Università degli Studi di Chieti
Clinica Pediatrica

UP TO DATE SUL DIABETE

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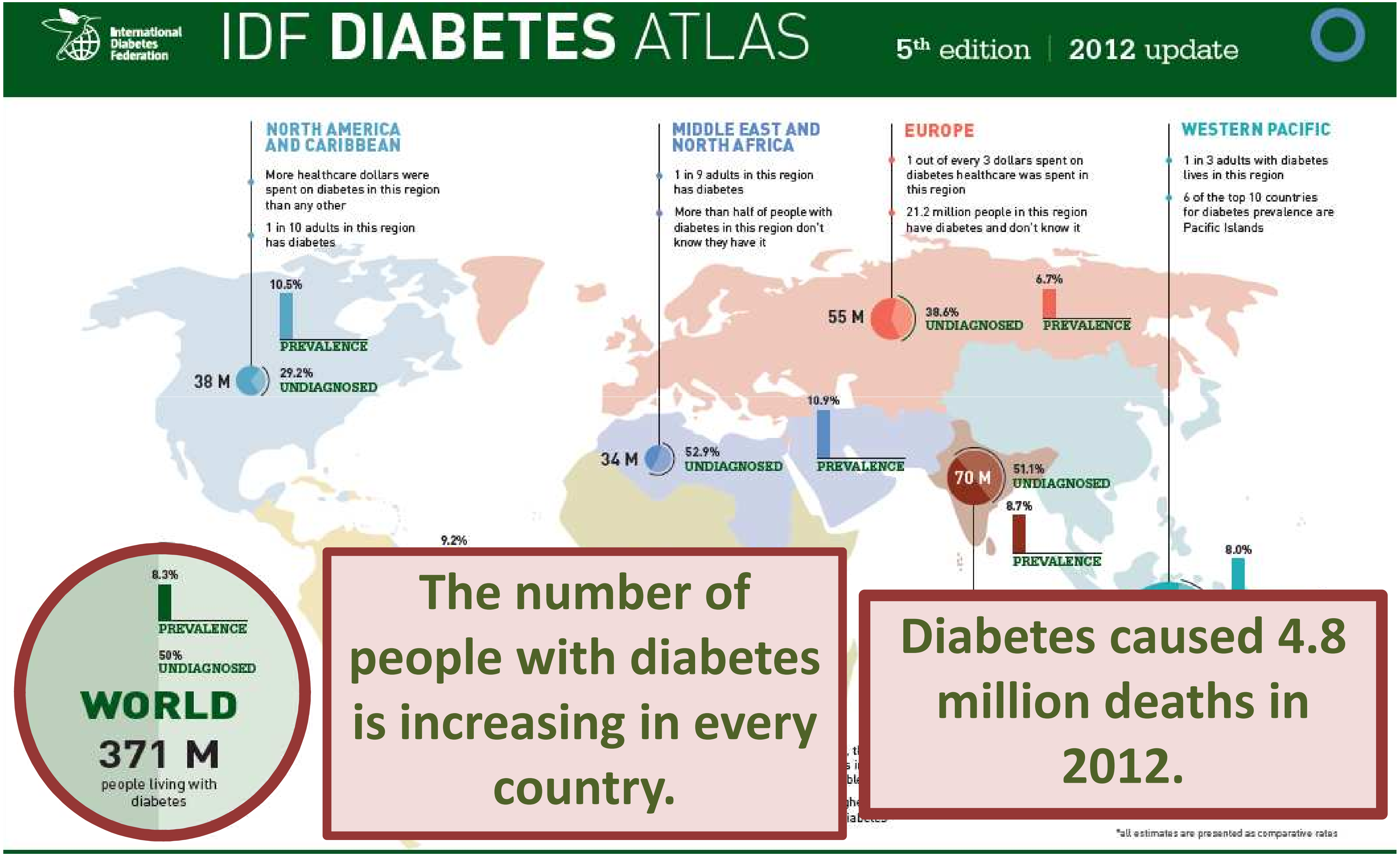
Outline

<u>An update on T1D & T2D</u>

- **Epidemiology of diabetes**
- **Pathogenesis**
- **Treatment**
- **Complications**

Diabetes: The global burden



The number of people with diabetes is increasing in every country.

Diabetes caused 4.8 million deaths in 2012.

