Summary

- Sultan – 12 yr old with T2DM
- Childhood T2DM is different from adult T2DM?
- Treatments for T2DM
- Published clinical trials in childhood T2DM
- Treatment guidelines for T2DM
- Future studies

BBC Panorama – diabetes the hidden killer

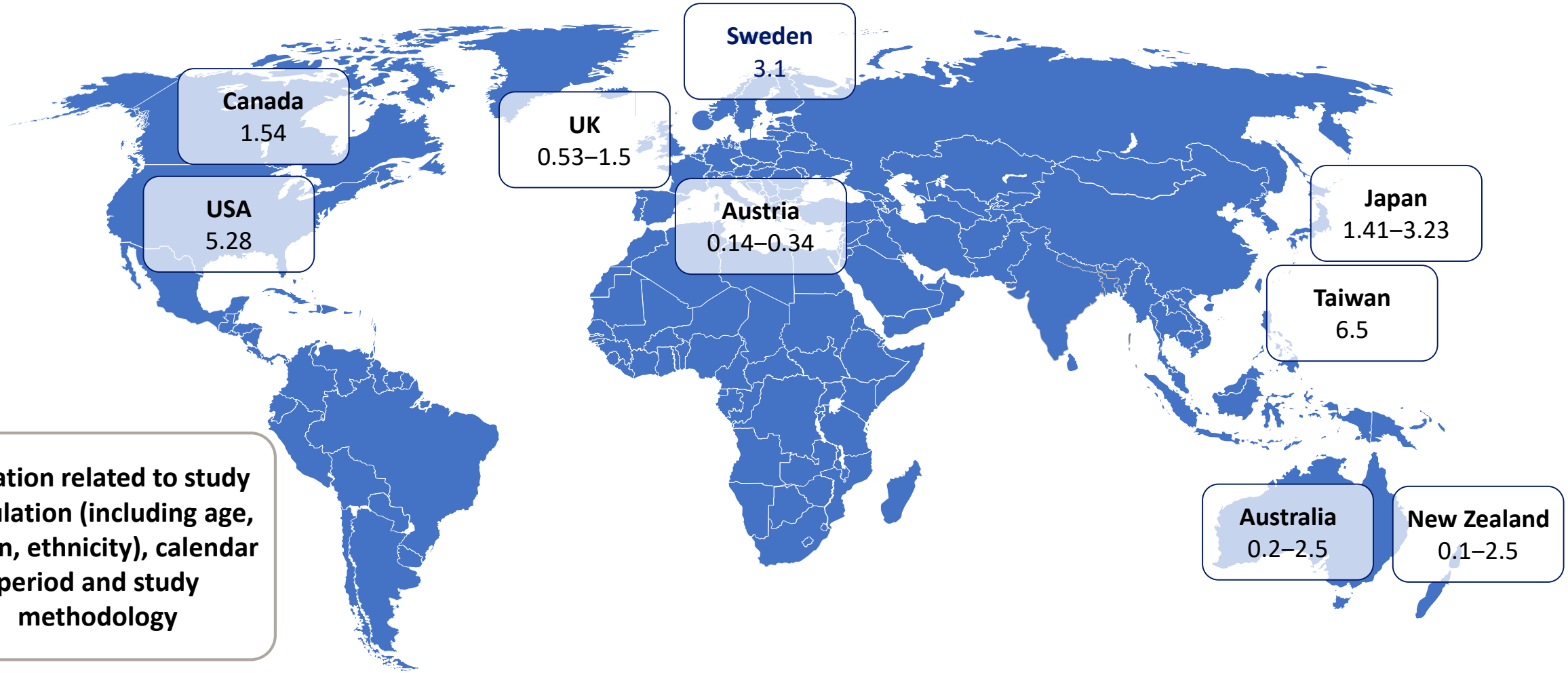
https://youtu.be/dWhSzQEcPMQ

Sultan

- Presented aged 12 years with foot pain
- Weight 96kg – above 99.6 centile for age and gender
- Random glucose 16mmol/L, HbA1c 8.5%
- Raised urate – gout – allopurinol
- Intensive input - dietetic and exercise advice
- Started metformin – increased dose to 1 gramme 12 hourly
- Enrolled into clinical trial of GLP-1 agonist – more intensive input
- Rescue basal insulin therapy
- Significant psychological issues

How common is T2D in children?

T2D incidence per 100,000 person-years in children and adolescents (0–19 years)*



Variation related to study population (including age, region, ethnicity), calendar period and study methodology

*as of 2013
T2D, type 2 diabetes
Adapted from Fazeli Farsani S et al. *Diabetologia* 2013 56:1471–1488 (systematic review of reported studies up to February 2013).

Is type 2 getting commoner? UK 2005- 2016

- **2006**
- 0.35/100,000/year (white UK)
- 1.25/100,000/yr S Asian UK
- 57% girls
- 43% ethnic minorities
- 83% obese,
- 57% acanthosis nigricans, 84% family history of diabetes
- 50% asymptomatic at diagnosis

- **2016**
- 0.44/100,000/year (white UK)
- 2.92/100,000/yr S Asian UK
- 67% female

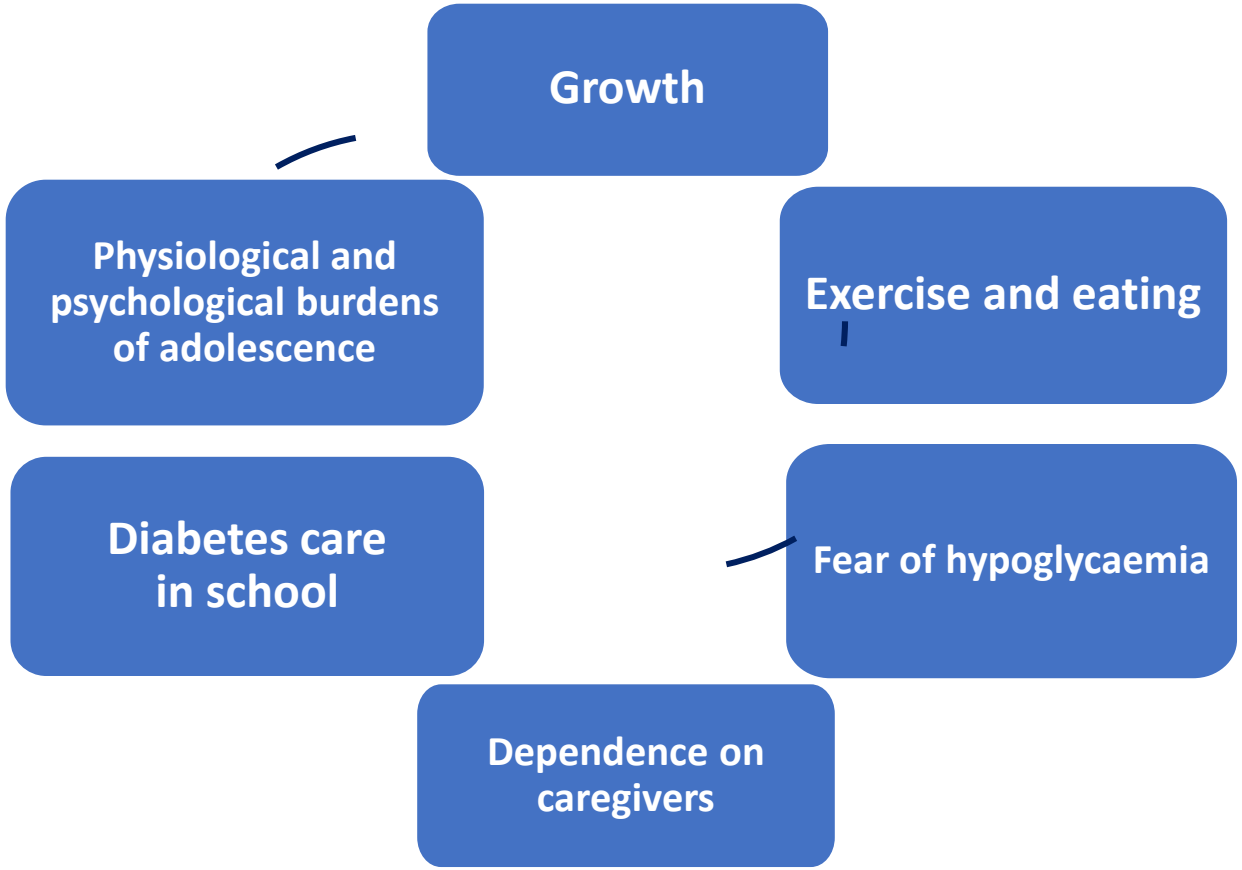
30% increase in white UK
Doubling in S Asian UK

(Candler T et al Diabet Med 2018)

(Haines L et al. Diabetes Care 2007)

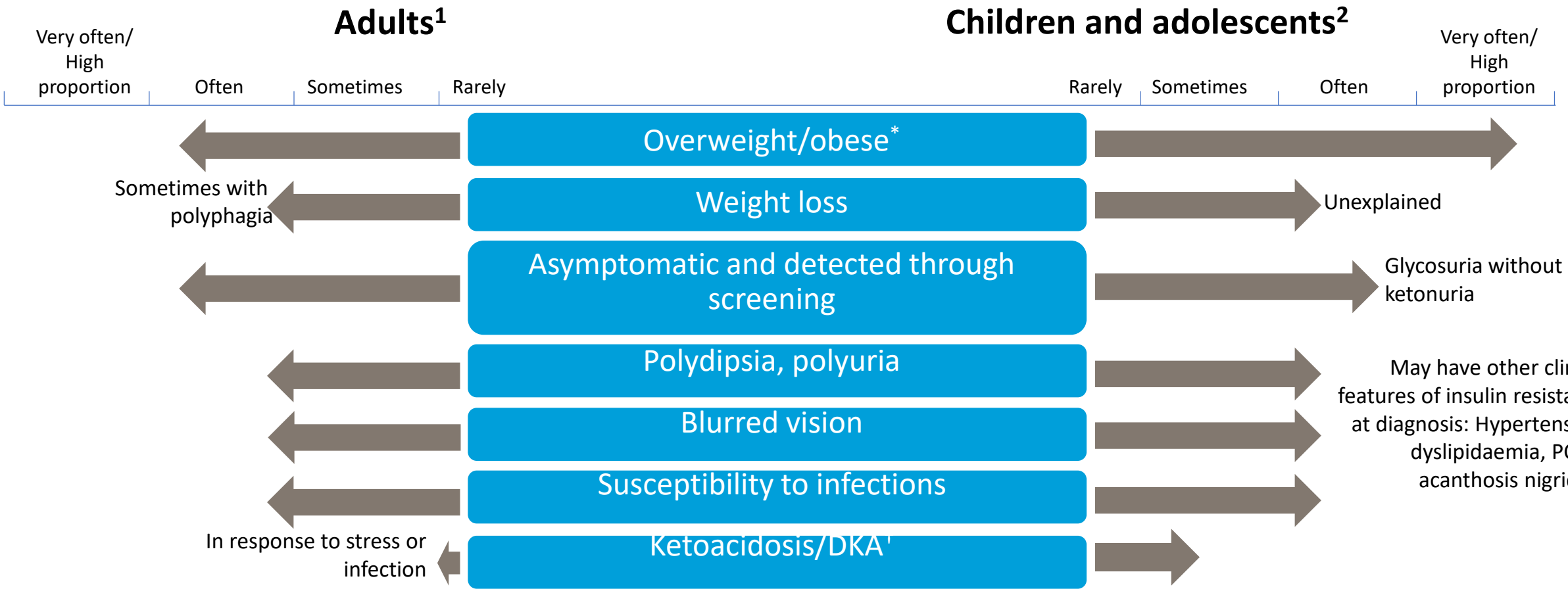
BPSU
British Paediatric Surveillance Unit

Children and adolescents with diabetes are different from adults with diabetes



ADA 2016 Standards of Care. *Diabetes Care* 2016;39 Suppl 1:S13–S22; Silverstein J et al. *Diabetes Care* 2005;28:186–212.

