Non-insulin treatment in Type 1 DM

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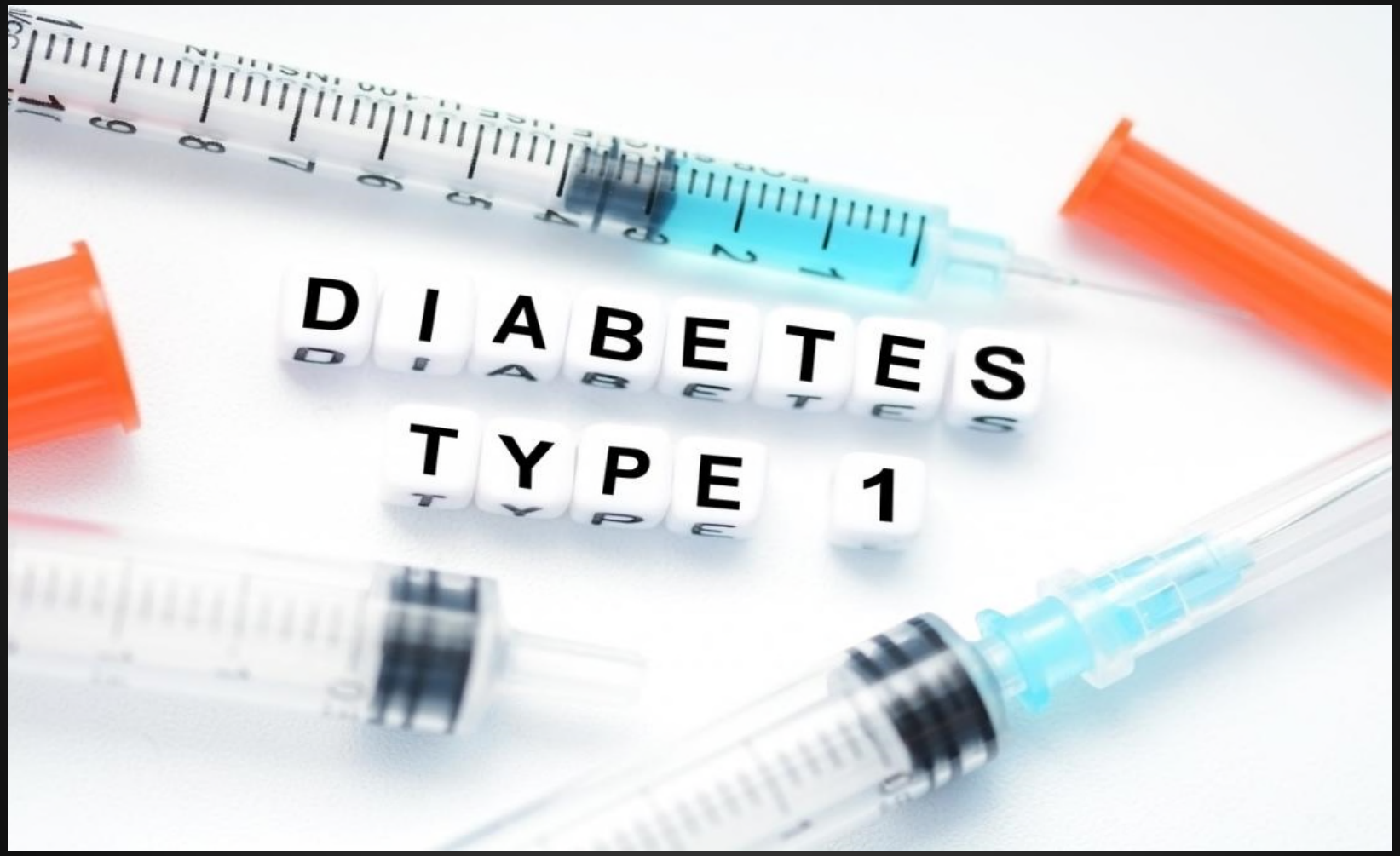
Conflict of interest disclosure

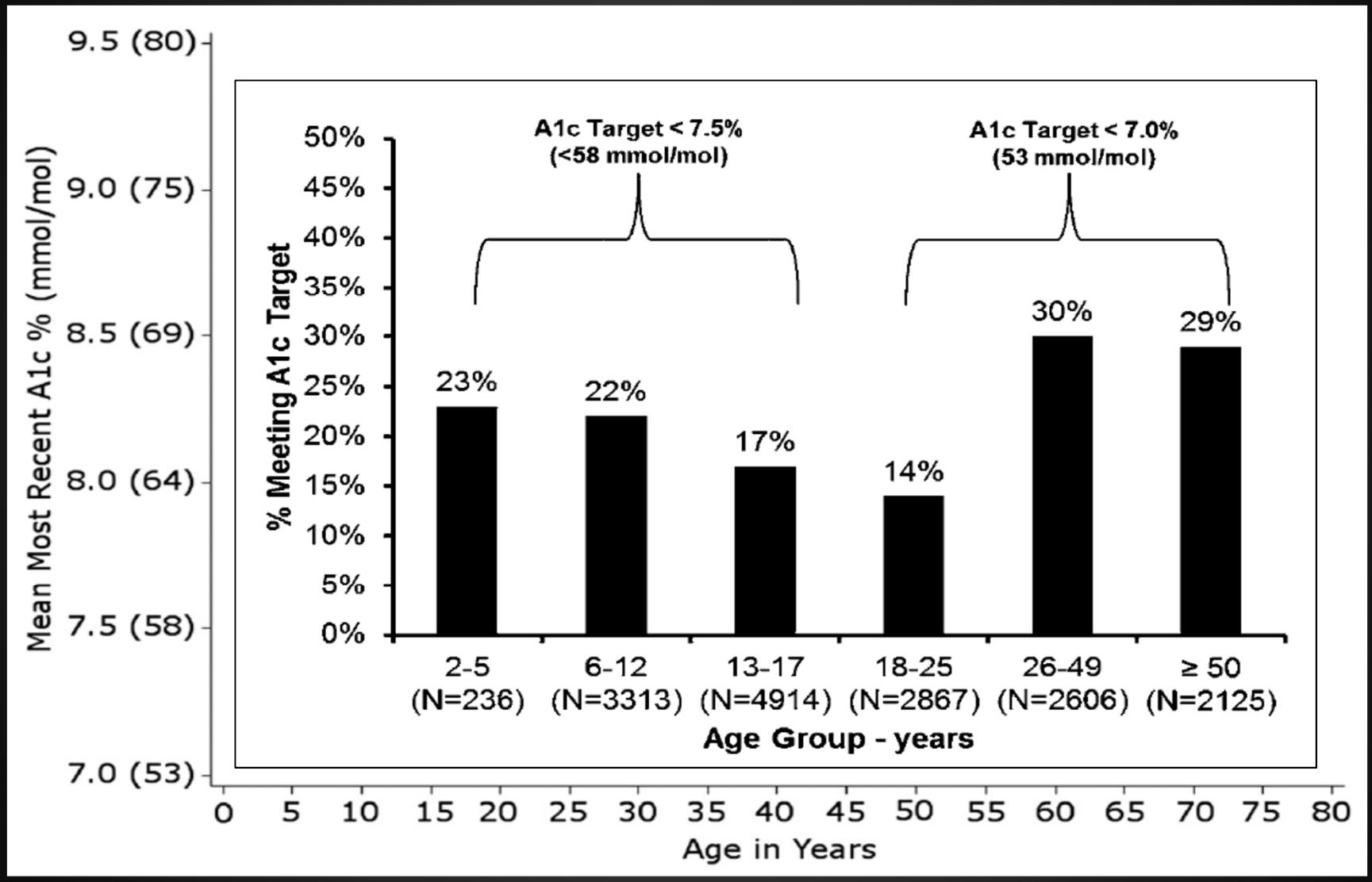
None

Committee of Scientific Affairs

Insulin therapy is the mainstay for T1DM

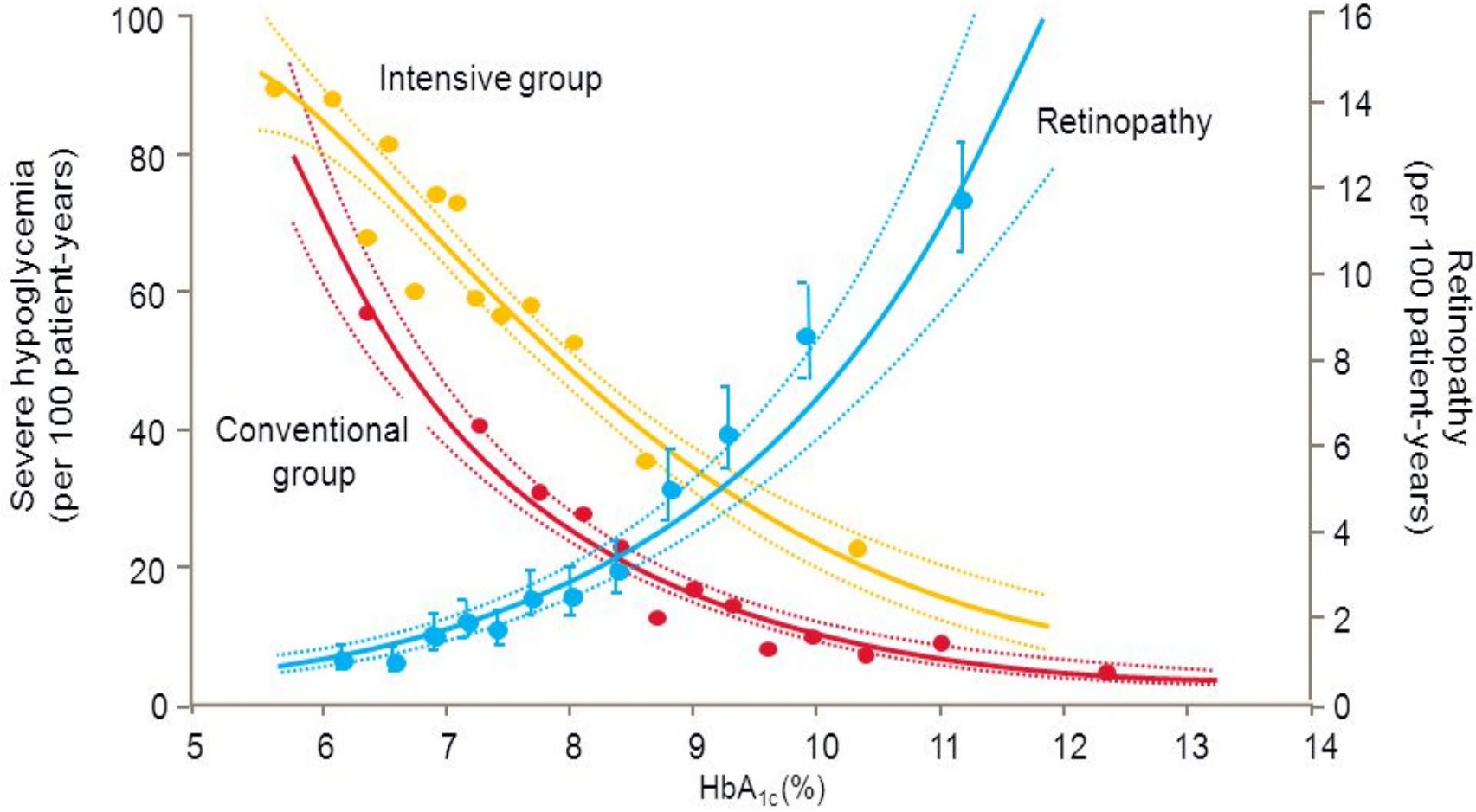


Unmet need in Type 1 diabetes



Diabetes Care 2015;38:971-8

Hypoglycemia: benefits and risks (DCCT)



DCCT, Diabetes Control and Complications Trial
DCCT Research Group. *N Engl J Med* 1993;329:977–86

Recent trend in Type 1 diabetic patients

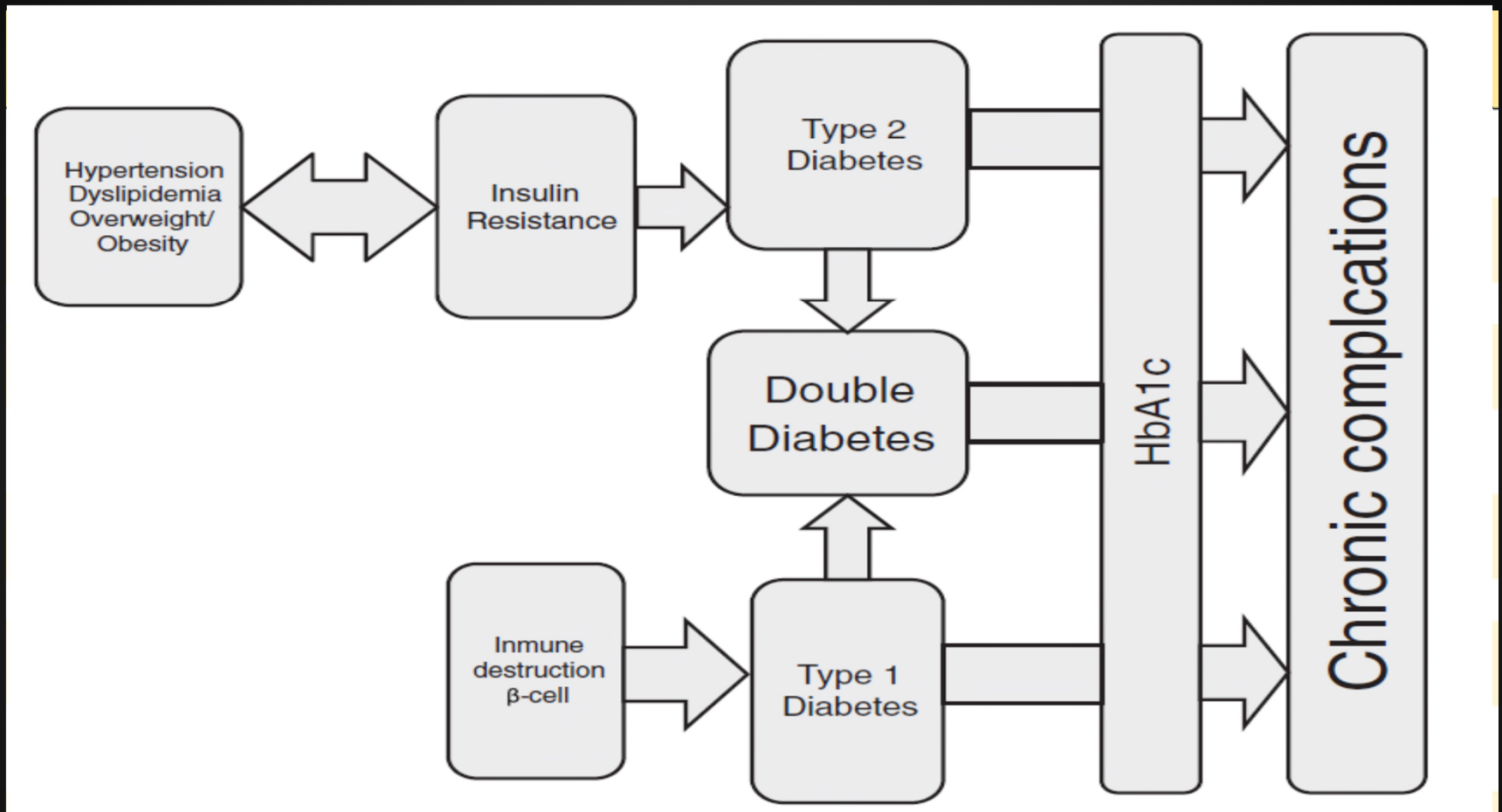


Fig. 1 – Physiopathologic aspects of type 1 and type 2 diabetes.

NR, not reported. [a]US Centers for Disease Control and Prevention or International Obesity Task Force criteria for overweight (BMI 85th to <95th percentile) and obesity (BMI ≥95th percentile). [b]German Working Group of Obesity in Childhood and Adolescence (AGA) criteria for overweight (BMI 90th to 97th percentile) and obesity (BMI ≥97th percentile). [c]BMI categories for overweight (BMI 25–30 kg/m^2) and obesity (BMI ≥30 kg/m^2).

