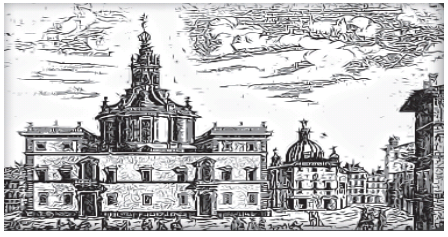
Gli inibitori di SGLT-2 possono essere impiegati nel diabete di tipo 1?

Raffaella Buzzetti
Dipartimento di Medicina Sperimentale



founded in 1303

Raffaella Buzzetti

Disclosures

La Prof.ssa Raffaella Buzzetti dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

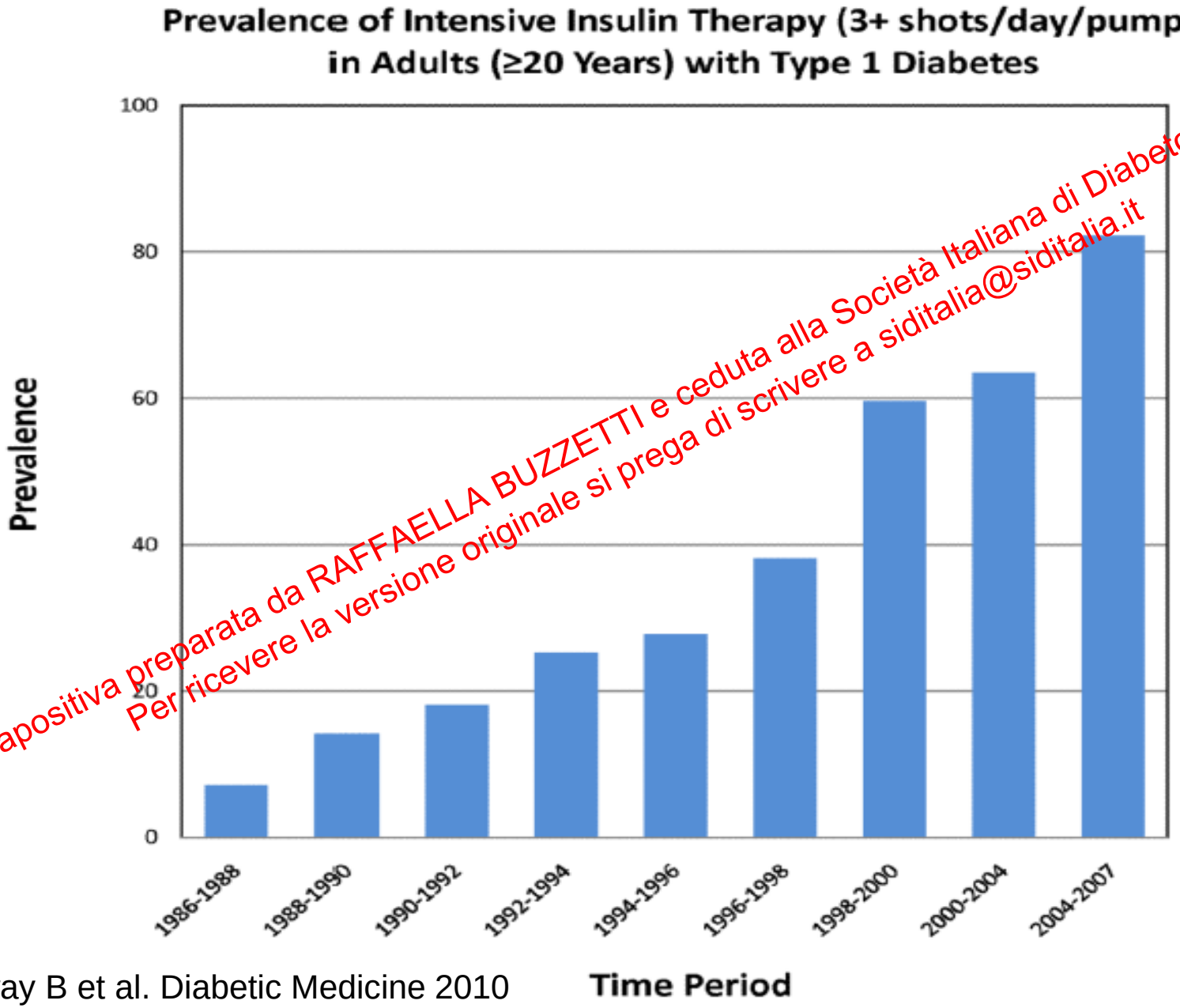
Sanofi

Eli Lilly

Medtronic

Novo Nordisk

Type 1 diabetes and insulin treatment

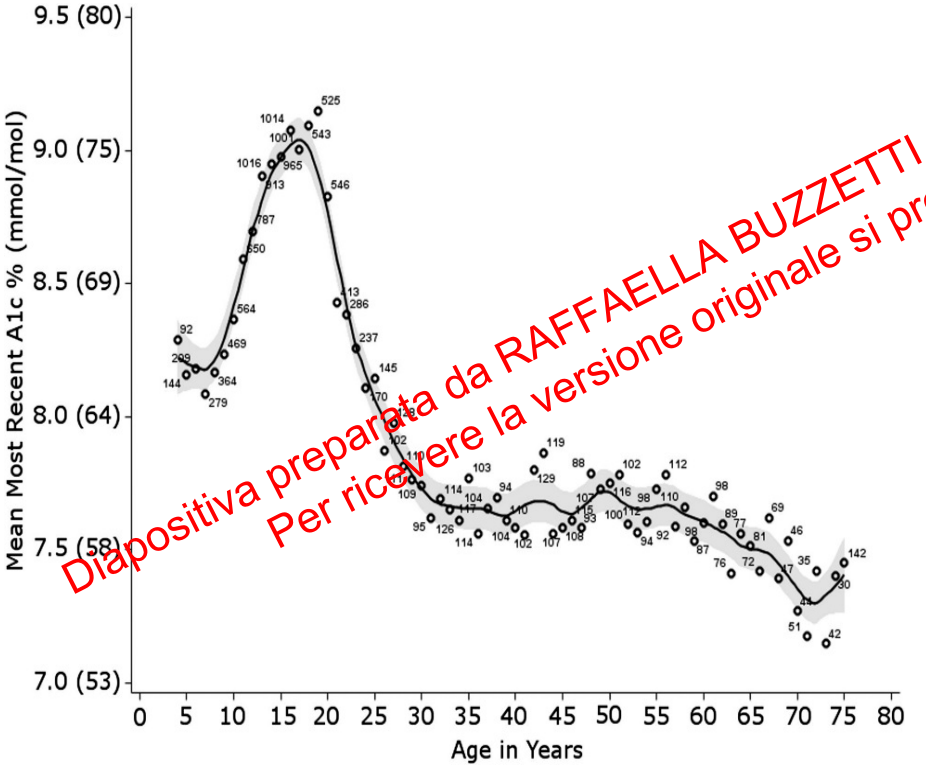


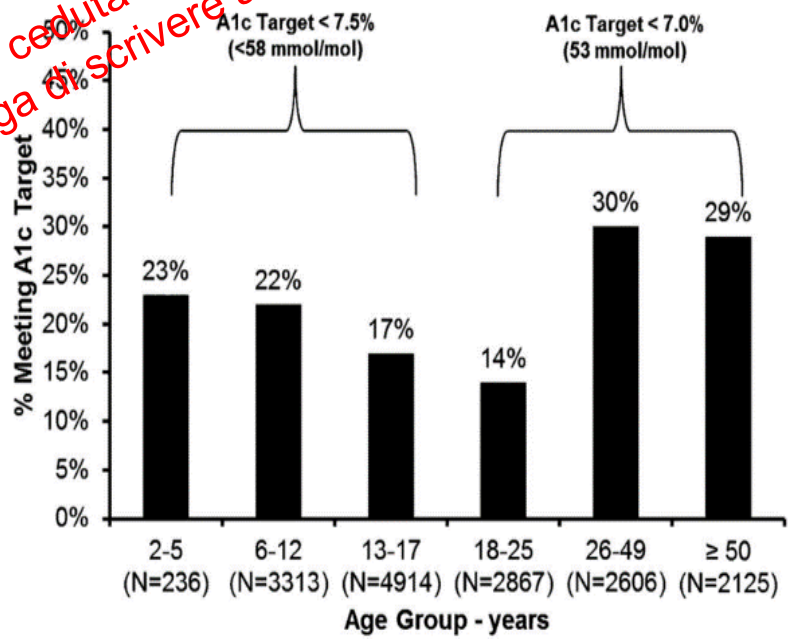
Conway B et al. Diabetic Medicine 2010

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

Type 1 diabetes: the reduced life expectancy

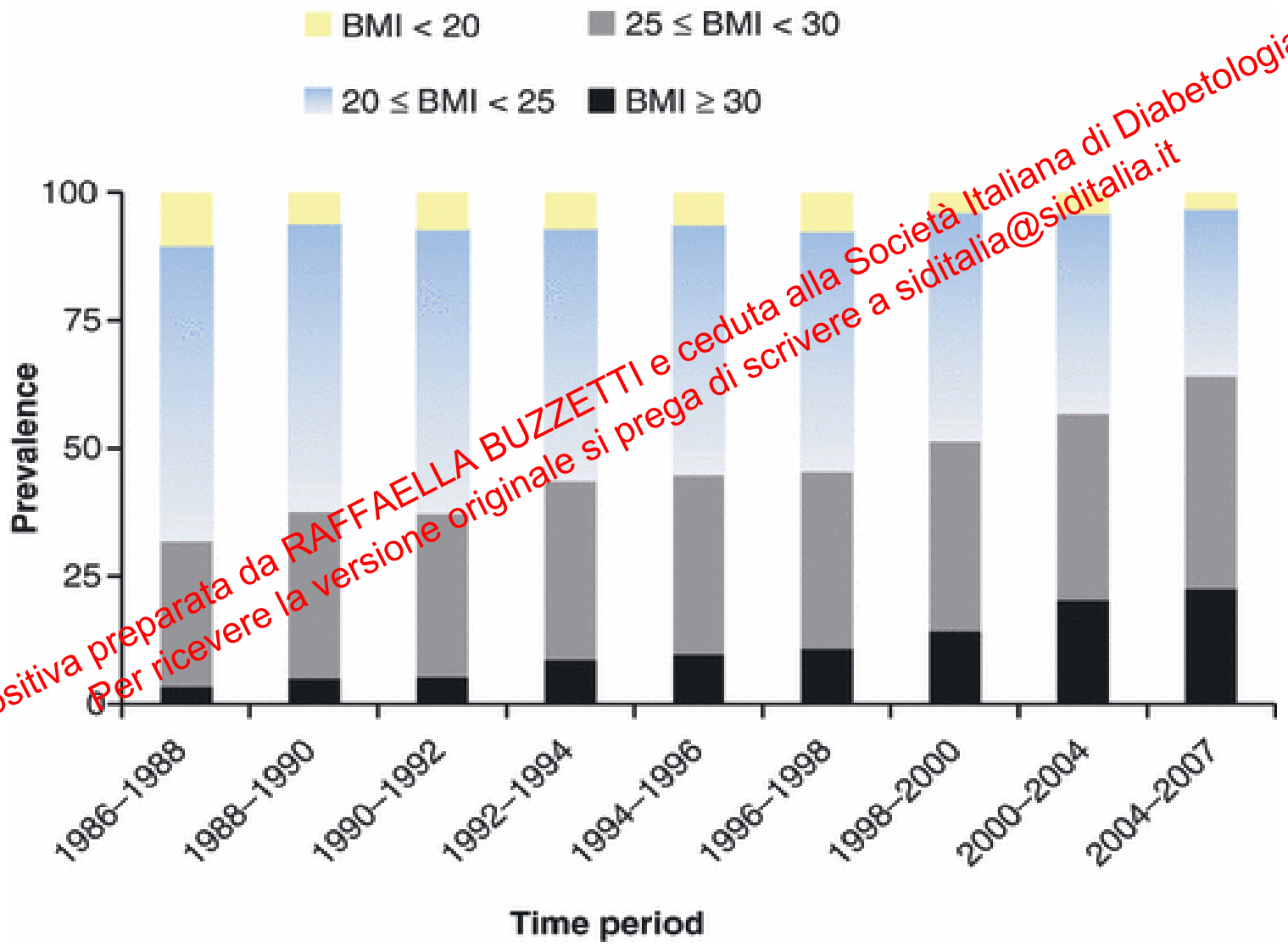
Hazard Ratios for Death from Any Cause and from Cardiovascular Causes among Patients with Type 1 Diabetes versus Controls,

(According to Time-Updated Mean Glycated Hemoglobin Level)

Variable	Hazard Ratio	
	Death from Any Cause	Death from Cardiovascular Disease
Time-updated mean glycated hemoglobin level — no. of events/total no.	7386/200,539	2326/200,539
Reference group (controls)	1.00	1.00
≤6.9%	2.36 (1.97–2.83)	2.92 (2.07–4.13)
7.0–7.8%	2.38 (2.02–2.80)	3.39 (2.49–4.61)
7.9–8.7%	3.11 (2.66–3.62)	4.44 (3.32–5.96)