Difference in presentation of T2D between adults vs children and adolescents



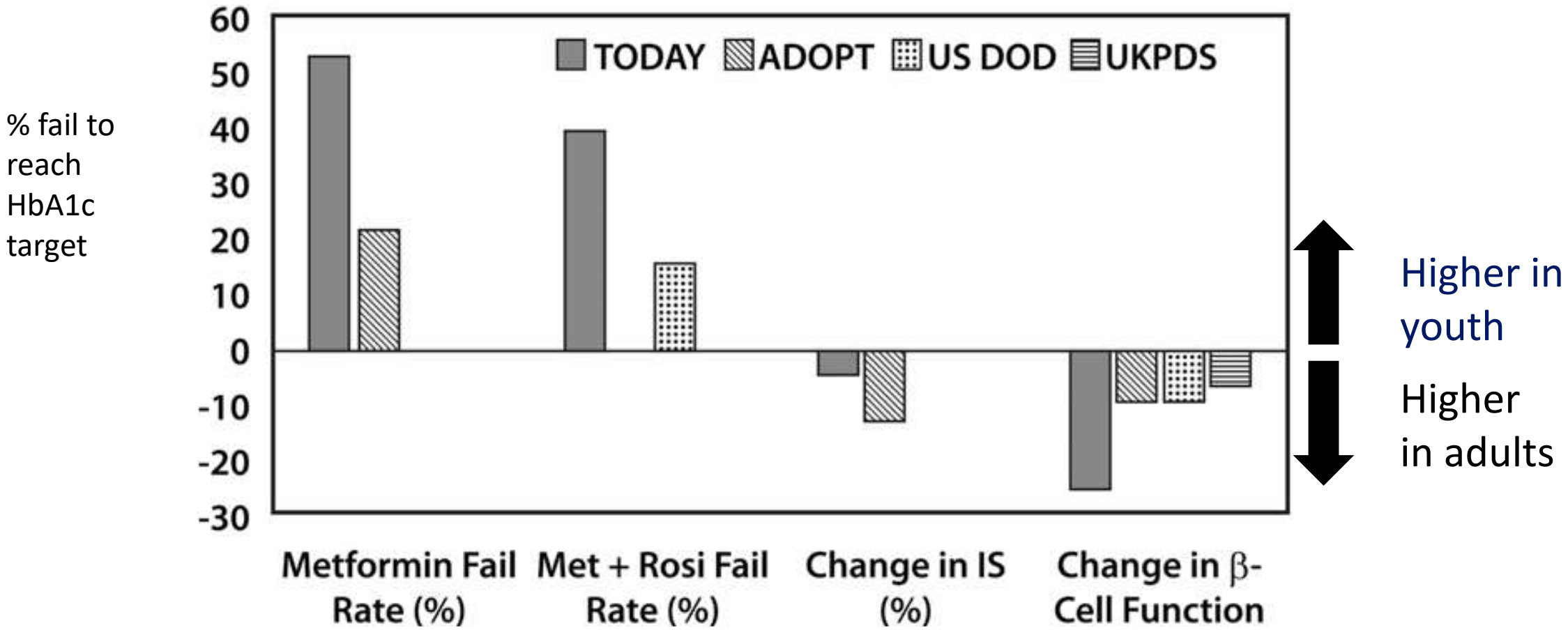
*Not the case in the Asian population

†Among children and adolescents with T2D in the SEARCH study (n=1425) DKA prevalence was 5.7% in 2008–2010 (decreased from 11.7% in 2002–2003). Higher prevalence of DKA was associated with younger age at diagnosis, minority race/ethnicity, and male gender[3]

DKA, diabetic ketoacidosis; PCOS, polycystic ovary syndrome

1. American Diabetes Association. *Diabetes Care* 2009;32 Suppl 1:S62–67; 2. Reinehr T. *Int J Obesity* 2005;29:S105–110; 3. Dabelea D et al. *Pediatrics* 2014;133:e938–945.

Beta cell failure rates in adults vs youth in T2DM



Nadeau K et al Diabetes Care 2016 ADOPT, A Diabetes Outcome Progression Trial; Met, metformin; TODAY, Treatment Options for type 2 Diabetes in Adolescents and Youth; US DOD, U.S. Department of Defense Database; UKPDS, United Kingdom. Prospective Diabetes Study.

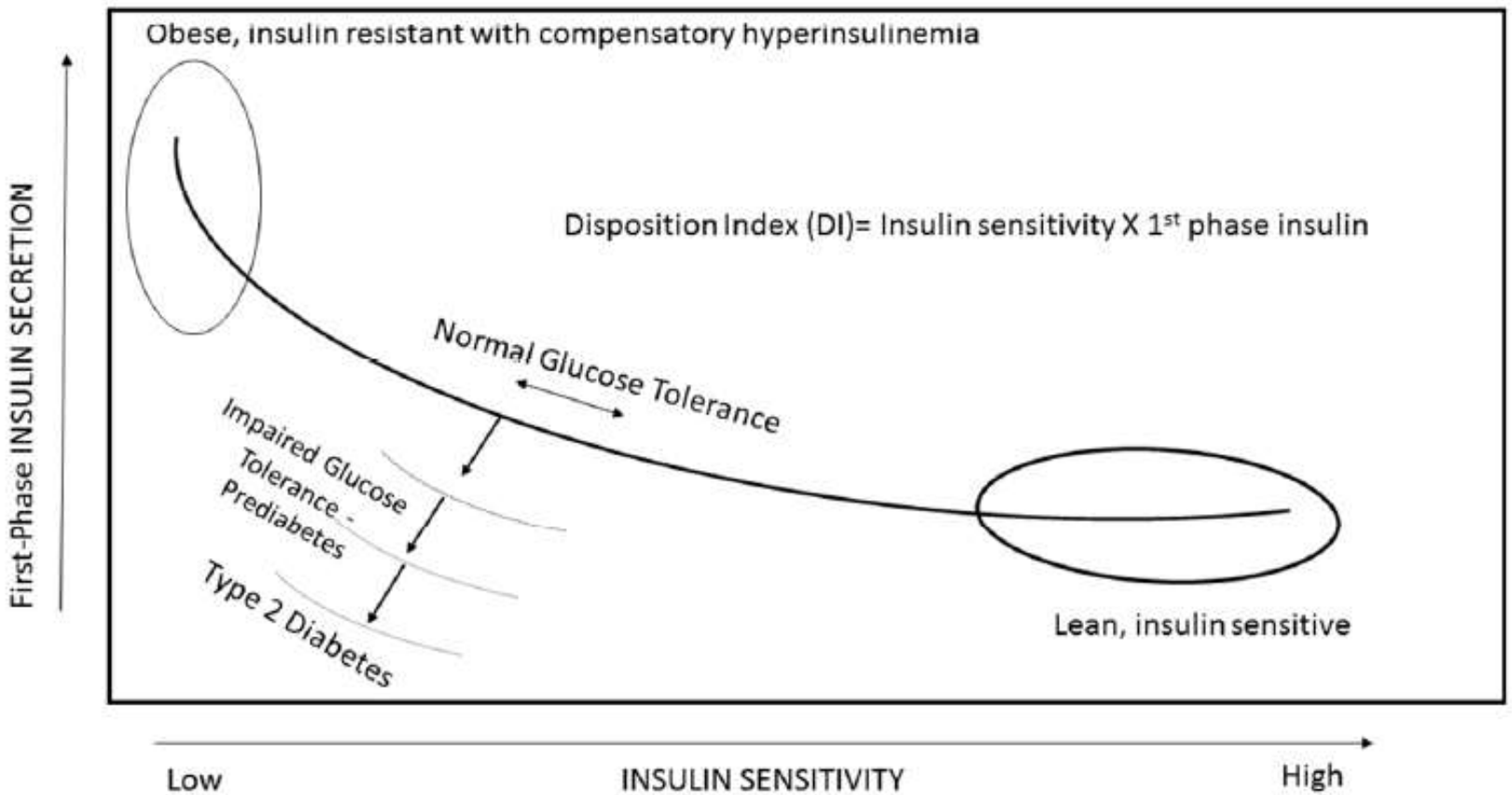
Natural history of T2D in children and adolescents

- Faster progression from insulin resistance to T2D than adults, particularly associated with obesity[1]
- Early onset associated with complication risk similar to adults and more rapid than in adolescents with T1D[2]
- High risk for early complications during most productive years of life[2]
- High risk for rapid loss of glycaemic control in adolescents if unable to attain a non-diabetes range HbA_{1c} on metformin initially[3,4]

HbA_{1c}, glycosylated haemoglobin; T1D, type 1 diabetes; T2D, type 2 diabetes

1. D'Adamo E, Caprio S. *Diabetes Care* 2011;34 Suppl 2:S161–S165; 2. Pinhas-Hamiel O, Zeitler P. *Lancet* 2007;369:1823–1831; 3. American Diabetes Association. *Diabetes Care* 2000;23:381–389; 4. Zeitler P et al *Diabetes Care* 2015;38:2285–2292.