Curr Opin Endocrinol Diabetes Obes. 2015;22(4):277-82

Pharmacologic approaches to glycemic treatment

Standards of medical care in diabetes -2018

PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES

Recommendations

- Most people with type 1 diabetes should be treated with multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion. **A**
- Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **A**
- Consider educating individuals with type 1 diabetes on matching prandial insulin doses to carbohydrate intake, premeal blood glucose levels, and anticipated physical activity. **E**
- Individuals with type 1 diabetes who have been successfully using continuous subcutaneous insulin infusion should have continued access to this therapy after they turn 65 years of age. **E**

Non-insulin agent	Investigational agents
Pramlintide	1. Metformin 2. Incretin-based therapies 3. SGLT-2 inhibitors

Diabetes Care 2018;41(Suppl. 1):S73–S85

Ideal non-insulin adjunctive therapy for T1DM

- Little impact on insulin secretion and action
- Safe profile for long-term use
- Provide additional non-glycemic benefit
- Reasonable price and insurance accepted

Diabetes Care 2015;38:971–978

Data from T1D exchange registry

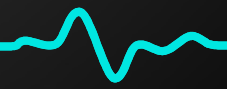
Table 1—Participant characteristics

	Overall *n* = 16,061	2–5 years old *n* = 236	6–12 years old *n* = 3,313	13–17 years old *n* = 4,914	18–25 years old *n* = 2,867	26–49 years old *n* = 2,606	≥50 years old *n* = 2,125
Demographic and clinical characteristics							
Race/ethnicity, *n* (%)							
White non-Hispanic	13,310 (83)	179 (76)	2,610 (79)	3,823 (78)	2,357 (82)	2,327 (89)	2,014 (95)
Black non-Hispanic	740 (5)	16 (7)	164 (5)	292 (6)	124 (4)	89 (3)	55 (3)
Hispanic or Latino	1,294 (8)	25 (11)	336 (10)	540 (11)	263 (9)	106 (4)	24 (1)
Other	699 (4)	16 (7)	194 (6)	255 (5)	121 (4)	81 (3)	32 (2)
Diabetes management							
Pump use, *n* (%)	9,530 (60)	146 (63)	2,131 (65)	2,810 (58)	1,555 (55)	1,625 (63)	1,263 (60)
CGM use, *n* (%)	1,703 (11)	31 (13)	263 (8)	249 (5)	193 (7)	590 (23)	377 (18)
SMBG, mean ± SD#	4.7 ± 2.7	7.4 ± 2.9	6.2 ± 2.6	4.2 ± 2.3	3.5 ± 2.4	4.3 ± 2.7	4.8 ± 2.7
0–3 times per day	3,630 (34)	3 (2)	253 (11)	1,316 (39)	994 (55)	689 (41)	375 (30)
4–6 times per day	4,781 (45)	63 (37)	1,174 (50)	1,575 (47)	625 (35)	712 (43)	632 (51)
6–9 times per day	1,566 (15)	75 (44)	627 (27)	360 (11)	124 (7)	193 (12)	187 (15)
≥10 times per day	578 (5)	28 (17)	286 (12)	87 (3)	48 (3)	73 (4)	56 (4)
Downloading of meter at home, *n* (%)§							
≥1 time per month	298 (12)	6 (13)	92 (17)	73 (16)	40 (9)	49 (7)	38 (9)
Never	1,671 (65)	33 (70)	277 (52)	252 (55)	310 (69)	506 (77)	293 (71)
Noninsulin medications for blood glucose control, *n* (%)							
Metformin	515 (3)	0	12 (<1)	121 (2)	100 (3)	168 (6)	114 (5)
GLP-1 agonist	116 (<1)	0	0	2 (<1)	18 (<1)	64 (2)	32 (2)
DPP-4*i*	12 (<1)	0	0	0	0	9 (<1)	3 (<1)
SGLT2*i*	14 (<1)	0	0	0	0	9 (<1)	5 (<1)
Pramlintide	128 (<1)	0	1 (<1)	2 (<1)	11 (<1)	61 (2)	53 (2)
Other‖	30 (<1)	0	0	0	1 (<1)	12 (<1)	17 (<1)

Diabetes Care 2015;38:971–978

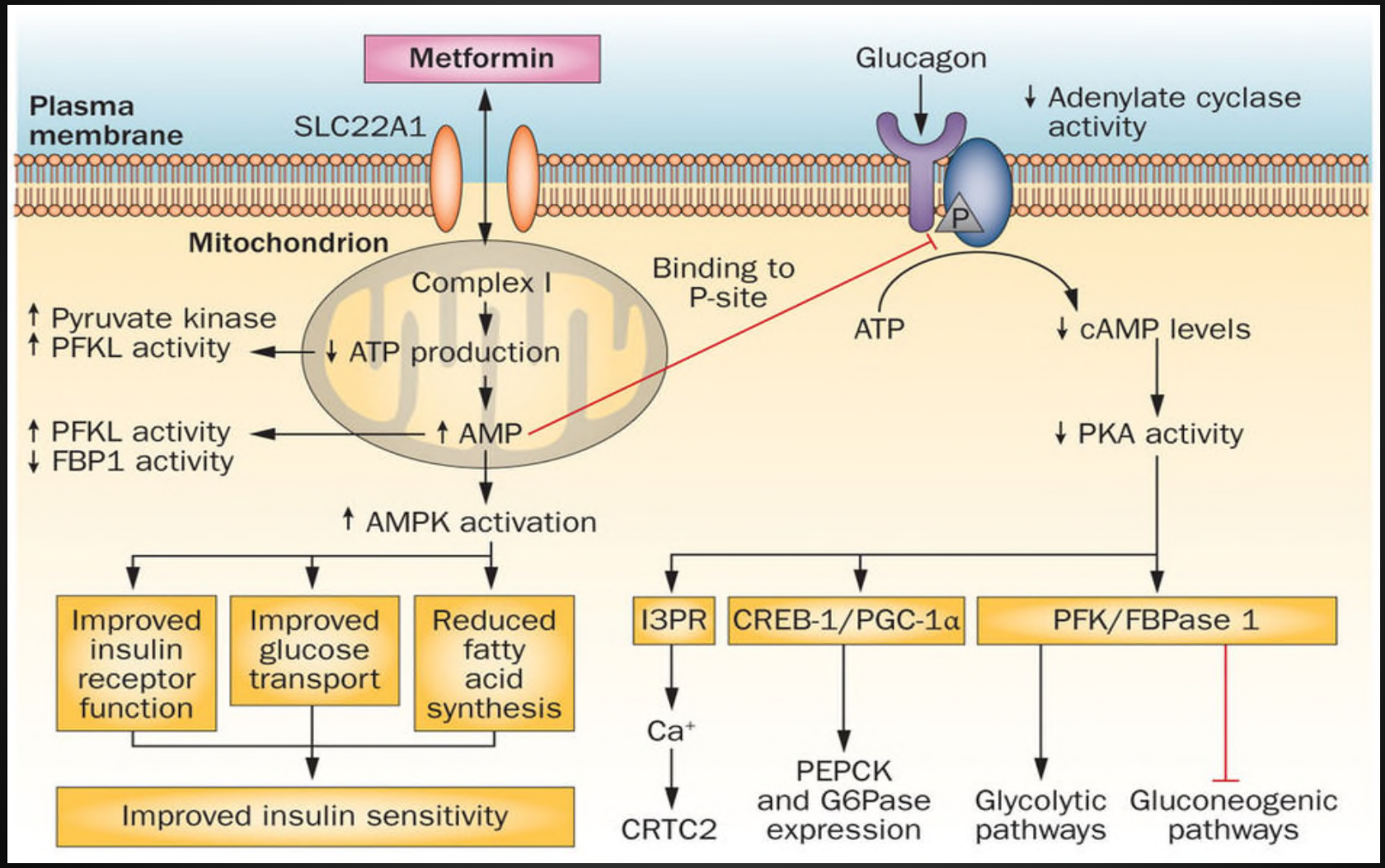
Possible non-insulin adjunctive therapy for T1DM

- Metformin
- α-glucosidase inhibitor
- Thiazolidinedione
- DPP-4 inhibitor
- GLP-1 Receptor agonist
- SGLT-2 inhibitor



Diabetes Care 2015;38:971–978

Metformin


Metformin
Glucagon
Plasma membrane
SLC22A1
↓ Adenylate cyclase activity
P
Mitochondrion
Complex I
Binding to P-site
↑ Pyruvate kinase
↑ PFKL activity
↓ ATP production
ATP
↓ cAMP levels
↑ PFKL activity
↓ FBP1 activity
↑ AMP
↓ PKA activity
↑ AMPK activation
Improved insulin receptor function
Improved glucose transport
Reduced fatty acid synthesis
I3PR
CREB-1/PGC-1α
PFK/FBPase 1
Ca+
PEPCK and G6Pase expression
Glycolytic pathways
Gluconeogenic pathways
CRTC2
Improved insulin sensitivity

Metformin in type 1 diabetes

The use of metformin in type 1 diabetes: a systematic review and efficacy

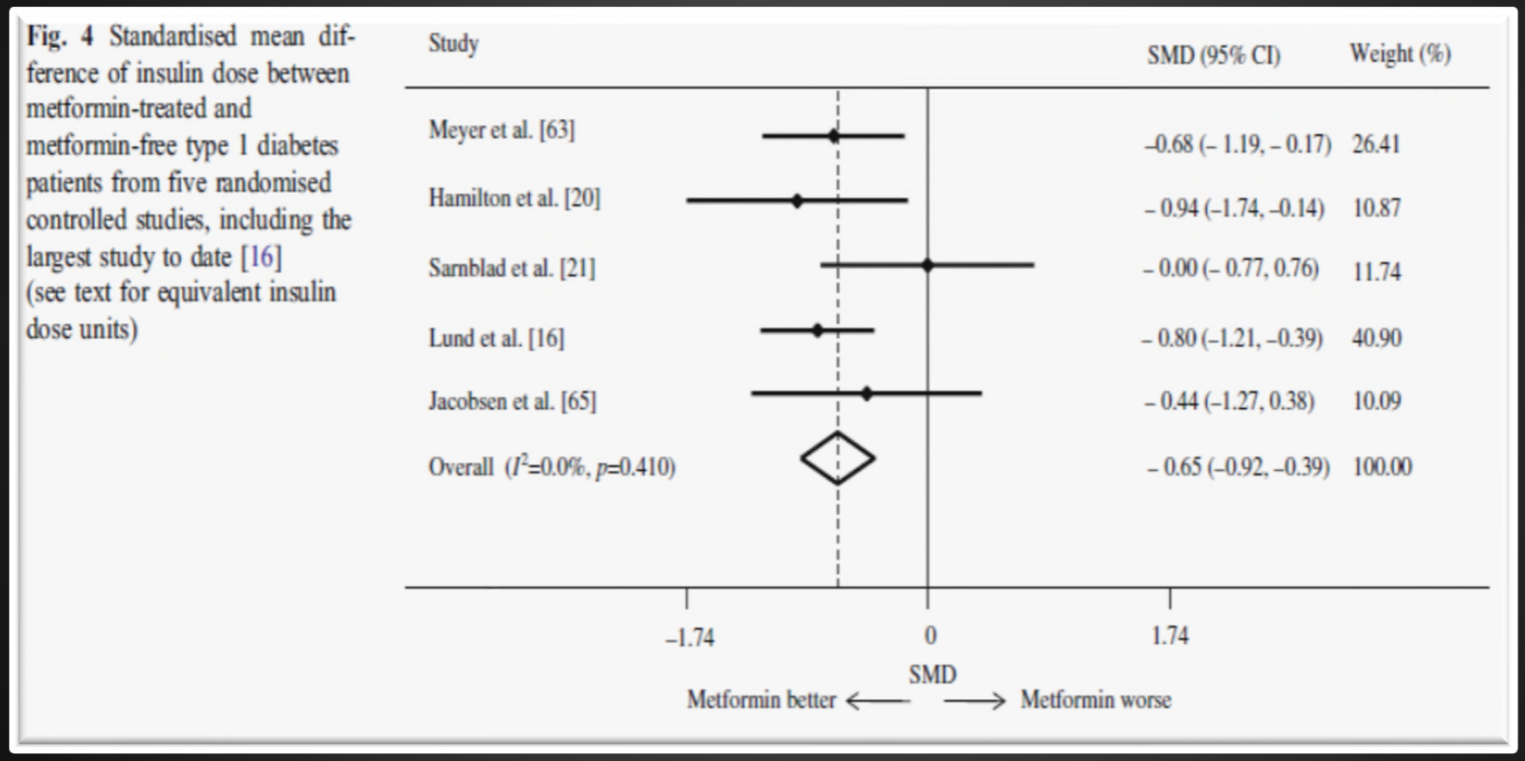
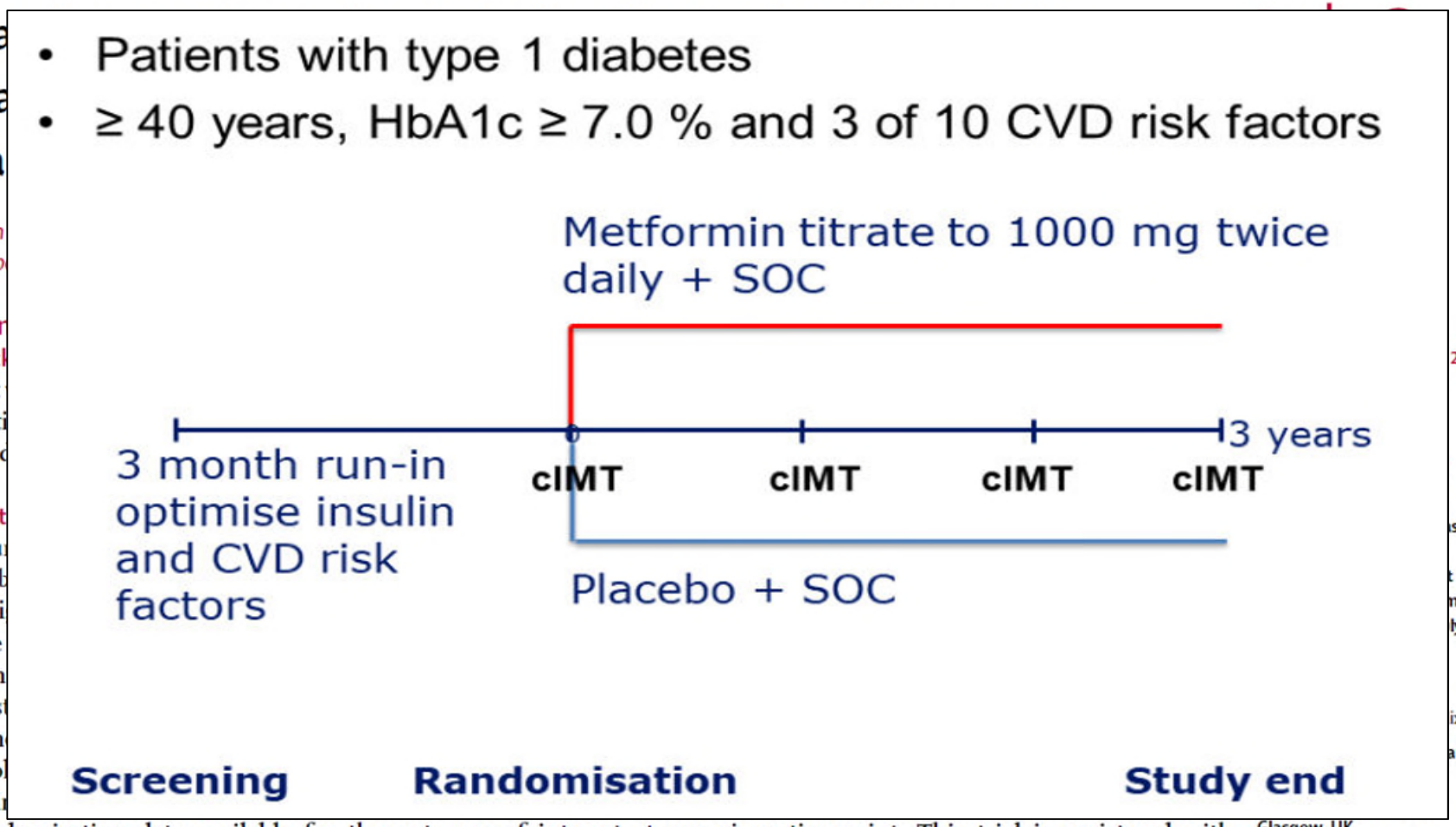


Fig. 4 Standardised mean difference of insulin dose between metformin-treated and metformin-free type 1 diabetes patients from five randomised controlled studies, including the largest study to date [16] (see text for equivalent insulin dose units)

Metformin was associated with reductions in weight (1.7–6.0 kg in three of six studies) and total cholesterol (0.3–0.41 mmol/l in three of seven studies).

Diabetologia (2010) 53:809–820

REMOVAL trial



randomisation data available for the outcome of interest at any given timepoint. This trial is registered with ClinicalTrials.gov, number NCT01483560.

Glasgow, UK (Prof J R Petrie FRCP, Prof N Sattar MD); Institute of

Lancet Diabetes Endocrinol 2017;5:597-609

REMOVAL trial - Outcomes

Primary:

Progression of mean far wall common carotid artery IMT at baseline, 12, 24, 36months

Secondary:

HbA1c, LDL-C, albuminuria, eGFR, retinopathy stage, weight, insulin dose, endothelial function.

Tertiary:

Frequency of hypoglycemia
Treatment satisfaction
Markers of endothelial function
Progression of maximal common carotid artery IMT
Vitamin B12 status

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REMOVAL trial – Study population

	Metformin (n=219)	Placebo (n=209)
Age (years)	55·2 (8·5)	55·8 (8·8)
Sex		
Male	129 (59%)	124 (59%)
Female		
Ethnic origin*		
White		
Other		
Diabetes duration (years)		
C-peptide (nmol/L)		
Existing CVD		
MI or stroke		
All†		
None		
Strong family history of CVD		
Yes		
No		
HbA_{1c}		
Absolute (mmol/mol)	64·8 (9·4)	64·1 (8·5)
% units	8·08 (0·86)	8·02 (0·78)
Insulin regimen		
Basal-bolus	128 (58%)	122 (58%)
Pump	73 (33%)	72 (34%)
Twice daily	5 (2%)	7 (3%)
Other	13 (6%)	8 (4%)
Total daily insulin dose (units per kg)		
Basal-bolus	0·67 (0·23)	0·74 (0·29)
Pump	0·54 (0·29)	0·57 (0·29)
Twice daily	0·73 (0·35)	0·64 (0·27)
Other	0·67 (0·23)	0·73 (0·26)
LDL cholesterol (mmol/L)	2·23 (0·70)	2·25 (0·72)
HDL cholesterol (mmol/L)	1·64 (0·56)	1·62 (0·59)
Triglycerides (mmol/L)	1·07 (0·77)	1·03 (0·57)
Smoking history		
Current	35 (16%)	22 (11%)
Former	73 (33%)	71 (34%)
Never	111 (51%)	116 (56%)
eGFR (mL/min/1·73m²)	92·9 (20·9)	91·1 (21·6)
Renal		
Normal		
(>90 mL/min/1·73m²)	128 (58%)	130 (62%)
Stage 1 CKD		
(>90 mL/min/1·73m²)		
Microalbuminuria	14 (6%)	14 (7%)
		8 (4%)
		48 (23%)
		9 (4%)
		16 (8%)
		132 (63%)
		39 (19%)
		19 (9%)
		3 (1%)
		28 (13%)
		157 (75%)
		103 (49%)
Angiotensin-receptor blocker	43 (20%)	49 (23%
Calcium-channel blocker	30 (14%)	38 (18%)
β blocker	19 (9%)	19 (9%)
α blocker	5 (2%)	7 (3%)
Statin	180 (82%)	169 (81%)
Antiplatelet drugs		
Aspirin	71 (32%)	80 (38%)
Clopidogrel	10 (5%)	6 (3%)

- Mean age: 55.5 years(SD: 8.6)
- Diabetes duration 33.8 years
- BMI 28.5 kg/m^2
- HbA1c 8.05%
- 58% used MDI, 34% used insulin pump
- BP: 129.5/72.3 mmHg (73% on hypertensive med)
- LDL-C : 85.8 mg/dL (82% on statin)

