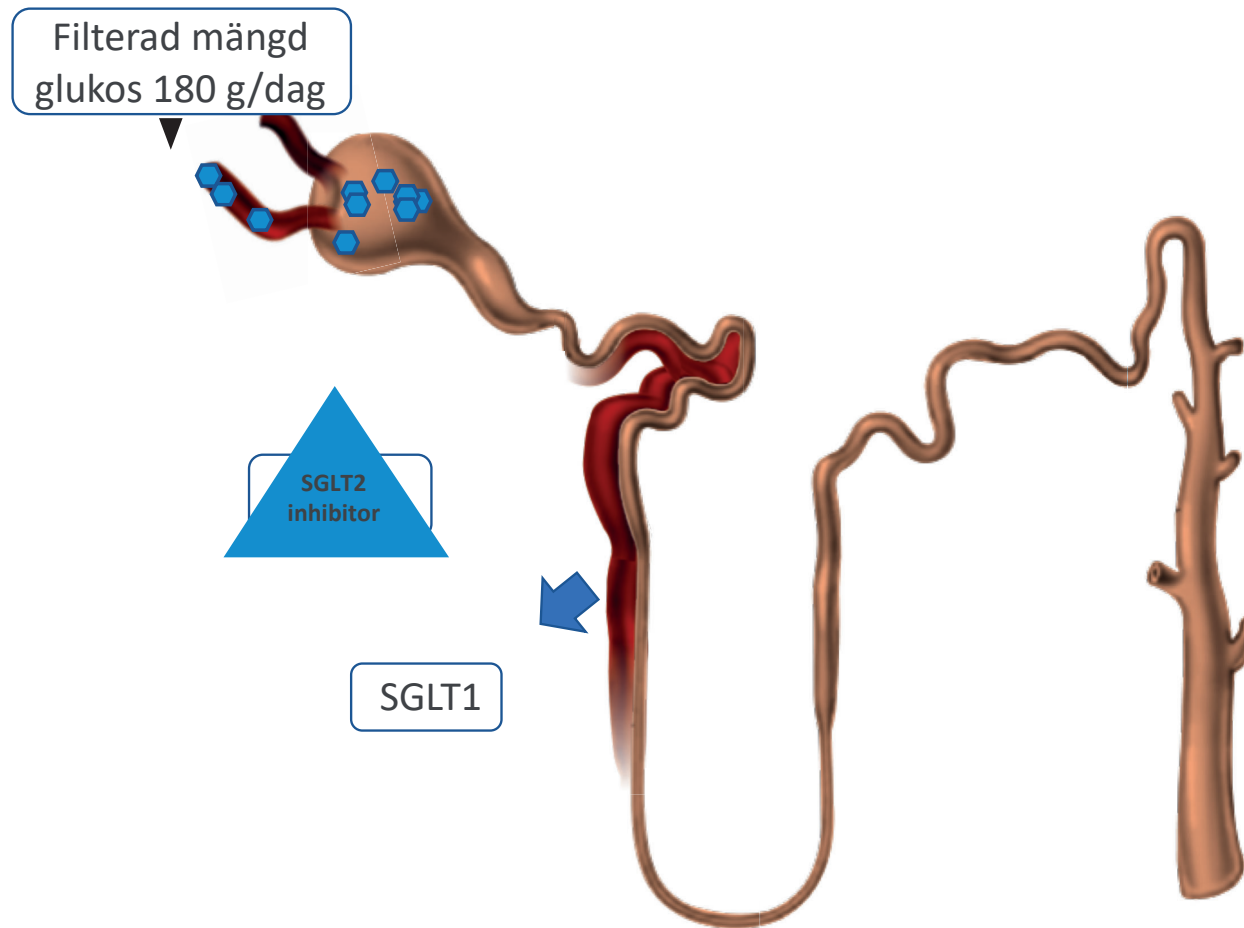
# Så fungerar njuren

Njurarna tar ~25% av cardiac output<sup>1</sup>  
(1,5 L/min hos en 70-kg man)



<sup>1</sup>Balat A. Kidney is in trouble with mediators. *Bosn J Basic Med Sci* 2010;10:S29–36.