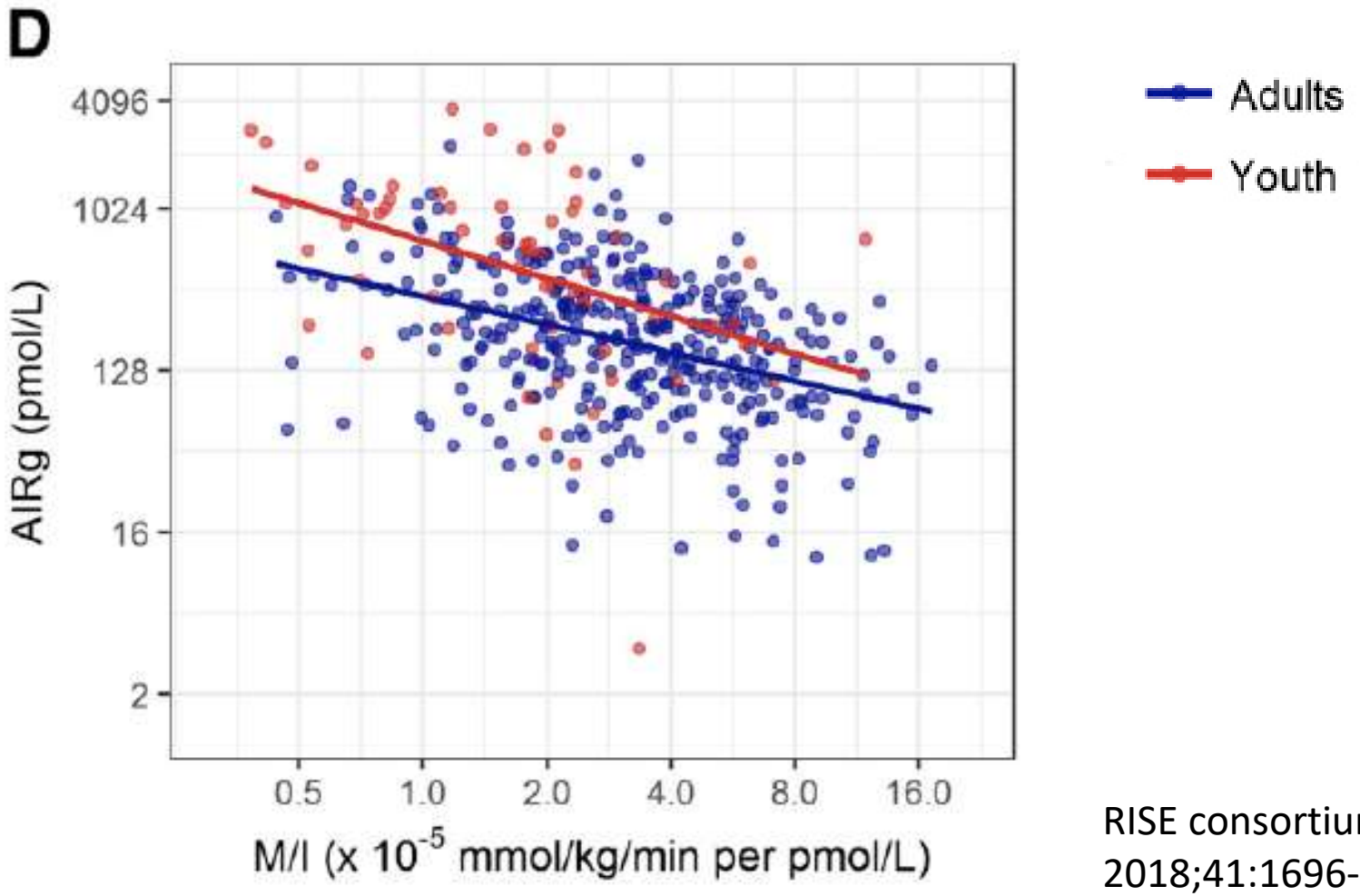
Disposition index



Hannon T et al Ann NY Acad Sci

Young people are more insulin resistant than adults, and insulin hypersecretors

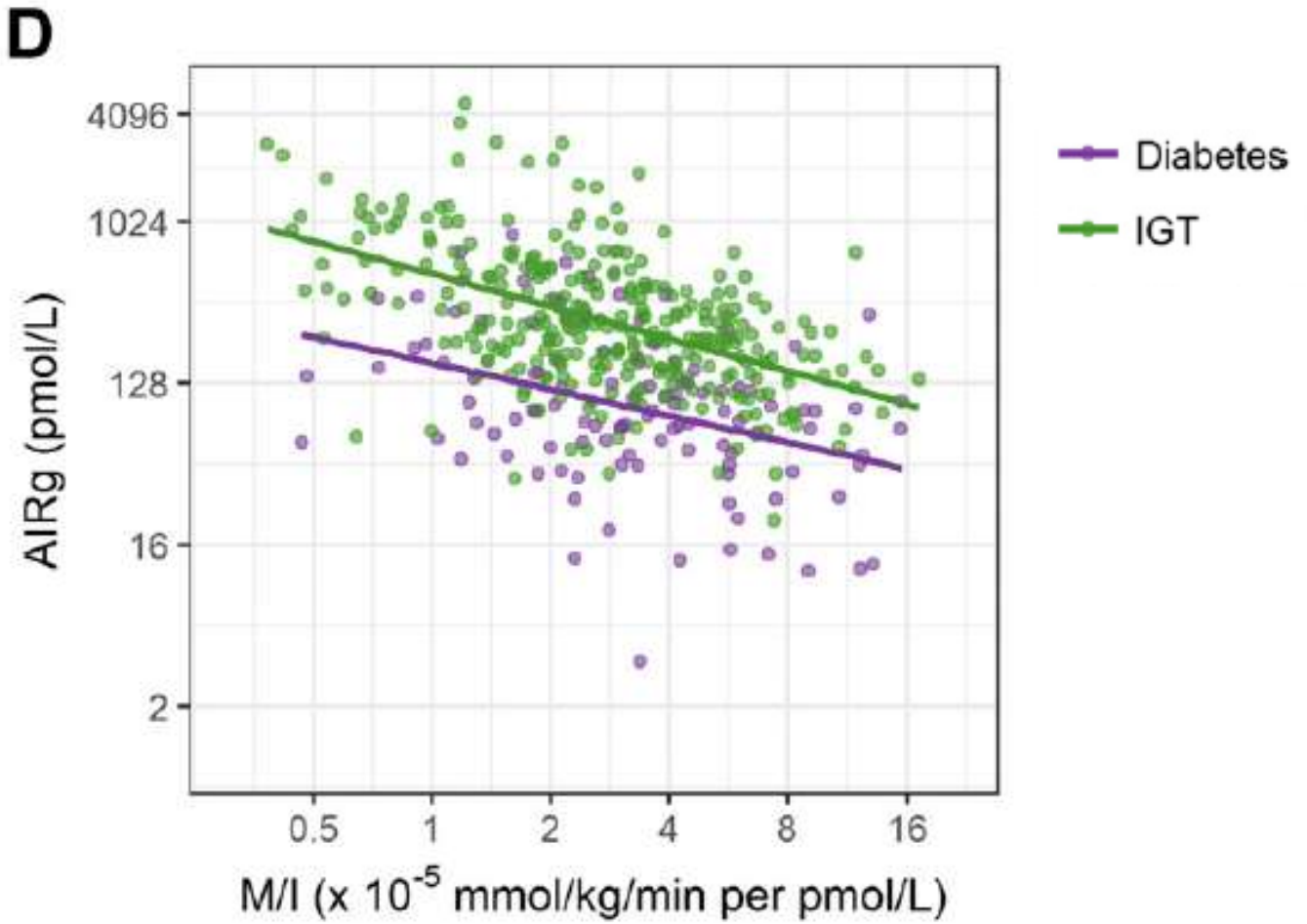
First phase insulin response to glucose



RISE consortium, Diabetes Care 2018;41:1696-1706

Reduced insulin responses from IGT to diabetes

First phase insulin response to glucose



Insulin sensitivity

RISE consortium, Diabetes Care 2018;41:1696-1706

Treatments for children and young people with T2DM

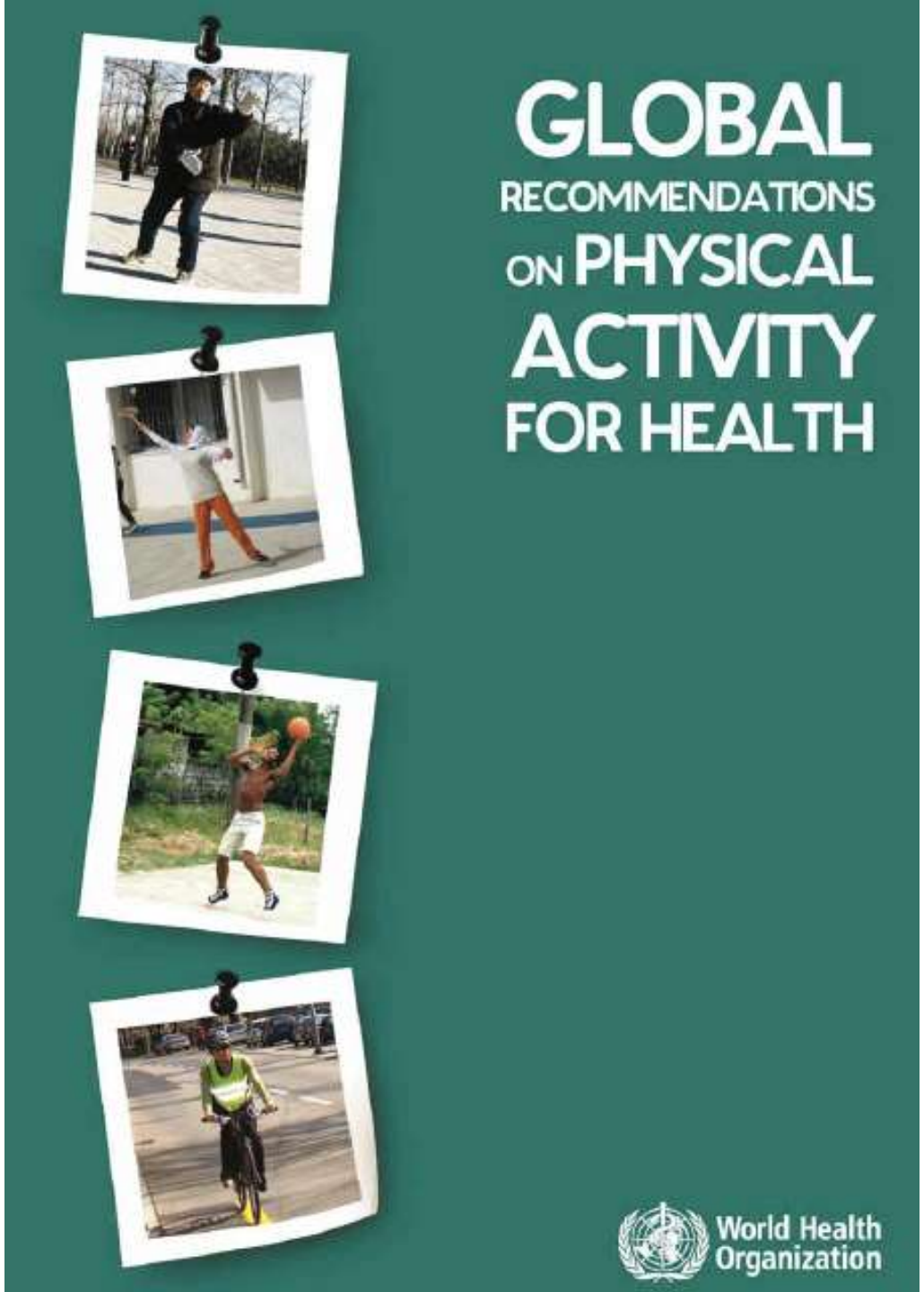
Treatment options of type 2 diabetes in children

Modality	Glycaemia reduction	b-cell enhancing	Insulin resistance lowering	Use	Notes
Diet and Exercise	Yes	No	Yes	Yes	First line
Insulin	Yes	No	No	Yes	Safe, used in children
Metformin	Yes	No	Yes	Yes	Safe
Sulphonylureas	Yes	Yes	No	?	Safe in adults
Meglitinides	Yes	Yes	No	?	Little safety data
Thiazolidinediones	Yes	?	Yes	?	Little used
Acarbose or orlistat	?	No	No	?	Side effects
Surgical treatment	Yes	No	Yes	?	

(Matthews et al, Hormone Research 2002;57(suppl 1):34-39).

Children and young people should have at least 60 minutes of moderate to vigorous physical exercise a day

Most of this exercise should be aerobic
Vigorous-intensity activities should be incorporated, including those that strengthen muscle and bone, at least 3 times a week.



Moderate to vigorous physical activity associated with lower cardiometabolic risk factors in children

- Data from 20,871 children collected between 1998 and 2009
- All studies from International Children's Accelerometry Database
- Data on time spent in moderate, vigorous physical activity, sedentary time
- Related to waist circumference, systolic BP, fasting TG's, HDL cholesterol, insulin

- Longer spent in moderate to vigorous physical activity by children was associated with better cardio-metabolic risk profiles regardless of the time spent sedentary

(Ekelund U et al JAMA 2012;307(7):704-712)

Physical activity associated with lower markers for metabolic syndrome

	Waist circumference (cm)	Systolic Blood Pressure (mmHg)[a]	Insulin (pmol/L)[b]	Triglycerides (mg/dl)[b]	HDL-Cholesterol (mg/dl)
Total PA (CMP)	−0.35 (−0.50;−0.16)	−0.10 (−0.26;0.05)	−0.026 (−0.033;−0.020)	−0.021 (−0.026;−0.016)	0.19 (−0.11;0.48)
MVPA (min/d)	−0.52 (−0.76;−0.28)	−0.15 (−0.30;−0.06)	−0.028 (−0.038;−0.017)	−0.017 (−0.025;−0.009)	0.25 (−0.034;0.53)
Sedentary (min/d)	0.13 (−0.094;0.358)	−0.043 (−0.21;0.20)	0.012 (0.0029;0.022)	0.014 (−0.0031;0.030)	−0.064 (−0.24;0.12)
MVPA adjusted for Sedentary (min/d)	−0.54 (−0.79;−0.30)	−0.17 (−0.30;−0.04)	−0.030 (−0.043;−0.017)	−0.014 (−0.023;−0.0046)	0.31 (0.036;0.59)
Sedentary adjusted for MVPA (min/d)	−0.12 (−0.32;0.09)	−0.10 (−0.21;0.02)	−0.009 (−0.026;0.008)	0.006 (−0.010;0.023)	0.096 (−0.098;0.29)

Meta-analysis 20,851 children

(Ekelund U et al JAMA 2012;307(7):704-712)

Oral anti-diabetic drugs: Metformin

- Biguanide: decreases hepatic gluconeogenesis, increases peripheral utilisation of glucose
- Needs circulating insulin to work.
- Insulin sensitiser, associated with lower incidence of weight gain, lower plasma insulin levels
- Gastro-intestinal side effects: abdo pain, nausea
- Contraindications: renal impairment; pregnancy

Metformin in children with type 2 diabetes:

Randomised controlled trial in 82 children 10-16yrs for up to 16 weeks.