International Diabetes Federation, http://www.idf.org/

Epidemiology of childhood diabetes: what is new?

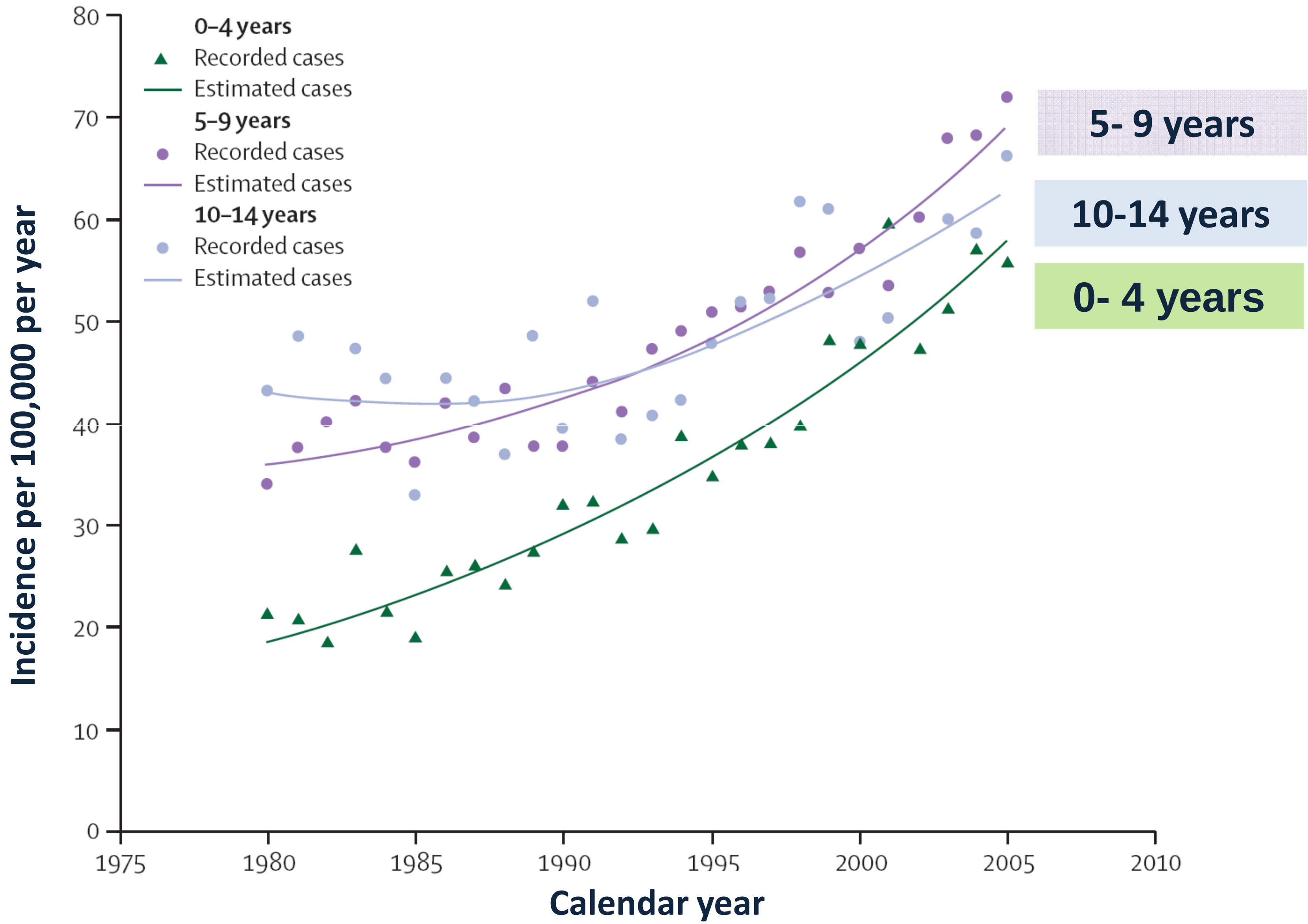
The Burden of Diabetes in Childhood

- Diabetes is one of the most common chronic diseases in children and adolescents.
- T1D accounts for over 90% of cases of newly- diagnosed diabetes in children and adolescents.