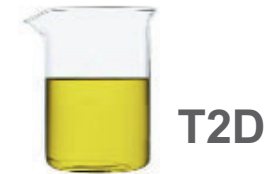
# Upptag av glukos i njure vid SGLT-2 hämmar behandling



\*Loss of ~ 80 g of glucose/day (~ 240 cal/day).  
Gerich JE. *Diabet Med.* 2010;27:136–142.

# Skillnader typ 1 och typ 2 diabetes

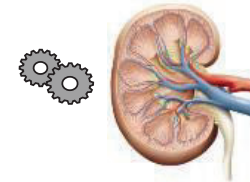
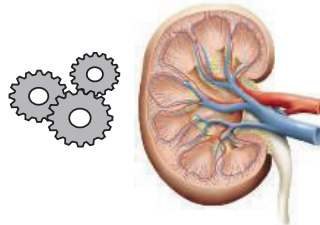
**Urinutsöndring av glukos**  
(↑ in T1D vs T2D)



**Glukos**  
(↑  
variabilitet/belastning)



**Njurfunktion**  
(↑ hyperfiltration)




**SGLT-2**  
(↑ expression/aktivitet)





# SGLT-2 hämmare som tilläggsbehandling vid typ 1 diabetes

Articles

 **Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial**

Paresh Dandona, Chantal Mathieu, Moshe Phillip, Lars Hansen, Steven C Griffen, Diethelm Tschöpe, Fredrik Thorén, John Xu, Anna Maria Langkilde, on behalf of the DEPICT-1 Investigators\*

**Summary**  
**Background** Dapagliflozin is a sodium-glucose cotransporter-2 inhibitor approved for the treatment of type 2 diabetes. We aimed to assess the efficacy and safety of dapagliflozin as an add-on to adjustable insulin in patients with inadequately controlled type 1 diabetes.

**Methods** DEPICT-1 was a double-blind, randomised, parallel-controlled, three-arm, phase 3, multicentre study done

Lancet Diabetes Endocrinol 2017; 5: 864-76  
Published Online September 14, 2017  
[http://dx.doi.org/10.1016/S2213-8587\(17\)30308-X](http://dx.doi.org/10.1016/S2213-8587(17)30308-X)

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.