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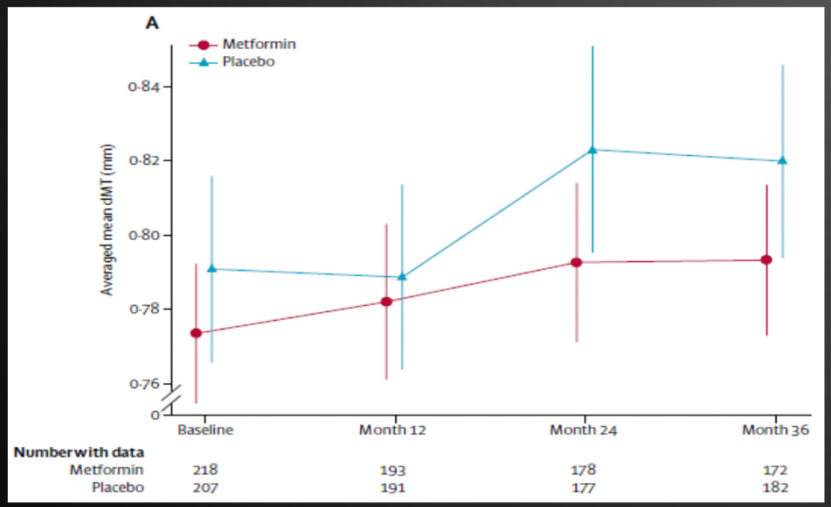
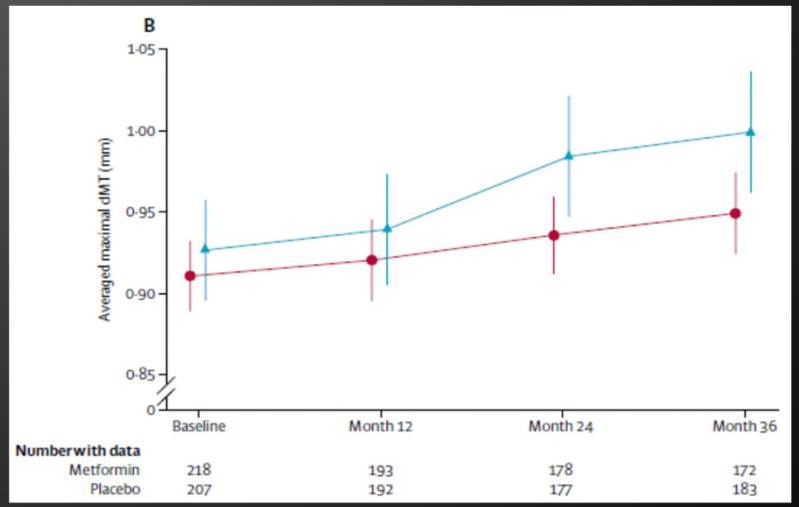
REMOVAL trial – Primary outcome

	Averaged mean far-wall cIMT (primary outcome)			Averaged maximal far-wall cIMT (tertiary outcome)		
	Metformin	Placebo	Difference (95% CI); p value	Metformin	Placebo	Difference (95% CI); p value
Baseline (mm)	0·773 (0·140)	0·791 (0·183)	..	0·910 (0·162)	0·926 (0·225)	..
12 months (mm)	0·782 (0·147)	0·788 (0·174)	..	0·920 (0·175)	0·939 (0·239)	..
24 months (mm)	0·792 (0·145)	0·823 (0·187)	..	0·936 (0·161)	0·984 (0·251)	..
36 months (mm)	0·793 (0·134)	0·820 (0·177)	..	0·949 (0·167)	0·999 (0·257)	..
Main analysis*						
Slope (95% CI; mm per year)	0·006 (0·001 to 0·011)	0·010 (0·006 to 0·015)	−0·005 (−0·012 to 0·002); p=0·1664	0·012 (0·005 to 0·019)	0·025 (0·018 to 0·032)	−0·013 (−0·024 to −0·003; p=0·0093)

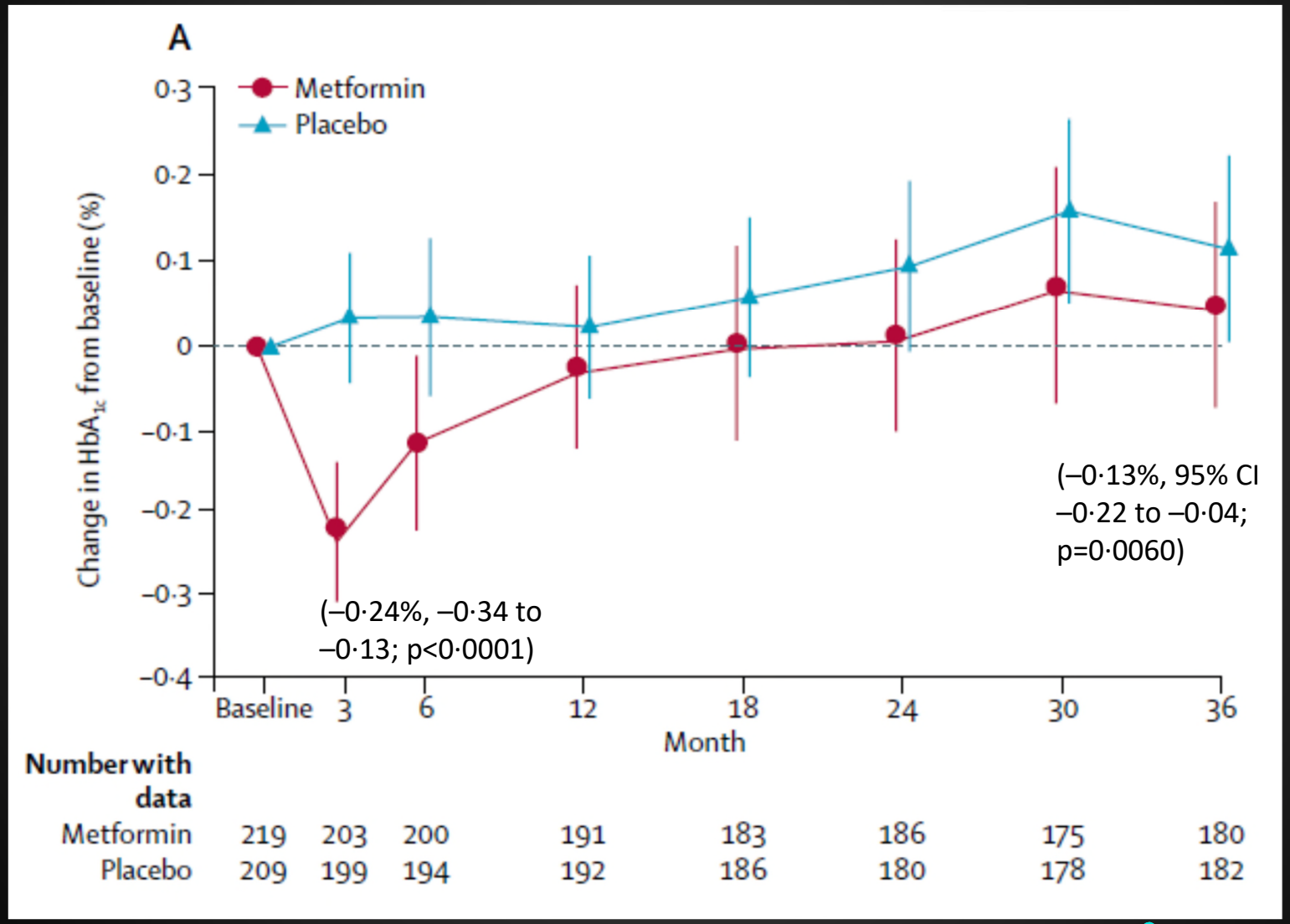
Data are mean (SD), unless otherwise indicated. Analyses are for modified intention-to-treat of participants with at least one measurement after baseline. cIMT=common carotid artery intima-media thickness. *Adjusted for baseline age, sex, cIMT, smoking status, systolic blood pressure, BMI, HbA_{1c}, and LDL cholesterol.

Table 2: **Repeated measures analysis of cIMT**





REMOVAL trial – HbA1c



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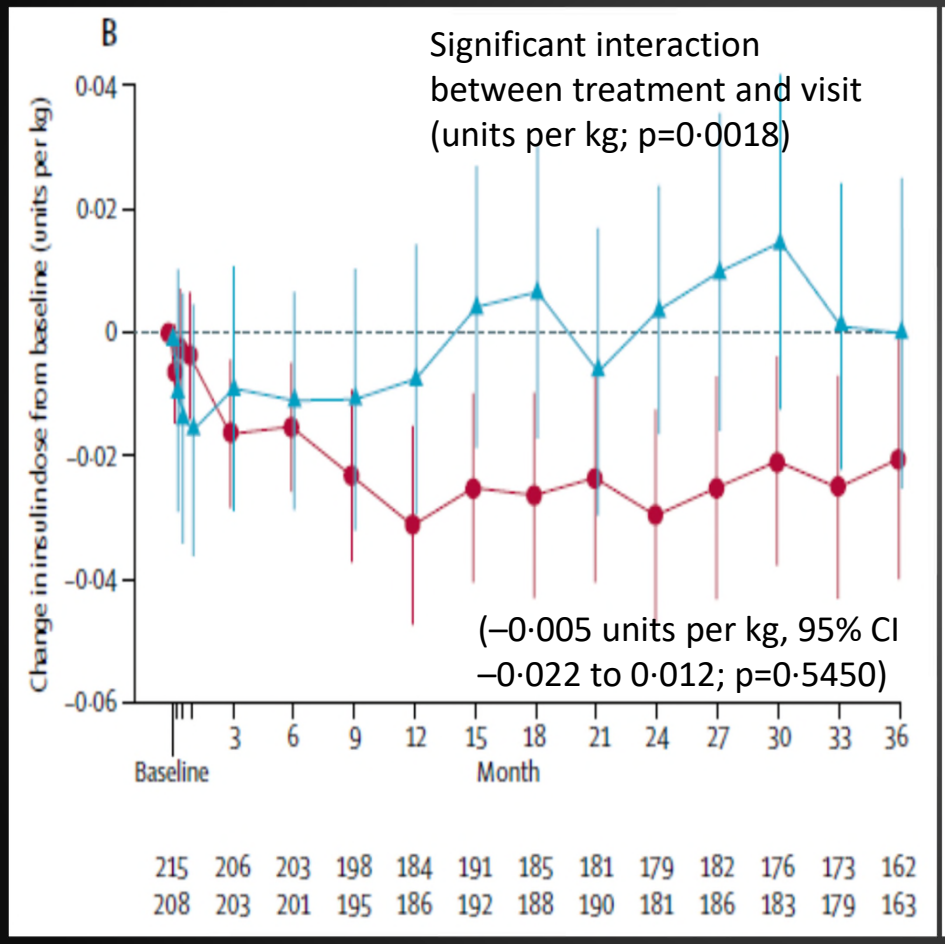
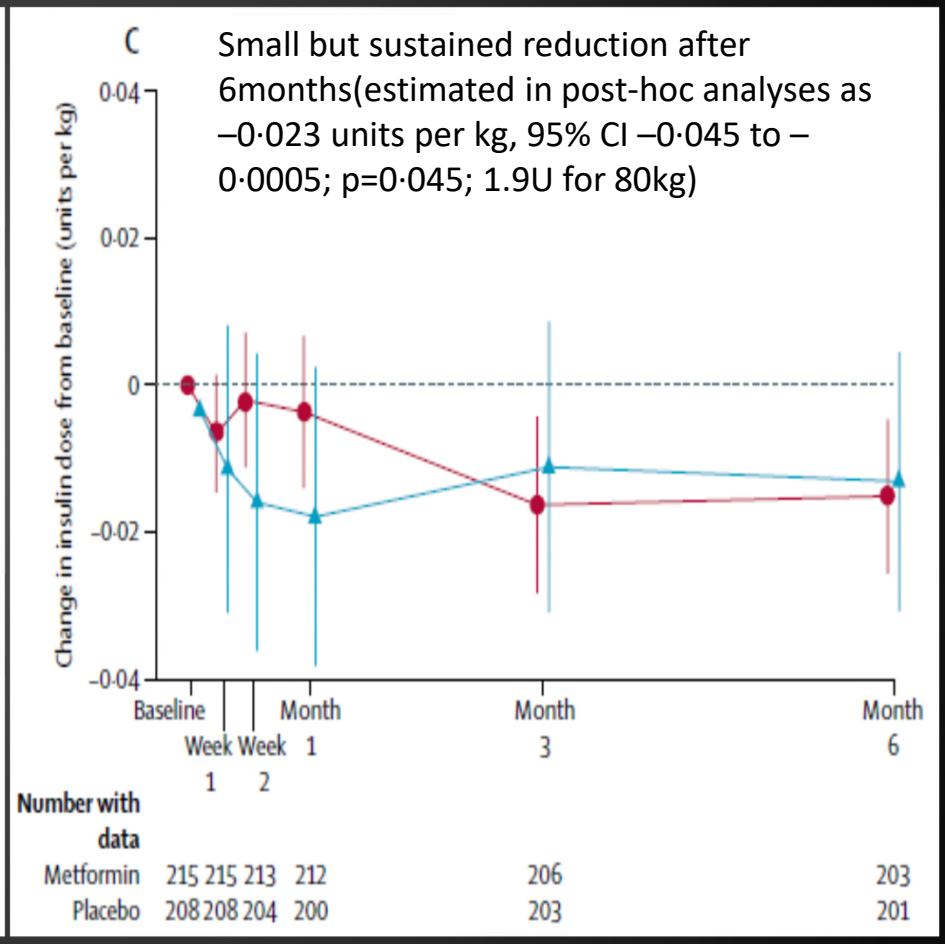
REMOVAL trial – Insulin dose



Significant interaction between treatment and visit (units per kg; p=0·0018)

(–0·005 units per kg, 95% CI –0·022 to 0·012; p=0·5450)



Small but sustained reduction after 6months(estimated in post-hoc analyses as –0·023 units per kg, 95% CI –0·045 to –0·0005; p=0·045; 1.9U for 80kg)

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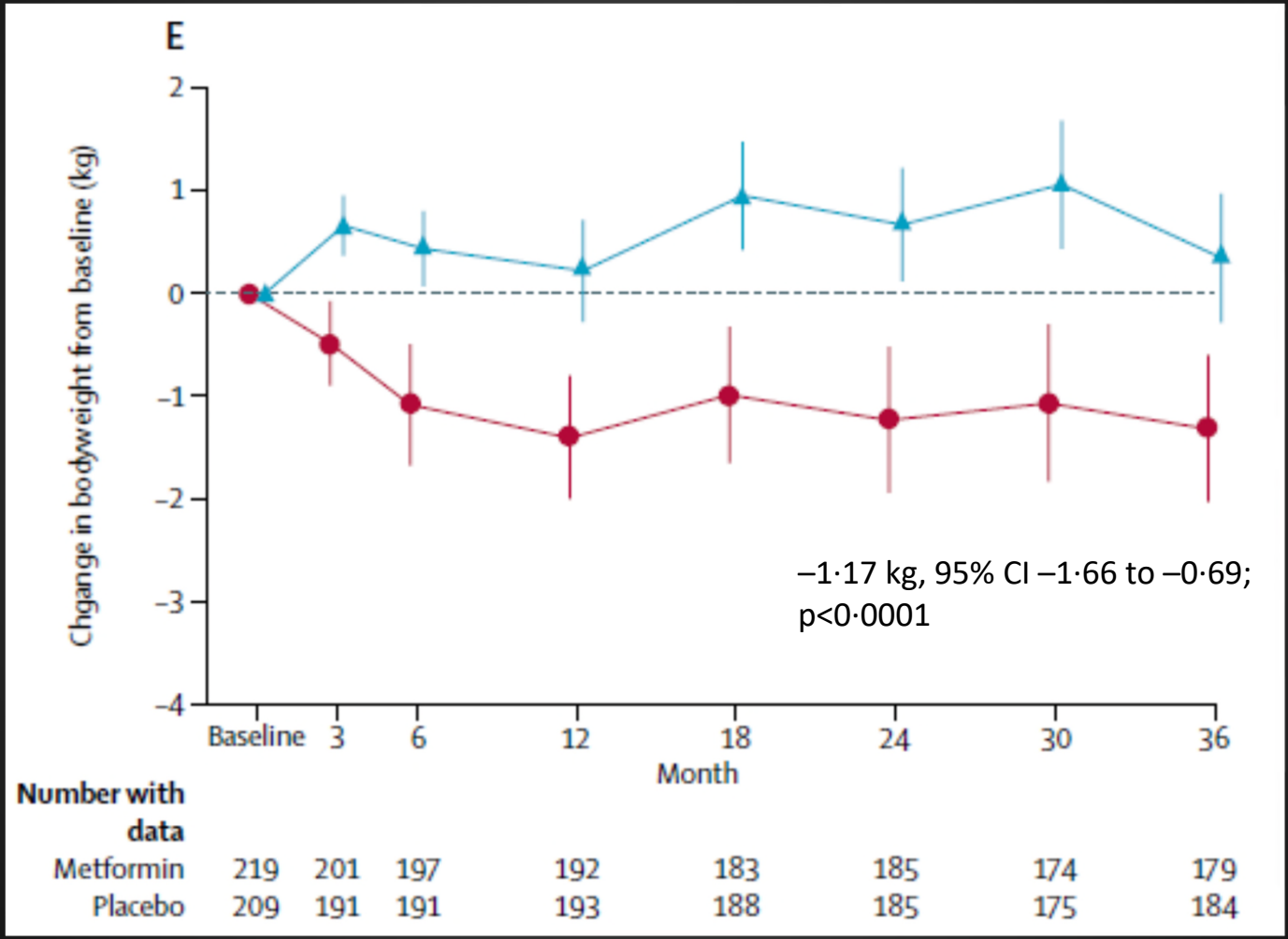
REMOVAL trial – Body weight



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REMOVAL trial – Tertiary outcomes

	Baseline		36 months		Change (ANCOVA)* or HR†/ IRR‡ (95% CI)	p value
	Metformin	Placebo	Metformin	Placebo		
Tertiary outcomes						
Hypoglycaemia (per patient-year)						
Minor events	37·2	38·8	54·6	49·1	1·12 (0·92 to 1·35)‡	0·2594
Major events	0·15	0·17	0·16	0·14	1·23 (0·73 to 2·05)‡	0·4419
Treatment satisfaction (units)	32·1 (3·6)	31·4 (4·2)	31·8 (4·2)	31·3 (4·8)	−0·12 (−0·72 to 0·47)*	0·6880
Vitamin B12 <150 pmol/L§	0	0	24/194 (12%)	9/192 (5%)	2·76 (1·28 to 5·95)†	0·0094
Adherence and safety						
Treatment discontinuation	..	..	59 (27%)	26 (12%)	..	0·0002
Gastrointestinal	..	..	34 (16%)	7 (3%)	..	..
Nausea	..	..	20 (9%)	5 (2%)	..	..
Diarrhoea	..	..	18 (8%)	3 (1%)	..	..
Reduced eGFR	..	..	0	0	..	..
Lactate >3·0 mmol/L (twice)	..	..	1 (<1%)	0	..	..
>5·0 mmol/L (any)	..	..	3 (1%)	0	..	..
Treatment down-titration	..	..	67 (31%)	18 (9%)	..	..
Study medication dose (mg per day)	..	..	1434 (612)	1674 (343)	..	..
Lactate (mmol/L)	1·31 (0·76)	1·23 (0·57)	1·30 (0·61)	1·19 (0·52)	0·08 (−0·03 to 0·19)*	0·1640
Deaths	..	..	5 (2%)	2 (1%)	..	..
Cancer	..	..	3¶	1‖	..	..
Cardiac	..	..	2**	1††	..	..

