Gli inibitori di SGLT-2 possono essere impiegati nel diabete di tipo 1?

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Disclosures

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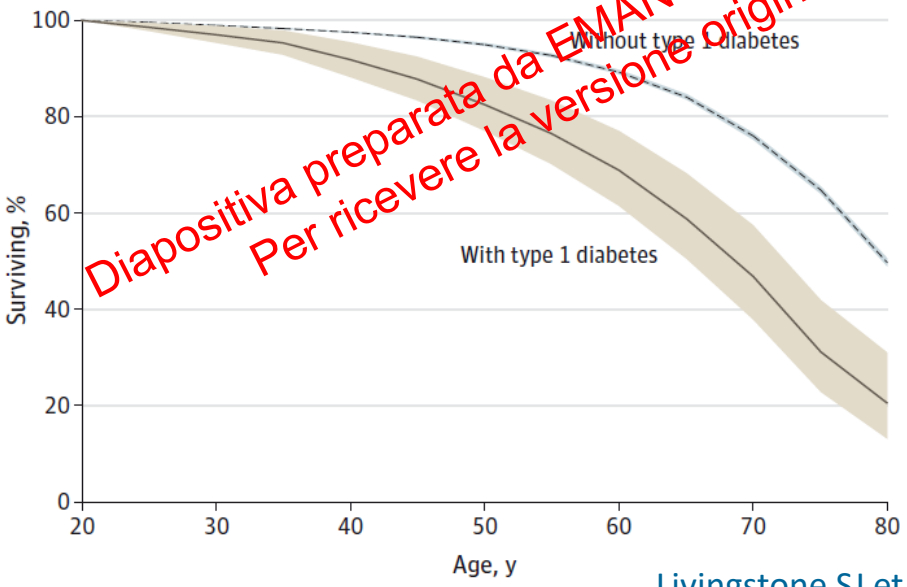
Type 1 diabetes: the reduced life expectancy

Original Investigation

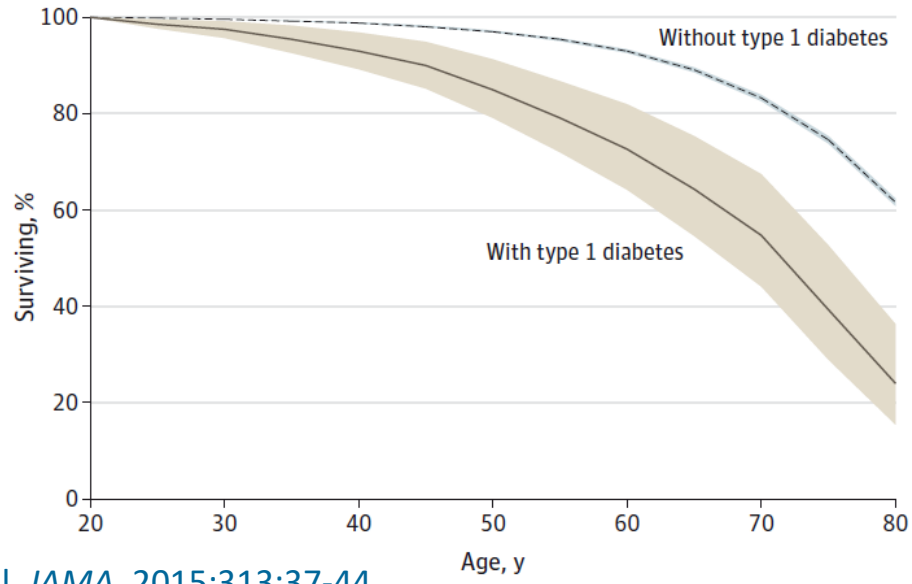
Estimated Life Expectancy in a Scottish Cohort With Type 1 Diabetes, 2008-2010

Shona J. Livingstone, MSc; Daniel Levin, MSc; Helen C. Looker, MBBS; Robert S. Lindsay, FRCP; Sarah H. Wild, FRCP; Nicola Joss, MD; Graham Leese, MD; Peter Leslie, MD; Rory J. McCrimmon, FRCP; Wendy Metcalfe, MD; John A. McKnight, FRCP; Andrew D. Morris, FRCP; Donald R. M. Pearson, FRCP; John R. Petrie, MD; Sam Philip, MD; Naveed A. Sattar, FRCP; Jamie P. Traynor, MD; Helen M. Colhoun, MD; for the Scottish Diabetes Research Network epidemiology group and the Scottish Renal Registry

- 11 years



- 13 years



Livingstone SJ et al. *JAMA*. 2015;313:37-44

Type 1 diabetes: the reduced life expectancy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glycemic Control and Excess Mortality in Type 1 Diabetes

Marcus Lind, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Mikhail Kosiborod, M.D., Soffia Gudbjörnsdottir, M.D., Ph.D., Aldina Pivodic, M.Sc., Hans Wedel, Ph.D., Sofia Dahlqvist, Mark Clements, M.D., Ph.D., and Annika Rosengren, M.D., Ph.D.

CONCLUSIONS

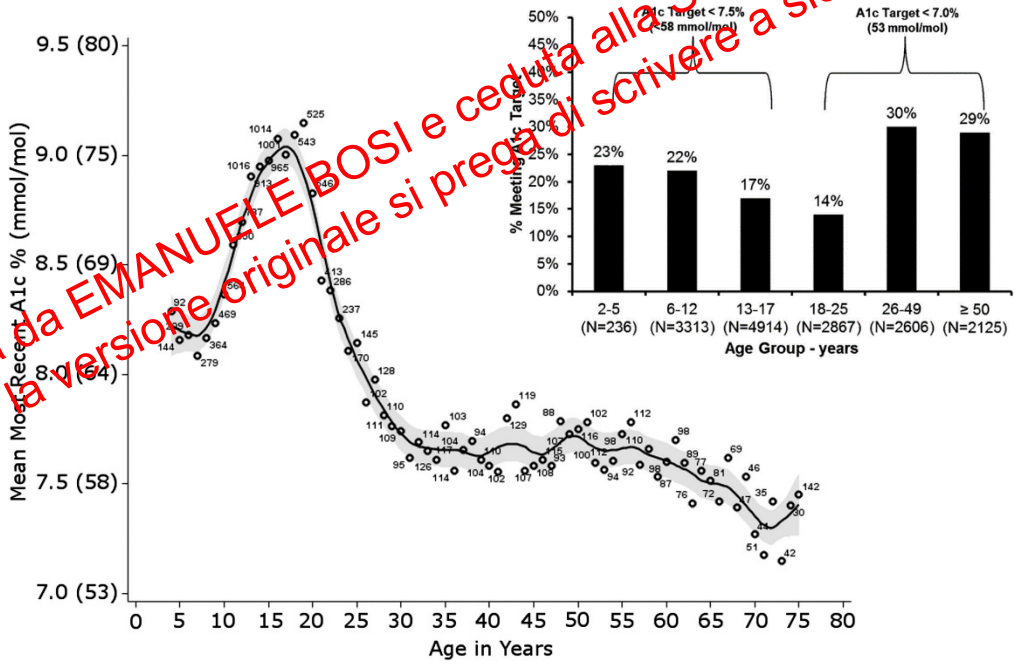
In our registry-based observational study, patients with type 1 diabetes and HbA1c ≤6.9% had a risk of death from any cause or from cardiovascular causes that was twice as high as the risk for matched controls.