International Diabetes Federation	
Number of children with T1D (0-14 yr, thousands)	**490.1**
Number of newly diagnosed cases per year (0-14 yr, thousands)	**77.8**
Annual increase incidence (%)	**3-5**

International Diabetes Federation, http://www.idf.org/

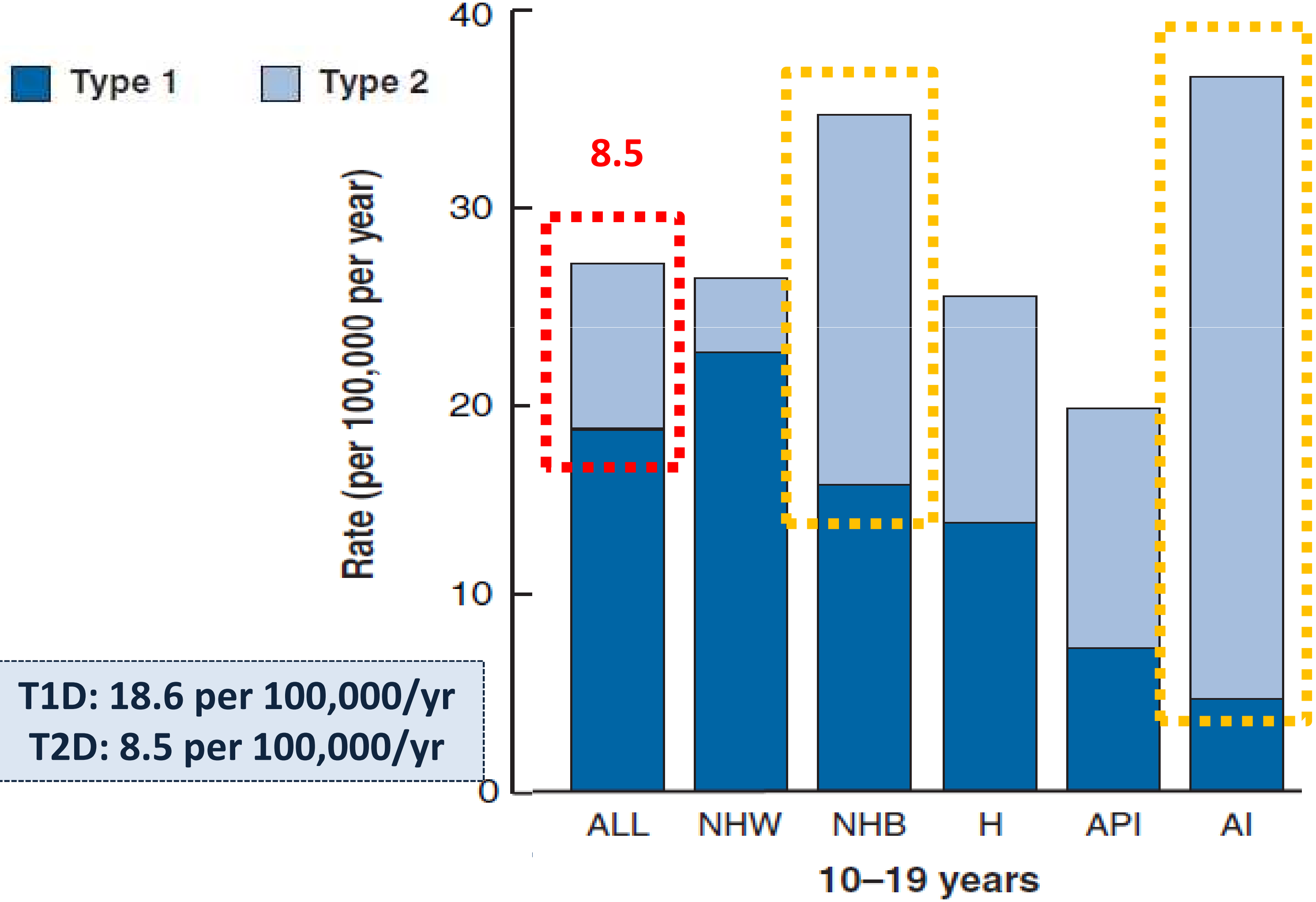
Time trends in age-specific incidence rates of T1D