Data are mean (SD) for continuous data or n (%) for categorical data, unless otherwise indicated. Treatment effect and corresponding 95% CIs are provided for metformin compared with placebo. eGFR=estimated glomerular filtration rate. *ANCOVA for the change from baseline, adjusted for the baseline value, for continuous data. †Hazard ratio (HR) and 95% CI for time to first event data obtained by Cox proportional-hazards model. ‡Incidence rate ratio (IRR) and 95% CI for count data are obtained by negative binomial regression models, including the logarithm of time as an offset; the frequency of minor hypoglycaemia events is further adjusted for the method of collection. §Vitamin B12 data were missing for 25 people in the metformin group and 17 in the placebo group. ¶ Two non-small-cell lung cancers, one malignant neoplasm of the tongue. ‖Glioblastoma. **One myocardial infarction, one sudden cardiac death. ††Myocardial infarction.

Table 4: **Tertiary outcomes, adherence, and safety**

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REMOVAL trial - Conclusion

1. The result of REMOVAL do not support the assertion by current guidelines that metformin treatment results in a clinically meaningful improvement in glycemic control.

2. Treatment with metformin was safe, but with the expected GI S/E leading to some discontinuation. And also, risk of biochemical vit-B12 deficiency was increased over 3 years.

3. Progression of the primary outcome mean cIMT was not significantly reduced with metformin.

4. The reduction in weight and the tertiary outcome maximal cIMT indicate that metformin may have a wider role in CV risk management.

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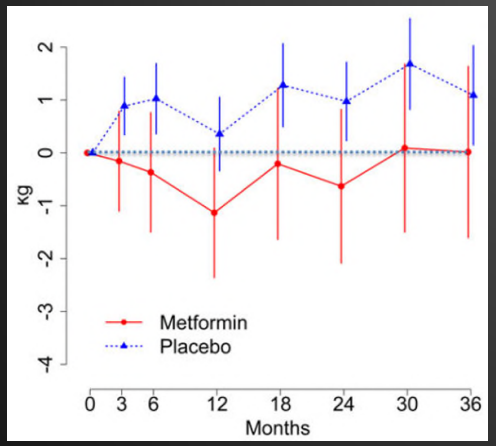
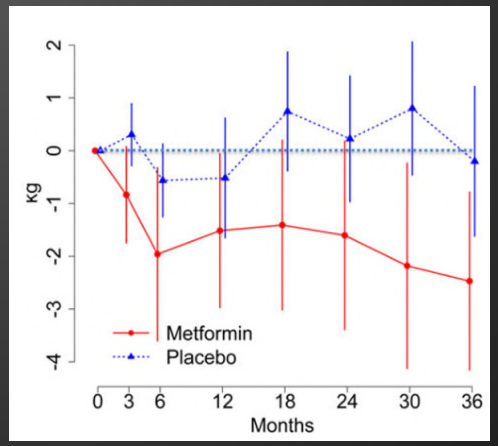
Further discussion

- Does metformin has an CV benefit?
- Dose reduction of insulin is meaningful?
- BW lowering effect is great in Obese T1D patients.
- Biochemical monitoring for Vit-B12 is necessary?



BMI
< 25



BMI
≥ 30

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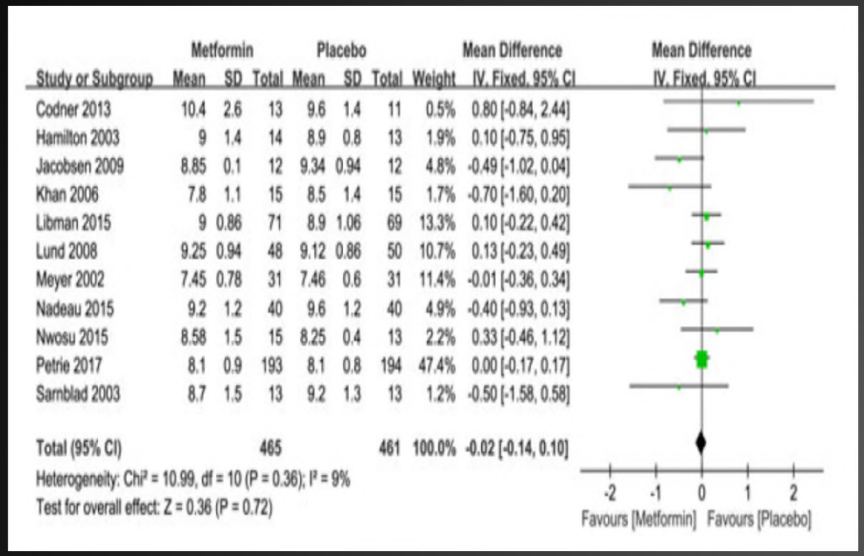
Metformin in type 1 diabetes

A1C

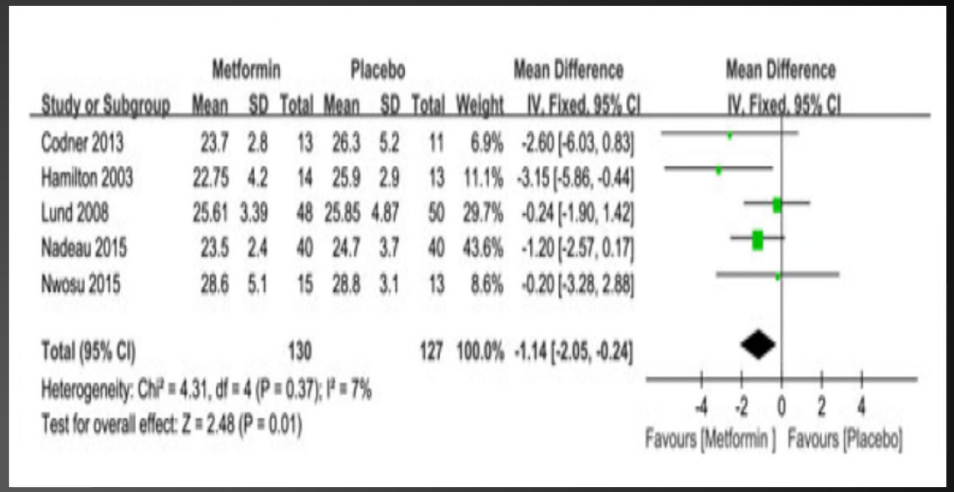


Study or Subgroup	Metformin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Codner 2013	10.4	2.6	13	9.6	1.4	11	0.5%	0.80 [-0.84, 2.44]
Hamilton 2003	9	1.4	14	8.9	0.8	13	1.9%	0.10 [-0.75, 0.95]
Jacobsen 2009	8.85	0.1	12	9.34	0.94	12	4.8%	-0.49 [-1.02, 0.04]
Khan 2006	7.8	1.1	15	8.5	1.4	15	1.7%	-0.70 [-1.60, 0.20]
Libman 2015	9	0.86	71	8.9	1.06	69	13.3%	0.10 [-0.22, 0.42]
Lund 2008	9.25	0.94	48	9.12	0.86	50	10.7%	0.13 [-0.23, 0.49]
Meyer 2002	7.45	0.78	31	7.46	0.6	31	11.4%	-0.01 [-0.36, 0.34]
Nadeau 2015	9.2	1.2	40	9.6	1.2	40	4.9%	-0.40 [-0.93, 0.13]
Nwosu 2015	8.58	1.5	15	8.25	0.4	13	2.2%	0.33 [-0.46, 1.12]
Petrie 2017	8.1	0.9	193	8.1	0.8	194	47.4%	0.00 [-0.17, 0.17]
Sarnblad 2003	8.7	1.5	13	9.2	1.3	13	1.2%	-0.50 [-1.58, 0.58]
Total (95% CI)			465			461	100.0%	-0.02 [-0.14, 0.10]

Heterogeneity: Chi² = 10.99, df = 10 (P = 0.36); I² = 9%
Test for overall effect: Z = 0.36 (P = 0.72)

Mean Difference IV, Fixed, 95% CI
-2 -1 0 1 2
Favours [Metformin] Favours [Placebo]

BMI

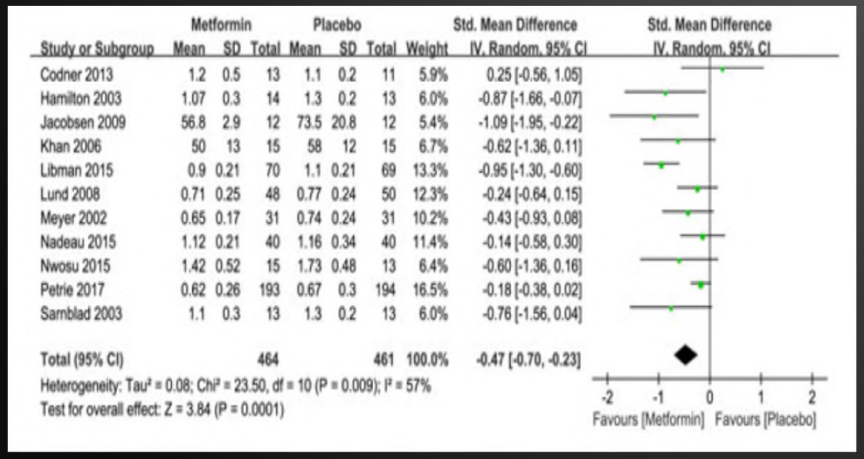


Study or Subgroup	Metformin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Codner 2013	23.7	2.8	13	26.3	5.2	11	6.9%	-2.60 [-6.03, 0.83]
Hamilton 2003	22.75	4.2	14	25.9	2.9	13	11.1%	-3.15 [-5.86, -0.44]
Lund 2008	25.61	3.39	48	25.85	4.87	50	29.7%	-0.24 [-1.90, 1.42]
Nadeau 2015	23.5	2.4	40	24.7	3.7	40	43.6%	-1.20 [-2.57, 0.17]
Nwosu 2015	28.6	5.1	15	28.8	3.1	13	8.6%	-0.20 [-3.28, 2.88]
Total (95% CI)			130			127	100.0%	-1.14 [-2.05, -0.24]

Heterogeneity: Chi² = 4.31, df = 4 (P = 0.37); I² = 7%
Test for overall effect: Z = 2.48 (P = 0.01)

Mean Difference IV, Fixed, 95% CI
-4 -2 0 2 4
Favours [Metformin] Favours [Placebo]

Insulin dose

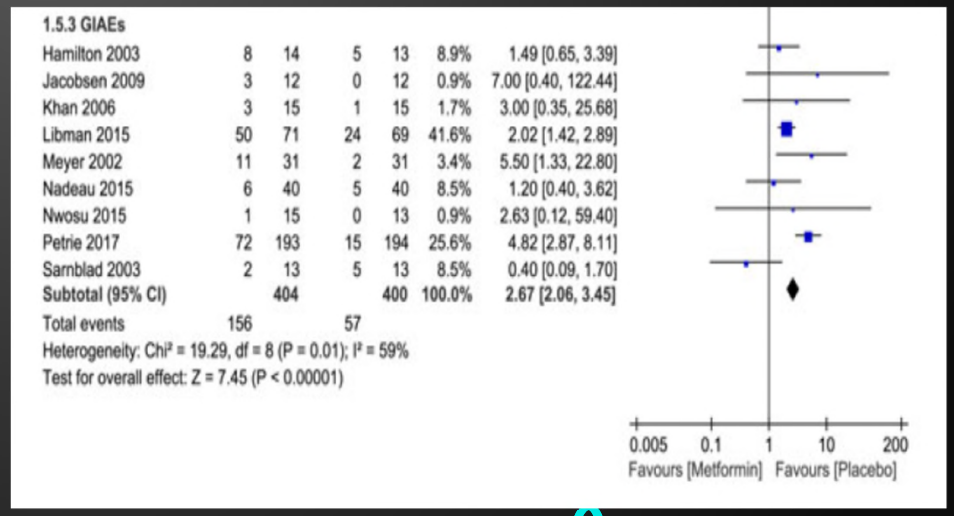


Study or Subgroup	Metformin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Codner 2013	1.2	0.5	13	1.1	0.2	11	5.9%	0.25 [-0.56, 1.05]
Hamilton 2003	1.07	0.3	14	1.3	0.2	13	6.0%	-0.87 [-1.66, -0.07]
Jacobsen 2009	56.8	2.9	12	73.5	20.8	12	5.4%	-1.09 [-1.95, -0.22]
Khan 2006	50	13	15	58	12	15	6.7%	-0.62 [-1.36, 0.11]
Libman 2015	0.9	0.21	70	1.1	0.21	69	13.3%	-0.95 [-1.30, -0.60]
Lund 2008	0.71	0.25	48	0.77	0.24	50	12.3%	-0.24 [-0.64, 0.15]
Meyer 2002	0.65	0.17	31	0.74	0.24	31	10.2%	-0.43 [-0.93, 0.08]
Nadeau 2015	1.12	0.21	40	1.16	0.34	40	11.4%	-0.14 [-0.58, 0.30]
Nwosu 2015	1.42	0.52	15	1.73	0.48	13	6.4%	-0.60 [-1.36, 0.16]
Petrie 2017	0.62	0.26	193	0.67	0.3	194	16.5%	-0.18 [-0.38, 0.02]
Sarnblad 2003	1.1	0.3	13	1.3	0.2	13	6.0%	-0.76 [-1.56, 0.04]
Total (95% CI)			464			461	100.0%	-0.47 [-0.70, -0.23]

Heterogeneity: Tau² = 0.08; Chi² = 23.50, df = 10 (P = 0.009); I² = 57%
Test for overall effect: Z = 3.84 (P = 0.0001)

Std. Mean Difference IV, Random, 95% CI
-2 -1 0 1 2
Favours [Metformin] Favours [Placebo]

GI S/E



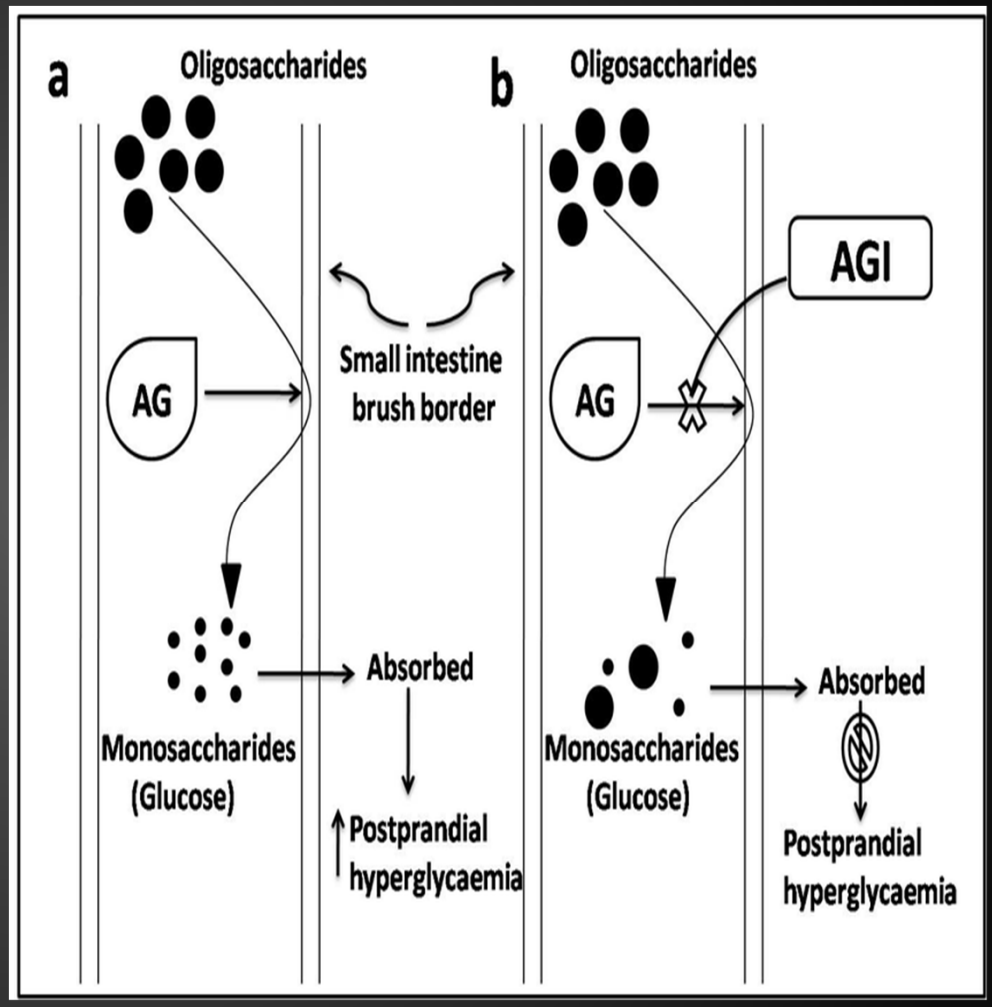
1.5.3 GIAEs						
Hamilton 2003	8	14	5	13	8.9%	1.49 [0.65, 3.39]
Jacobsen 2009	3	12	0	12	0.9%	7.00 [0.40, 122.44]
Khan 2006	3	15	1	15	1.7%	3.00 [0.35, 25.68]
Libman 2015	50	71	24	69	41.6%	2.02 [1.42, 2.89]
Meyer 2002	11	31	2	31	3.4%	5.50 [1.33, 22.80]
Nadeau 2015	6	40	5	40	8.5%	1.20 [0.40, 3.62]
Nwosu 2015	1	15	0	13	0.9%	2.63 [0.12, 59.40]
Petrie 2017	72	193	15	194	25.6%	4.82 [2.87, 8.11]
Sarnblad 2003	2	13	5	13	8.5%	0.40 [0.09, 1.70]
Subtotal (95% CI)		404		400	100.0%	2.67 [2.06, 3.45]
Total events	156		57			

Heterogeneity: Chi² = 19.29, df = 8 (P = 0.01); I² = 59%
Test for overall effect: Z = 7.45 (P < 0.00001)

0.005 0.1 1 10 200
Favours [Metformin] Favours [Placebo]

α-glucosidase inhibitor

- Mechanism – insulin independent
- Low hypoglycemia
- No weight gain
- Advantage in controlling post-prandial hyperglycemia



Efficacy and safety of acarbose in the treatment of Type 1 diabetes mellitus: a placebo-controlled, double-blind, multicentre study

Table 1 Baseline features of patients included in 'intention to treat' analysis

Parameter	Acarbose ($n = 57$)	Placebo ($n = 59$)
Male:female (%)	47:53	42:58
Age (years)	32.6 ± 11.78	36.3 ± 15.35
BMI (kg/m^2)	24.62 ± 3.53	24.74 ± 3.05
Fasting weight (kg)	66.1 ± 11.58	68.1 ± 10.54
HbA_{1c} (%)	9.1 ± 1.37	9.1 ± 1.34
Triglyceride (mmol/l)	1.31 ± 1.84	1.09 ± 0.57
Cholesterol (mmol/l)	5.24 ± 1.17	5.03 ± 0.98
HDL-cholesterol (mmol/l)	1.47 ± 0.36	1.37 ± 0.36
Insulin dose (U/day)	39 ± 15	42 ± 16

Mean ± SD.