N Engl J Med 2014;371:1972-82.

Type 1 diabetes: the unacceptable glucose control

Mean HbA_{1c} by age

Individuals with type 1 diabetes participating in the T1D Exchange clinic registry. Data from 16,061 participants updated between 1 September 2013 and 1 December 2014



Miller KE et al. Diabetes Care 2015;38:971-978

Rationale for non insulin compounds in T1D

- Insulin treatment in type 1 diabetes has shortcomings and most patients are not at target;
- Therefore, the search for possible advantages (e.g. reduced hyperglycemia, hypoglycemia and glucose variability, body weight, blood pressure, etc.) by adding a non-insulin compound is fully justified;
- Among old and novel agents, almost all compounds used in type 2 diabetes may have some appeal;
- Recent experiences with metformin (REMOVAL) and the GLP-1 receptor agonist Liraglutide (ADJUNCT ONE) have not been convincing;
- SGLT-2 inhibitors look very attractive.

SGLT-2 (and SGLT-1) Inhibition: Potential Clinical Benefit in Type 1 Diabetes

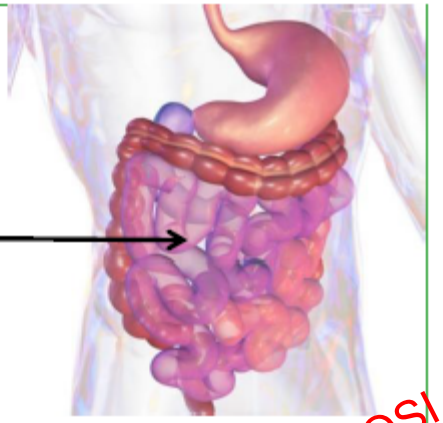
- **Glucose lowering**
  - Decrease in glucose variability
  - Reduced glucotoxicity
  - Reduced insulin need
- **Insulin-independent mechanisms**
  - Ability to combine with insulin
  - Ability to work at all stages of disease
- **Osmotic diuresis**
  - Weight loss
  - Decrease in blood pressure
- **Loss of excess calories in the urine**
  - Sustained weight loss when required
  - Mitigation of weight gain from insulin therapy

SGLT-2 and SGLT-2/1 Inhibition in Type 1 Diabetes

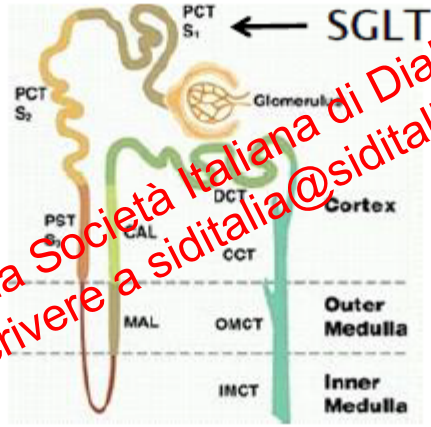
Preliminary experiences:

- Dapagliflozin
- Canagliflozin
- Empagliflozin
- Sotagliflozin

Sotagliflozin:
First-in-Class Dual SGLT1/SGLT2 Inhibitor for Diabetes



- SGLT1 is the primary transporter for glucose and galactose in the gastrointestinal (GI) tract
- Inhibiting SGLT1 in the GI tract **reduces post-prandial glucose** and **elevates GI hormones** such as GLP-1 and PYY that have been associated with metabolic benefits
- Mechanism is independent of insulin and is not affected by declining renal function



- SGLT2 reabsorbs 90% of filtered glucose in the kidney
- Inhibiting SGLT2 in the kidney **increases glucose excretion in the urine**, resulting in reduced blood glucose
- Mechanism is independent of insulin but diminishes in effect with declining renal function

Dual SGLT1/SGLT2 inhibition, involving inhibition of SGLT1 in the GI tract and associated effects on post-prandial glucose, is characterized by less urinary glucose excretion than seen when inhibiting SGLT2 alone, and in type 1 diabetes, changes only in mealtime insulin needs (no change in basal insulin requirements)

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SGLT-2 inhibitors in T1D: RCTs

INHIBITION OF SODIUM–GLUCOSE COTRANSPORTERS

Exploring the Potential of the SGLT2 Inhibitor Dapagliflozin in Type 1 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

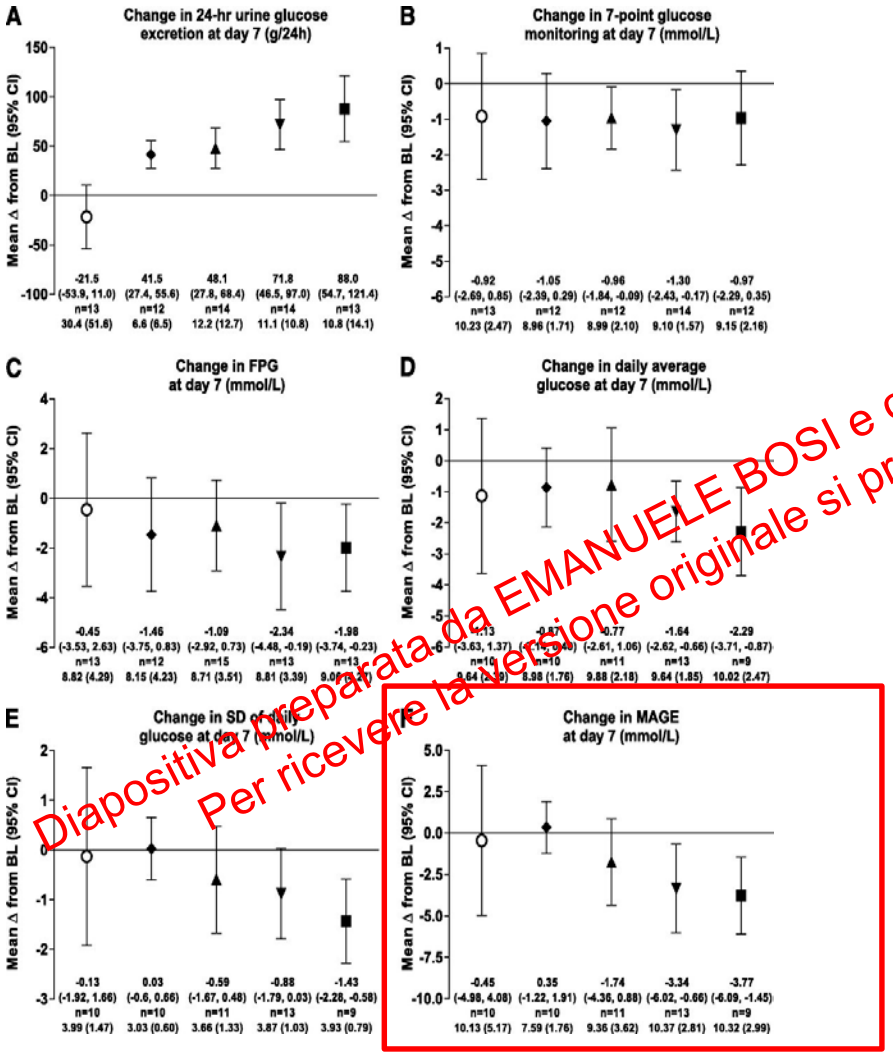
Robert R. Henry,[1,2] Julio Rosenstock,[3] Steven Edelman,[1,2] Sunder Mudaliar,[1,2] Alexandros-Georgios Chalamandaris,[4] Sreeneeranj Kasichayanula,[5] Allyson Bogle,[5] Nayyar Iqbal,[5] James List,[5] and Steven C. Griffen[5]