Multicentre: 35 in US, 9 Eastern Europe

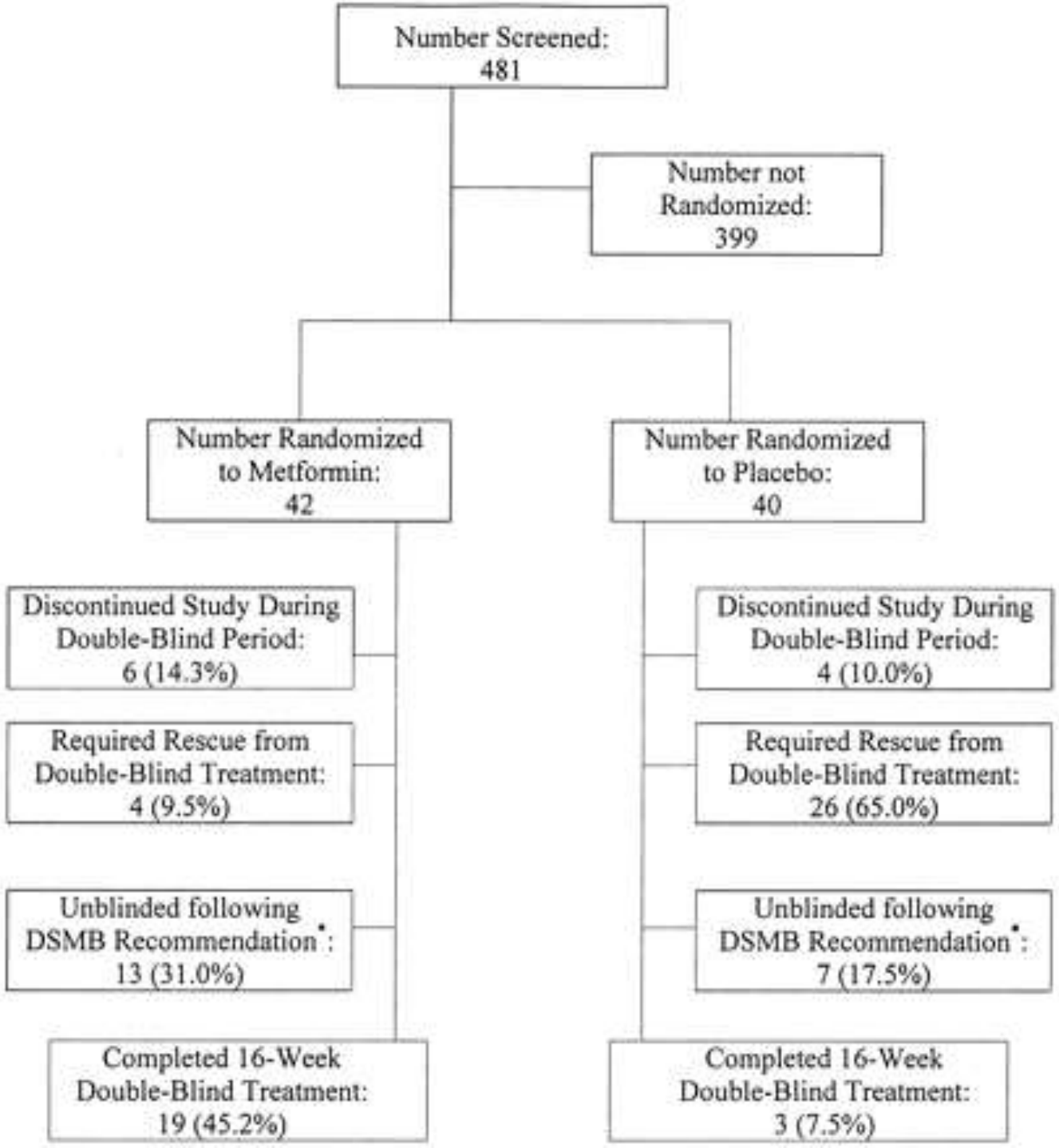
Included if: FPG 7.0-13mmol/L; HbA1c≥7.0%, C-peptide ≥0.5nmol/L, BMI >50th centile

Excluded if: diabetes antibodies; DKA; on insulin; hepatic dysfunction

(Lee Jones et al, Diabetes Care;2002:89-94).

Screened healthy children with known risk factors

Trial stopped early due to convincing efficacy of metformin

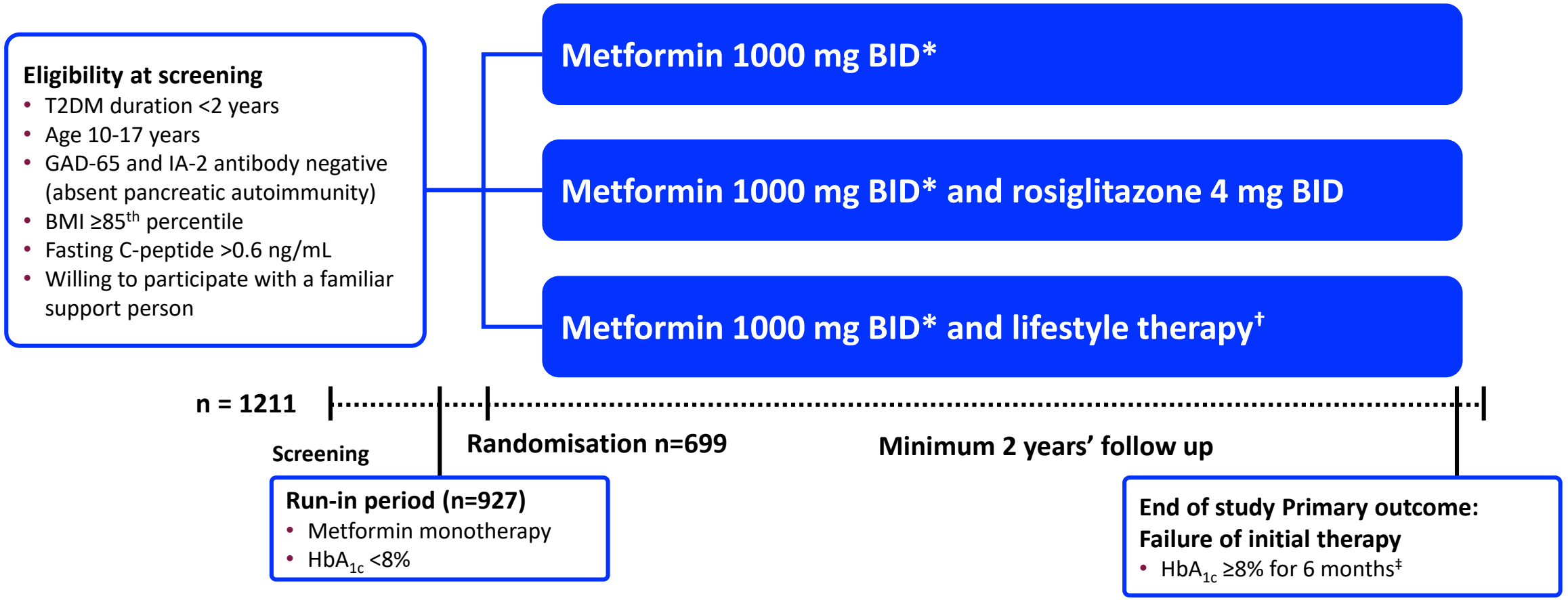


Glycaemic control measurements at baseline and last double-blind visit

Variable	Metformin	Placebo	Difference
Baseline FPG	9.0+/-2.7	10.7+/-2.7	
Last visit	7.0+/-2.2	11.5+/-4.5	
Change	-2.4+/-0.5	1.2+/-0.5	-3.6+/-0.8*
Baseline HbA	8.2+/-1.3	8.9+/-1.4	
Last visit	7.2+/-1.2	8.9+/-1.6	
Adjusted mean	7.5+/-0.2	8.6+/-0.2	-1.2+/-0.2*

*** P<0.001**

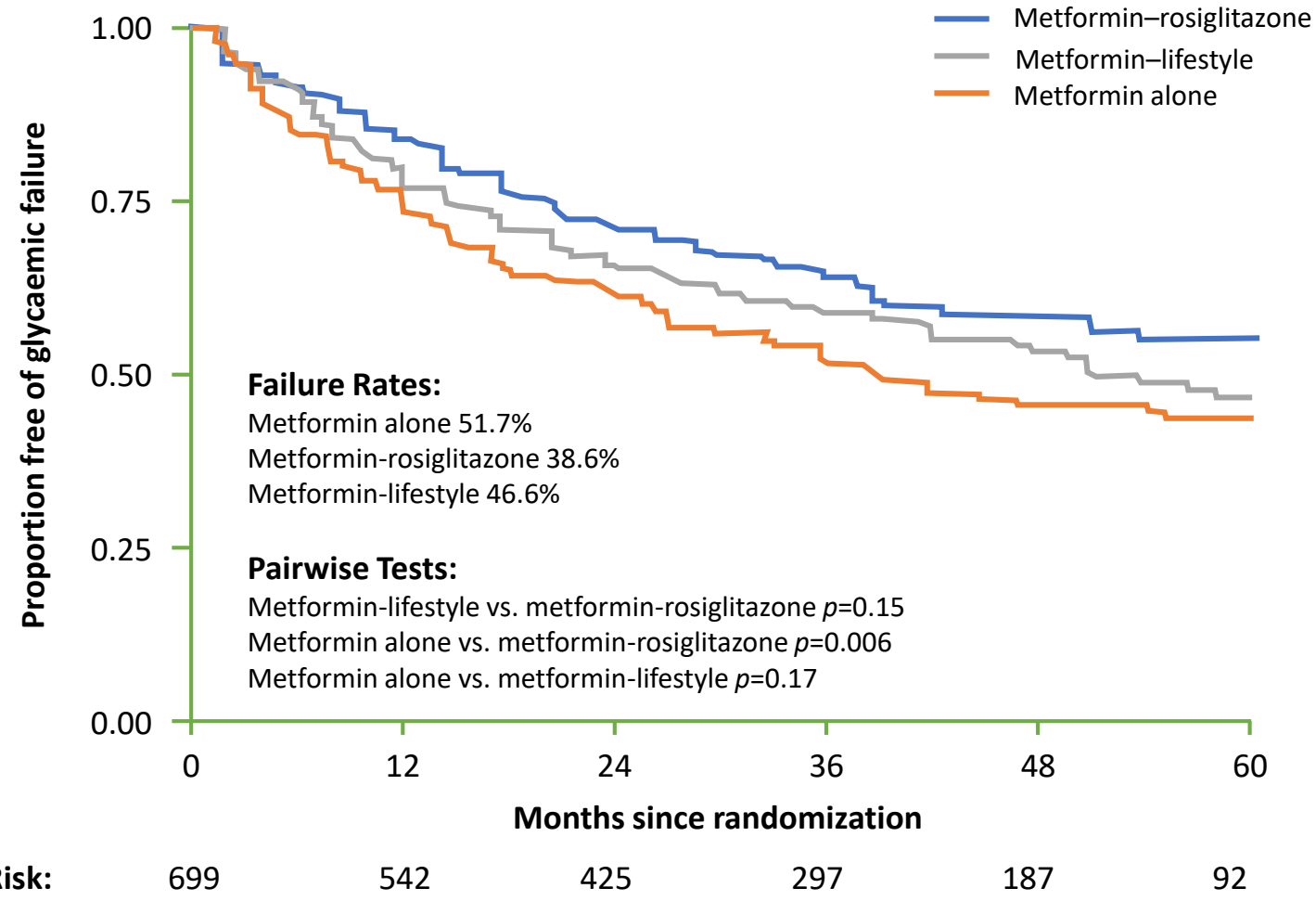
TODAY study design



TODAY Study Group. *N Engl J Med.* 2012;366:2247-56

Primary outcome

- Survival curves for freedom from glycaemic failure
  - HbA_{1c} ≥8.0% for 6 months or persistent metabolic decompensation



HbA1c, glycosylated haemoglobin; TODAY, Treatment Options for type 2 Diabetes in Adolescents and Youth
TODAY Study Group. *N Engl J Med.* 2012;366:2247-56

Ellipse Study: efficacy and safety of Liraglutide in children with type 2 diabetes

- The ELLIPSE study was conducted to **meet the unmet medical need** for treatment of adolescents with T2D and to **satisfy regulatory requirements** from the EMA and FDA
- A phase 2 study of the **GLP-1RA liraglutide** demonstrated that approved adult dose ranges may also be appropriate for a paediatric population[1]
- The ELLIPSE study subsequently investigated the efficacy and safety of liraglutide as a new treatment option for children and adolescents with T2D

ELLIPSE is the first phase 3 non-metformin trial completed in children and adolescents with T2D

EMA, European Medicines Agency; FDA, Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonist