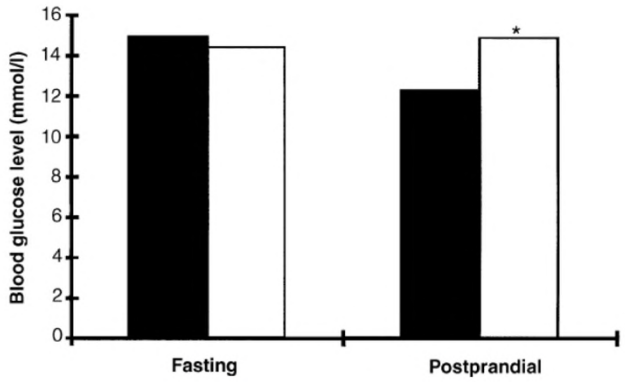


Figure 1 Acarbose vs. placebo: effects on fasting and postprandial blood glucose levels after 6 months' treatment (intention to treat). *$P < 0.02$. ■, acarbose; □, placebo. Data are lsmeans adjusted by covariance analysis on centre and baseline values.

Parameter	Acarbose ($n = 57$)	Placebo ($n = 59$)	95% CI for the treatment difference
Fasting weight (kg)	66.4 ± 0.3	66.7 ± 0.3	−1.0 ÷ +0.5
HbA_{1c} (%)	8.67 ± 0.14	8.90 ± 0.14	−0.61 ÷ +0.15
Triglyceride (mmol/l)	1.19 ± 0.06	1.10 ± 0.06	−0.07 ÷ +0.25
Cholesterol (mmol/l)	5.23 ± 0.10	5.37 ± 0.10	−0.0.41 ÷ +0.13
HDL-cholesterol (mmol/l)	1.39 ± 0.03*	1.50 ± 0.03	−0.20 ÷ −0.02
Insulin dose (U/day)	38.1 ± 0.7	39.3 ± 0.6	−2.9 ÷ +0.4
Hypoglycaemic events (n)	6.8 ± 0.96	6.4 ± 0.96	−2.1 ÷ +2.9

*$P < 0.02$.
lsmeans ± SEM.
Data represent lsmeans adjusted by covariance analysis on centre and baseline values.

75% patients in the acarbose group and 39% patients in the placebo group reported at least one adverse event during the double-blind period of the study. Most adverse events were mild and most were confined to the gastrointestinal tract.

Diabet Med 16;228-232:1999

Effects of acarbose (Glucobay®) in persons with type 1 diabetes: a multicentre study

Table 2
Results (per-protocol analysis)

	Screening	Start study				
Treatment		Plac	Plac	Acarb	Acarb	Plac
Weeks	−4	0	8	16	24	32
HbA_{1c} (%)	9.1 ± 1.1	8.9 ± 1.1	8.5 ± 0.9	8.1 ± 0.9	8.2 ± 0.9	8.6 ± 0.9
Blood glucose (mmol/l)						
Fasting	11.1	9.9	10.3	9.5	10.7	9.8
90 min after breakfast	11.7	11.0	11.0	9.1	10.0	11.5
Before lunch	10.5	10.1	8.5	7.9	8.9	9.0
90 min after lunch	11.3	11.1	10.2	8.1	8.4[a]	11.0
Before dinner	9.9	10.6	8.8	8.5	10.0	10.1
90 min after dinner	11.7	10.7	10.0	9.0	9.8	11.7
At bedtime	10.1	10.3	9.8	9.6	10.1	11.0

Data are shown as mean; Acarb, acarbose; Plac, placebo.
[a] $P < 0.01$ stop acarbose (week 24) vs. start acarbose (week 8).

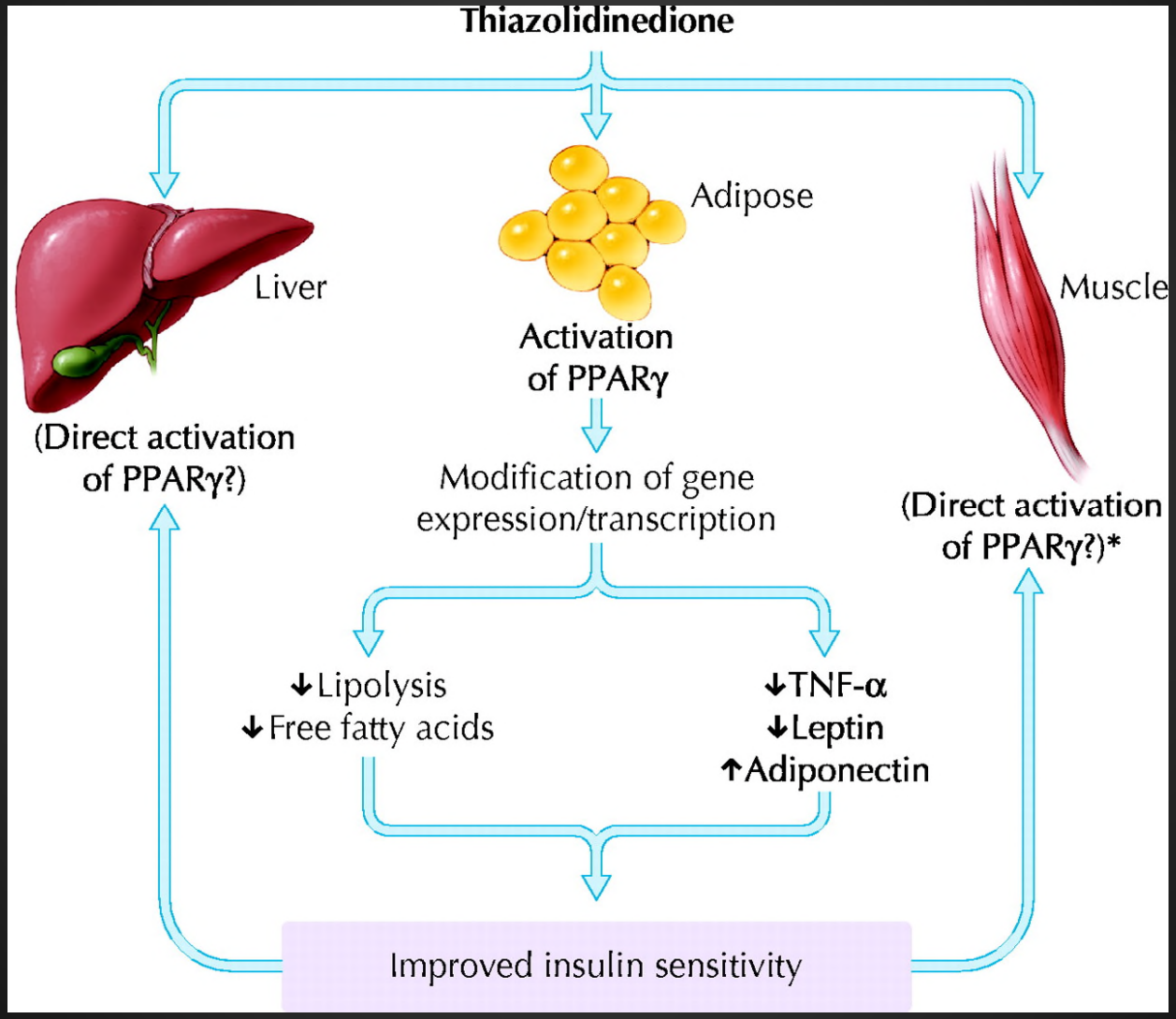
In total 214 adverse events were reported for 73(81%) patients, of which 71 (33%) occurred during placebo run-in phase, 124 (58%) during acarbose and 13 (6%) during placebo run-out phase. The most frequent reported adverse events were flatulence (43%), diarrhoea (27%), abdominal pain(11%).

Diab Res Clin Prac 41;139-145:1998

α-glucosidase inhibitor

- Overall, AGIs tend to be well tolerated and help reduce post-prandial glycemic excursions in individuals with T1DM.
- Modest HbA1c reduction and relatively high incidence of S/E are main barrier to prolong use of this drug.
- Balanced trial for long-term outcomes is needed.

Thiazolidinedione



The effect of rosiglitazone on overweight T1D

Table 1 — *Baseline characteristics*

	Rosiglitazone + insulin	Placebo + insulin
n	25	25
Age (years)	43.7 ± 13.3	41.1 ± 9.2
Sex (M/F)	16/9	18/7
Ethnic group (*n*)	22 Caucasian, 3 African American	23 Caucasian, 1 African American, 1 Hispanic
Duration of diabetes (years)	20.7 ± 13.3	18.1 ± 9.3
Waist-to-hip ratio	0.91 ± 0.07	0.93 ± 0.06
Fasting C-peptide (ng/ml)	0.3 ± 0.3	0.3 ± 0.3

Data are means ± SD or *n*.

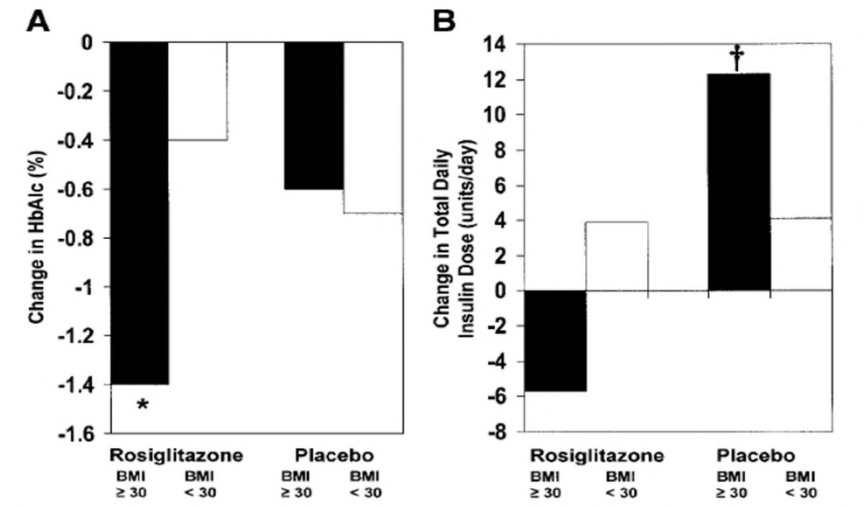


Figure 1—*Change in mean A1C level (A) and total daily insulin dose (B) based on baseline BMI in type 1 diabetic subjects after 8 months of treatment with insulin and rosiglitazone or insulin and placebo. *P < 0.05 vs. rosiglitazone-treated subjects with a BMI <30 kg/m²; †P < 0.05 vs. rosiglitazone-treated subjects with a BMI ≥30 kg/m².*

Table 2—*Results before and 32 weeks after treatment with rosiglitazone and insulin or placebo and insulin*

	Rosiglitazone and insulin		Placebo and insulin	
	Baseline	Week 32	Baseline	Week 32
Weight (kg)	97.2 ± 11.8	100.6 ± 16.0*	96.4 ± 12.2	99.1 ± 15.0*
BMI (kg/m²)	32.7 ± 5.4	34.0 ± 7.4*	31.1 ± 3.1	32.0 ± 4.2*
Systolic blood pressure (mmHg)	137.4 ± 15.6†	128.8 ± 14.8*	125.8 ± 10.0	127.5 ± 14.0
Diastolic blood pressure (mmHg)	87.2 ± 9.4	79.4 ± 7.2‡	84.7 ± 7.0	83.2 ± 7.1
Insulin dose (units/day)	77.5 ± 28.6	75.3 ± 33.1	74.0 ± 33.8	82.0 ± 48.9*
Fasting plasma glucose (mg/dl)	172.6 ± 68.3	153.3 ± 66.4	185.8 ± 90.6	173.4 ± 64.8
A1C (%)	7.9 ± 1.3	6.9 ± 0.7‡	7.7 ± 0.8	7.0 ± 0.9‡
Total cholesterol (mg/dl)	201.9 ± 37.6†	195.2 ± 37.5§	177.9 ± 33.1	175.1 ± 31.7
LDL cholesterol (mg/dl)	117.8 ± 32.0	120.1 ± 35.0	103.4 ± 25.2	102.6 ± 25.4
HDL cholesterol (mg/dl)	53.9 ± 20.5	53.6 ± 19.4	47.8 ± 15.0	49.1 ± 15.8
VLDL cholesterol (mg/dl)	15.8 ± 13.2	16.4 ± 9.8	13.8 ± 9.4	14.6 ± 15.6
Triglycerides (mg/dl)	108.1 ± 64.6	101.8 ± 53.8	92.8 ± 38.9	85.4 ± 39.7
VLDL triglycerides (mg/dl)	66.8 ± 57.6	61.9 ± 46.6	55.8 ± 31.6	48.8 ± 33.0
Hemoglobin (gm/dl)	14.4 ± 1.5	13.6 ± 1.9†§	14.5 ± 1.0	14.5 ± 1.0
Hematocrit (%)	42.0 ± 3.9	39.8 ± 5.1†§	42.3 ± 3.0	42.2 ± 2.9

Data are means ± SD. *$P < 0.05$ vs. baseline; †$P < 0.05$ vs. placebo and insulin at baseline; ‡$P < 0.0001$ vs. baseline; §$P < 0.05$ vs. placebo and insulin at week 32.

Rosiglitazone in combination with insulin resulted in improved glycemic control and blood pressure without an increase in insulin requirements, compared with insulin- and placebo-treated subjects, whose improved glycemic control required an 11% increase in insulin dose.

Diabetes Care 28:1562–1567, 2005

Effect of pioglitazone in lean T1D

Comparison of glycemic control, insulin requirement and lipid profile at baseline and 6 months following pioglitazone and placebo therapy

Parameters	Pioglitazone group			Placebo group		
	Baseline	6 months	*p*	Baseline	6 months	*p*
Weight (kg)	48.9 ± 5.6	48.7 ± 4.8	0.57	50.0 ± 6.9	49.9 ± 7.1	0.75
BMI (kg/m^2)	19.7 ± 1.4	19.6 ± 1.7	0.64	19.6 ± 1.67	19.6 ± 1.7	0.63
WC (cm)	82.3 ± 6.1	82.2 ± 5.8	0.85	81.3 ± 6.3	81.5 ± 6.4	0.77
HC (cm)	96.1 ± 3.6	96.3 ± 3.7	0.14	95.0 ± 4.7	95.2 ± 4.6	0.19
WHR	0.86 ± 0.1	0.85 ± 0.1	0.13	0.87 ± 0.1	0.86 ± 0.1	0.27
SBP (mmHg)	115.7 ± 5.1	116.5 ± 4.7	0.12	118.4 ± 9.3	120.3 ± 8.4	0.23
DBP (mmHg)	79.4 ± 5.6	80.0 ± 4.9	0.41	74.4 ± 5.1	77.0 ± 5.2	0.07
FPG (mmol/L)	6.5 ± 1.5	6.4 ± 0.9	0.71	6.4 ± 1.5	6.2 ± 1.2	0.99
PPPG (mmol/L)	9.1 ± 1.7	8.4 ± 1.3	0.002	8.3 ± 2.3	7.8 ± 1.8	0.06
HbA_{1c} (%)	7.08 ± 0.48	6.86 ± 0.45	0.001	7.30 ± 0.37	7.24 ± 0.33	0.74
Insulin requirement (units/day)	48.6 ± 5.8	48.9 ± 6.2	0.21	51.5 ± 6.7	51.8 ± 6.7	0.33
TC (mmol/L)	4.5 ± 0.6	4.4 ± 0.5	0.11	4.6 ± 0.7	4.6 ± 0.5	0.9
LDL (mmol/L)	2.8 ± 0.4	2.7 ± 0.4	0.07	2.9 ± 0.7	2.8 ± 0.7	0.08
HDL (mmol/L)	1.2 ± 0.2	1.3 ± 0.1	0.16	1.1 ± 0.1	1.2 ± 0.1	0.06
TG (mmol/L)	1.6 ± 0.7	1.4 ± 0.7	0.77	1.3 ± 2.2	1.2 ± 0.6	0.27