Diabetes Care 2015;38:412–419 | DOI: 10.2337/dc13-2955

CONCLUSIONS

This exploratory study of dapagliflozin in adults with type 1 diabetes demonstrated acceptable short-term tolerability and expected pharmacokinetic profiles and increases in urinary glucose excretion. Within the dapagliflozin groups, dose-related reductions in 24-h glucose, glycemic variability, and insulin dose were suggested, which provide hope that SGLT2 inhibition may prove in larger randomized controlled trials to be efficacious in reducing hyperglycemia in type 1 diabetes.

Dapagliflozin in T1D



Mean changes from baseline at day 7 in 24-h urinary glucose excretion (A);
average daily glucose derived from 7-point glucose monitoring (B);
FPG (C);
DAG from 24-h CGM (D);
SD of glucose values from 24-h CGM (E);
and mean amplitude of glycemic excursion from 24-h CGM (F). ○, placebo plus insulin; ◆, dapagliflozin 1 mg plus insulin; ▲, dapagliflozin 2.5 mg plus insulin; ▼, dapagliflozin 5 mg plus insulin; and ■, dapagliflozin 10 mg plus insulin.

American Diabetes Association.

Henry RR et al. Diabetes Care 2015;38:412-419

SGLT-2 inhibitors in T1D: RCTs

SPECIAL ARTICLE COLLECTION: INSULIN

Efficacy and Safety of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-on to Insulin in Patients With Type 1 Diabetes

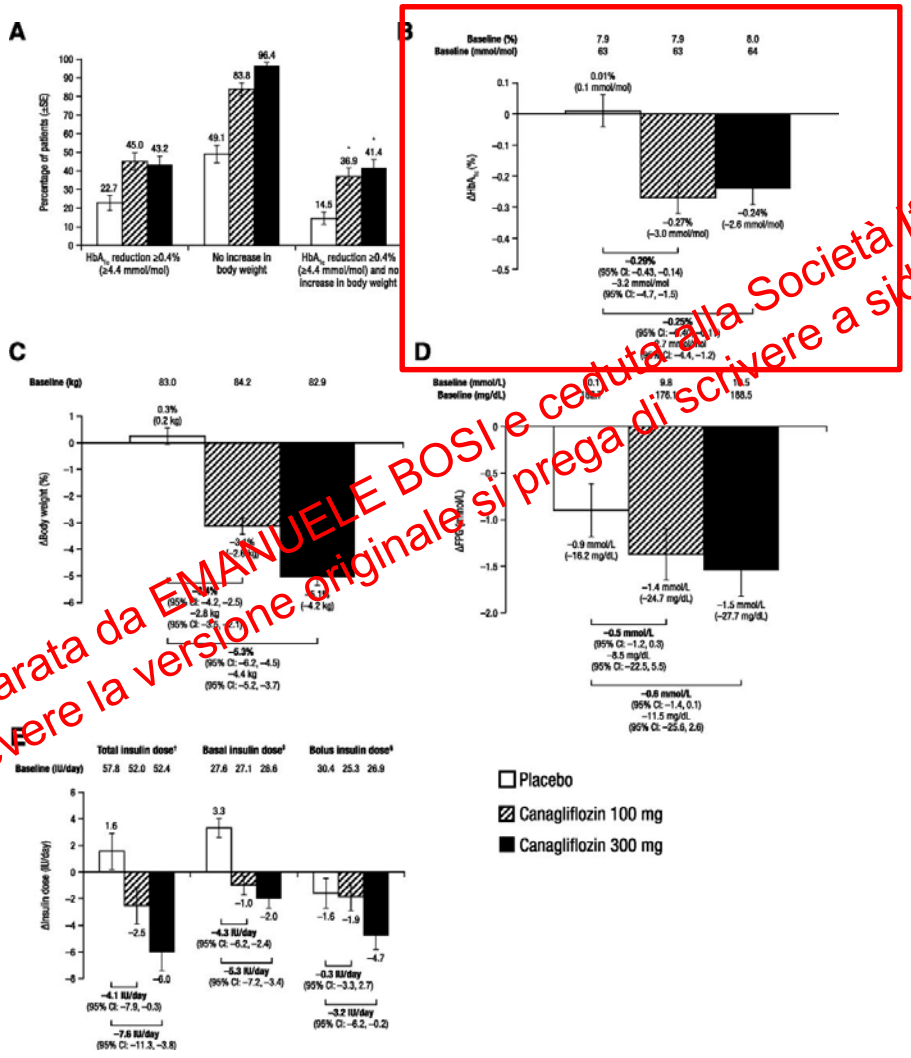
Robert R. Henry,[1,2] Payal Thakkar,[3] Cindy Tong,[3] David Polidori,[4] and Maria Alba[3]

Diabetes Care 2015;38:2258–2265 | DOI: 10.2337/dc15-1730

CONCLUSIONS

Canagliflozin provided reductions in HbA_{1c}, body weight, and insulin dose with no increase in hypoglycemia, but increased rates of ketone-related AEs, including DKA, in adults with type 1 diabetes inadequately controlled with insulin.

Canagliflozin in T1D



Proportion of patients with HbA1c reduction ≥0.4% (≥4.4 mmol/mol) from baseline and no weight gain (A), change from baseline in HbA1c (B), percentage change from baseline in body weight (C), change from baseline in FPG (D), and change from baseline in insulin dose at week 18 (E).

American Diabetes Association.

Henry RR et al. Diabetes Care 2015;38:2258-2265

SGLT-2 inhibitors in T1D: RCTs

original article

Diabetes, Obesity and Metabolism 17: 928–935, 2015.