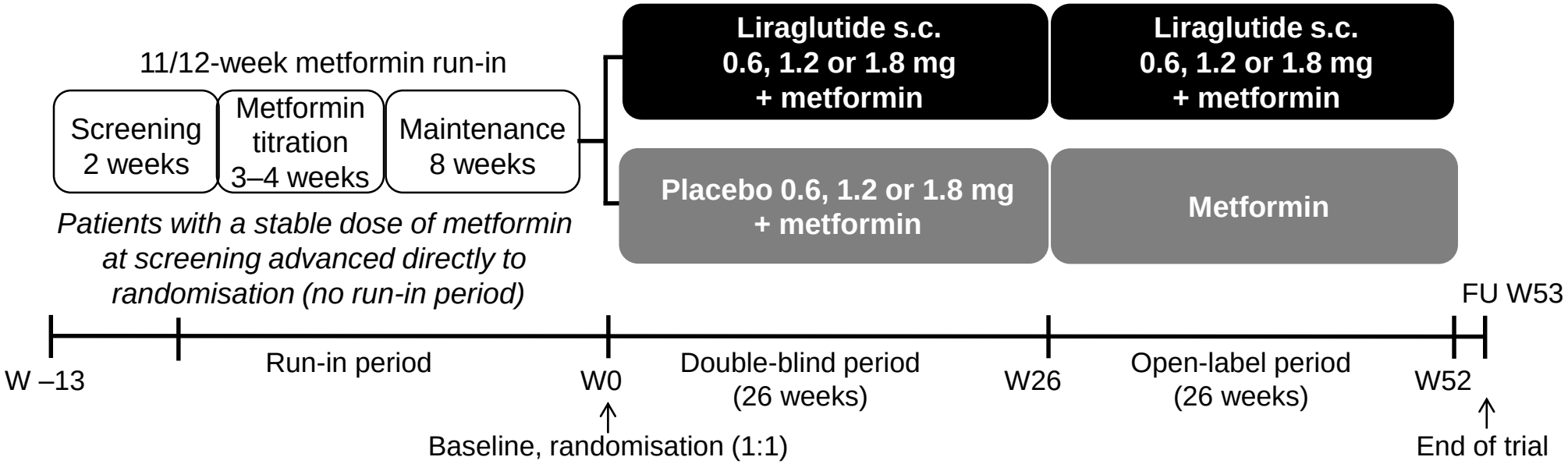
1. Klein DJ et al. *Diabetes Technol Ther* 2014;16:679–687

Ellipse: trial design

307 patients screened

134 patients treated

- Multicentre trial
- Stratified according to sex and age at end of treatment†



Key inclusion criteria

- T2D
- Children and adolescents aged 10 to <17 years at randomisation
- HbA_{1c}
  - ≥7.0% and ≤11% if diet and exercise-treated
  - ≥6.5% and ≤11% if treated with metformin ± insulin
- BMI >85th percentile (with age- and sex-matched population as reference)

Key exclusion criteria

- Type 1 diabetes
- Maturity-onset diabetes of the young
- Fasting C-peptide <0.6 ng/mL
- History of pancreatitis or a personal or family history of MTC or MEN

†(≤14; >14 years). BMI, body mass index; FU, follow-up; s.c., subcutaneous; MEN, multiple endocrine neoplasia 2; MTC, medullary thyroid cancer; T2D, type 2 diabetes; W, week

Study endpoints

Primary endpoint

- Change from baseline in HbA_{1c} at 26 weeks[†]

Secondary endpoints (assessed at week 26)[†]

- Change from baseline in FPG
- Percentage of patients reaching HbA_{1c} <7%
- Change from baseline in BMI SDS

Safety was assessed throughout the trial

[†]Also measured at week 52. BMI SDS, body mass index standard deviation score; FPG, fasting plasma glucose

Baseline characteristics (1/2)

Characteristic	Liraglutide (N = 66)	Placebo (N = 68)	Total (N = 134)
Age – years	14.6±1.7	14.6±1.7	14.6±1.7
Female sex – %†	62.1	61.8	61.9
Age of 10 to 14 years at end of trial – no. (%)	21 (31.8)	19 (27.9)	40 (29.9)
Region – no. (%)			
Asia	6 (9.1)	6 (8.8)	12 (9.0)
Europe	24 (36.4)	21 (30.9)	45 (33.6)
North America	28 (42.4)	35 (51.5)	63 (47.0)
Rest of the world	8 (12.1)	6 (8.8)	14 (10.4)

Characteristic	Liraglutide (N = 66)	Placebo (N = 68)	Total (N = 134)
Race or ethnic group – no. (%)			
White	42 (63.6)	45 (66.2)	87 (64.9)
Black	9 (13.6)	7 (10.3)	16 (11.9)
Asian	10 (15.2)	8 (11.8)	18 (13.4)
American Indian or Alaska Native	2 (3.0)	1 (1.5)	3 (2.2)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	3 (4.5)	7 (10.3)	10 (7.5)

Data are mean ± standard deviation, or proportion of patients (%). †Fulfilling regulatory requirement of including ≥40% females.

Baseline characteristics (2/2)

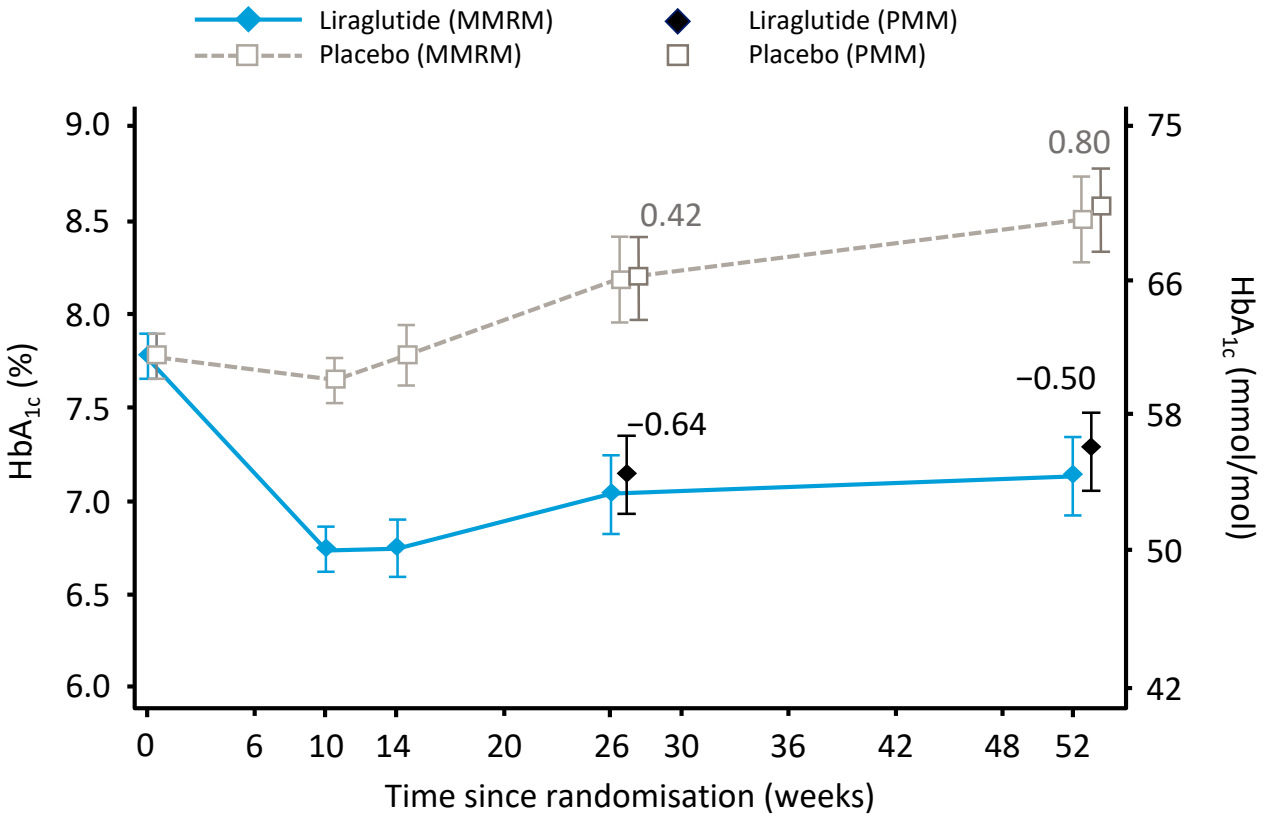
Characteristic	Liraglutide (N = 66)	Placebo (N = 68)	Total (N = 134)
Hispanic or Latino ethnic group – no. (%)			
Yes	16 (24.2)	23 (33.8)	39 (29.1)
No	50 (75.8)	45 (66.2)	95 (70.9)
Duration of diabetes – years	1.9±1.7	1.9±1.3	1.9±1.5
Body weight – kg	93.3±31.0	89.8±22.1	91.5±26.8
BMI	34.55±10.87	33.27±7.36	33.90±9.25
BMI SDS score	3.03±1.47	2.86±1.11	2.94±1.30
HbA_{1c} – %	7.87±1.35	7.69±1.34	7.78±1.34

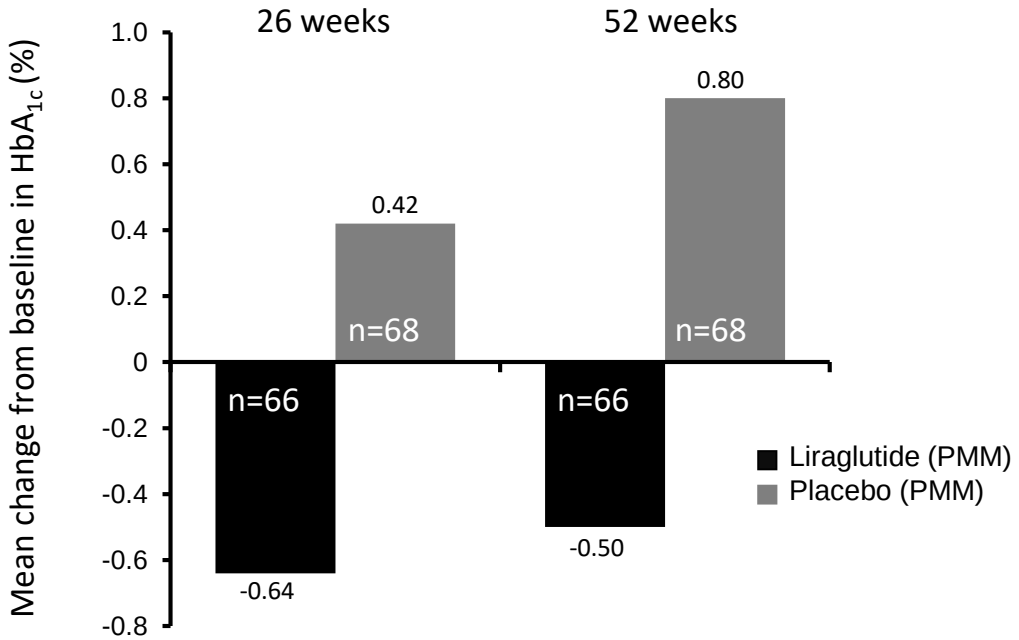
Characteristic	Liraglutide (N = 66)	Placebo (N = 68)	Total (N = 134)
Fasting plasma glucose – mg/dl	156.8±52.2	146.8±38.3	151.7±45.8
Blood pressure – mm Hg			
Systolic	118.4±11.4	115.3±12.0	116.8±11.8
Diastolic	73.2±8.5	71.2±7.6	72.2±8.1
Metformin dose at baseline – mg	1912±286	1877±384	1894±339
Basal insulin use at baseline			
No. (%) of patients	15 (22.7)	10 (14.7)	25 (18.7)
Mean dose – U	29.6±19.5	29.6±17.7	29.6±18.4

Baseline characteristics and demographics overall were similar across both groups

Data are mean ± standard deviation, or proportion of patients (%). Adapted from Table 1, Tamborlane *et al*., Liraglutide in Children and Adolescents with Type 2 Diabetes, *N Engl J Med* 2019;381:637–46.