8.8–9.6%	3.65 (3.11–4.30)	5.35 (3.94–7.26)
≥9.7%	8.51 (7.24–10.01)	10.46 (7.62–14.37)

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

Temporal patterns in overweight and obesity in Type 1 diabetes



Conway B et al. Diabetic Medicine 2010

Quali sono le possibili cause del persistere dello scompenso metabolico nella media dei soggetti con diabete tipo 1 soprattutto nella età adolescenziale nonostante i miglioramenti nel trattamento?

A. Incremento del BMI verificatosi nelle ultime decadi
B. Modifiche nella qualità dell'alimentazione verificatesi nelle ultime decadi
C. Difficoltà da parte dei diabetologi nel seguire i soggetti con diabete tipo 1 determinata dall'aumento di incidenza
D. Cambiamenti generazionali nell'attitudine dei giovani a seguire prescrizioni mediche soprattutt limitative nella gestione del quotidiano

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 **some 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

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

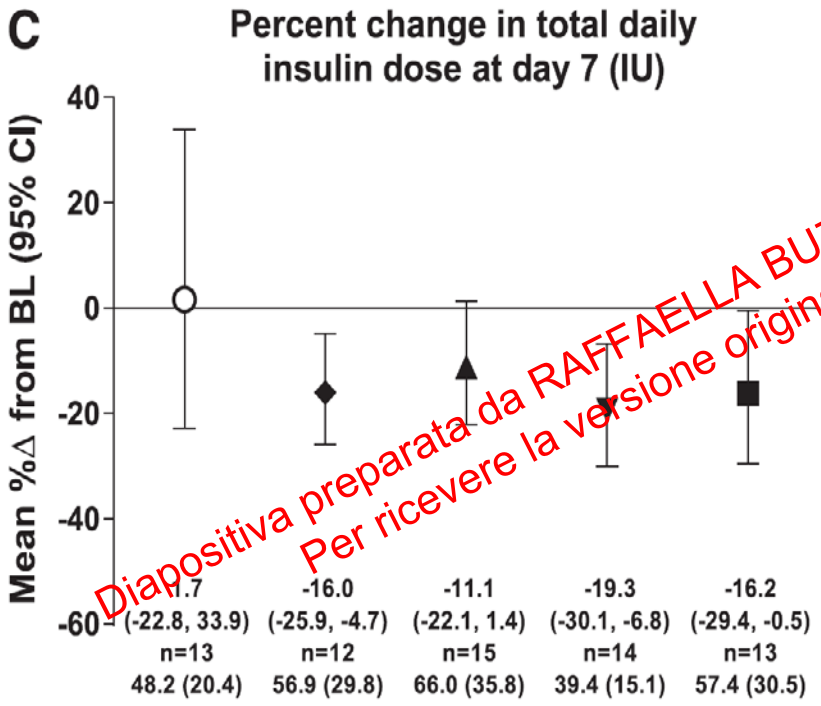
. **The primary objective of this study was to assess short-term safety of dapagliflozin in combination with insulin; secondary objectives included pharmacokinetic, pharmacodynamic, and efficacy parameters.**