ORIGINAL ARTICLE

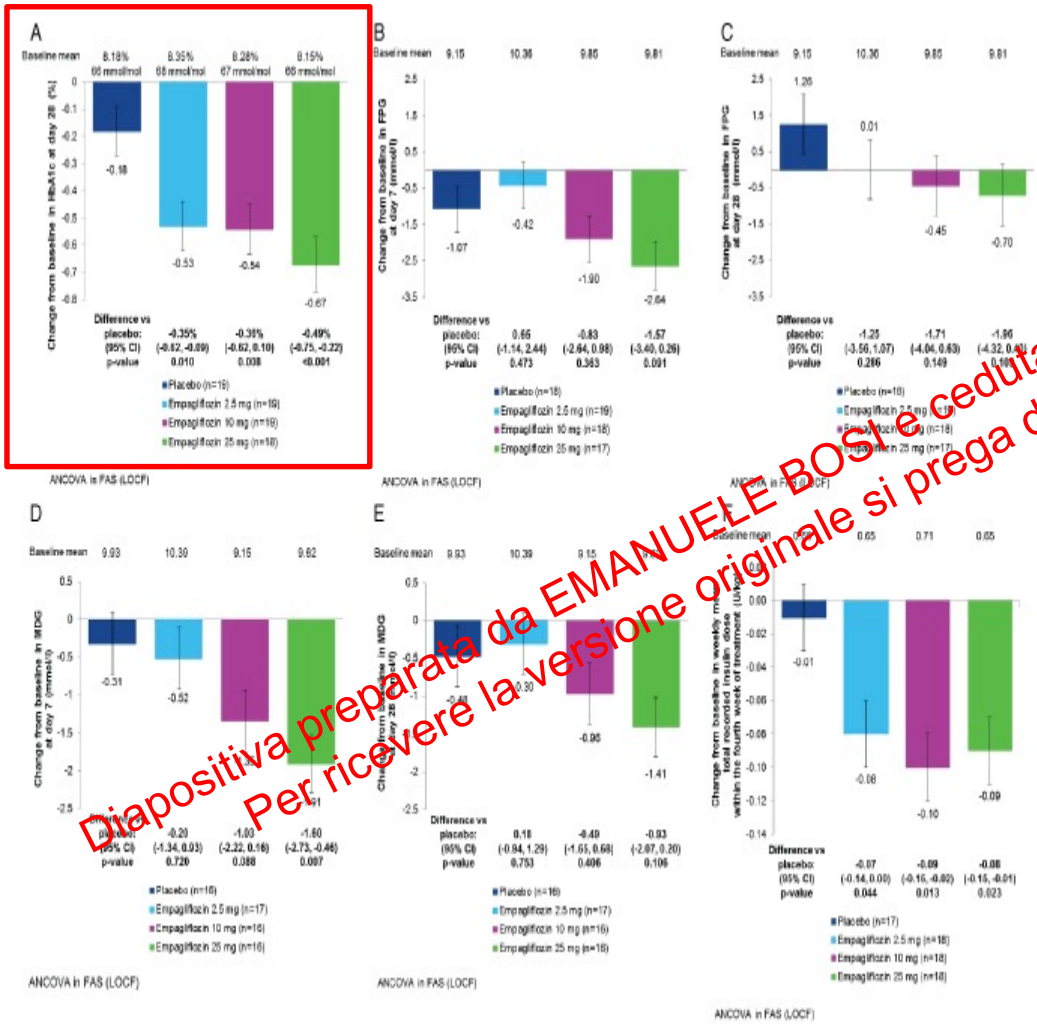
Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1)

T. R. Pieber[1,†], S. Famulla[2,†], J. Eilbracht[3], J. Cescutti[4], N. Soleymanlou[5], O. E. Johansen[6], H. J. Woerle[7], U. C. Broedl[7] & S. Kaspers[7]

Conclusions: In patients with type 1 diabetes, empagliflozin for 28 days as adjunct to insulin increased UGE, improved HbA1c and reduced weight with lower insulin doses compared with placebo and without increasing hypoglycaemia.

Pieber TR et al. Diabetes Obes Metab 17: 928-935, 2015

Empagliflozin in T1D



A) Change from baseline in glycated haemoglobin (HbA1c) on day 28.
B) Change from baseline in fasting plasma glucose (FPG) on day 7.
C) Change from baseline in FPG on day 28
D) Change from baseline in mean daily glucose (MDG) at day 7
E) Change from baseline in MDG on day 28
F) Change from baseline in weekly mean total recorded insulin dose within the fourth week of treatment

Data are adjusted mean (standard error) values. CI, confidence interval.

Pieber TR et al. Diabetes Obes Metab 17: 928-935, 2015

Sotagliflozin in T1D

Sotagliflozin, a Dual SGLT1 and SGLT2 Inhibitor, as Adjunct Therapy to Insulin in Type 1 Diabetes

DOI: 10.2337/dc14-2805

Arthur T. Sands,[1] Brian P. Zambrowicz,[1] Julio Rosenstock,[2] Pablo Lapuerta,[1] Bruce W. Bode,[3] Satish K. Garg,[4] John B. Buse,[5] Phillip Banks,[1] Rubina Heptulla,[6] Marc Rendell,[7] William T. Cefalu,[8] and Paul Strumph[1]

Sands AT et al. Diabetes Care 2015; 38; 1181

Summary on SGLT-2 and SGLT-2/1 in T1D on preliminary (phase II) studies

Preliminary experience with SGLT-2 and dual SGLT-1/2 inhibitors in T1D indicates beneficial trends on several measures:

- HbA1c
- glucose variability
- body weight
- insulin dose

Neutral effect on hypoglycemia;

Increased risk of DKA.

SGLT-2 and SGLT-2/1 Inhibition in Type 1 Diabetes

The large trials:

- Dapagliflozin: DEPICT-1, DEPICT-2
- Sotagliflozin: inTandem1, inTandem2, inTandem3