Harjutsalo V et al., Lancet 2008

Rates of new cases of T1D and T2D among youth, by race/ethnicity, 2002-2005

T2D: 15-87% of new cases of diabetes inthe USA



T1D: 18.6 per 100,000/yr
T2D: 8.5 per 100,000/yr

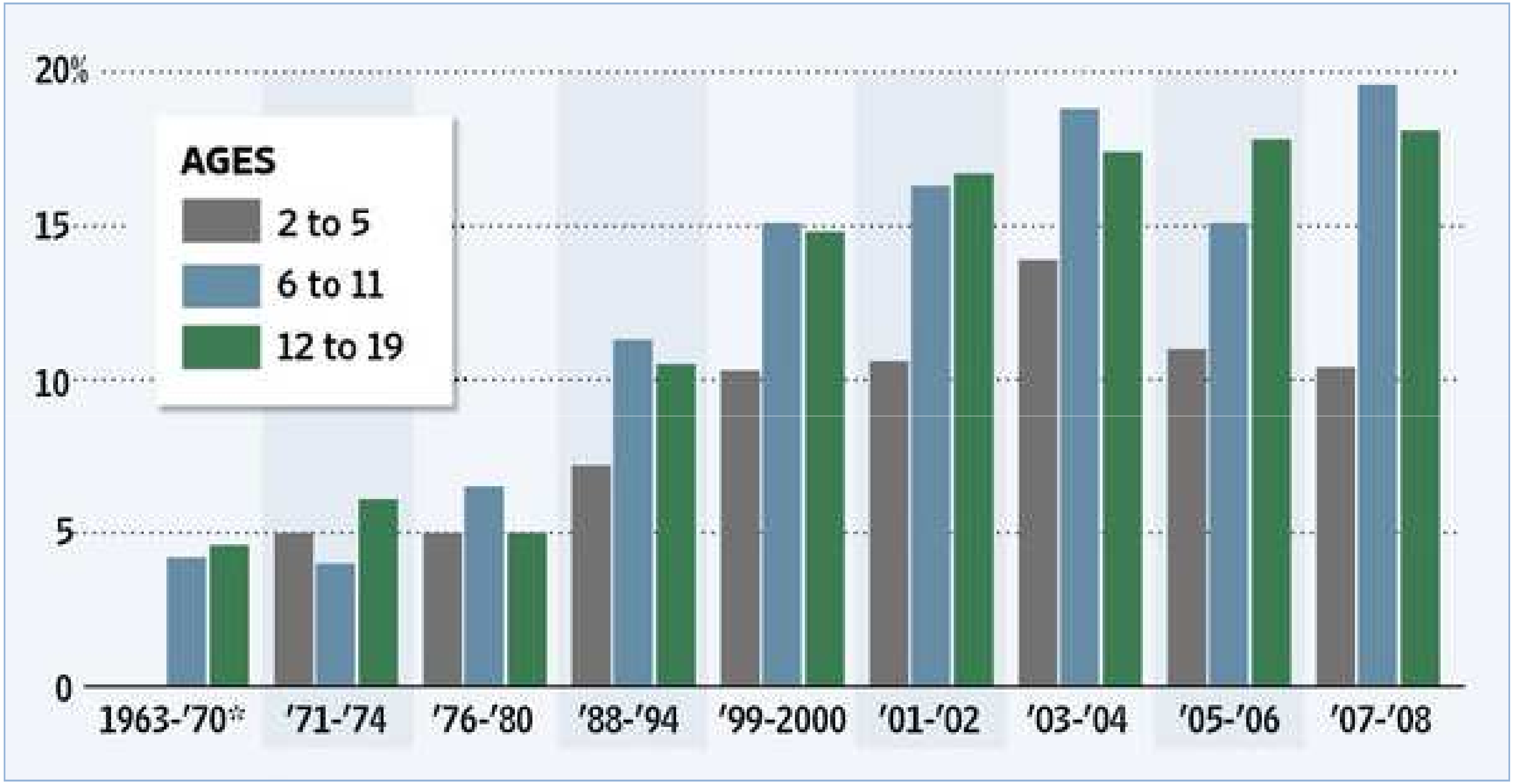
http://diabetes.niddk.nih.gov/dm/pubs/statistics/DM_Statistics_508.pdf