Diab Res Clin Pract 78;349–354:2007

The addition of rosiglitazone to insulin in T1D

Table 2. Changes in outcome parameters during treatment arms

	Placebo			Rosiglitazone			
	Pre	Post	Change in parameters†	Pre	Post	Change in parameters†	p
HbA1c (%)	8.7 ± 1.0	8.5 ± 1.5	−0.1 ± 1.1	8.6 ± 1.0	8.4 ± 1.0	−0.3 ± 1.1	0.57
Fasting blood glucose (mmol/L)	11.12 ± 1.2	11.17 ± 2.2	−0.8 (−5.2, 5.4)	10.37 ± 2.9	11.1 ± 2.1	0.8 (−5.6, 5)	0.78
Insulin dose (units/kg/day)	1.5 ± 0.36	1.6 ± 0.43	0.12 ± 0.3	1.57 ± 0.39	1.52 ± 1.51	−0.11 ± 0.4*	0.01
% change in insulin dose			9.4 ± 0.22			−5.8 ± 0.25*	0.02
BMI-SDS	1.1 (−0.6 to 2.6)	1.1 (−0.8 to 2.6)	0.04 ± 0.22	1.0 (−0.1 to 2.4)	1.1 (−0.4 to 2.6)	0.08 ± 0.33	0.5
Waist circumference (cm)	75.4 ± 9.7	77.44 ± 10.3	2.5 (−8 to 7.2)	78.35 ± 10.49	80.7 ± 9.67	1.7 (−9.5 to 15)	0.78
Sum skinfolds (cm)	20.8 ± 12.87	20.39 ± 10.39	−0.76 ± 6.2	20.44 ± 10.39	23.46 ± 14.19	3.5 ± 9.7	0.05
Cholesterol (mmol/L)	4.57 ± 0.79	4.53 ± 0.86	0 ± 0.6	4.43 ± 0.86	4.46 ± 1.57	0.5 ± 0.9*	0.02
HDL (mmol/L)	1.29 ± 0.48	1.25 ± 0.42	−0.05 ± 0.3	1.24 ± 0.45	1.30 ± 0.41	0.05 ± 0.3	0.2
LDL (mmol/L)	2.44 ± 0.87	2.79 ± 1.08	−0.08 ± 0.5	2.68 ± 0.76	2.55 ± 0.88	0.34 ± 0.6*	0.01
Triglycerides (mmol/L)	2.68 ± 0.76	2.55 ± 0.88	0.0 ± 1.0	2.44 ± 0.87	2.79 ± 1.08	0.1 ± 0.6	0.9
Adiponectin (ng/L)	23.5 ± 9.0	16.6 ± 6.1	−5.2 ± 9.7	16.0 ± 5.7	27.9 ± 9.6	11.9 ± 10	<0.01
% change in adiponectin			−25 (−77 to 16)			84.8 (6.6 to 423)	<0.01
IGF-1	309.2 (142.1–496.5)	315.1 (152.5–506.2)	27.1 ± 79.5	339.5 (193.7–472.6)	344.9 (138–489)	−5.6 ± 126.2	
% change in IGF-1			4 (−22.8 to 58.6)			0 (−40.4 to 40.4)	0.9

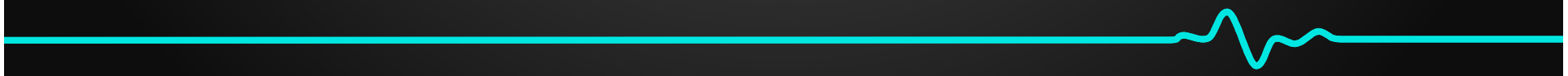
Raw data includes the mean and SD before and after each arm of the trial.
HbA1c, haemoglobin A1c; BMI-SDS, body mass index standard deviation scores; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*$p < 0.05$ for difference between means.
†Data are mean ± SD or median (range) of the difference in outcome during treatment with rosiglitazone (for group A week 52 compared with 24, for group B week 24 compared with week 0) and placebo (for group A week 24 compared with week 0, for group B week 52 compared with week 24). Paired *t*-tests, (or sign rank test for skewed data) were used to test the statistical significance between changes in parameters during treatment with rosiglitazone or placebo.

Only two of the seven subjects had an improvement in insulin sensitivity of greater than 10% on rosiglitazone. The improvement in these subjects could not be predicted by initial HbA1c, age, BMI-SDS, pubertal stage or compliance.

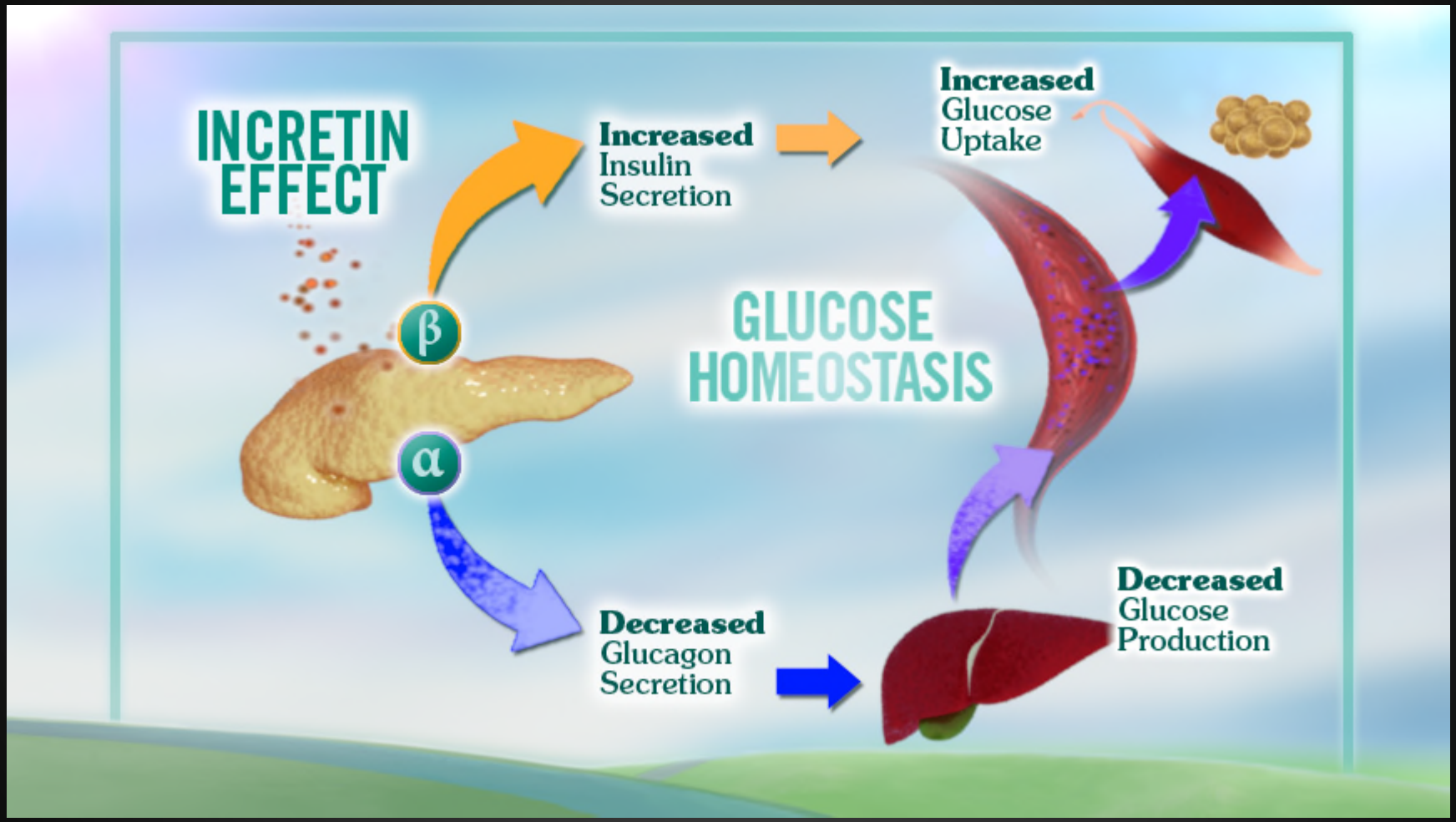
Pediatric Diabetes 2008: 9: 326–334

Thiazolidinedione

- Thus, the benefits of thiazolidinedione treatment are modest, although insulin requirement slightly decreased.
- However, the greatest effect of rosiglitazone occurred in subjects with more pronounced markers of insulin resistance, we might be consider this treatment in severe insulin-resistant patients.
- When we consider the potential risk of edema and weight gain, a thiazolidinedione as an add-on to insulin cannot be considered as a potential future treatment of patients with type 1 diabetes.
- Moreover, concerns exist about bone metabolism and long-term use of these drugs.

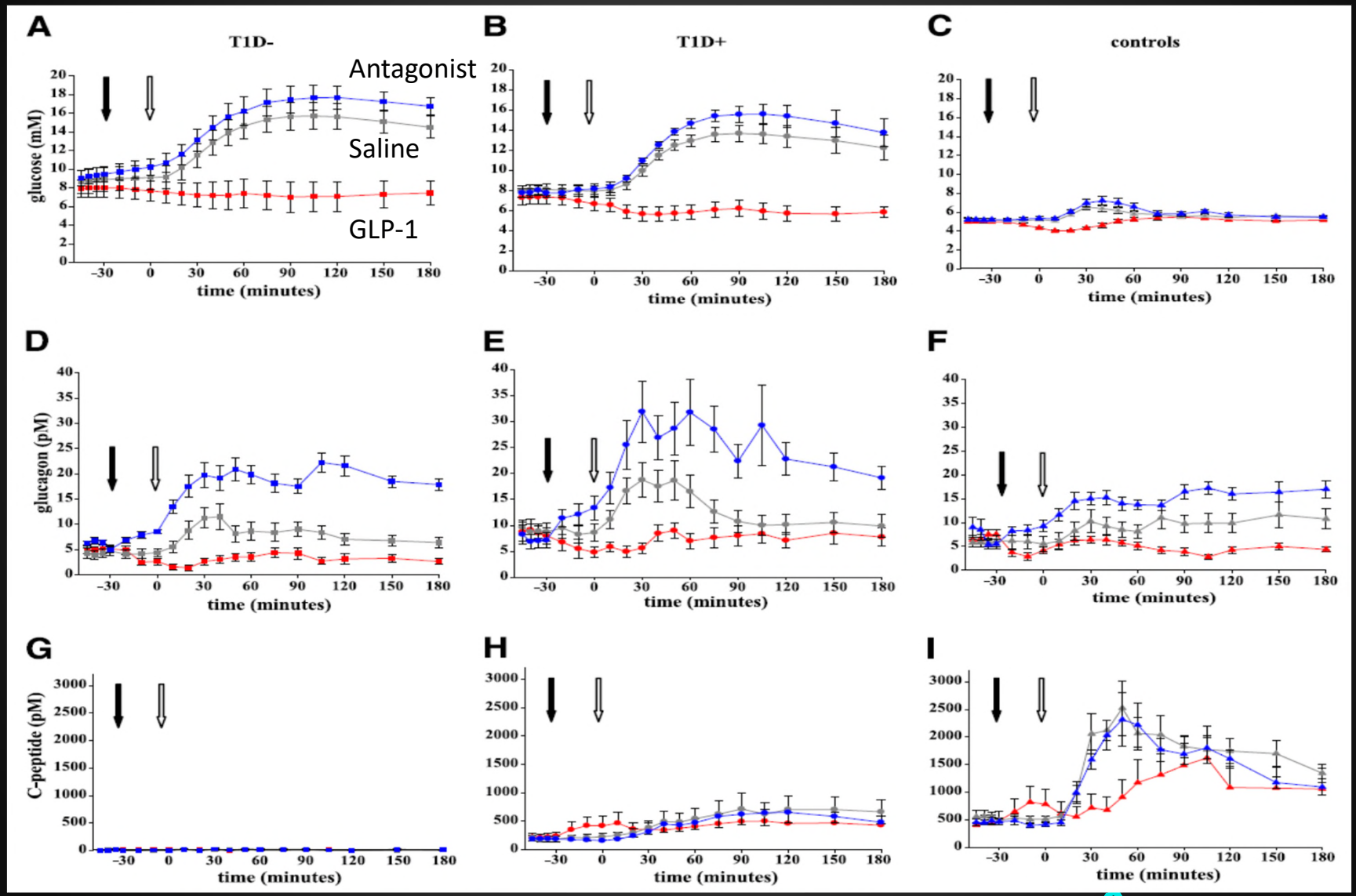


Incretin-based therapy



KS1

Antidiabetic actions of GLP-1 in T1D



Diabetes 60:1599–1607, 2011

KS1 환자 baseline character 넣을건지?

Kim Sangyong, 2018-04-30

Clinical trials for GLP-1 agonist in T1D

	Number of participants	Baseline HbA_{1c} (%)	EOT HbA_{1c} (%)	Basal insulin change (%)	Bolus insulin change (%)	Bodyweight change (% or kg)
Frandsen et al[52]						
12 weeks, RDBPC; insulin treatment: flexible dosing; study population: patients with type 1 diabetes, C-peptide negative (without residual β-cell function), BMI 18–<25 kg/m², normotensive, with no severe late diabetic complications; mean diabetes duration: 18·3 years (SD 2·0) in liraglutide group, 19·6 years (1·6) in placebo group						
1·2 mg liraglutide once per day	18	8·8%	8·2%	0	−11%	−4·1% (−3·1 kg)
Placebo once per day	18	8·7%	8·2%	0	0	+1·5% (1·1 kg)
Dejgaard et al[53]						
26 weeks, RDBPC; insulin treatment: flexible dosing; study population: patients with type 1 diabetes, C-peptide positive and negative (with and without residual β-cell function), BMI >25 kg/m², normotensive, with no severe late diabetic complications; mean diabetes duration: 20 years (SD 12) in liraglutide group, 25 years (12) in placebo group						
1·8 mg liraglutide once per day	46	8·7%	8·2%	12%	2%	−6·3% (−5·8 kg)
Placebo once per day	44	8·7%	8·4%	24%	20%	+0·2 (0·2 kg)
Kuhadiya et al[51]*						
12 weeks, RDBPC; insulin treatment not defined; study population: patients with type 1 diabetes, C-peptide negative (without residual β-cell function), BMI >25 kg/m²						
0·6 mg liraglutide once per day	10	..	..	..	..	−4·1% (3·1 kg)
1·2 mg or 1·8 mg liraglutide once per day†	23	7·6%	7·1%	0	0	−5·1% (4·5 kg)
Placebo once per day	14	..	..	..	..	..
ADJUNCT ONE[54]*						
52 weeks, RDBPC in 1398 patients with type 1 diabetes; insulin treatment: flexible dosing						
0·6 mg liraglutide once per day	..	..	..	..	..	..
1·2 mg liraglutide once per day	..	8·2%	7·7%	..	..	−3 to 4 kg
1·8 mg liraglutide once per day	..	8·2%	7·7%	..	..	−3 to 4 kg
Placebo once per day	..	8·2%	7·9%	..	..	+1 kg
ADJUNCT TWO[55]*						
26 weeks, RDBPC in 835 patients with type 1 diabetes; insulin treatment: fixed dosing						
0·6 mg liraglutide once per day	..	8·2%	7·9% to 8·0%	..	..	−2 to 5 kg
1·2 mg liraglutide once per day	..	8·2%	7·9% to 8·0%	..	..	−2 to 5 kg
1·8 mg liraglutide once per day	..	8·2%	7·9% to 8·0%	..	..	−2 to 5 kg
Placebo once per day	..	8·2%	8·2%	..	..	0

Clinical trials for GLP-1 agonist in T1D

	Number of participants	Baseline HbA_{1c} (%)	EOT HbA_{1c} (%)	Basal insulin change (%)	Bolus insulin change (%)	Bodyweight change (% or kg)
(Continued from previous page)						
Kuhadiya et al[44]						
24 weeks, restrospective; insulin treatment: flexible dosing; study population: patients with type 1 diabetes, C-peptide negative (without residual β-cell function), BMI >30 kg/m², mean diabetes duration: 21·1 years (SD 2·1)						
1·8 mg liraglutide once per day	27	7·9%	7·5%	−6%	−28%	−4·8% (−4·6 kg)
Harrison et al[45]						
Retrospective; insulin treatment: flexible dosing; study population: patients with type 1 diabetes, BMI >25 kg/m², mean diabetes duration: 17·3 years (SD 9·3)						
10 weeks 1·8 mg liraglutide once per day	11	7·4%	7·0%	−14%	−24%	−4·2% (−3·0 kg)
20 weeks 1·8 mg liraglutide once per day	7	7·5%	6·6%	−12%	−19%	−5·0% (−3·6 kg)
Varanasi et al[46]						
24 weeks, open-label; insulin treatment: flexible dosing‡; study population: patients with type 1 diabetes, C-peptide negative (without residual β-cell function), BMI 20–<30 kg/m², mean diabetes duration: 24·0 years (SD 4·0)						
1·8 mg liraglutide once per day	8	6·5%	6·1%	−49%	−45%	−6·6% (−4·5 kg)
Kielgast et al[47]						
4 weeks, open-label; insulin treatment: flexible dosing; study population: patients with type 1 diabetes, C-peptide positive and negative (with and without residual β-cell function), BMI 18–<27 kg/m², with no severe late diabetic complications; patients with preserved β-cell function had mean diabetes duration of 3·7 years (SD 0·8), those without preserved β-cell function had mean diabetes duration of 17·3 years (SE 2·5), those given insulin alone had mean diabetes duration of 23·1 years (1·6)						
C-peptide positive patients; 1·2 mg liraglutide once per day	10	6·6%	6·4%	−29%	−46%	−3·6% (−2·8 kg)
C-peptide negative patients; 1·2 mg liraglutide once per day	9	7·5%	7·0%	−6%	−28%	−2·2% (−1·8 kg)
Insulin only	10	7·1%	6·9%	..	..	+0·2 kg

Clinical trials for GLP-1 agonist in T1D

	Number of participants	Baseline HbA_{1c} (%)	EOT HbA_{1c} (%)	Basal insulin change (%)	Bolus insulin change (%)	Bodyweight change (% or kg)
Rother et al[48]						
24 weeks, open-label; insulin treatment: flexible dosing; study population: patients with type 1 diabetes, BMI 20–30 kg/m², with no severe late diabetic complications; mean diabetes duration: 21·0 years (SD 11·0)						
10 µg exenatide four times per day	14	6·6%	6·5%	0	-28%	-5·4% (-4·1 kg)
Traina et al[50]						
12 weeks, retrospective; insulin treatment not defined; study population: patients with type 1 diabetes, C-peptide negative (without residual β-cell function), mean BMI 30 kg/m² (SD 5), diabetes duration: 39 years (range 11–47)						
2·0 mg exenatide once per week	11	7·7%	7·1%	+15%	-32%	-3·7% (··kg)
Hari Kumar et al[49]						
56 weeks, open-label; insulin treatment: flexible dosing; study population: patients with new-onset type 1 diabetes						
10 µg exenatide twice per day	6	9·7%	7·9%	-70% total daily dose	··	+0·9% (+0·5 kg)
Insulin only	6	9·9%	7·4%	-26% total daily dose	··	+6·8% (+ 4·0kg)
100 mg sitagliptin once per day	6	9·6%	7·5%	-49·4% total daily dose	··	+4·7% (+2·7 kg)