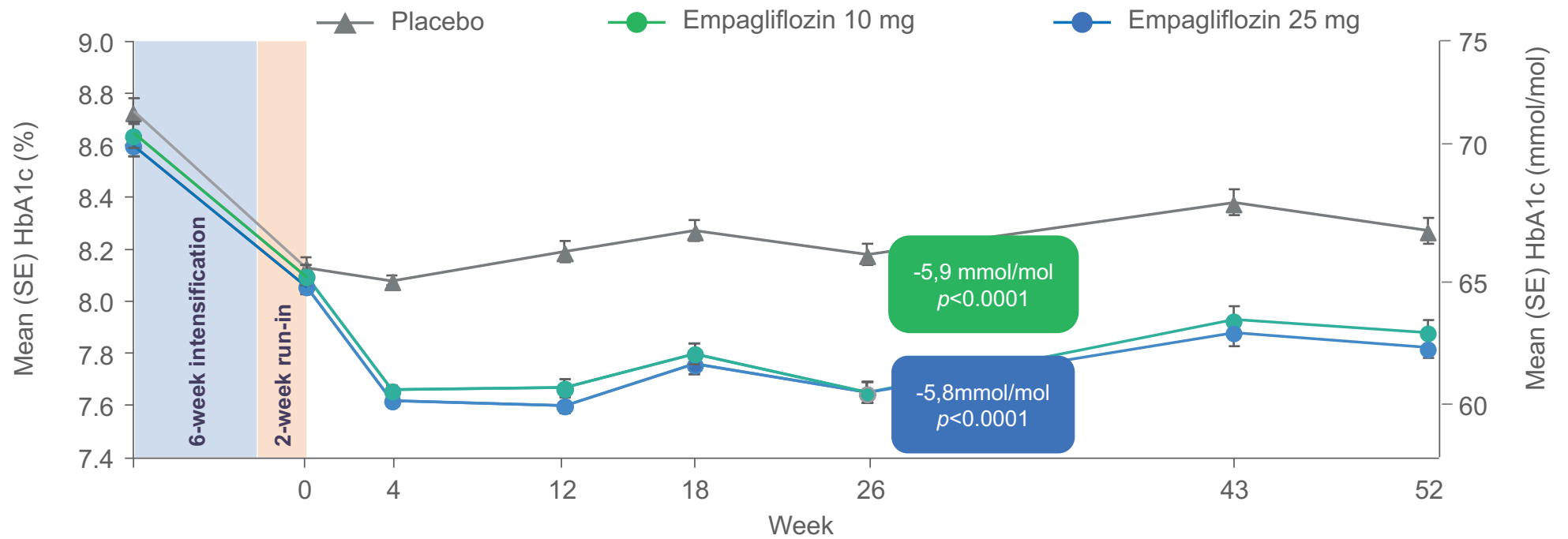
ABSTRACT

**BACKGROUND**  
In most patients with type 1 diabetes, adequate glycemic control is not achieved with insulin therapy alone. We evaluated the safety and efficacy of sotagliflozin, an oral inhibitor of sodium-glucose cotransporters 1 and 2, in combination with insulin treatment in patients with type 1 diabetes.

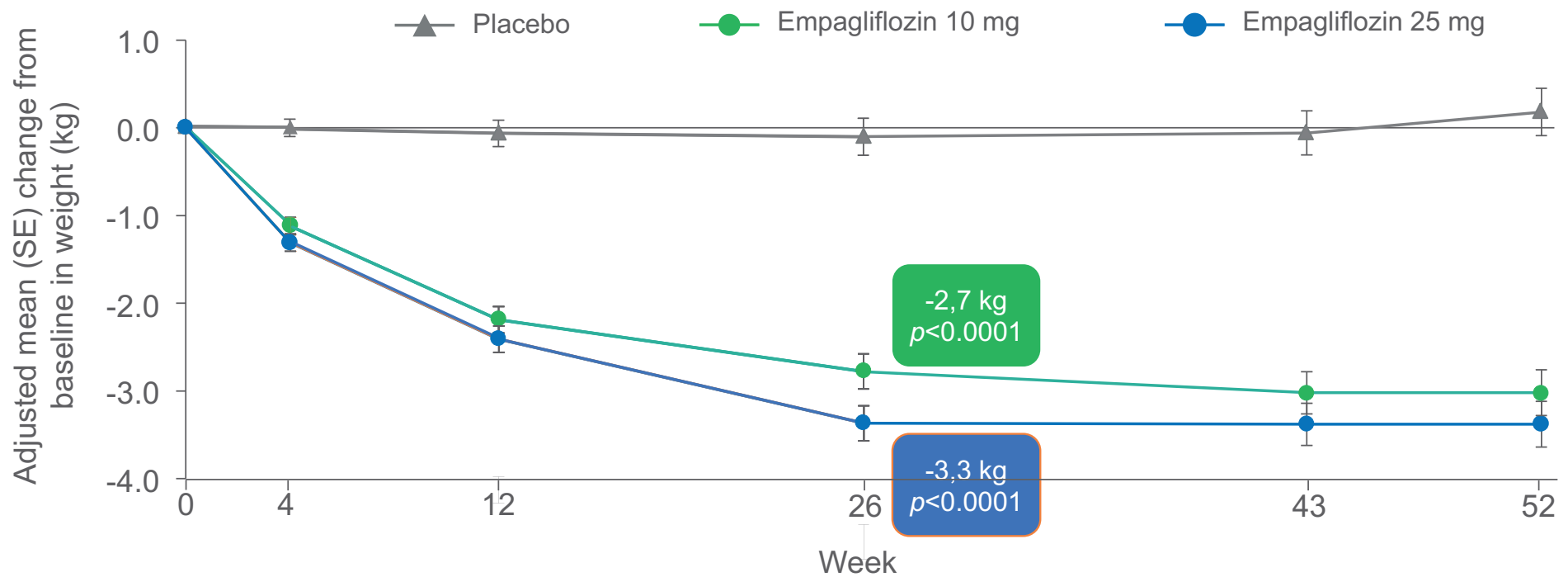
**METHODS**  
In this phase 3, double-blind trial, which was conducted at 133 centers worldwide, we randomly assigned 1402 patients with type 1 diabetes who were receiving treatment with any insulin therapy (pump or injections) to receive sotagliflozin (400 mg per day) or placebo for 24 weeks. The primary end point was a glycated hemoglobin level