Change from baseline in HbA_{1c}



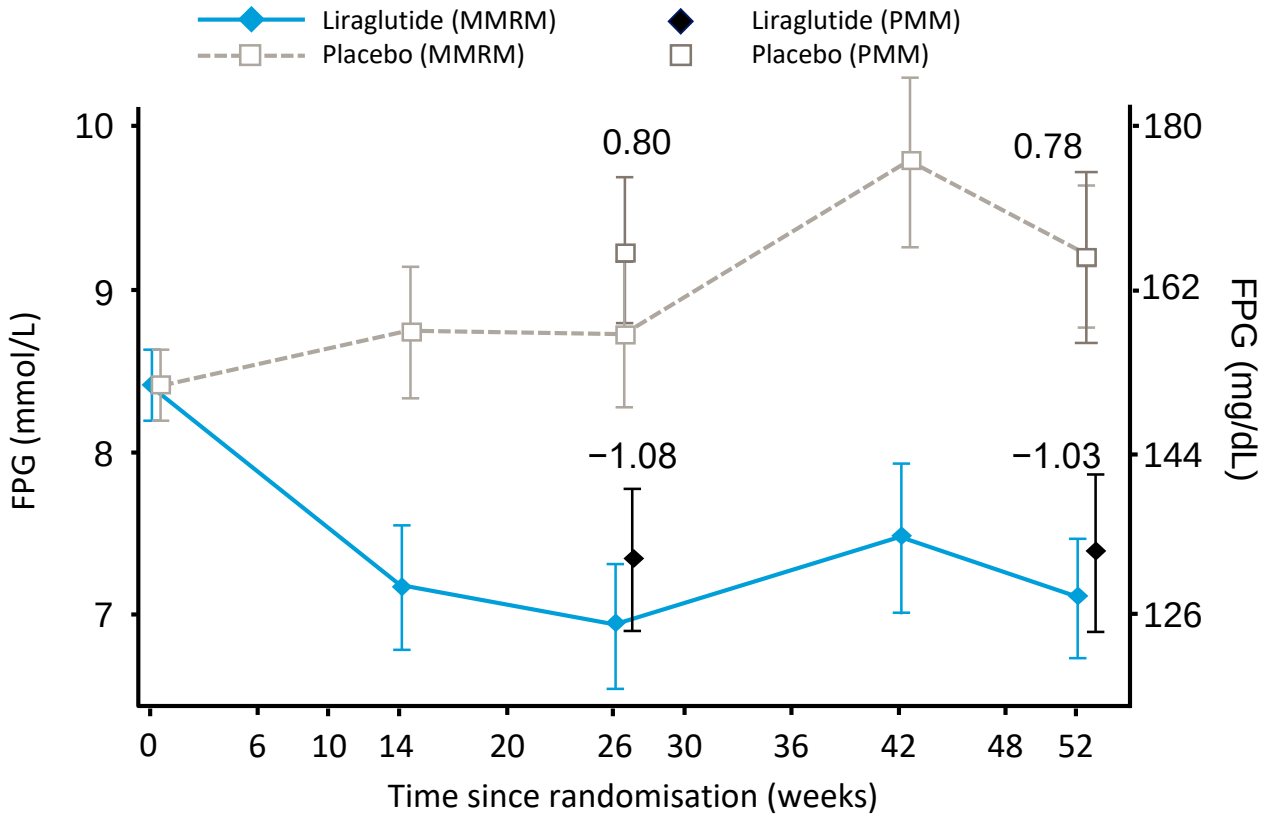


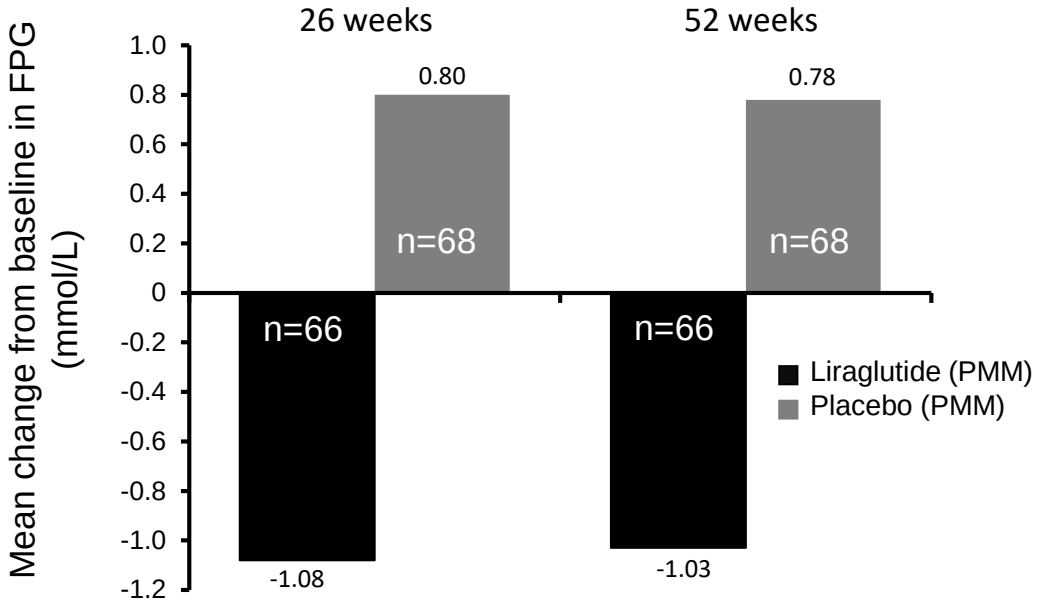
Week 26 (confirmatory)
ETD (95% CI) from PMM:
–1.06% (–1.65;–0.46)
p<0.001

Week 52
ETD (95% CI) from PMM:
–1.30% (–1.89;–0.70)

Error bars: ± standard error (mean). Means are estimated from MMRM containing treatment, sex and age group as fixed effects and baseline value as covariate, all nested within visit, during the 52-week trial period. For MMRM results, data collected after initiation of rescue medication were handled as missing data. Liraglutide: all doses of liraglutide. CI, confidence interval; ETD, estimated treatment difference from the PMM; MMRM, mixed model repeated measurements; PMM, pattern mixture model. Adapted from Figure 2, Tamborlane *et al*., Liraglutide in Children and Adolescents with Type 2 Diabetes, *N Engl J Med* 2019;381:637–46.

Change from baseline in FPG



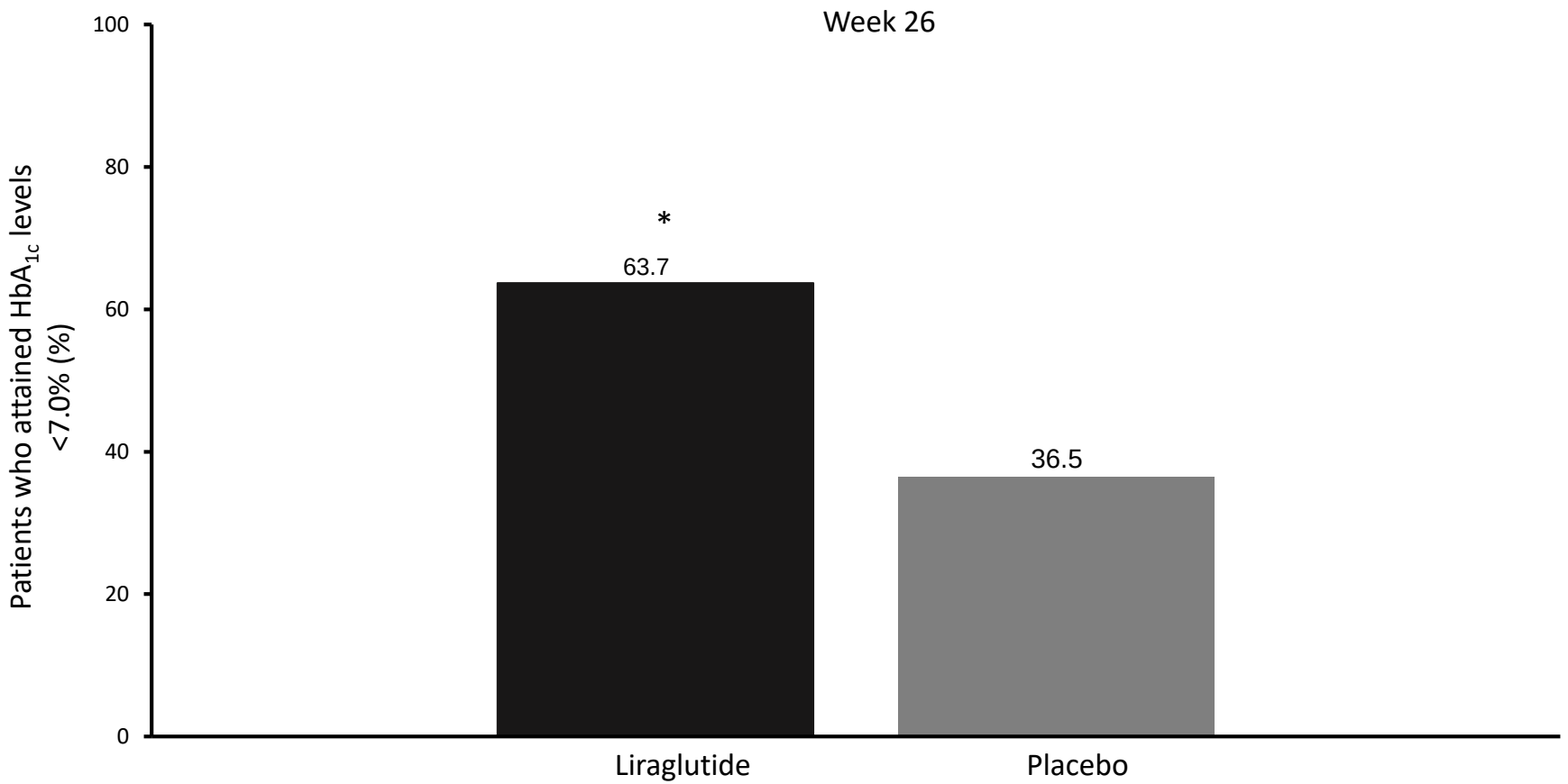


Week 26 (confirmatory)
ETD (95% CI) from PMM:
–1.88 mmol/L (–3.09;–0.66)
[–33.8 mg/dL (–55.7;–11.92)]
p=0.002

Week 52
ETD (95% CI) from PMM:
–1.81 mmol/L (–3.17;–0.44)
[–32.6 mg/dL (–57.2;–7.9)]

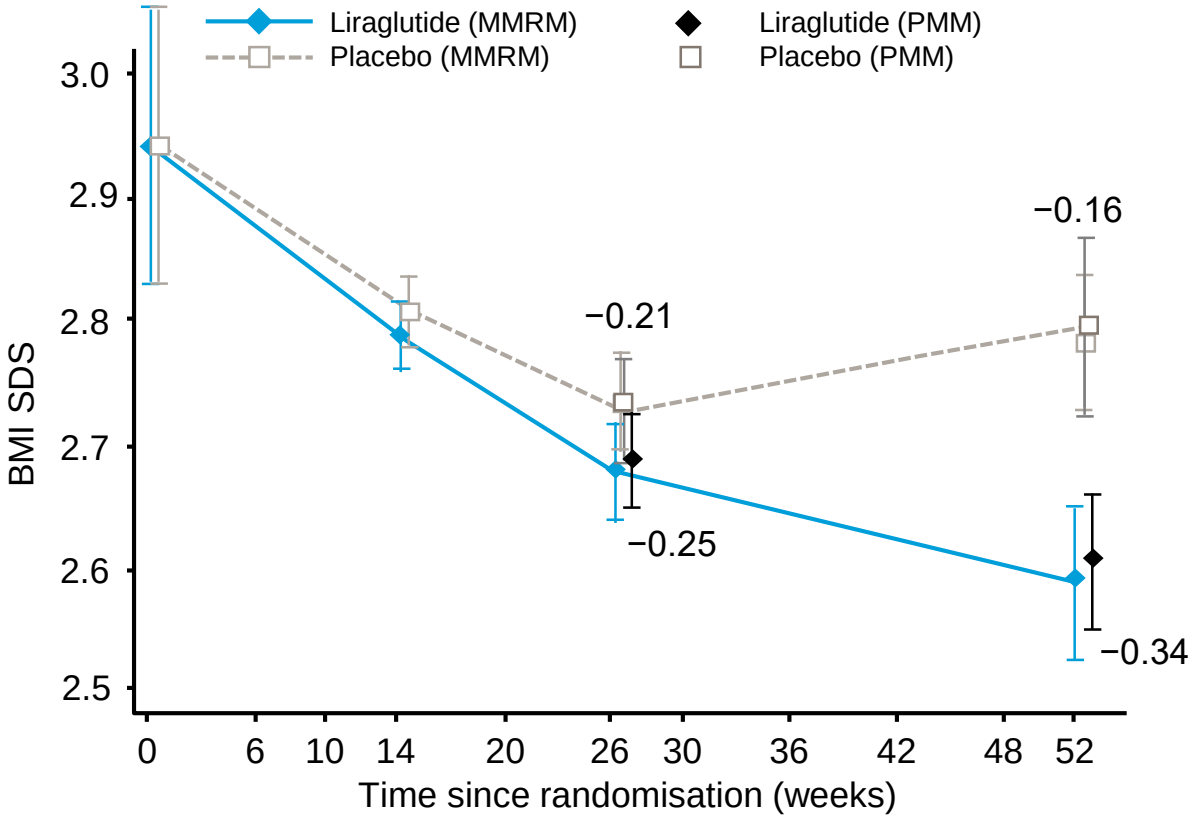
Error bars: ± standard error (mean). Means are estimated from MMRM containing treatment, sex and age group as fixed effects and baseline value as covariate, all nested within visit during the 52-week trial period. For MMRM results, data collected after initiation of rescue medication were handled as missing data. Liraglutide: all doses of liraglutide. CI, confidence interval; ETD, estimated treatment difference from the PMM; FPG, fasting plasma glucose; MMRM, mixed model of repeated measurements; PMM, pattern mixture model.