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**

Dandona P et al. Lancet Diabetes Endocrinol 2017;5:864-876

Dapagliflozin in T1D: DEPICT-1
Baseline patient characteritics

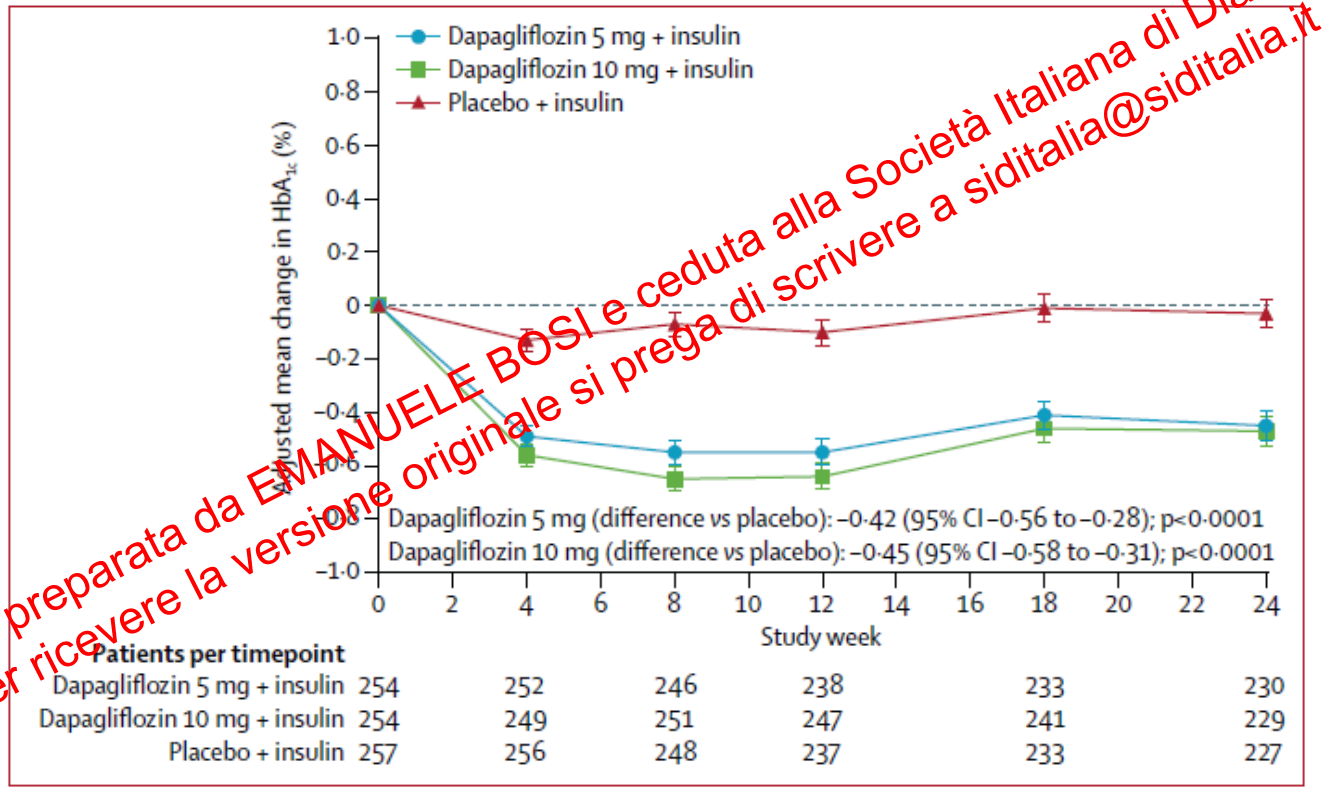
	Dapagliflozin 5 mg plus insulin (n=259)	Dapagliflozin 10 mg plus insulin (n=259)	Placebo plus insulin (n=260)
Sex			
Men	111 (43%)	130 (50%)	132 (51%)
Women	148 (57%)	129 (50%)	128 (49%)
Age (years)	41·9 (14·1)	42·7 (14·1)	42·7 (13·6)
Bodyweight (kg)	80·8 (18·2)	82·0 (17·3)	84·3 (18·3)
BMI (kg/m²)	28·3 (5·8)	28·1 (5·1)	28·6 (5·2)
Ethnic origin			
White	248 (96%)	247 (95%)	249 (96%)
Black or African-American	5 (2%)	7 (3%)	3 (1%)
Asian	0	0	1 (<1%)
Other	6 (2%)	5 (2%)	7 (3%)
Geographical region			
North America	68 (26%)	72 (28%)	70 (27%)
Latin America	30 (12%)	24 (9%)	25 (10%)
Europe	146 (56%)	154 (59%)	161 (62%)
Asia-Pacific	15 (6%)	9 (3%)	4 (2%)
Duration of type 1 diabetes (years)	19·7 (12·0)	19·9 (11·1)	21·2 (12·2)
HbA_{1c} (%)	8·53% (0·61)	8·52% (0·64)	8·53% (0·67)
HbA_{1c} (mmol/mol)	69·6 (7·8)	69·6 (7·0)	69·7 (7·3)
Total baseline insulin dose			
Dose (IU)	62·1 (44·2)	59·4 (28·2)	63·1 (29·3)
Dose/weight (IU/kg)	0·76 (0·52)	0·71 (0·26)	0·74 (0·25)
Method of insulin administration			
MDI	162 (63%)	165 (64%)	165 (63%)
CSII	97 (37%)	94 (36%)	95 (37%)
Use of CGM	85 (33%)	86 (33%)	86 (33%)
HbA_{1c} range at randomisation			
≥7·5% to <9·0% (≥58·5 to <74·9 mmol/mol)	194 (75%)	198 (76%)	194 (75%)
≥9·0% to ≤10·5% (≥74·9 to ≤91·3 mmol/mol)	65 (25%)	61 (24%)	66 (25%)

Data are n (%) or mean (SD). MDI=multiple daily injections. CSII=continuous subcutaneous insulin infusion. CGM=continuous glucose monitoring.

Table 1: **Demographic and baseline characteristics**

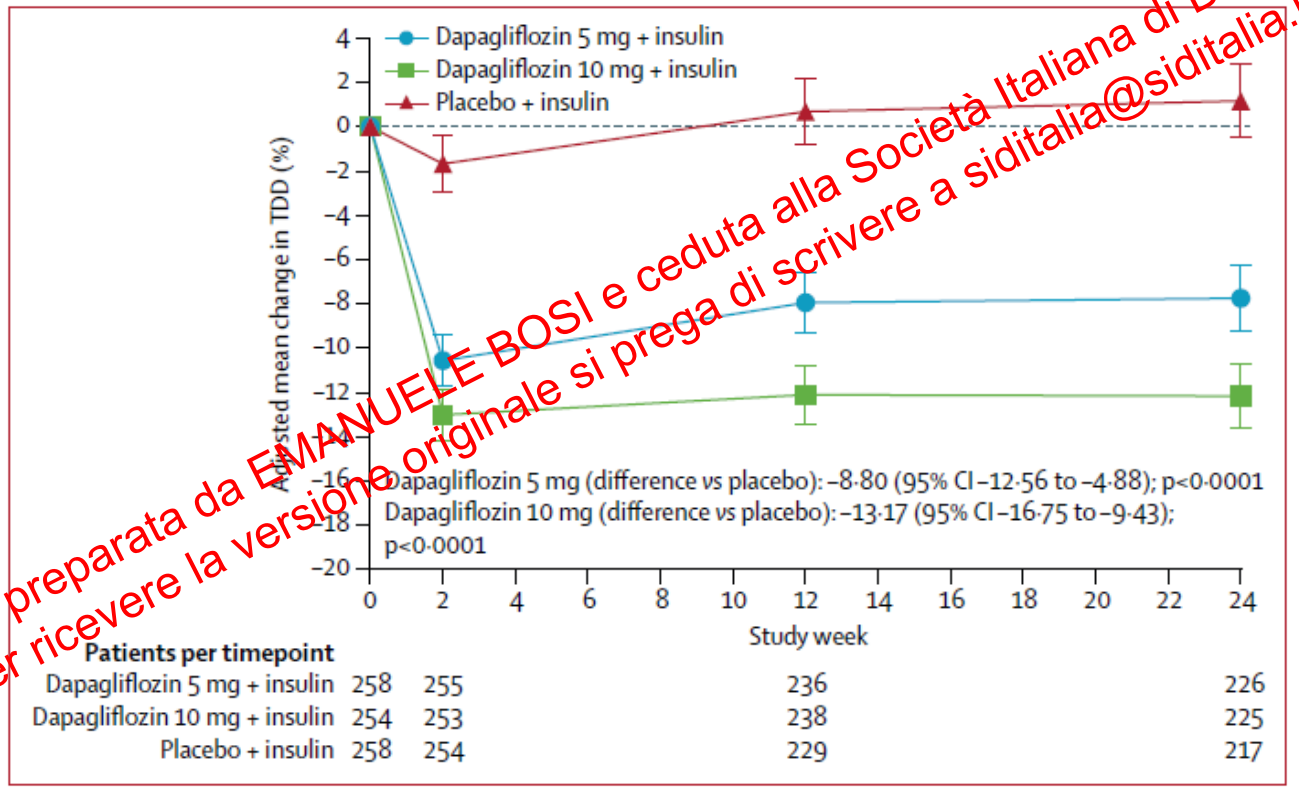
Dandona P et al. Lancet Diabetes Endocrinol 2017;5:864-876