From the University of Colorado Denver, Aurora (S.K.G.); the University of California at San Diego, San Diego (R.R.H.); Lexicon Pharmaceuticals, The Woodlands (P.B., D.G.-P., P.L., P.S.), the University of Texas Southwestern Medical Center, Dallas (D.K.M.), and Baylor College of Medicine and Texas Children's Hospital, Houston (J.A.K.) — all in Texas; the Diabetes Research Center, University of North Carolina School of Medicine, Durham (J.B.B.); the University of Leicester and University Hospitals of Leicester NHS Trust, Leicester

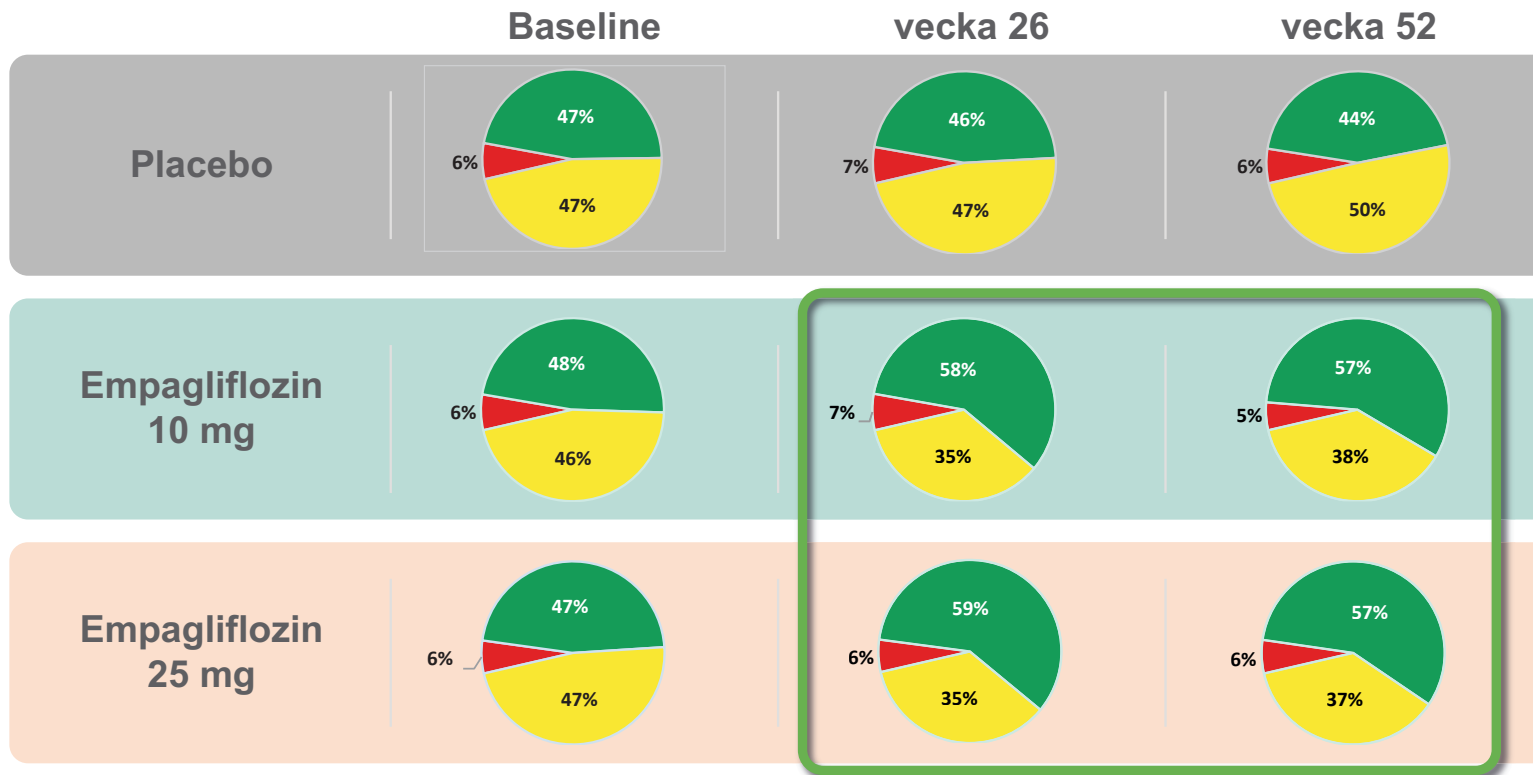
# EASE-2: HbA1c



# EASE-2: kroppsvikt



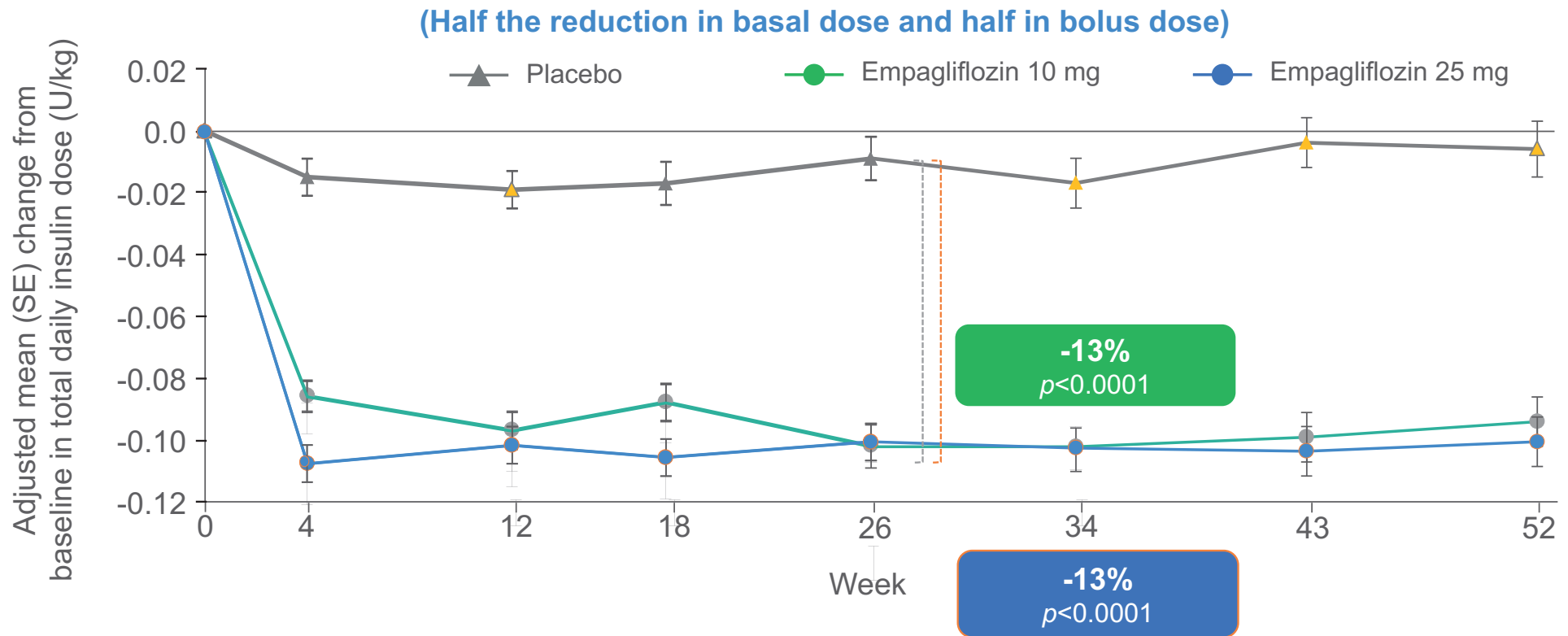
# EASE-2: CGM resultat



**Empagliflozin ökar tid inom målområde (TIR) 3 tim/dag**

■ Glukos  $\leq 3,9$  mmol/L   ■ Glukos  $> 3,9 - \leq 10$  mmol/L   ■ Glukos  $> 10$  mmol/L