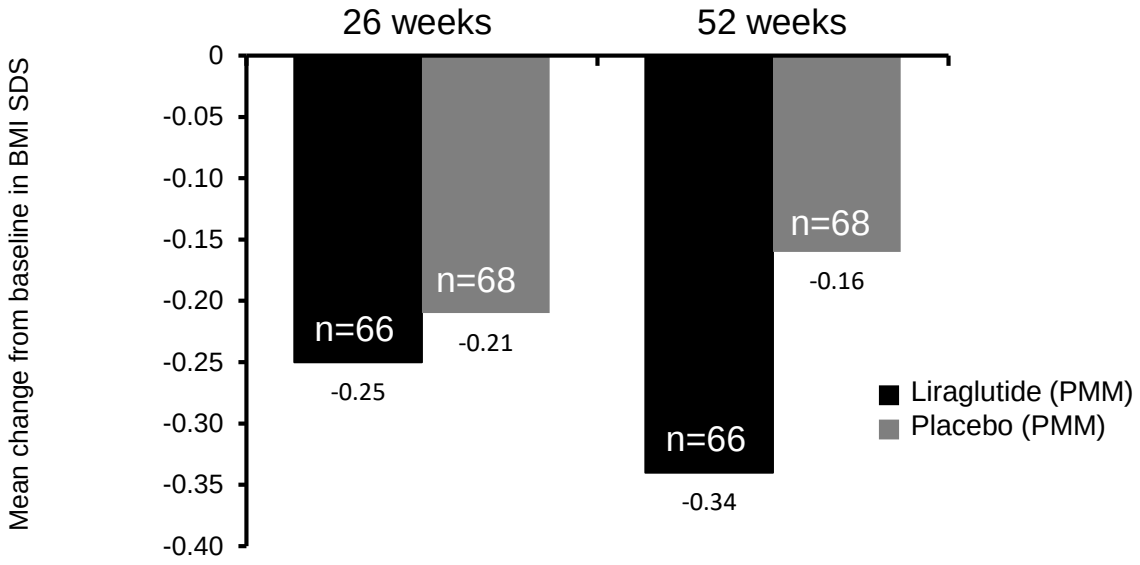
Proportion of patients who attained HbA_{1c} <7.0% at week 26



**p*<0.001. Liraglutide: all doses of liraglutide.

Change from baseline in BMI SDS





Week 26 (confirmatory)
ETD (95% CI) from PMM:
–0.05 (–0.15;0.06)
p=0.39

Week 52
ETD (95% CI) from PMM:
–0.18 (–0.33;–0.03)

Error bars: ± standard error (mean). Means are estimated from MMRM containing treatment, sex and age group as fixed effects and baseline value as covariate, all nested within visit during the 52-week trial period. For MMRM results, data collected after initiation of rescue medication were handled as missing data. Liraglutide: all doses of liraglutide. BMI SDS, body mass index standard deviation score; CI, confidence interval; ETD, estimated treatment difference from the PMM; MMRM, mixed model of repeated measurements; PMM, pattern mixture model.

Key treatment-emergent AEs – entire 52-week study period

	Liraglutide n=66	Placebo n=68
Events, n (%)	56 (84.8)	55 (80.9)
SAEs, n (%)	9 (13.6)	4 (5.9)
MESIs, n (%)	6 (9.1)	3 (4.4)
AEs leading to treatment discontinuation, n (%)	1 (1.5)[†]	1 (1.5)
Key AEs (≥5%), n (%)		
Nausea	19 (28.8)	9 (13.2)
Vomiting	17 (25.8)	6 (8.8)
Diarrhoea	15 (22.7)	11 (16.2)
Headache	14 (21.2)	13 (19.1)
Abdominal pain	12 (18.2)	5 (7.4)
Nasopharyngitis	11 (16.7)	19 (27.9)

	Liraglutide n=66	Placebo n=68
Key AEs (≥5%), n (%) (cont.)		
Dizziness	8 (12.1)	2 (2.9)
Gastroenteritis	7 (10.6)	2 (2.9)
Upper respiratory tract infection	6 (9.1)	5 (7.4)
Dyspepsia	5 (7.6)	1 (1.5)
Rash	4 (6.1)	1 (1.5)
Constipation	4 (6.1)	1 (1.5)
Dysmenorrhoea	3 (4.5)	6 (8.8)
Abdominal pain upper	2 (3.0)	8 (11.8)
Rhinorrhoea	1 (1.5)	4 (5.9)
Alanine aminotransferase increased	0 (0.0)	4 (5.9)

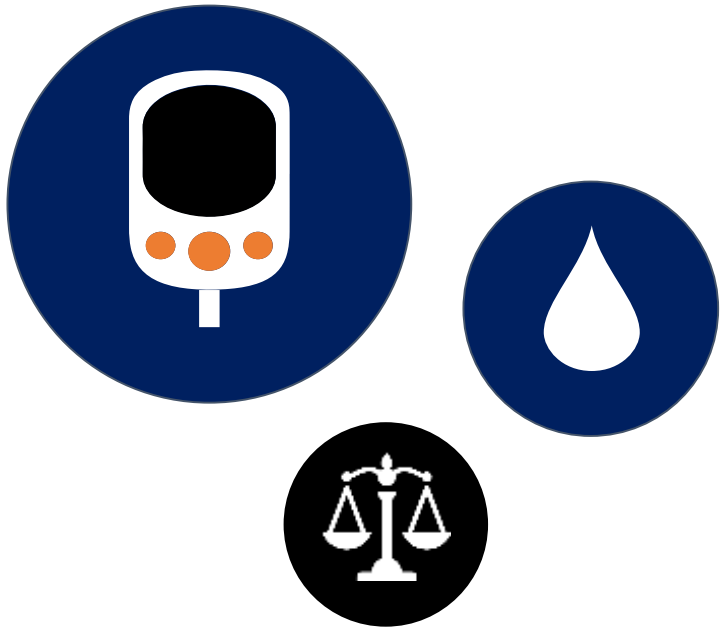
[†]One patient on liraglutide with hyperglycaemia AE leading to treatment discontinuation was withdrawn due to non-compliance. Liraglutide: all doses (0.6, 1.2 and 1.8 mg). AE, adverse event; MESI, medical event of special interest; SAE, serious adverse event. Adapted from Suppl Table 5, Tamborlane *et al*., Liraglutide in Children and Adolescents with Type 2 Diabetes, *N Engl J Med* 2019;381:637–46.

Hypoglycaemic episodes – entire 52-week study period

Hypoglycaemia	Liraglutide n=66	Placebo n=68
Minor,[†] n (%)	16 (24.2)	7 (10.3)
All hypoglycaemic episodes[‡]	30 (45.5)	17 (25.0)
Severe	0 (0.0)	1 (1.5)
Documented symptomatic	19 (28.8)	6 (8.8)
Asymptomatic	21 (31.8)	12 (17.6)

[†]Minor: symptomatic or asymptomatic hypoglycaemic episode with plasma glucose <3.1 mmol/L. [‡]ADA classification. Liraglutide: all doses (0.6, 1.2 and 1.8 mg). ADA, American Diabetes Association. Adapted from Suppl Table 5, Tamborlane *et al*., Liraglutide in Children and Adolescents with Type 2 Diabetes, *N Engl J Med* 2019; 381:637–46.

ELLIPSE study summary



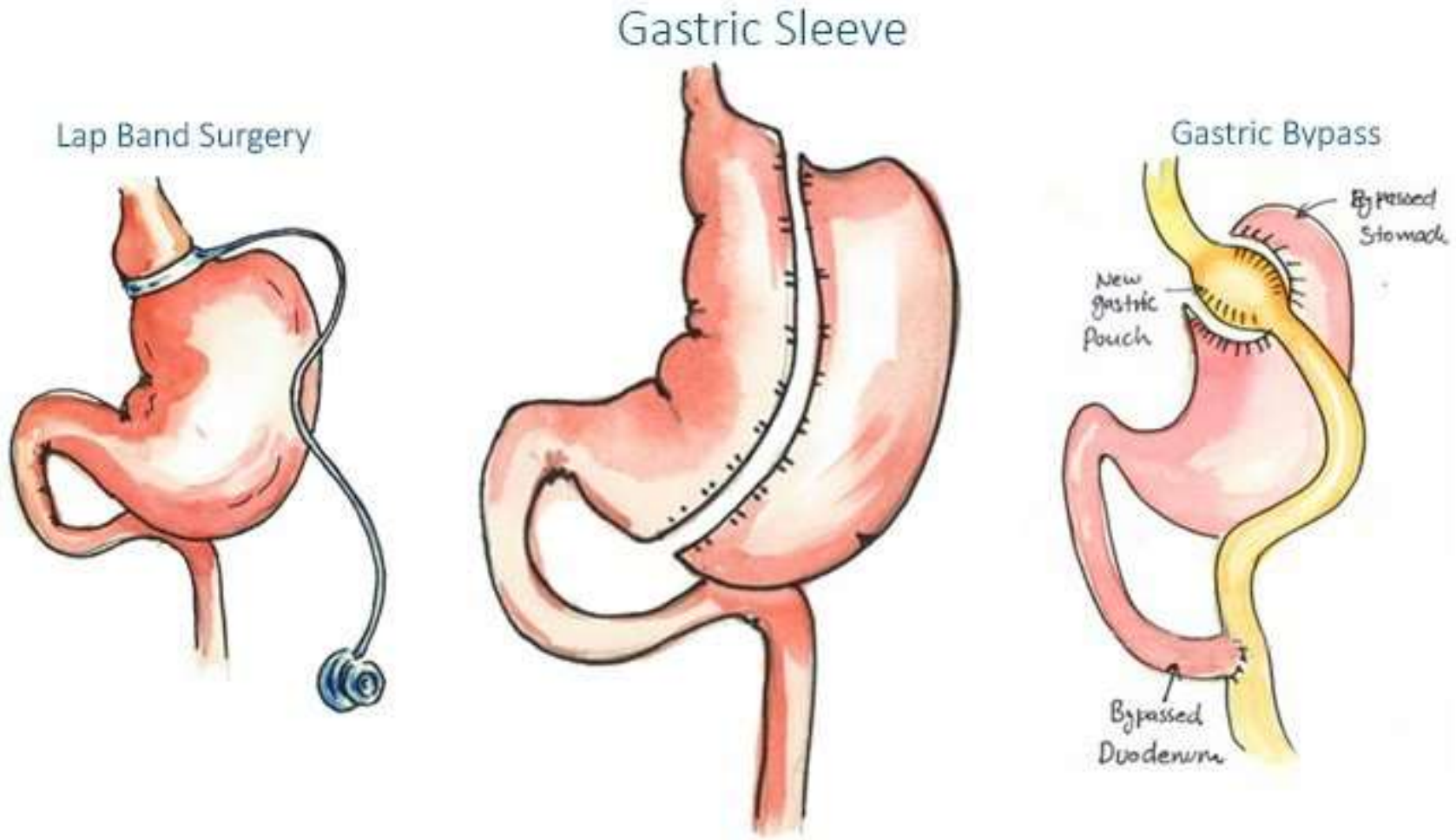
- At Week 26 and Week 52, liraglutide demonstrated reductions in HbA_{1c} and FPG compared with placebo; superiority* was confirmed at Week 26
- The percentage of participants achieving HbA_{1c} <7% at Week 26 was superior* with liraglutide compared with placebo
- >50% of participants reached liraglutide doses up to 1.8 mg
- Overall, the safety profile of liraglutide is similar to that in adults, although the frequency of hypoglycaemic events was higher in liraglutide than in placebo
  - No episodes of severe hypoglycaemia were observed in liraglutide-treated participants