Incidence of T2D in children and adolescents

Country	Age	Ethnicity	Incidence (100,000)	Years
Australia	10-18	Mixed	**2.5**	2001-2006
Japan	6-15	North-East Asian	**2.5**	1996-2002
Taiwan	6-18	North East Asian	**6.5**	1999
Libya	10-19	Arab	**3.9**	1981-1990
Finland	15-19	Finnish residents	**0.5**	1992-2002
Sweden	10-19	Caucasian 95%	**5.6**	1998-2001
Austria	0-14	Caucasian	**0.3**	1999-2001
UK	0-16	Caucasian 60%, South Asian 18%, Black 17%	**0.6**	2004-2005
Italy	3-18	Caucasian	**0.4**	2010

Modified from Craig ME et al., Pediatr Child Health 2009

Obesity: single most important risk factor for T2D

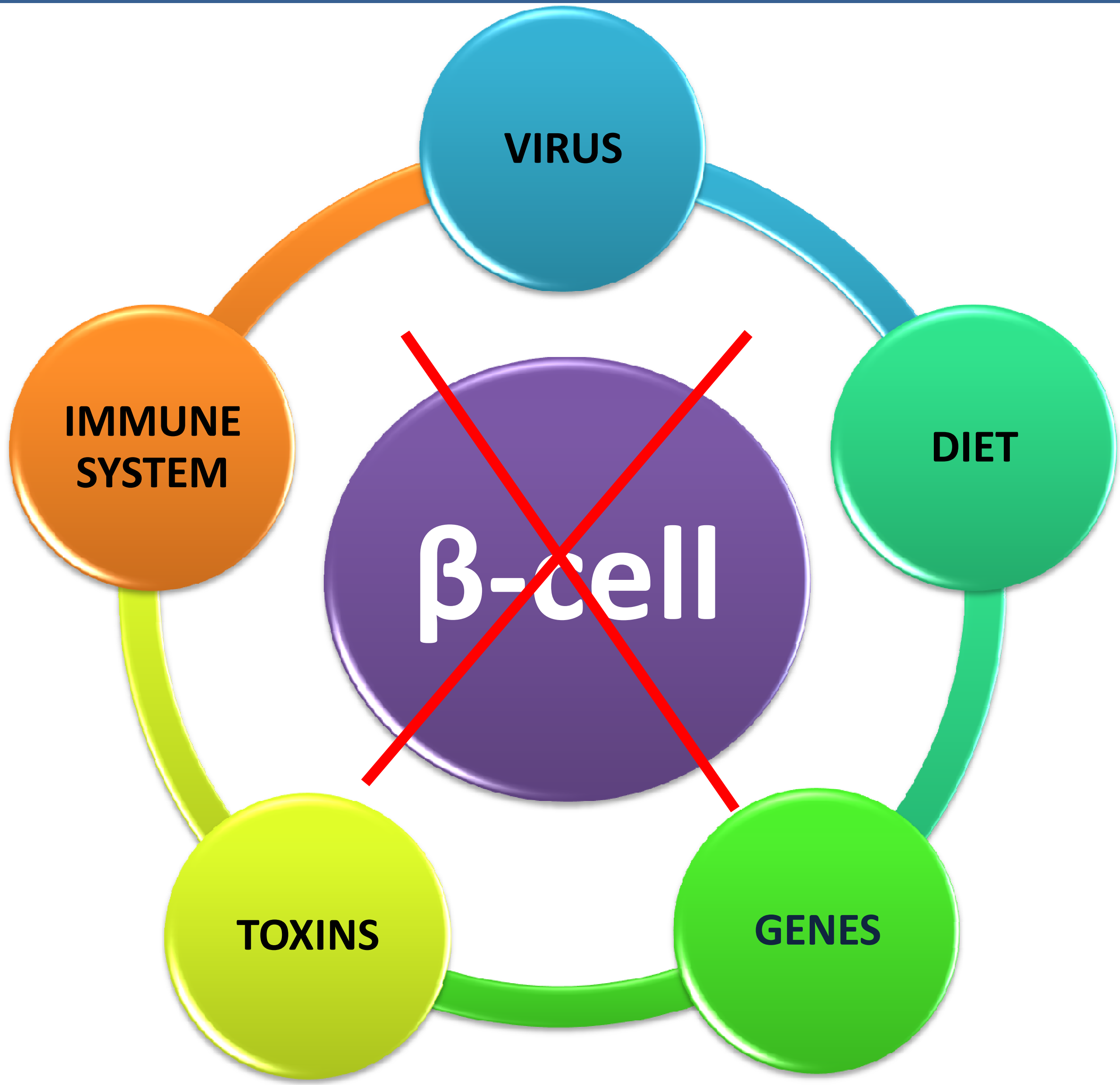


- **Clinical presentation of T2D may be indistinguishable from T1D, due to the increasing number of obese children.**