# EASE-2: Totala insulin doser



# Diabetisk ketoacidosis

	Pooled placebo (n=484)	Pooled empagliflozin 10 mg (n=491)	Pooled empagliflozin 25 mg (n=489)	EASE-3 placebo (n=241)	EASE-3 empagliflozin 2.5 mg (n=241)
<b>Patients with certain DKA, n (%)</b>	6 (1.2)	21 (4.3)	16 (3.3)	3 (1.2)	2 (0.8)
Certain DKA events, n	6	21	18	3	2
<b>Incidence rate per 100 patient-years</b>	<b>1.77</b>	<b>5.94</b>	<b>5.05</b>	<b>2.52</b>	<b>1.65</b>
Events by severity, n					
Mild	1	6	4	1	2
Moderate	4	13	8	1	0
Severe	1	2	6	1	0
Fatal	0	0	1	0	0

# Diabetic ketoacidosis and pre-disposing factors

	Pooled* placebo (n=484)	Pooled empagliflozin 10 mg (n=491)	Pooled empagliflozin 25 mg (n=489)	EASE-3 placebo (n=241)	EASE-3 empagliflozin 2.5 mg (n=241)
<b>Patients with certain DKA, n (%)</b>	6 (1.2)	21 (4.3)	16 (3.3)	3 (1.2)	2 (0.8)
Certain DKA events with BG <13,9 mmol/L, n	0	9	5	0	1
<b>Certain DKA events, n</b>	6	21	18	3	2
<b>Pre-disposing factors, number of episodes</b>					
Concomitant illness/infection	2	7	12	2	0
Inadequate insulin administration (including insulin delivery malfunction)	1	11	10	0	1
Dietary changes/carbohydrate depletion	1	4	1	0	0
Severe dehydration	1	1	4	1	0
Other	3	9	4	2	2
None	0	0	0	0	0

# Hantera risken för DKA vid SGLT-2 hämmar behandling (STICH protocol)<sup>1,2</sup>



**ST**

- **STop SGLT2 inhibitor<sup>a</sup>**



**I**

- **Insulin administration to be continued**  
(take extra insulin)



**C**

- **Carbohydrate consumption**  
(consider taking extra carbohydrates if glucose levels are normal or low)



**H**

- **Hydration with suitable drink**  
(consider drinking water)

<sup>a</sup>Restart SGLT2 inhibitor once well, unless advised otherwise  
SGLT2, sodium–glucose co-transporter 2.

1. Danne T, et al. Diabetes Care 2019 [Epub ahead of print]; 2. AstraZeneca. Dapagliflozin Summary of Product Characteristics



# Hypoglykemie

	Empagliflozin		Placebo		Event Rate Ratio (95% CI)	Event Rate Ratio (95% CI)	p-value
	N	Patients/E vents, n	N	Patients/E vents, n			
<b>Severe hypoglycaemia</b>							
<b>EASE-2 and EASE-3</b>							
Empagliflozin 10 mg	491	20/33	484	15/21	1.47 (0.70, 3.10)		0.3095
Empagliflozin 25 mg	489	13/14	484	15/21	0.55 (0.23, 1.29)		0.1695
<b>EASE-3</b>							
Empagliflozin 2.5 mg	241	3/9*	241	6/6	0.18 (0.03, 1.15)		0.0698
<b>All nocturnal patient-reported (symptomatic and asymptomatic) hypos with BG &lt;54 mg/dl</b>							
Empagliflozin 2.5 mg	241	331	241	514	0.65 (0.48, 0.86)		0.0030
Empagliflozin 10 mg	491	1166	484	1844	0.65 (0.54, 0.78)		<0.0001
Empagliflozin 25 mg	489	1310	484	1844	0.72 (0.60, 0.87)		0.0005

0,0      0,1      0,3      1,0      4,0

← Favours empagliflozin      Favours placebo →

# Summering

## Empagliflozin 10 and 25 mg

- HbA1c (> 4.9 mmol/mol)
- Kroppsvikt (-3.4 kg)
- Insulindos (-13%)
- Systoliskt blodtryck (-3.9 mmHg)
- Tid i målområde för glukos (+3 tim/dag)
- Ökad risk DKA

## Empagliflozin 2.5 mg

- HbA1c: -3.1 mmol/mol
- Kroppsvikt (-1.8 kg)
- Insulindos (-6.4%)
- Systoliskt blodtryck (-2.1 mmHg)
- Tid i målområde för glukos (+1 tim/dag)
- DKA ej ökad risk