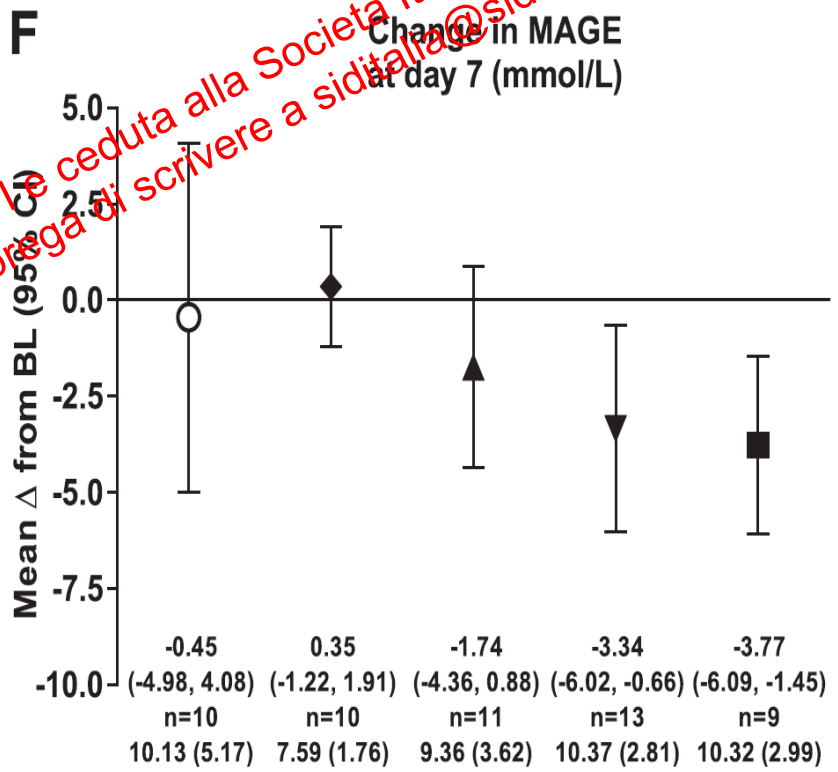
CONCLUSIONS

This exploratory study of dapagliflozin in adults with type 1 diabetes demonstrated acceptable short-term tolerability and expected pharmacokinetic profiles

Dapagliflozin in T1D

○, 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.





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

SGLT-2 inhibitors in T1D: RCTs

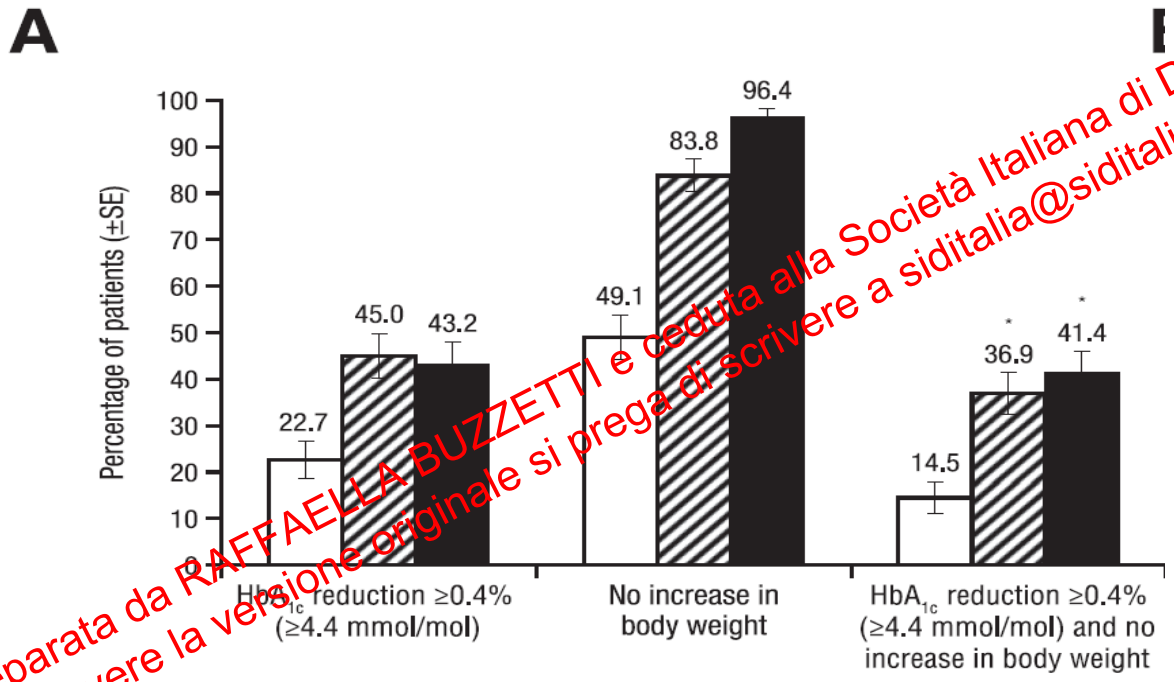
Efficacy and Safety of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-on to Insulin in Patients With Type 1 Diabetes

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

The primary end point was the proportion of patients achieving at week 18 both HbA_{1c} reduction from baseline and no increase in body weight.

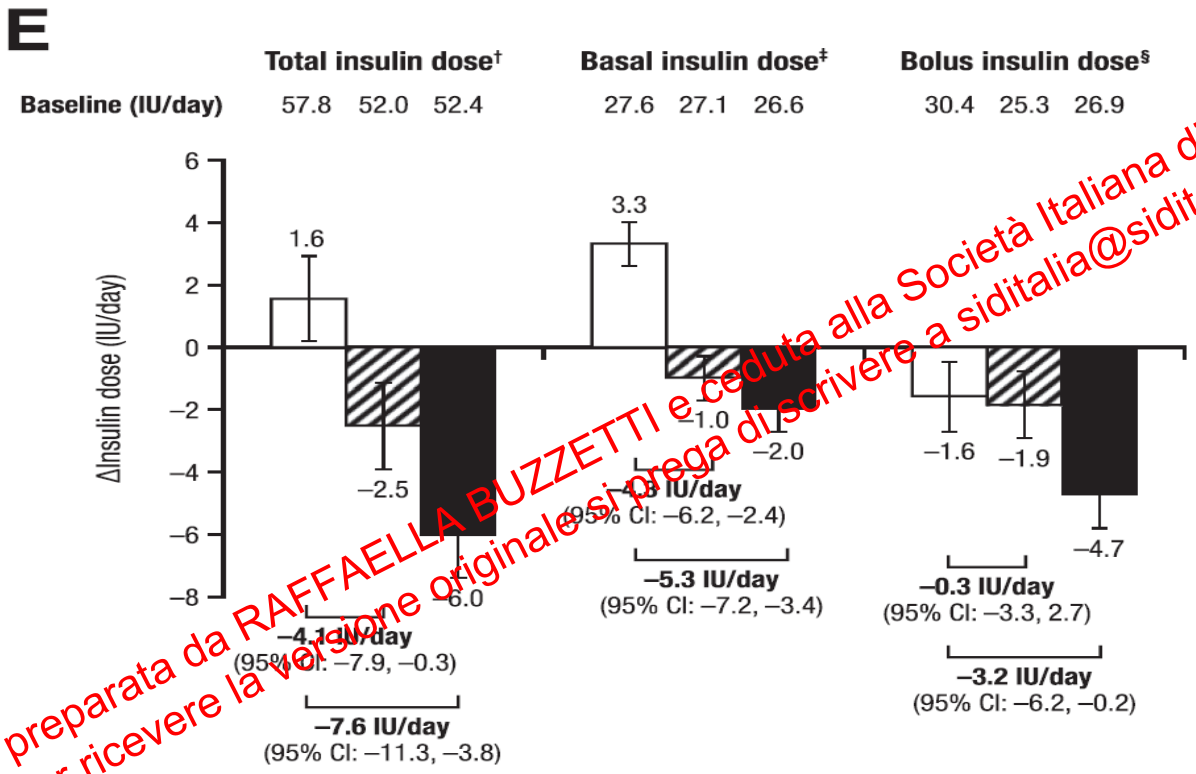
Efficacy and Safety of Canagliflozin as add-on to insulin in patients with T1D



Canagliflozin provided reductions in HbA1c, body weight, and insulin dose with no increase in hypoglycemia, but increased rates of ketone-related AEs, including DKA, in adults with T1D inadequately controlled with insulin.