Lancet Diabetes Endocrinol 2016;4:766–80

ADJUNCT-1 trial

Table 2—Safety: AEs and SAEs

	Liraglutide 1.8 mg			Liraglutide 1.2 mg			Liraglutide 0.6 mg			Placebo		
	N	%	*R*	*N*	%	*R*	*N*	%	*R*	*N*	%	*R*
Participants, *N*	347			348			350			348		
Exposure years	278.9			286.3			315.5			296.6		
AEs	313	90.2	7.7	302	86.8	6.0	298	85.1	5.3	275	79.0	4.8
SAEs	29	8.4	0.14	36	10.3	0.17	35	10.0	0.15	38	10.9	0.18
Leading to premature treatment discontinuation	51	14.7	0.30	44	12.6	0.29	17	4.9	0.08	12	3.4	0.06
Hypoglycemic episodes												
All	329	94.8	50.2	322	92.5	49.4	334	95.4	45.4	321	92.2	42.7
Symptomatic*	290	83.6	16.5	285	81.9	16.1	277	79.1	15.7	276	79.3	12.3
Severe or BG confirmed**	306	88.2	21.1	300	86.2	20.0	294	84.0	19.2	290	83.3	16.9
ADA classification	329	94.8	50.1	322	92.5	49.3	333	95.1	45.4	321	92.2	42.6
Severe	28	8.1	0.17	22	6.3	0.11	32	9.1	0.13	37	10.6	0.19
Documented symptomatic	309	89.0	34.4	303	87.1	34.0	311	88.9	32.6	302	86.8	27.7
Asymptomatic	295	85.0	15.2	272	78.2	14.8	276	78.9	12.2	278	79.9	14.0
Probable symptomatic	40	11.5	0.30	31	8.9	0.28	39	11.1	0.34	40	11.5	0.39
Pseudo-hypoglycemia	18	5.2	0.08	21	6.0	0.12	20	5.7	0.11	22	6.3	0.35
Hyperglycemic episodes												
All	307	88.5	33.5	293	84.2	30.9	309	88.3	29.5	312	89.7	34.7
Episodes with ketosis***	39	11.2	0.28	26	7.5	0.15	22	6.3	0.17	24	6.9	0.12
Gastrointestinal disorders												
All	237	68.3	2.7	212	60.9	1.9	175	50.0	1.3	116	33.3	0.76
Nausea	172	49.6	0.97	142	40.8	0.69	112	32.0	0.47	42	12.1	0.18
EAC-confirmed SAEs	*N*		Events	*N*		Events	*N*		Events	*N*		Events

Change in fasting body weight (kg)

Diabetes Care 2016;39:1702–1710

Clinical trials of DPP-4 inhibitor

	Baseline HbA_{1c} (%)	EOT HbA_{1c} (%)	Change in TDD insulin (%)	Bodyweight change (% or kg)
Foley et al[62]				
4 weeks, double-blind, crossover; insulin treatment not defined; study population: 12 patients with type 1 diabetes, mean BMI 24 kg/m² (SD 3); mean diabetes duration: 20·0 years (SD 10·0)				
100 mg vildagliptin twice per day	7·6%	..	..	..
Placebo twice per day	7·6%	..	..	..
Ellis et al[63]				
4 weeks, double-blind, crossover; insulin treatment: fixed dosing; study population: 20 patients with type 1 diabetes, BMI around 27 kg/m², with no severe late diabetic complications; diabetes duration around 15–20 years				
100 mg sitagliptin once per day	Between-group difference at end of treatment 0·3% in favour of sitagliptin	..	..	..
Placebo once per day	..	..	..	..
Farngren et al[64]				
4 weeks, double-blind, crossover. Insulin treatment: not defined. Study population: 28 patients with type 1 diabetes, mean BMI 25 kg/m² (SD 3); with no severe late diabetic complications. Mean diabetes duration: 11·0 years (SD 4·0)				
100 mg vildagliptin twice per day	7·5%	7·2%	..	..
Placebo twice per day	7·5%	7·4%	..	..
Hari Kumar et al[49]				
52 weeks, open-label; insulin treatment: flexible dosing; study population: 18 patients with new-onset type 1 diabetes, BMI 20–<25 kg/m²				
100 mg sitagliptin once per day	9·6%	7·5%	−49·4%	+4·7% (+2·7 kg)
10 µg exenatide twice per day	9·7%	7·4%	−70·4%	−0·9% (−0·5 kg)
Insulin only	9·9%	7·4%	−26%	+6·8% (+ 4·0kg)
Garg et al[65]				
16 weeks, RDBPC; insulin treatment: fixed dosing; study population: 141 patients with type 1 diabetes, C-peptide positive and negative (with and without residual β-cell function), BMI 25–30 kg/m²; mean diabetes duration: 22·0 years (SD 11·0) in sitagliptide group, 20·0 years (SD 11·0) in placebo group				
100 mg sitagliptin once per day	8·2%	8·2%	−3·5%	+0·1% (+0·1 kg)
Placebo once per day	8·6%	8·5%	+0·4%	0
Schopman et al[66]				
6 weeks, double-blind, crossover; insulin treatment not defined; study population: 16 patients with type 1 diabetes, C-peptide negative (without residual β-cell function), BMI 24 kg/m² (range 21–25) with no severe late diabetic complications; diabetes duration: 11 years (range 6–15)				
100 mg sitagliptin once per day	8·3%	..	..	..
Placebo once per day	8·1%	..	..	..

Meta-analysis for incretin based therapy in T1D

Study or Subgroup	Incretin Mean	Incretin SD	Incretin Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ahren 2016	-6.12	8.85	626	-2.16	13.07	211	22.5%	-3.96 [-5.85, -2.07]
Dejgaard 2016	4.1	25.61	50	13.4	9.66	50	4.0%	-9.30 [-16.89, -1.71]

Table 3 – Safety of incretin in treatment of patients with type 1 diabetes.

Outcomes	No. of trials	Events/total		RR (95%CI)	P value	I^2
		Incretin	Control			
Hypoglycemia						
Severe hypoglycemia	6	127/1813	56/671	0.79 (0.58, 1.06)	0.11	0%
Hyperglycemia with ketosis and ketoacidosis						
Ketosis	2	137/1671	33/554	1.37 (0.95, 1.97)	0.10	0%
Ketoacidosis	3	9/1682	0/560	2.62 (0.31, 21.99)	0.37	0%
Gastrointestinal disorders						
Nausea	6	838/1805	93/646	3.02 (2.14, 4.27)	<0.00001	53%
Vomiting	4	118/748	12/292	3.25 (1.06, 9.94)	0.04	48%
Diarrhea	4	86/792	24/309	1.33 (0.41, 4.31)	0.63	57%
Other adverse effects						
Pancreatitis	2	1/1671	0/554	1.00 (0.04, 24.51)	1.00	–
CV events (acute coronary syndromes)	2	4/1671	2/554	0.66 (0.12, 3.60)	0.63	0%

Heterogeneity: $Tau^2 = 0.79$; $Chi^2 = 13.40$, $df = 2$ ($P = 0.001$); $I^2 = 85\%$
Test for overall effect: $Z = 1.57$ ($P = 0.12$)

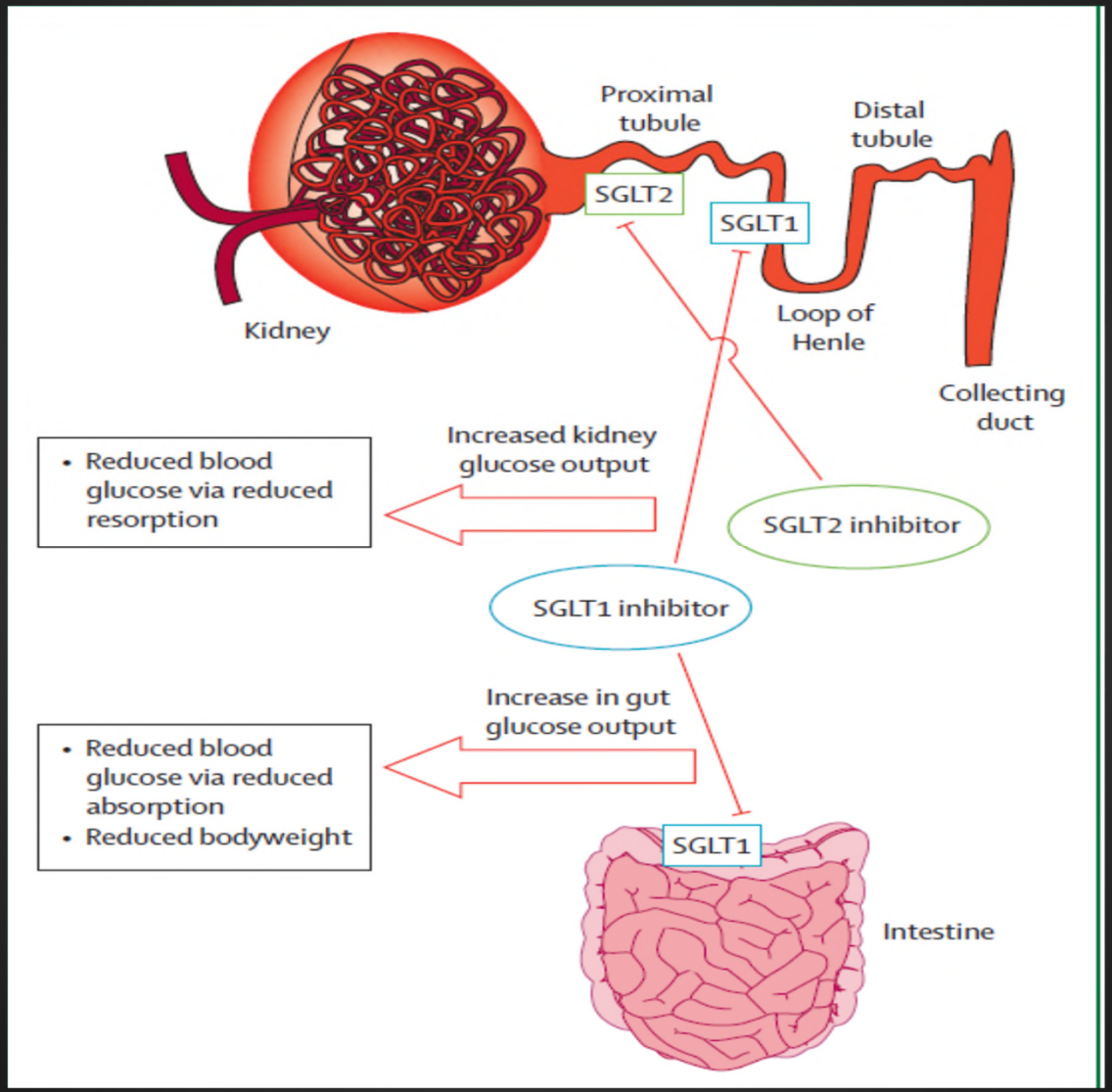
Fig. 5 – Change in fasting c-peptide among patients with type 1 diabetes receiving incretin-based drugs versus control.

Diabetes Res Clin Pract 2017;129:213-23.

Incretin-based therapy

- In patients with type 1 diabetes, the amount of meal-induced GLP-1 secretion is similar to that of healthy individuals.
- Findings from clinical trials suggest that incretin-based therapy induce weight loss and reduce insulin requirements, with either improved or unaltered glycemic control.
- DPP-4 inhibitors as add-on to insulin modestly improve HbA1c with no raised risk of hypoglycemia and no effect on body weight or the daily doses of insulin needed.
- GLP-1RA added to insulin therapy reduced HbA1c levels, total insulin dose, and body weight in type 1 diabetes, accompanied by increased rates of symptomatic hypoglycemia and hyperglycemia with ketosis, thereby limiting clinical use in this group.

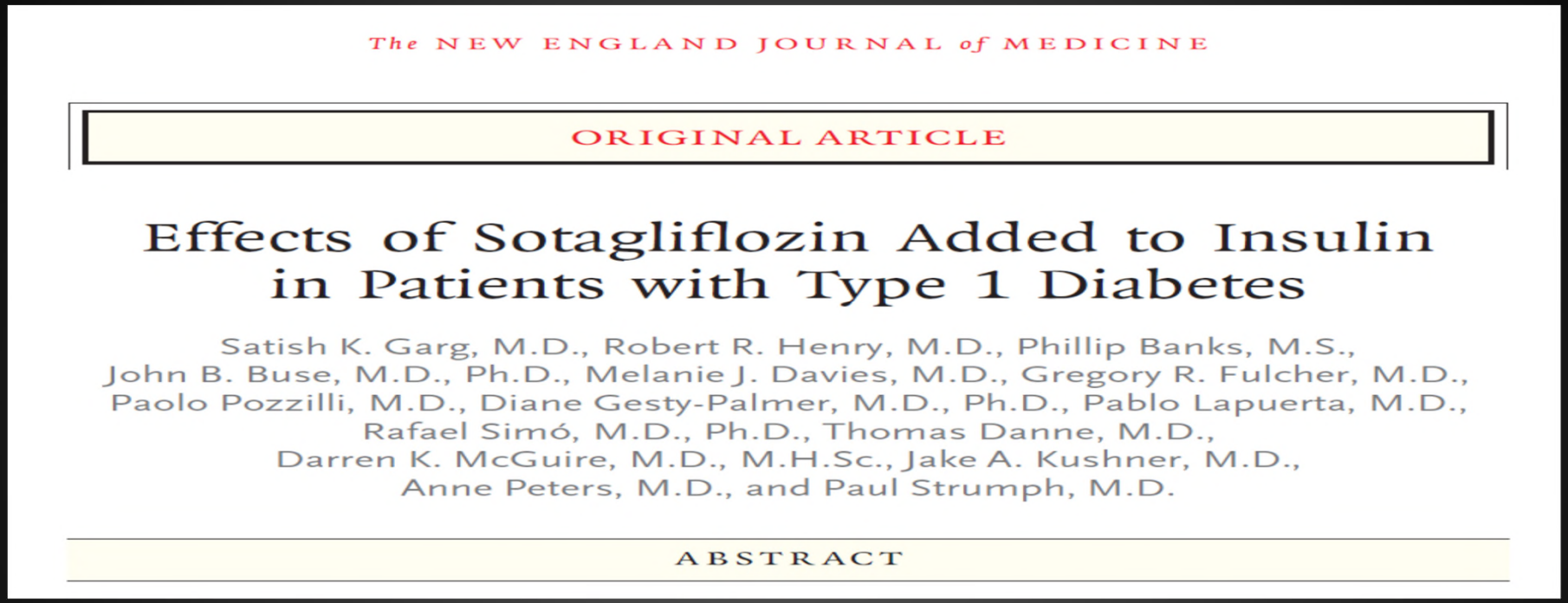
SGLT-2 inhibitor



Clinical trials of SGLT-2 inhibitor in T1D

	Number of patients	Baseline HbA_{1c} (%)	EOT HbA_{1c} (%)	Basal insulin change (%)	Bolus insulin change (%)	Bodyweight change (%)
Sands et al[68]						
4 weeks, RDBPC; insulin treatment: flexible dosing; study population: patients with type 1 diabetes, BMI 25–30 kg/m²; diabetes duration: median 18·5 years (range 4·7–40·8) for placebo group, 16·8 (3·4–42·9) for sotagliflozin						
400 mg sotagliflozin once per day	16	8·0%	7·4%	−2·4%	−32·1%	−2·3% (−1·7 kg)
Placebo once per day	17	7·9%	7·9%	+0·2%	−6·4%	+0·7% (+0·5 kg)
Perkins et al[69]						
8 weeks, open-label; insulin treatment: flexible dosing; study population: patients with type 1 diabetes, BMI 20– <25 kg/m², normotensive, with no severe late diabetic complications; diabetes duration: 17 years (SD 7)						
25 mg empagliflozin once per day	40	8·0%	7·6%	−24·1%	−6·9%	−3·6% (−2·6 kg)
Pieber et al[70] (EASE-1)						
4 weeks, open-label; insulin treatment: flexible dosing;* study population: patients with type 1 diabetes, BMI 25–30 kg/m²; normotensive, with no severe late diabetic complications; diabetes duration: 21 years (SD 13) for placebo, 20 years (12) for empagliflozin 2·5 mg, 16 years (8) for empagliflozin 10 mg, 24 years (15) for empagliflozin 25 mg						
2·5 mg empagliflozin once per day	19	8·4%	7·9%	−0·08 TWD (U/kg)	..	−1·8% (−1·4 kg)
10 mg empagliflozin once per day	19	8·3%	7·8%	−0·10 TWD (U/kg)	..	−1·8% (−1·6 kg)
25 mg empagliflozin once per day	19	8·2%	7·5%	−0·09 TWD (U/kg)	..	−2·2% (−1·7 kg)
Placebo once per day	18	8·2%	8·0%	−0·01 TWD (U/kg)	..	+0·3% (+0·2 kg)
Henry et al[71]						
18 weeks, RDBPC; insulin treatment: flexible dosing; study population: patients with type 1 diabetes, BMI 20– <25 kg/m², normotensive, with no severe late diabetic complications; diabetes duration: 22 years (SD 11)						
300 mg canagliflozin per day once per day	117	8·0%	7·8%	−7·5%	−17·5%	−5·1% (−4·2 kg)
100 mg canagliflozin per day once per day	117	7·9%	7·6%	−3·7%	−7·5%	−3·1% (−2·6 kg)
Placebo once per day	117	7·9%	7·9%	+12·0%	−5·3%	+0·3% (+0·2 kg)

Clinical trials of Sotagliflozin



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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ABSTRACT

Phase 3, double-blind trial, 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 lower than 7.0% at week 24, with no episodes of severe hypoglycemia or diabetic ketoacidosis after randomization. Secondary end points included the change from baseline in glycated hemoglobin level, weight, systolic blood pressure, and mean daily bolus dose of insulin.