Dapagliflozin in T1D: DEPICT-1
HbA1c at 24 weeks



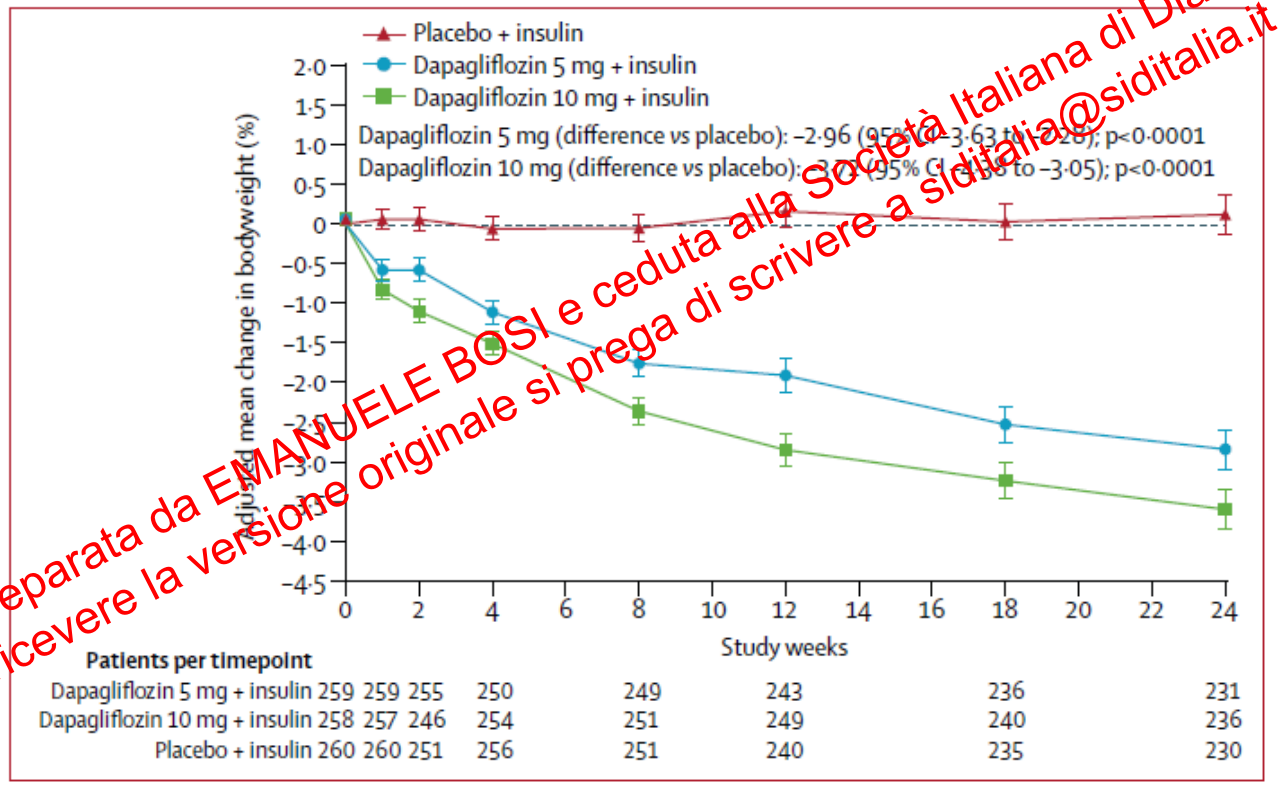
Dandona P et al. Lancet Diabetes Endocrinol 2017;5:864-876

Dapagliflozin in T1D: DEPICT-1
Insulin dose at 24 weeks



Dandona P et al. Lancet Diabetes Endocrinol 2017;5:864-876

Dapagliflozin in T1D: DEPICT-1
Body weight at 24 weeks



Dandona P et al. Lancet Diabetes Endocrinol 2017;5:864-876

Dapagliflozin in T1D: DEPICT-1
CGM at 24 weeks

	Dapagliflozin 5 mg plus insulin (n=259)	Dapagliflozin 10 mg plus insulin (n=259)	Placebo plus insulin (n=260)
CGM mean value (mg/dL)			
N*	238	239	234
Baseline mean (SD)	192·9 (29·9)	189·4 (27·3)	192·4 (29·4)
Week 24 mean (SD)	178·3 (31·8)	173·6 (26·7)	192·1 (34·2)
Adjusted mean change from baseline (SE)	−10·3 (1·9)	−13·0 (1·9)	5·1 (1·9)
Difference from placebo (95% CI)	−15·3 (−20·2 to −10·5)	−18·0 (−23·0 to −13·1)	NA
p value†	<0·0001	<0·0001	NA
CGM MAGE (mg/dL)			
N*	238	239	234
Baseline mean (SD)	170·7 (31·1)	171·0 (31·4)	169·1 (34·3)
Week 24 mean (SD)	152·2 (34·5)	150·5 (32·8)	168·1 (34·9)
Adjusted mean change from baseline (SE)	−14·9 (2·0)	−16·6 (2·0)	2·4 (2·0)
Difference from placebo (95% CI)	−17·3 (−22·5 to −12·1)	−18·9 (−24·1 to −13·7)	NA
p value†	<0·0001	<0·0001	NA
24 h CGM values within >70 mg/dL to ≤180 mg/dL			
N*	238	239	234
Baseline mean (SD)	43·2 (12·4)	44·6 (12·4)	44·4 (12·9)
Week 24 mean (SD)	52·3 (14·8)	54·6 (13·1)	43·8 (14·7)
Adjusted mean change from baseline (SE)	7·0 (0·9)	8·5 (0·9)	−2·1 (0·9)
Difference from placebo (95% CI)	9·1 (6·8 to 11·4)	10·7 (8·4 to 12·9)	NA
p value†	<0·0001	<0·0001	NA

CGM=continuous glucose monitoring. NA=not applicable. MAGE=mean amplitude of glucose excursion. *N is the number of participants in the full-analysis set with no missing baseline data and at least one post-baseline value. †Nominal p value.