Henry RR et al, Diabetes Care 2015

Efficacy and Safety of Canagliflozin as add-on to insulin in patients with T1D



Canagliflozin provided reductions in insulin dose with no increase in hypoglycemia, but increased rates of ketone-related AEs, including DKA, in adults with T1D inadequately controlled with insulin.

Henry RR et al, Diabetes Care 2015

SGLT-2 inhibitors in T1D: RCTs

original article

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

ORIGINAL ARTICLE

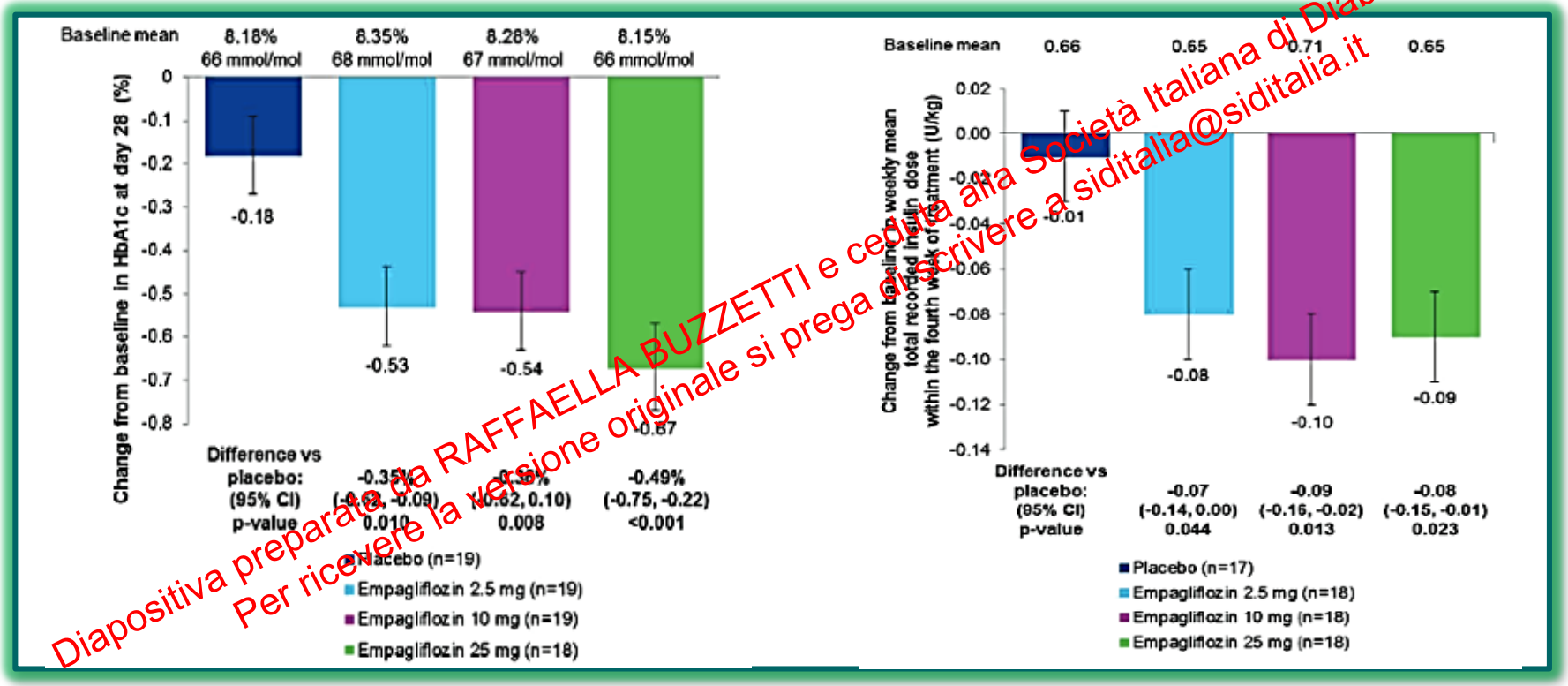
Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1)

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

Aim: To investigate the pharmacodynamics, efficacy and safety of empagliflozin as adjunct to insulin in patients with type 1 diabetes

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

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



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

Pieber TR et al, Diabetes Obesity and Metabolism 2015

Sotagliflozin in T1D

Diabetes Care 1

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

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]

DOI: 10.2337/dc14-2806

To assess the safety and efficacy of dual sodium–glucose cotransporter (SGLT) 1 and SGLT2 inhibition with sotagliflozin as adjunct therapy to insulin in type 1 diabetes.

CONCLUSIONS As adjunct to insulin, dual SGLT1 and SGLT2 inhibition with sotagliflozin improved glycemic control and the CGM profile with bolus insulin dose reduction, weight loss, and no increased hypoglycemia

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 (phase III):

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

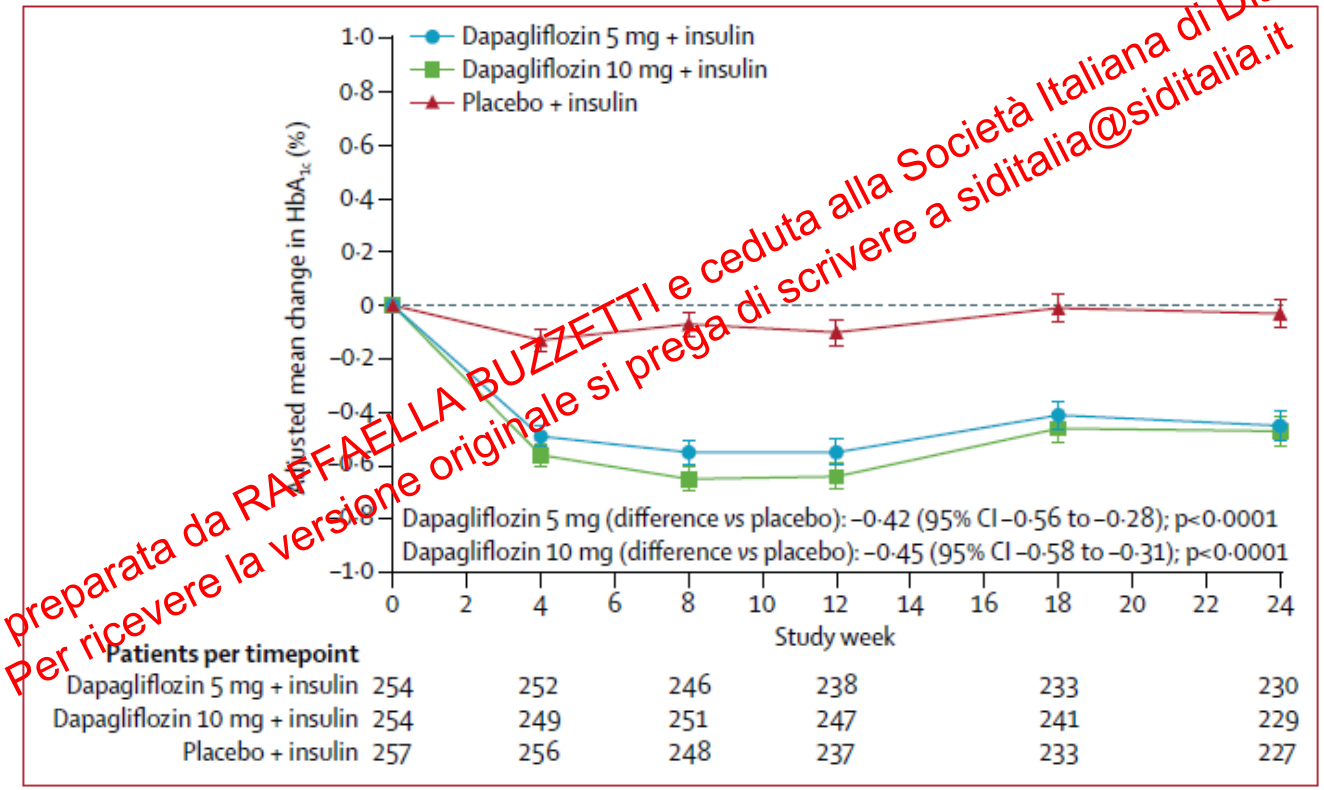
Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial

*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**

The aim of the present study was to assess if dapagliflozin (5 mg or 10 mg once daily) added to adjustable insulin can safely improve glycaemic control in people with type 1 diabetes over 24 weeks.

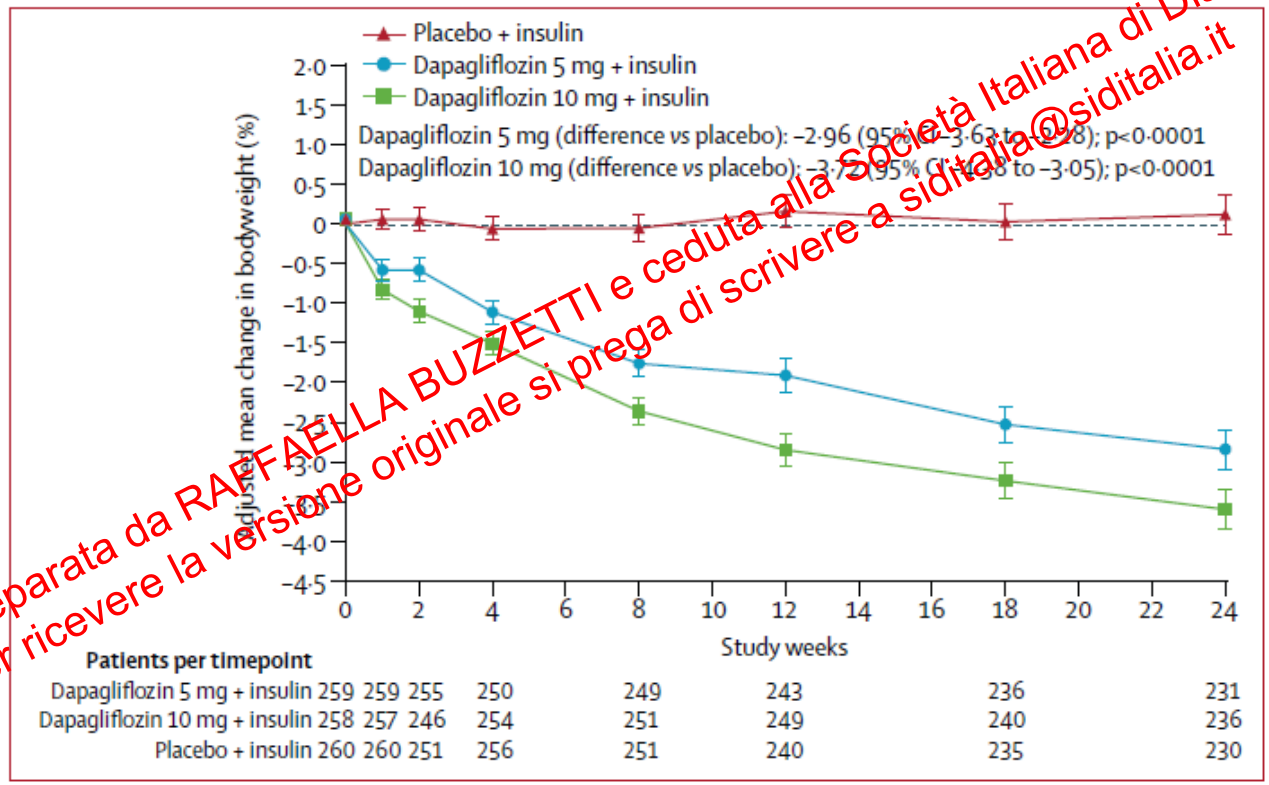
Dandona P et al. Lancet Diabetes Endocrinol 2017;5:864-876

Dapagliflozin in T1D: DEPICT-1 HbA1c at 24 weeks



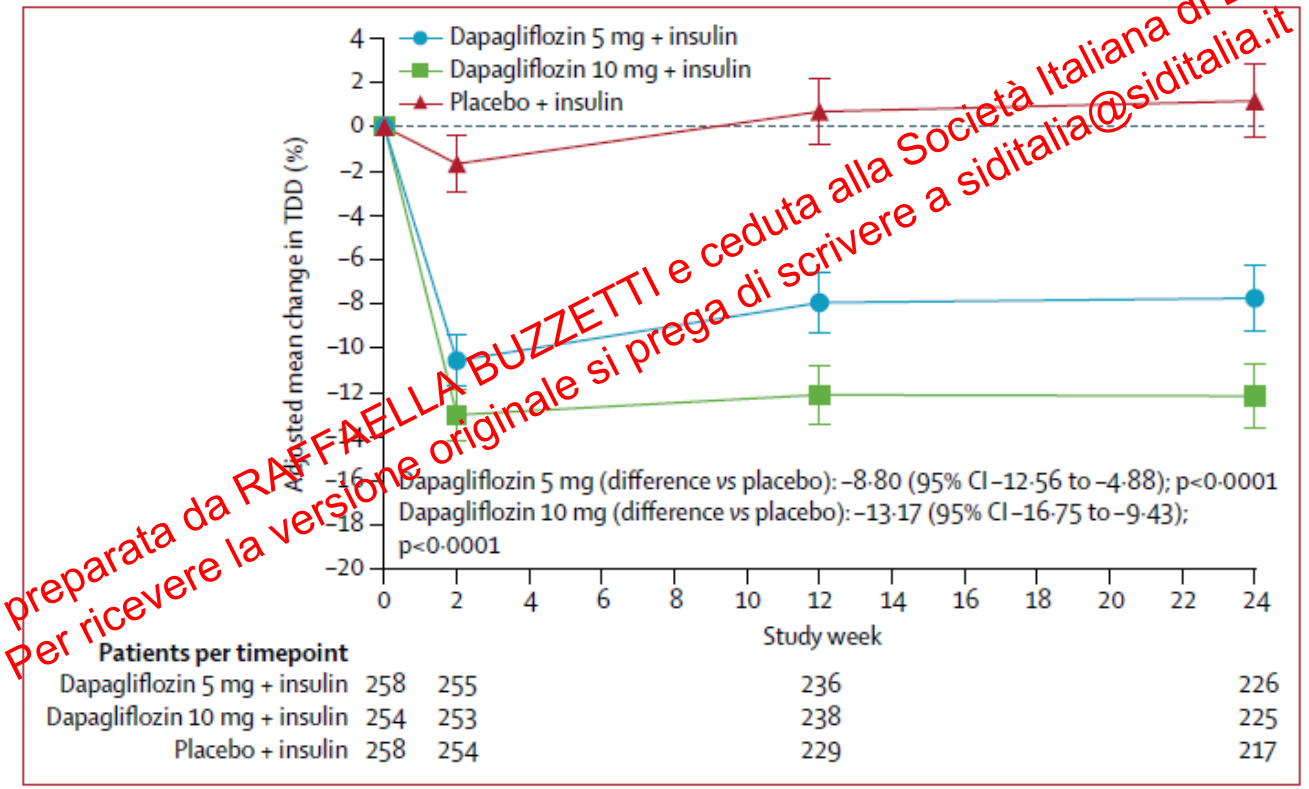
Dandona P et al. Lancet Diabetes Endocrinol 2017;5:864-876

Dapagliflozin in T1D: DEPICT-1
Body weight 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
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%)	3 (1%)
Number of events of definite DKA	4	5	3
Incidence rate per 100 patient-years	3·29	3·38	2·64
Severity of events as adjudicated			
Mild	2	1	1
Moderate	1	3	1
Severe	1	1	1
Number of events of euglycaemic* DKA	1	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., Dianne 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 primary end point was a glycated hemoglobin level lower than 7.0% at week 24, with no episodes of severe hypoglycemia or diabetic ketoacidosis after randomization.