N Engl J Med. 2017 Sep 13. [Epub ahead of print]

Clinical trials of Sotagliflozin

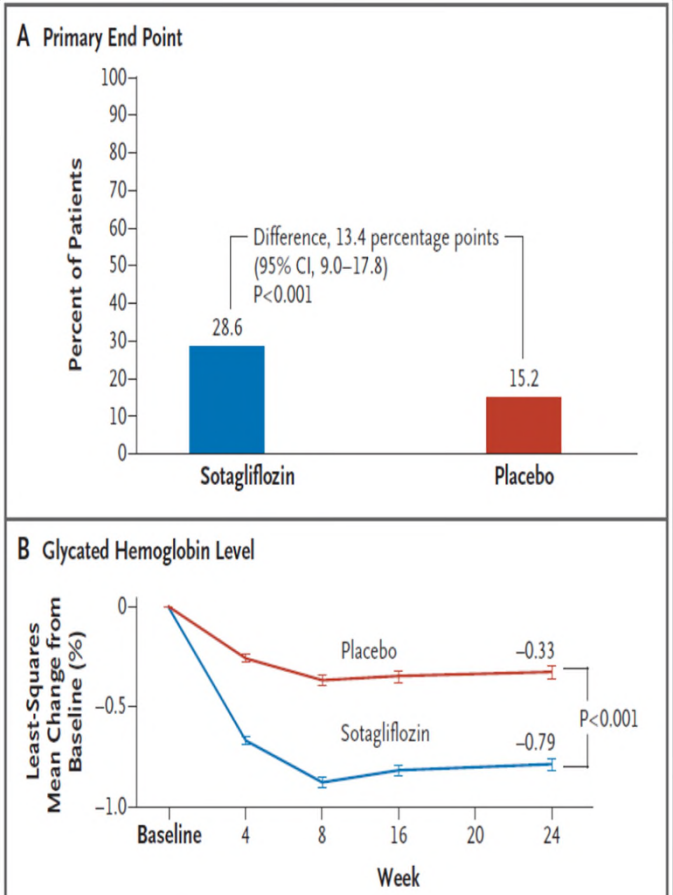


Figure 1. Primary and Secondary End Points.

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 hemo-

Positively adjudicated adverse events		
Severe hypoglycemia, ≥1 episode‡	21 (3.0)	17 (2.4)
Severe nocturnal hypoglycemia, ≥1 episode‡	2 (0.3)	5 (0.7)
Severe hypoglycemia in a patient who used insulin pump, ≥1 episode§	10 (3.6)	5 (1.8)
Severe hypoglycemia in a patient who did not use insulin pump, ≥1 episode§	11 (2.6)	12 (2.8)
Diabetic ketoacidosis, ≥1 episode	21 (3.0)	4 (0.6)
Diabetic ketoacidosis in a patient who used insulin pump, ≥1 episode§	12 (4.4)	2 (0.7)
Diabetic ketoacidosis in a patient who did not use insulin pump, ≥1 episode§	9 (2.1)	2 (0.5)
Major adverse cardiovascular events	2 (0.3)	0
Investigator-reported events of special interest		
Volume depletion	13 (1.9)	2 (0.3)
Genital mycotic infection	45 (6.4)	15 (2.1)
Urinary tract infection	25 (3.6)	27 (3.8)
Diarrhea¶	29 (4.1)	16 (2.3)
Pancreatitis	0	0
Bone fracture	4 (0.6)	5 (0.7)
Potential drug-induced liver injury	2 (0.3)	0
Renal event	5 (0.7)	3 (0.4)
Cancer	1 (0.1)	2 (0.3)
Documented hypoglycemia‡	673 (96.3)	670 (95.3)
Documented nocturnal hypoglycemia‡	521 (74.5)	553 (78.7)

N Engl J Med. 2017 Sep 13. [Epub ahead of print]

Clinical trials of Dapagliflozin

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**

DEPICT-1 was a double-blind, randomised, parallel-controlled, three-arm, phase 3, multicentre study done at 143 sites in 17 countries. Eligible patients were aged 18–75 years and had inadequately controlled type 1 diabetes (HbA1c between ≥7·7% and ≤11·0% [≥61·0 mmol/mol and ≤97·0 mmol/mol]) and had been prescribed insulin for at least 12 months before enrolment. The primary efficacy outcome was the change from baseline in HbA1c after 24 weeks of treatment in the full analysis set, which consisted of all randomly assigned patients who received at least one dose of study drug.

Lancet Diabetes Endocrinol. 2017;5(11):864-876

Clinical trials of Dapagliflozin

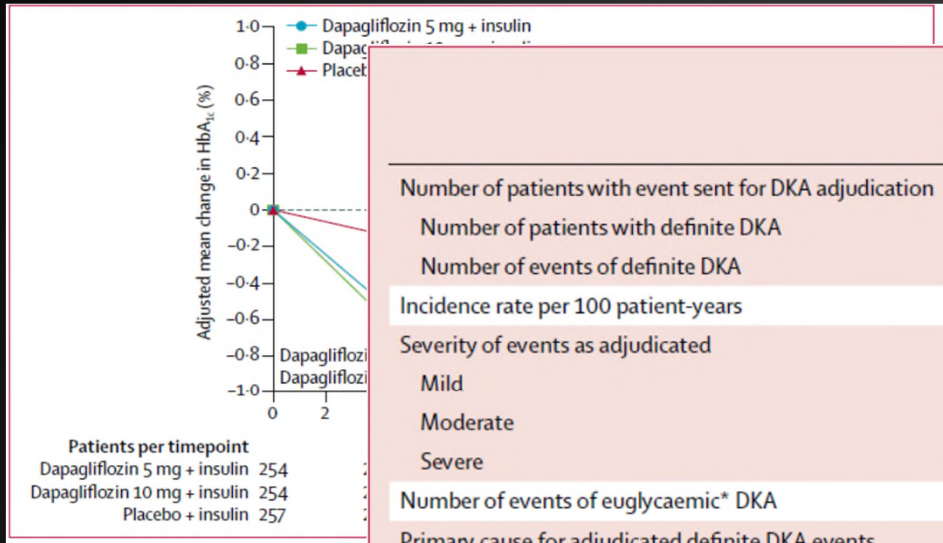


Figure 2: Change in HbA_{1c} over 24 weeks

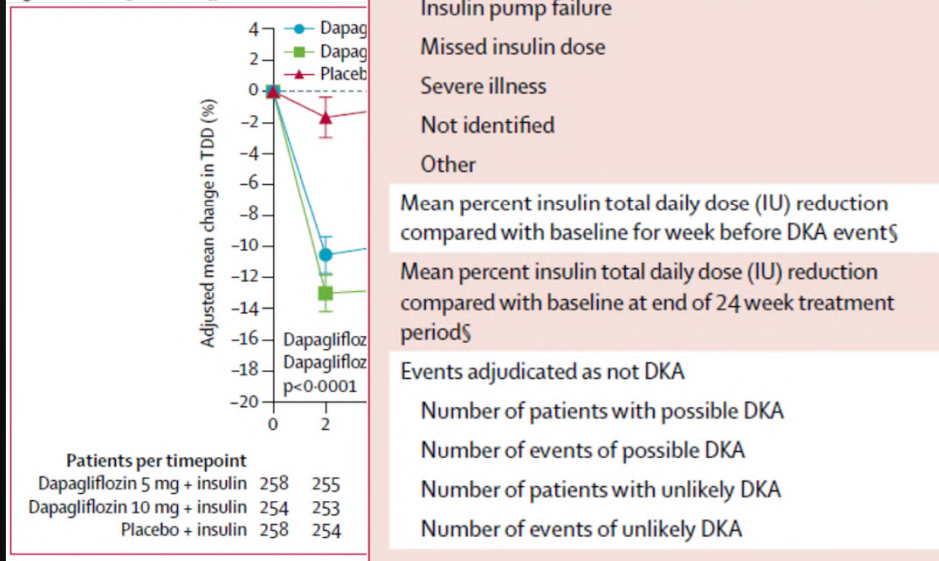


Figure 3: Change in total daily dose of insulin

	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	3·78	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	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

bo): −2·96 (95% CI −3·63 to −2·28); p<0·0001
ebo): −3·72 (95% CI −4·38 to −3·05); p<0·0001

agliflozin g plus ulin 277)*	Dapagliflozin 10 mg plus insulin (n=296)*	Placebo plus insulin (n=260)
7 (68%)	207 (70%)	160 (62%)
) (29%)	82 (28%)	31 (12%)
5 (2%)	8 (3%)	9 (3%)
4 (12%)	33 (11%)	7 (3%)
) (7%)	11 (4%)	13 (5%)
4 (1%)	2 (1%)	0
4 (1%)	3 (1%)	3 (1%)
)	1 (<1%)	2 (1%)
2 (4%)	13 (4%)	2 (1%)
1 (<1%)§	2 (1%)¶	0
) (7%)	24 (8%)	15 (6%)
5 (2%)	9 (3%)	1 (<1%)
3 (1%)	4 (1%)	3 (1%)
1 (<1%)	2 (1%)	1 (<1%)
1 (<1%)	0	1 (<1%)
5 (2%)	8 (3%)	2 (1%)
1 (<1%)	5 (2%)	0
)	0	1 (<1%)

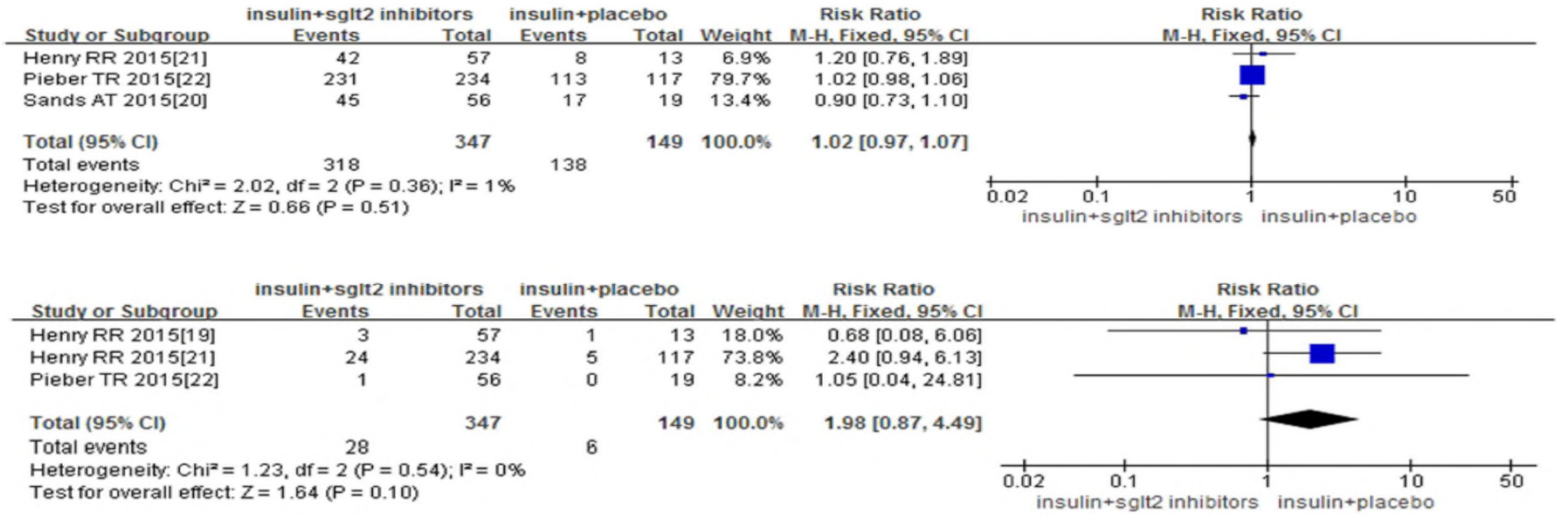
Lancet Diabetes Endocrinol. 2017;5(11):864-876

Meta-analysis for SGLT-2i therapy in T1D

Study or Subgroup	insulin+sglt2 inhibitors Events	Total	insulin+placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Henry RR 2015[19]	25	57	8	13	9.5%	0.71 [0.42, 1.20]
Henry RR 2015[21]	144	234	64	117	62.3%	1.13 [0.93, 1.37]
Pieber TR 2015[22]	50	56	18	19	19.6%	0.94 [0.82, 1.08]
Sands AT 2015[20]	14	16	12	17	8.5%	1.24 [0.87, 1.77]
Total (95% CI)		363		166	100.0%	1.06 [0.92, 1.22]
Total events	233		102			

Heterogeneity: Chi² = 6.04, df = 3 (P = 0.11); I² = 50%
Test for overall effect: Z = 0.83 (P = 0.41)

Figure 6. Forest plot for meta-analyses comparing SGLT-2 inhibitor with placebo in Total AEs. RR = related risk.



Study or Subgroup	insulin+sglt2 inhibitors Events	Total	insulin+placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Henry RR 2015[21]	42	57	8	13	6.9%	1.20 [0.76, 1.89]
Pieber TR 2015[22]	231	234	113	117	79.7%	1.02 [0.98, 1.06]
Sands AT 2015[20]	45	56	17	19	13.4%	0.90 [0.73, 1.10]
Total (95% CI)		347		149	100.0%	1.02 [0.97, 1.07]
Total events	318		138			

Heterogeneity: Chi² = 2.02, df = 2 (P = 0.36); I² = 1%
Test for overall effect: Z = 0.66 (P = 0.51)

Study or Subgroup	insulin+sglt2 inhibitors Events	Total	insulin+placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Henry RR 2015[19]	3	57	1	13	18.0%	0.68 [0.08, 6.06]
Henry RR 2015[21]	24	234	5	117	73.8%	2.40 [0.94, 6.13]
Pieber TR 2015[22]	1	56	0	19	8.2%	1.05 [0.04, 24.81]
Total (95% CI)		347		149	100.0%	1.98 [0.87, 4.49]
Total events	28		6			

Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)

Figure 8. Forest plot for meta-analyses comparing SGLT-2 inhibitor with placebo in urinary tract or genital infection. RR = related risk.

Main problem of SGLT-2 inhibitor use in T1D

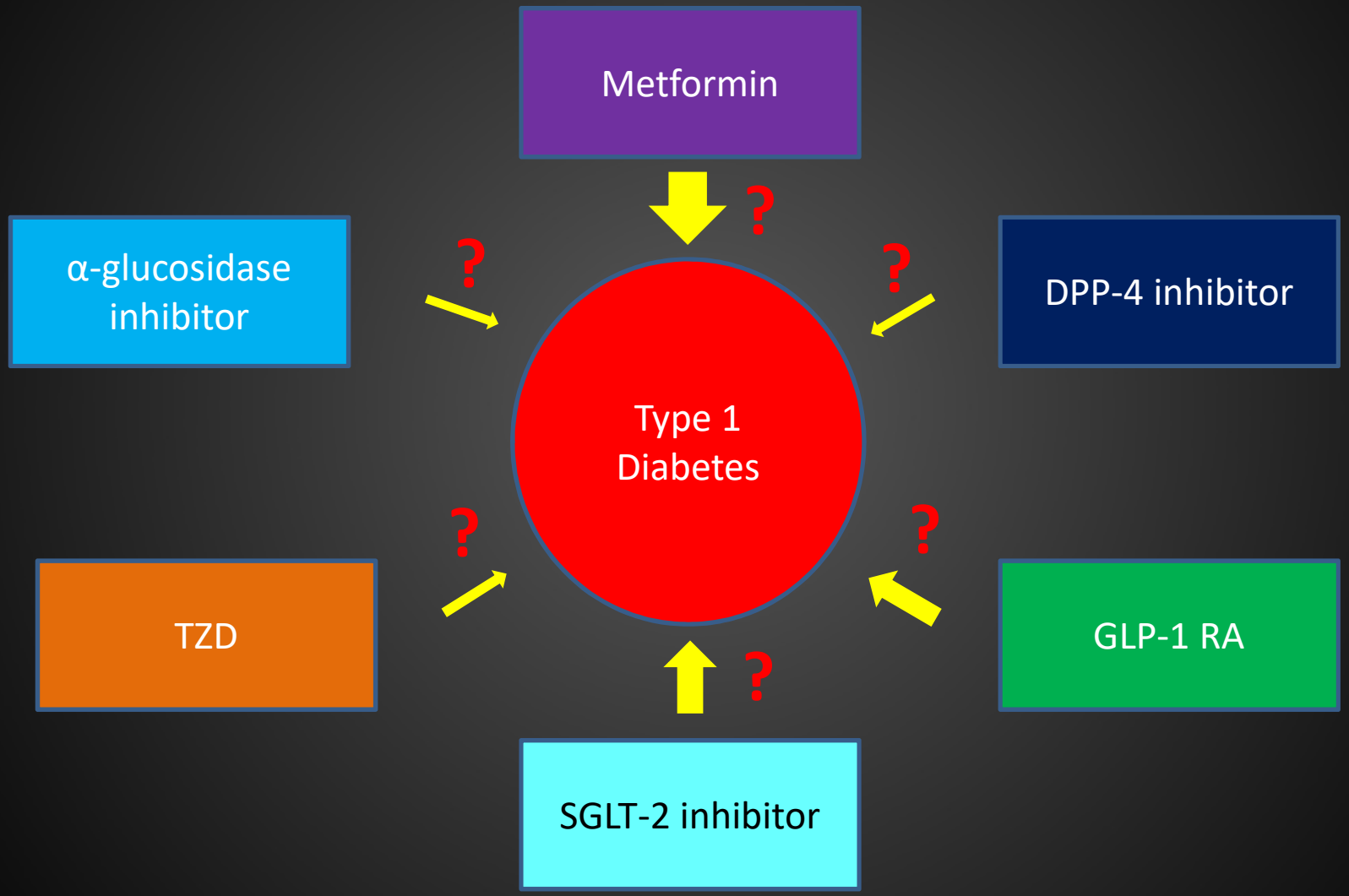
- Inhibition of SGLT2, the major sodium–glucose cotransporter in the kidney, directly reduces hyperglycemia through an insulin-independent mechanism and could provide new possibilities for patients with type 1 diabetes.

- Some SGLT-2 inhibitors adjunct to insulin for the treatment of type 1 diabetes shows the improvement in HbA1c and weight loss, with a lower risk of hypoglycemia.

- Although there are primary cause for DKA events such as pump failure, missed insulin dose, the event rate increased in the group that using SGLT-2 inhibitors.

- Interest is increasing about the relation between use of SGLT2 inhibition and development of DKA in both type 1 and type 2 diabetes, and the FDA has recommended that SGLT2 inhibitor use should be avoided in patients with type 1 diabetes.

Non-insulin agents for type 1 diabetes



Conclusion

- Despite the proven benefits of tight glycemic control in individuals with type 1 diabetes in reducing diabetic complications, the risk and fear of hypoglycemia and the potential for weight gain are limitations of treatment.
- With regard to the rising problem of severe obesity and insulin resistance in individuals with type 1 diabetes, trials focusing on adding non-insulin hypoglycemic agent to treatment will be of interest for type 1 diabetic patients.
- However, the non-insulin hypoglycemic agents do not hold promise for achieving improved glycemic control with type 1 diabetes except some antidiabetic agent.
- Large and long-term randomized, controlled clinical trials should be done to further explore the non-insulin drugs: Ideally, both lean and obese people with and without residual β-cell function, should be included in the studies.

Thanks for your attention!!