Liraglutide at doses up to 1.8 mg/day (when added to metformin ± basal insulin) offers a new, efficacious and durable treatment option, with an acceptable safety profile, for children and adolescents with T2D in need of improved glycaemic control

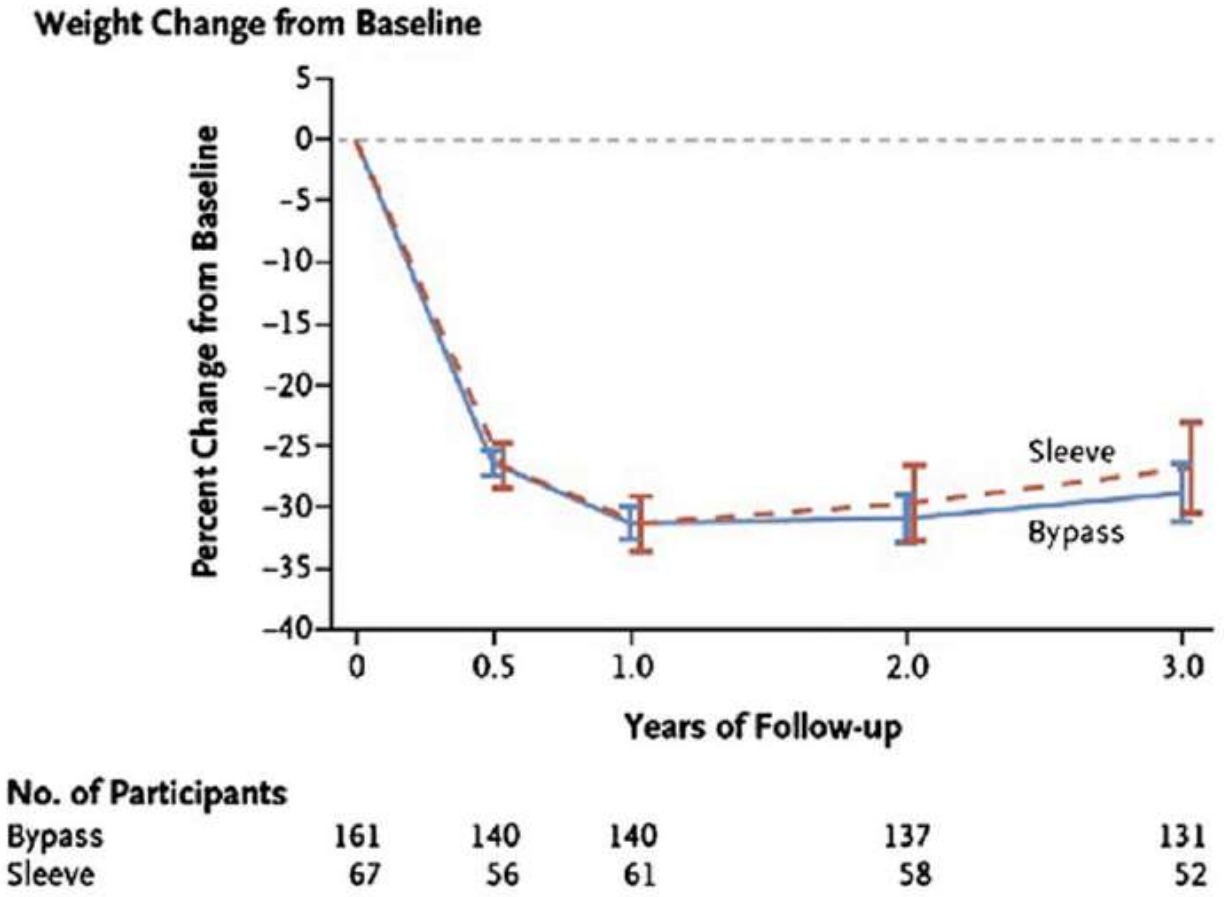
*Superiority testing only pre-specified for confirmatory endpoints at Week 26

Tamborlane WV et al. *N Engl J Med* 2019;381:637–646

What about bariatric surgery?



Weight change following bariatric surgery in young people

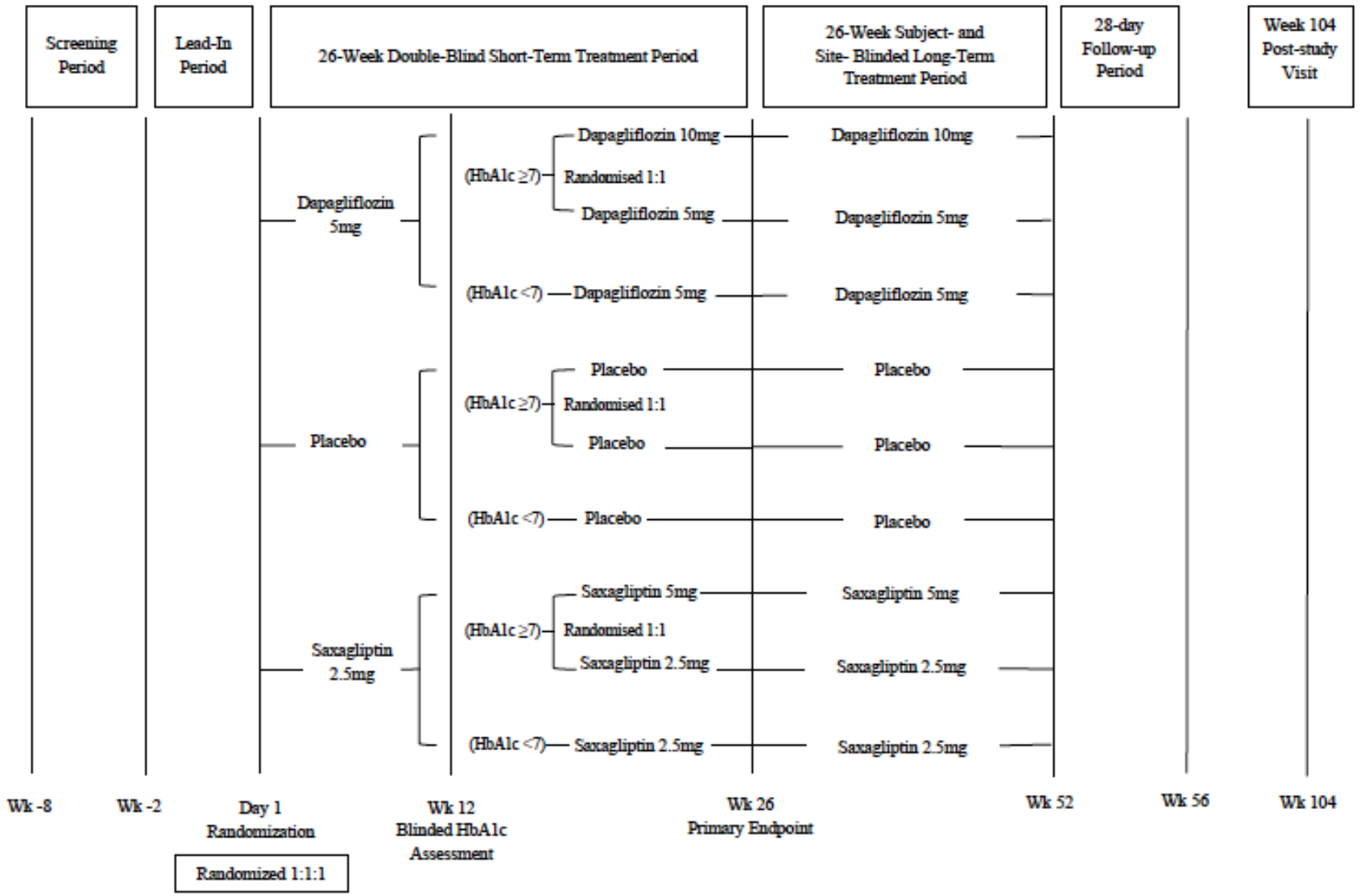


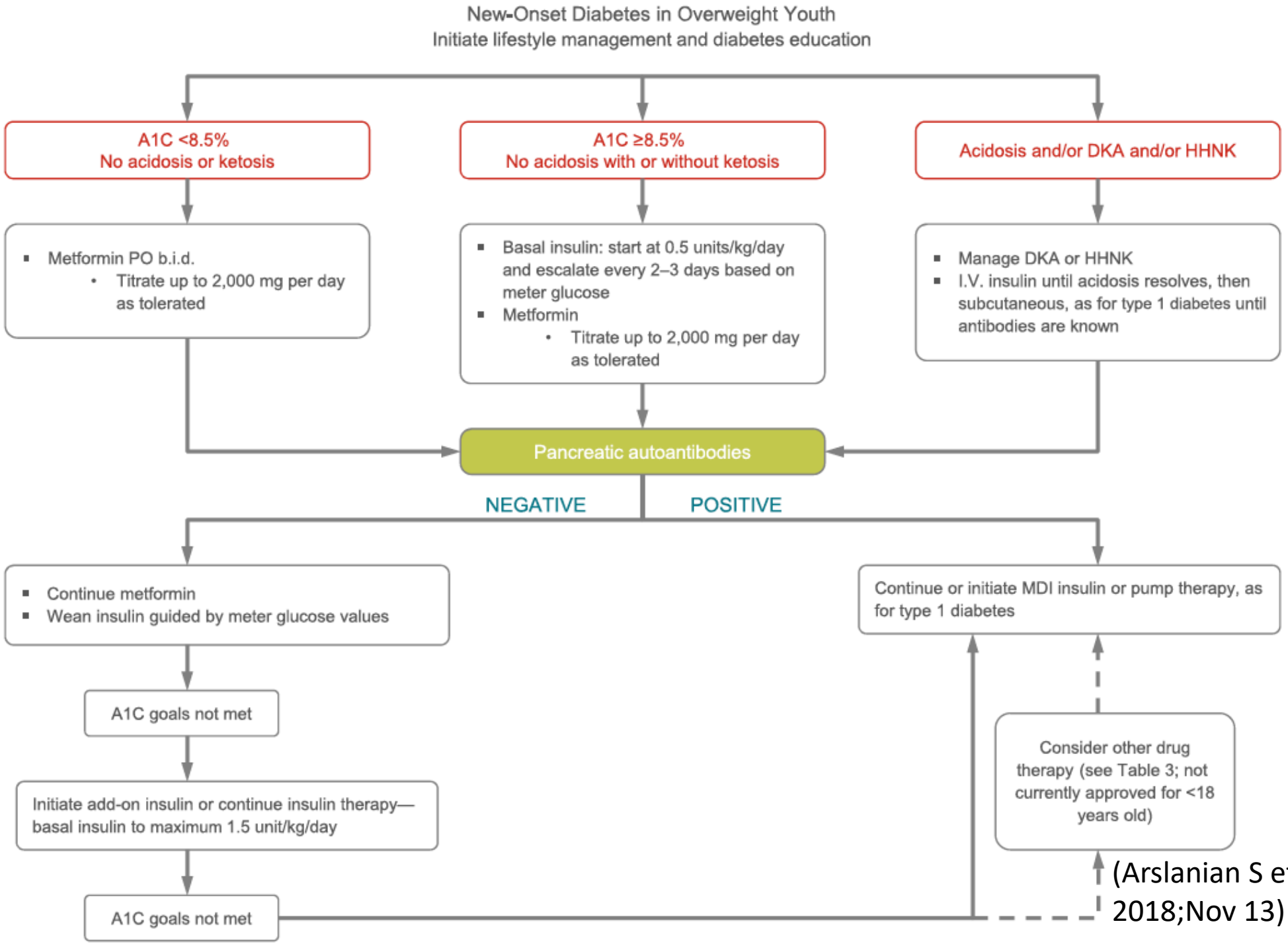
T2DM remission after 3 years:

94% (gastric bypass)
68% (sleeve gastrectomy)

(Inge T et al New Engl J Med 2016;374:113-123)

Ongoing clinical trials – SGLT2 inhibitor Dapagliflozin





(Arslanian S et al Diabetes Care 2018;Nov 13)

Summary

- Type 2 diabetes in childhood an emerging health problem in UK
- T2DM a more aggressive disease in children than in adults
- First line treatment always lifestyle, exercise and diet + metformin
- Second line treatment – are now licensed alternatives to insulin
- All children under 16yrs should be seen in secondary care, managed in partnership with primary care colleagues

Thankyou!

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