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

Sotagliflozin in T1D: inTandem3 Efficacy at 24 weeks

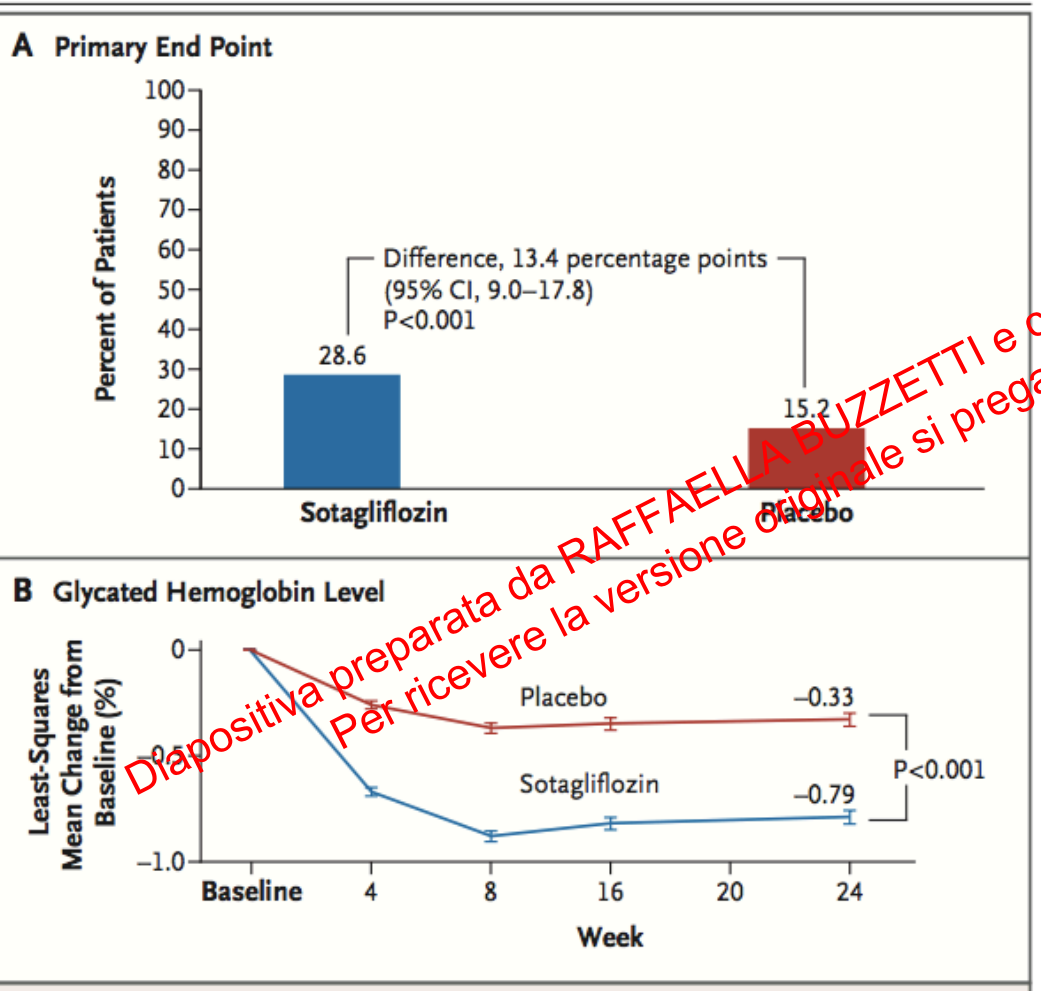


Figure 1. Primary and Secondary End Points.

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

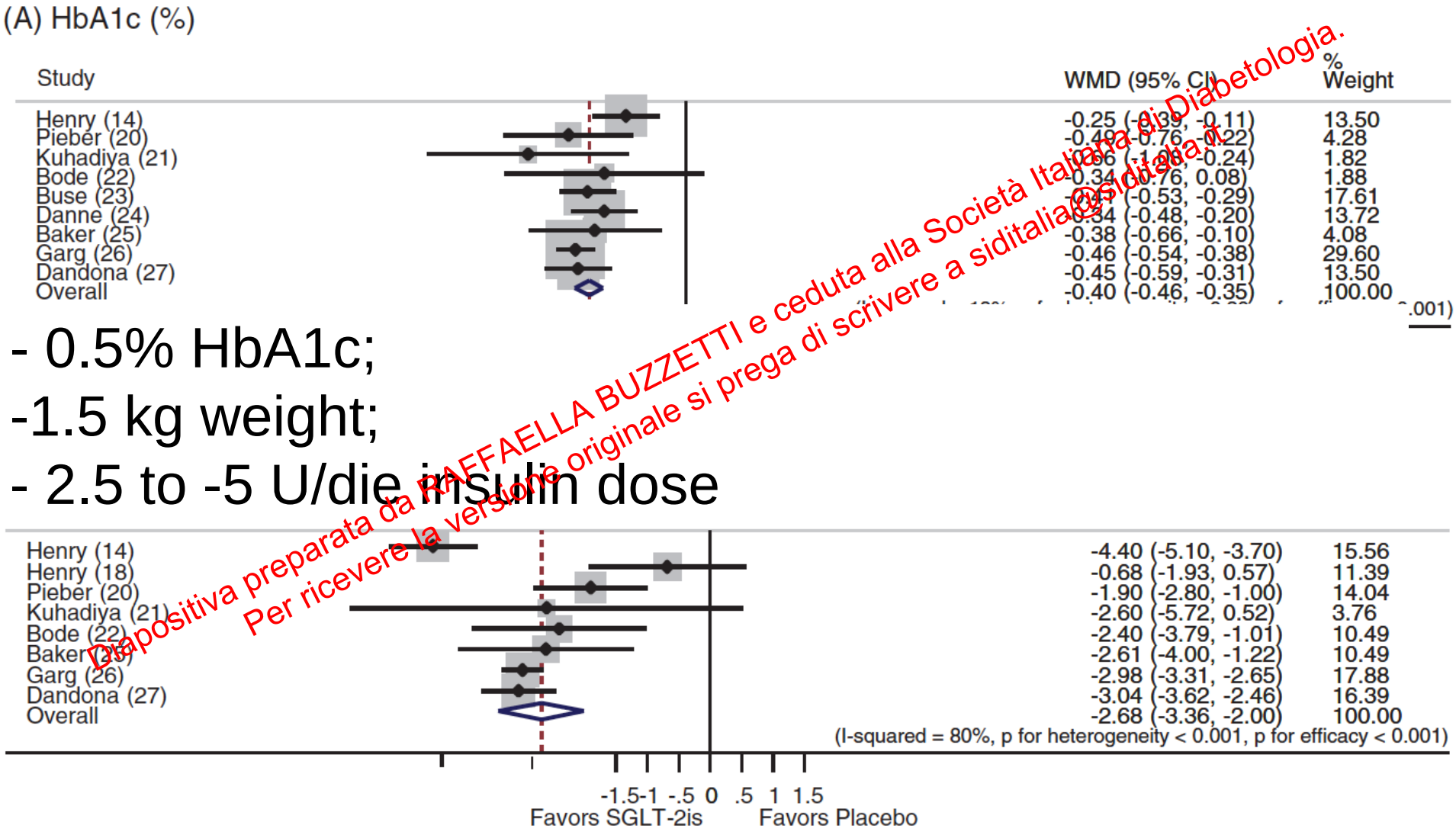
Sotagliflozin in T1D: inTandem1 and inTandem2 HbA1c