Dandona P et al. Lancet Diabetes Endocrinol 2017;5:864-876

Dapagliflozin in T1D: DEPICT-1
Adverse events at 24 weeks

	Dapagliflozin 5 mg plus insulin (n=277)*	Dapagliflozin 10 mg plus insulin (n=296)*	Placebo plus insulin (n=260)
Adverse events			
One or more adverse events	187 (68%)	207 (70%)	160 (62%)
One or more adverse events related to the study drug	79 (29%)	82 (28%)	31 (12%)
Adverse event leading to study discontinuation	6 (2%)	9 (3%)	9 (3%)
Adverse events of special interest			
Genital infection	34 (12%)	33 (11%)	7 (3%)
Urinary tract infection	19 (7%)	11 (4%)	13 (5%)
Renal impairment or failure†	4 (1%)	2 (1%)	0
Fractures	4 (1%)	3 (1%)	3 (1%)
Hypotension, dehydration, or hypovolaemia	0	1 (<1%)	2 (1%)
Hypersensitivity‡	12 (4%)	13 (4%)	2 (1%)
Cardiovascular events	1 (<1%)§	2 (1%)¶	0
Serious adverse events			
One or more serious adverse events	19 (7%)	24 (8%)	15 (6%)
One or more serious adverse events related to the study drug	5 (2%)	9 (3%)	1 (<1%)
Serious adverse event leading to study discontinuation	3 (1%)	4 (1%)	3 (1%)
Hypoglycaemia			
At least one serious adverse event of hypoglycaemia	1 (<1%)	2 (1%)	1 (<1%)
Hypoglycaemia leading to study discontinuation	1 (<1%)	0	1 (<1%)
Ketone-related events			
One or more ketone-related serious adverse events	5 (2%)	8 (3%)	2 (1%)
DKA leading to study discontinuation	1 (<1%)	5 (2%)	0
Death	0	0	1 (<1%)

Dapagliflozin in T1D: DEPICT-1
DKA at 24 weeks

	Dapagliflozin 5 mg plus insulin (n=277)	Dapagliflozin 10 mg plus insulin (n=296)	Placebo plus insulin (n=260)
Number of patients with event sent for DKA adjudication	16 (6%)	19 (6%)	6 (2%)
Number of patients with definite DKA	4 (1%)	5 (2%)	1 (<1%)
Number of events of definite DKA	4	5	3
Incidence rate per 100 patient-years	3·29	3·78	3·64
Severity of events as adjudicated			
Mild	2	1	1
Moderate	1	3	1
Severe	1	1	1
Number of events of euglycaemic* DKA	0	2	0
Primary cause for adjudicated definite DKA events			
Insulin pump failure	2	1	1
Missed insulin dose	1	3	1
Severe illness	0	0	0
Not identified	1	0	0
Other	0	1†	1‡
Mean percent insulin total daily dose (IU) reduction compared with baseline for week before DKA event§	−8·9	−25·3	−7·8
Mean percent insulin total daily dose (IU) reduction compared with baseline at end of 24 week treatment period§	−11·0	−21·6	30·8
Events adjudicated as not DKA			
Number of patients with possible DKA	5 (2%)	7 (2%)	1 (<1%)
Number of events of possible DKA	7	8	3
Number of patients with unlikely DKA	8 (3%)	8 (3%)	3 (1%)
Number of events of unlikely DKA	15	10	8

Data reported are for 24 week treatment period and include all patients with an onset from day 1 of the 24 week treatment period up to and including 4 days after the last dose date in this period, or up to the start date of the 28 week extension period, whichever came first. DKA=diabetic ketoacidosis. *Self-monitored blood glucose of less than 250 mg/dL (13·9 mmol/L). †Reason was excessive alcohol intake. ‡Reason was stress. §Means apply for patients with definite DKA.

Table 5: **Summary of events sent for diabetic ketoacidosis adjudication**

Sotagliflozin in T1D: the inTandem phase 3 Clinical Trial program

Phase 3 Studies in T1DM	Enrollment Objective; Dose	Primary Endpoint	Top-Line Results	Study Completion
inTandem1	• 750 patients • Placebo, 200mg, 400mg once-daily	Reduction of A1C vs. placebo on optimized insulin	Reported (24 week primary efficacy endpoint)	2017 (52 week total study duration)
inTandem2	• 750 patients • Placebo, 200mg, 400mg once-daily	Reduction of A1C vs. placebo on optimized insulin	Reported (24 week primary efficacy endpoint)	2017 (52 week total study duration)
inTandem3	• 1,400 patients • Placebo, 400mg once-daily	Proportion with A1C 7.0% and no SH and no DKA	Mid 2017 (24 week study)	

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., Annie Peters, M.D., and Paul Strumph, M.D.