	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	8.40	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 Hypoglycemia and DKA

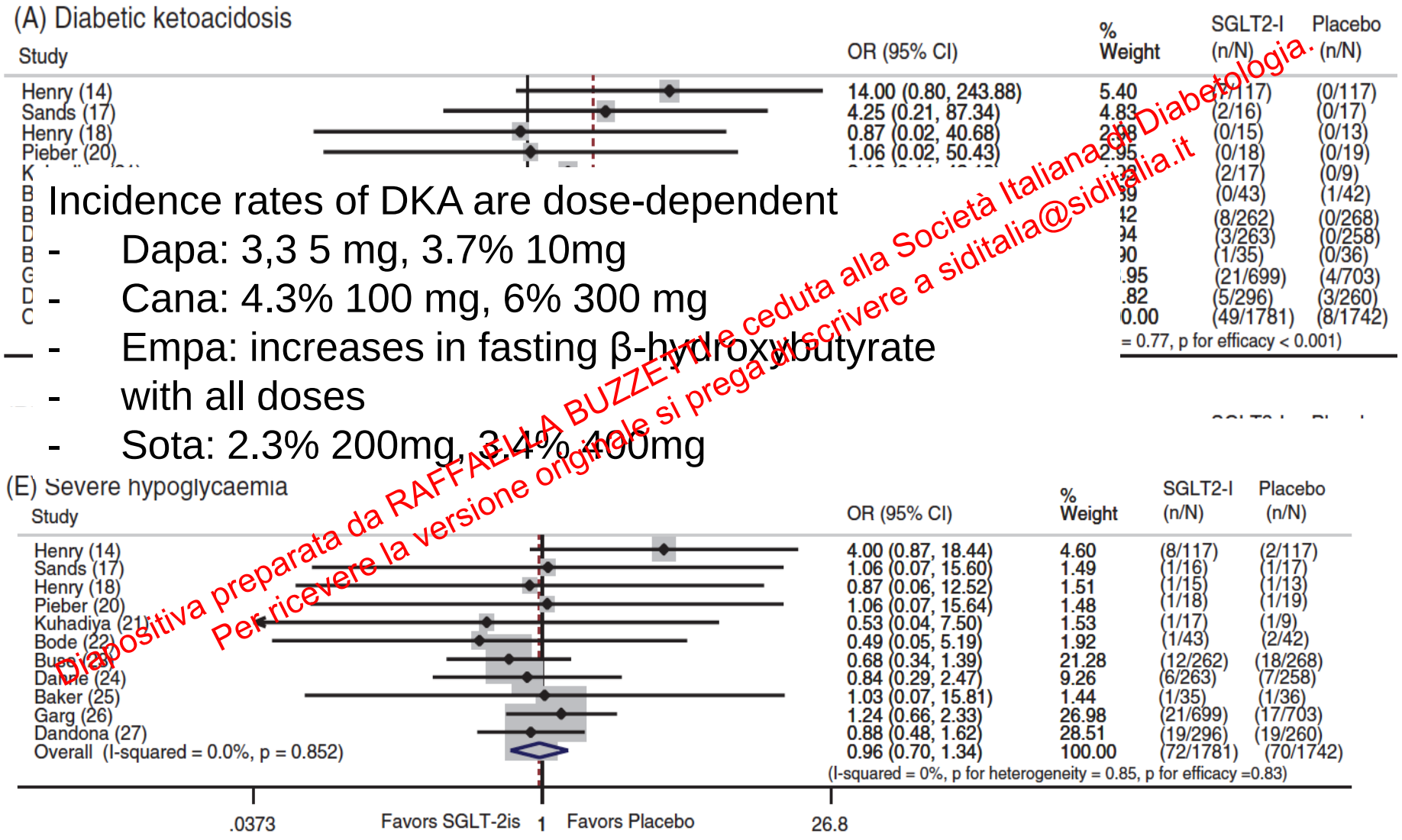
	inTandem1			inTandem2		
	Optimized Insulin + Placebo	Optimized Insulin + Sotagliflozin 200 mg	Optimized Insulin + Sotagliflozin 400 mg	Optimized Insulin + Placebo	Optimized Insulin + Sotagliflozin 200 mg	Optimized Insulin + Sotagliflozin 400 mg
Number of patients	268	263	262	257	261	263
Severe hypoglycemic 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%

Summary of the efficacy of sodium-glucose co-transporter inhibitors published in clinical trials in type 1 diabetes



Yamada T et al. Diabetes Obes Metab. 2018;20:1755–17

Summary of the side effects of sodium-glucose co-transporter inhibitors published in clinical trials in type 1 diabetes



- Incidence rates of DKA are dose-dependent
  - Dapa: 3,3 5 mg, 3.7% 10mg
  - Cana: 4.3% 100 mg, 6% 300 mg
  - Empa: increases in fasting β-hydroxybutyrate
  - with all doses
  - Sota: 2.3% 200mg, 3.4% 400mg

Yamada T et al. Diabetes Obes Metab. 2018;20:1755–17

Dapagliflozin in T1D: DEPICT-2
DKA at 24 weeks

Diabetes Care

Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes (the DEPICT-2 Study): 24-Week Results From a Randomized Controlled Trial

Chantal Mathieu,[1] Paresa Dandona,[2] Pieter Gillard,[1] Roger Senior,[3] Christoph Weissmann,[4] Eiichi Araki,[5] Marcus Lind,[6,7] Stephen C. Bain,[8] Serge Jabbour,[9] Niki Arya,[10] Lars Hansen,[11] Fredrik Thorén,[12] and Anna Maria Langkilde,[12] on behalf of the DEPICT-2 Investigators*

https://doi.org/10.2337/dc18-0623 2018

This 24-week, double-blinded, phase 3 clinical trial (DEPICT-2; NCT02460978) evaluated efficacy and safety of dapagliflozin as adjunct therapy to adjustable insulin in patients with inadequately controlled type 1 diabetes (glycated hemoglobin [HbA_{1c}] 7.5–10.5%).

Dapagliflozin in T1D: DEPICT-2
DKA at 24 weeks

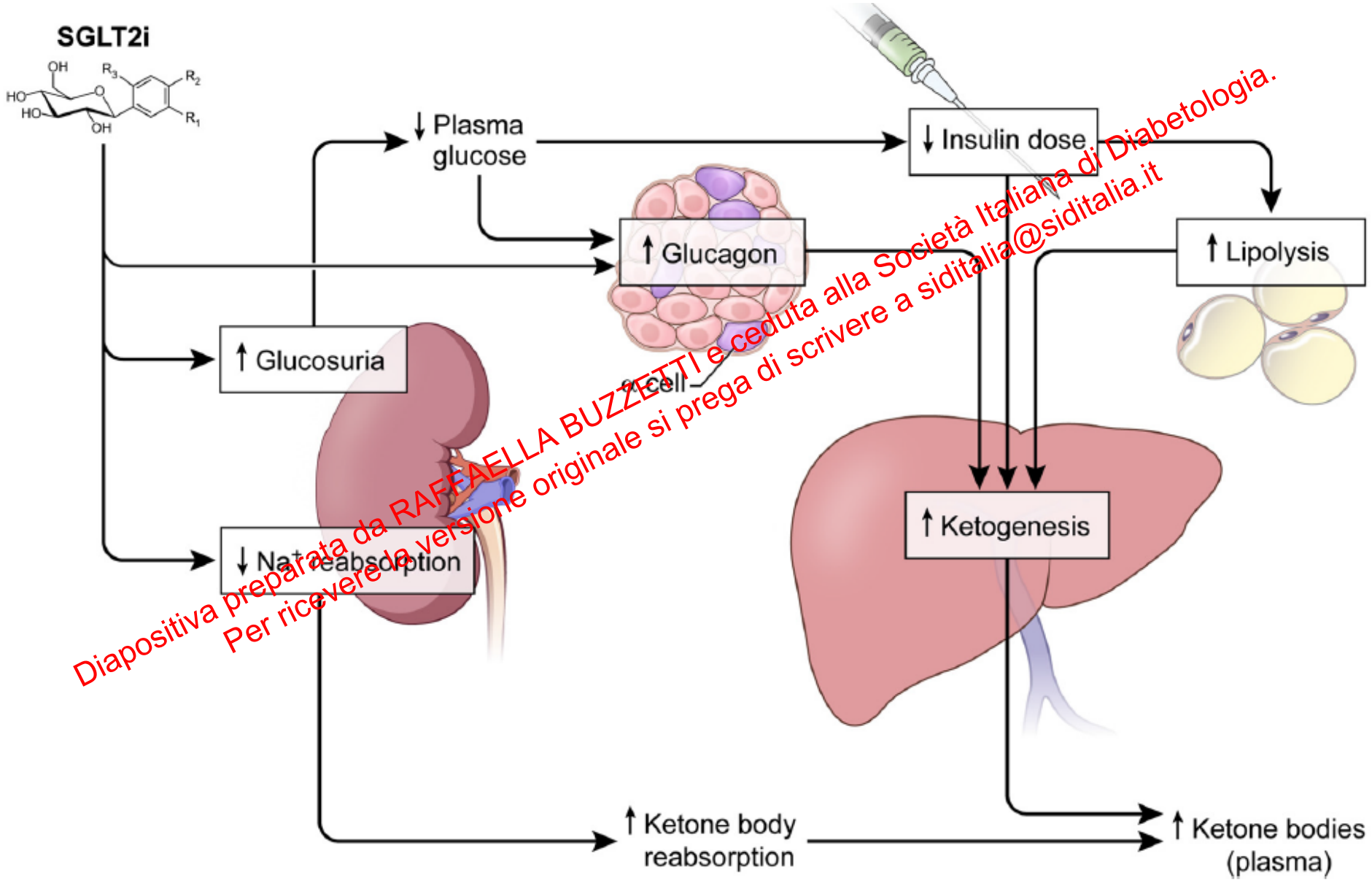
Table 2–Safety summary

Characteristic	Dapagliflozin 5 mg + insulin (*n* = 271)	Dapagliflozin 10 mg + insulin (*n* = 270)	Placebo + insulin (*n* = 272)
Adjudicated definite DKA			
Number of patients with definite DKA	7 (2.6%)	6 (2.2%)	0
Number of events adjudicated as definite DKA	7 (25.0%)	6 (33.3%)	0
Incidence rate per 100 patient-years	5.83	4.99	0
Number of CSII users experiencing definite DKA	6 (6.5%)	3 (3.3%)	0
Male-to-female ratio in patients experiencing definite DKA	2:5	1:5	0

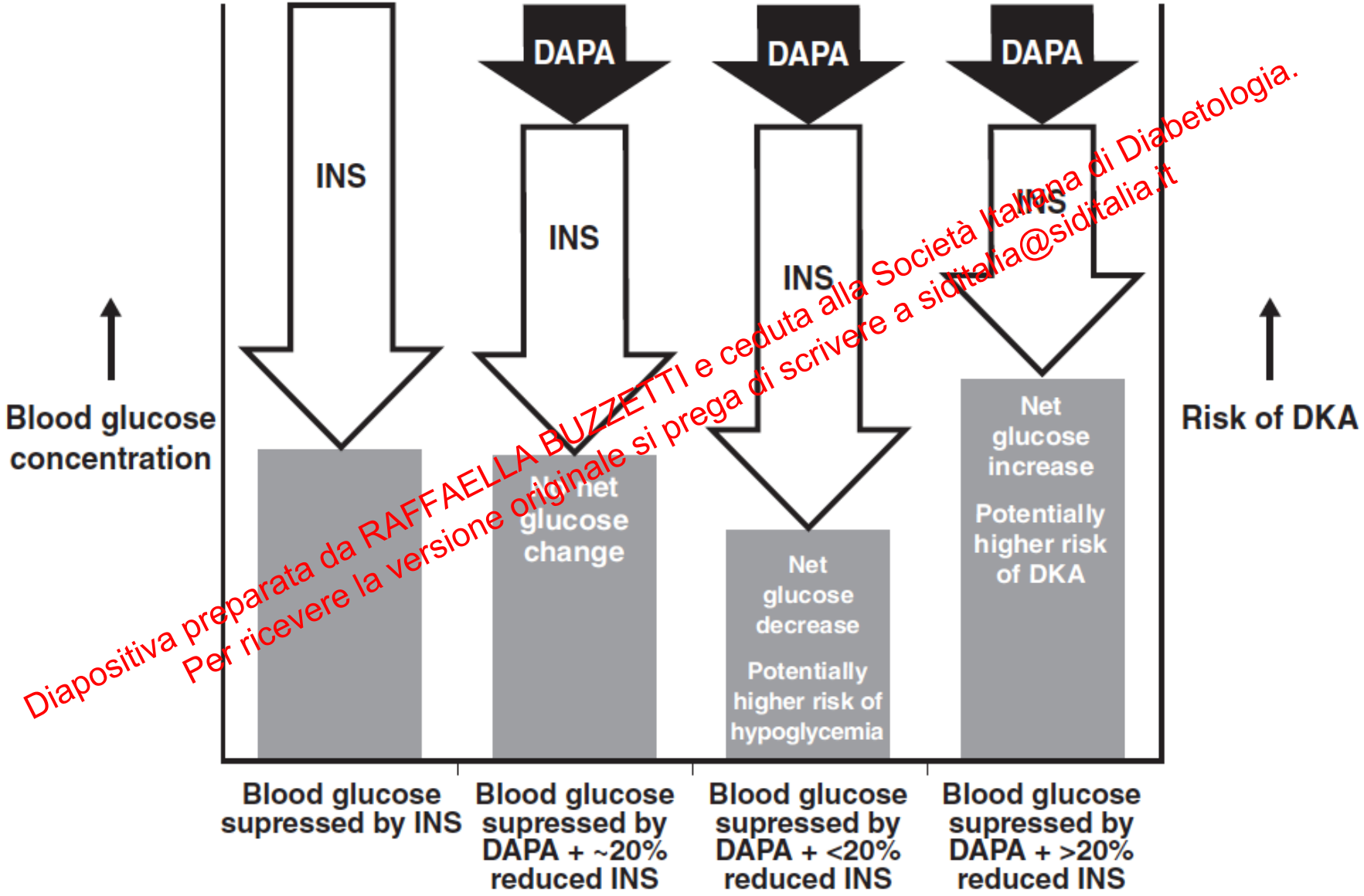
Conclusion

The imbalance in DKA events seen in the dapagliflozin versus placebo groups in DEPICT-2, despite receiving the same education and monitoring instructions as in DEPICT-1, **suggests that if approved for the indication, the DKA risk should be carefully considered if using dapagliflozin for the treatment of type 1 diabetes in the real world**.

Potential mechanisms of adjunctive therapy with SGLT2 inhibitors to promote ketosis and increase the risk of ketoacidosis in T1D patients



Impact of varying insulin dose eductions on glycaemic control and risk of DKA when considered in combination with dapagliflozin.



Henry RR, Diabetes Obes Metab. 2017

In quali soggetti con diabete tipo 1 aggiungeresti la terpia con SGLT2i?

A. Soltanto nei soggetti con HbA1c >8.5%
B. Soltanto nei pazienti con HbA1c >8.5% sovrappeso od obesi
C. Soltanto nei pazienti con HbA1c >8.5% con BMI nella norma
D. Nei pazienti con elevata sensibilità insulinica a rischio di ipoglicemia severa

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 (especially when fatigue, abdominal pain, fasting, vomiting, physical activity, alcohol use, fever, reduction of insulin therapy, surgery
- **Never run out of insulin, especially basal**