Garg S et al. N Engl J Med 2017;377:2337-48

Sotagliflozin in T1D: inTandem3 Efficacy at 24 weeks

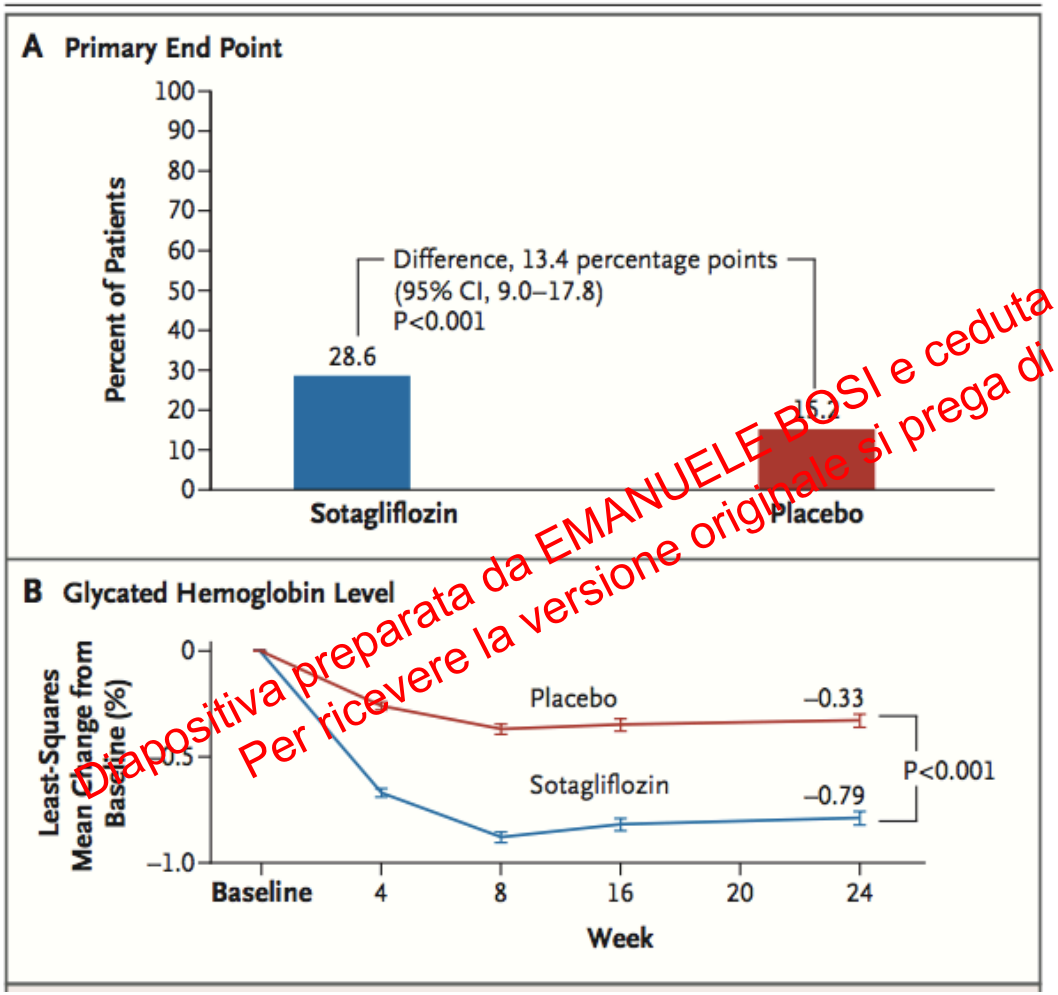


Figure 1. Primary and Secondary End Points.
Panel A shows the percentage of patients who achieved the primary end point of a glycated hemoglobin level lower than 7.0% at week 24, with no episodes of severe hypoglycemia or diabetic ketoacidosis after randomization. Panel B shows the least-squares mean change in the glycated hemoglobin level from baseline to week 24.

Garg S et al. N Engl J Med 2017;377:2337-48

Sotagliflozin vs Dapagliflozin in T1D: incidence of DKA in inTandem3 and DEPICT-1

Table 1. Comparison of Rates of Diabetic Ketoacidosis in DEPICT-1 and inTandem3 Trials after Standardization of the Criteria Used.*

Variable	inTandem3		DEPICT-1		
	Placebo (N=703)	Sotagliflozin, 400 mg (N=699)	Placebo (N=260)	Dapagliflozin, 5 mg (N=277)	Dapagliflozin, 10 mg (N=296)
All patients with certain, definite, probable, or possible diabetic ketoacidosis — no. (%)	4 (0.6)	21 (3.0)	4 (1.5)	9 (3.2)	12 (4.1)
Percent difference between treatment and placebo among patients with ≥1 event	—	2.4	—	1.7	2.5

* DEPICT-1 denotes Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes.

Garg S, Strumph P. N Engl J Med 2018;378:966-968

Sotagliflozin in T1D: the inTandem phase 3 Clinical Trial program

Phase 3 Studies in T1DM	Enrollment Objective; Dose	Primary Endpoint	Top-Line Results	Study Completion
inTandem1	• 750 patients • Placebo, 200mg, 400mg once-daily	Reduction of A1C vs. placebo on optimized insulin	Reported (24 week primary efficacy endpoint)	2017 (52 week total study duration)
inTandem2	• 750 patients • Placebo, 200mg, 400mg once-daily	Reduction of A1C vs. placebo on optimized insulin	Reported (24 week primary efficacy endpoint)	2017 (52 week total study duration)
inTandem3	• 1,400 patients • Placebo, 400mg once-daily	Proportion with A1C 7.0% and no SH and no DKA	Mid 2017 (24 week study)	

Sotagliflozin in T1D: inTandem1 and inTandem2 HbA1c

	inTandem1			inTandem2		
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Mean A1C at screening (before optimization)	8.21	8.26	8.20	8.38	8.35	8.38
Mean A1C at baseline (after 6-week insulin optimization period)	7.55	7.61	7.57	7.80	7.74	7.71
Mean A1C at Week 24	7.50	7.17	7.08	7.79	7.36	7.35
	Primary Endpoint: Change from baseline in A1C at Week 24					
N	246	245	242	239	239	241
LS Mean	−0.06	−0.43	−0.49	−0.03	−0.39	−0.37
p-value	0.027	<0.001	<0.001	0.54	<0.001	<0.001
	Summary of treatment comparison					
LS Mean difference from placebo		−0.35	−0.41		−0.36	−0.35
p-value		<0.001	<0.001		<0.001	<0.001

Sotagliflozin in T1D: inTandem1 and inTandem2 Adverse events of special interest

	inTandem1			inTandem2		
	Optimized Insulin + Placebo	Optimized Insulin + Sotagliflozin 200 mg	Optimized Insulin + Sotagliflozin 400 mg	Optimized Insulin + Placebo	Optimized Insulin + Sotagliflozin 200 mg	Optimized Insulin + Sotagliflozin 400 mg
Number of patients	268	263	262	257	261	263
Diarrhea	5.6%	7.2%	9.9%	3.9%	5.4%	7.2%
Discontinuation of study drug due to diarrhea	0.4%	0.0%	0.4%	0.4%	0.4%	0.8%
Genital mycotic infection	3.4%	6.1%	10.3%	1.6%	7.3%	8.4%
Discontinuation of study drug due to genital mycotic infection	0.0%	0.4%	0.0%	0.4%	0.8%	0.4%

Sotagliflozin in T1D: inTandem1 and inTandem2 Hypoglycemia and DKA

	inTandem1			inTandem2		
	Optimized Insulin + Placebo	Optimized Insulin + Sotagliflozin 200 mg	Optimized Insulin + Sotagliflozin 400 mg	Optimized Insulin + Placebo	Optimized Insulin + Sotagliflozin 200 mg	Optimized Insulin + Sotagliflozin 400 mg
Number of patients	268	263	262	252	261	263
Severe hypoglycemic event	18	11	12	7	10	6
Severe hypoglycemic %	6.7%	4.2%	4.6%	2.7%	3.8%	2.3%
Discontinuation of study drug due to severe hypoglycemic event	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%
DKA events	0	3	8	0	1	3
DKA %	0.0%	1.1%	3.1%	0.0%	0.4%	1.1%
Discontinuation of study drug due to DKA event	0.0%	0.4%	0.8%	0.0%	0.0%	0.8%

SGLT-2 and SGLT-2/1 inhibitors in T1D: Conclusions

Large trials with SGLT-2 and dual SGLT-1/2 inhibitors in T1D confirm, on a larger basis:

- beneficial effect on several measures: HbA1c, glucose variability, body weight, insulin dose;
- Neutral effect on hypoglycemia;
- Increased risk of DKA.

Needs associated with the use of SGLT-2 and dual SGLT-1/2 inhibitors in T1D:

- High patient compliance
- Check ketones
- Never run out of insulin, especially basal

Future studies will clarify the real potential as add on therapy to insulin of these compounds in T1D

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