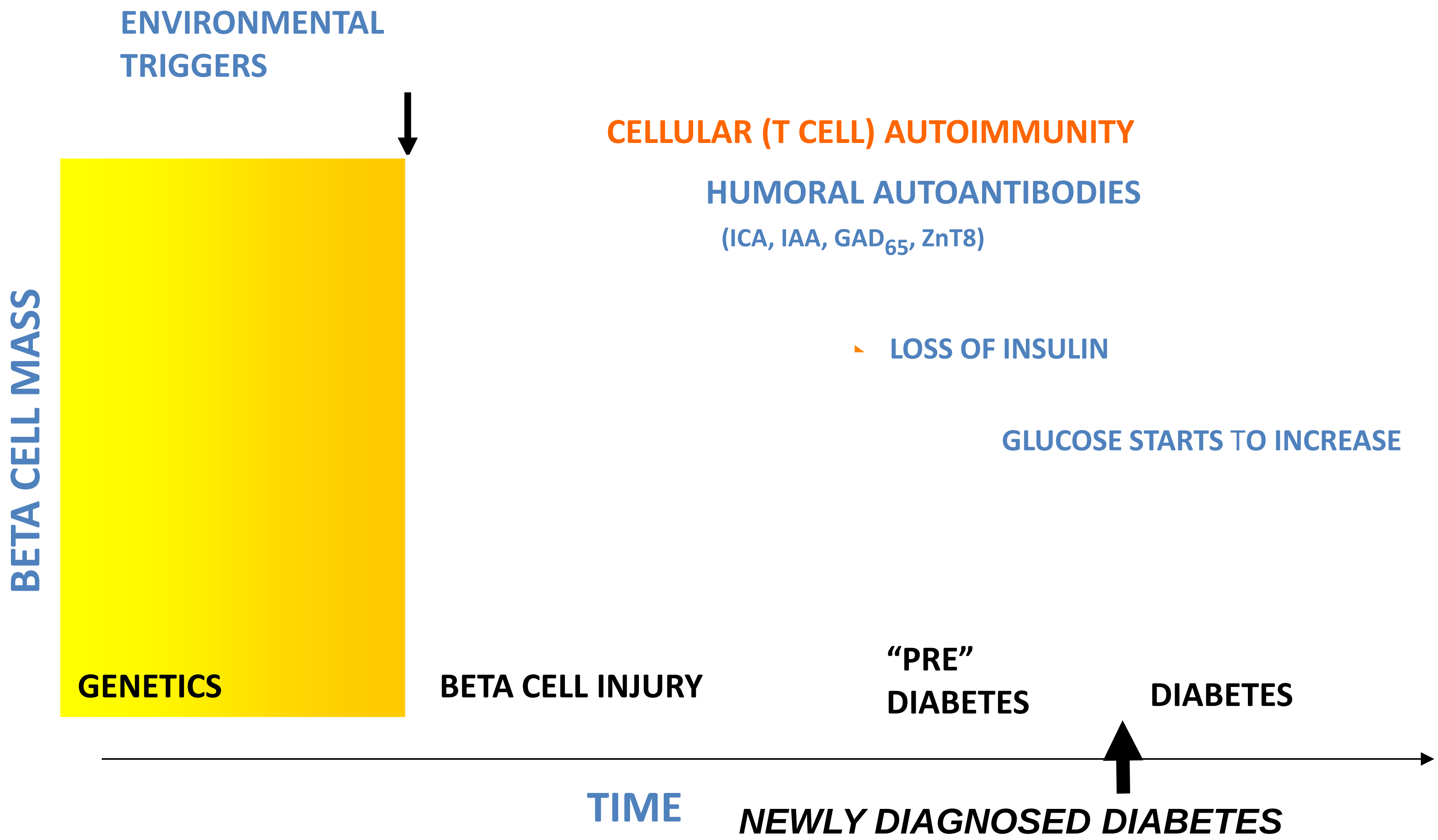
Badaru A et al., Curr Diab Rep 2012

An update on the pathogenesis of Type 1 diabetes

T1D: a complex pathogenesis

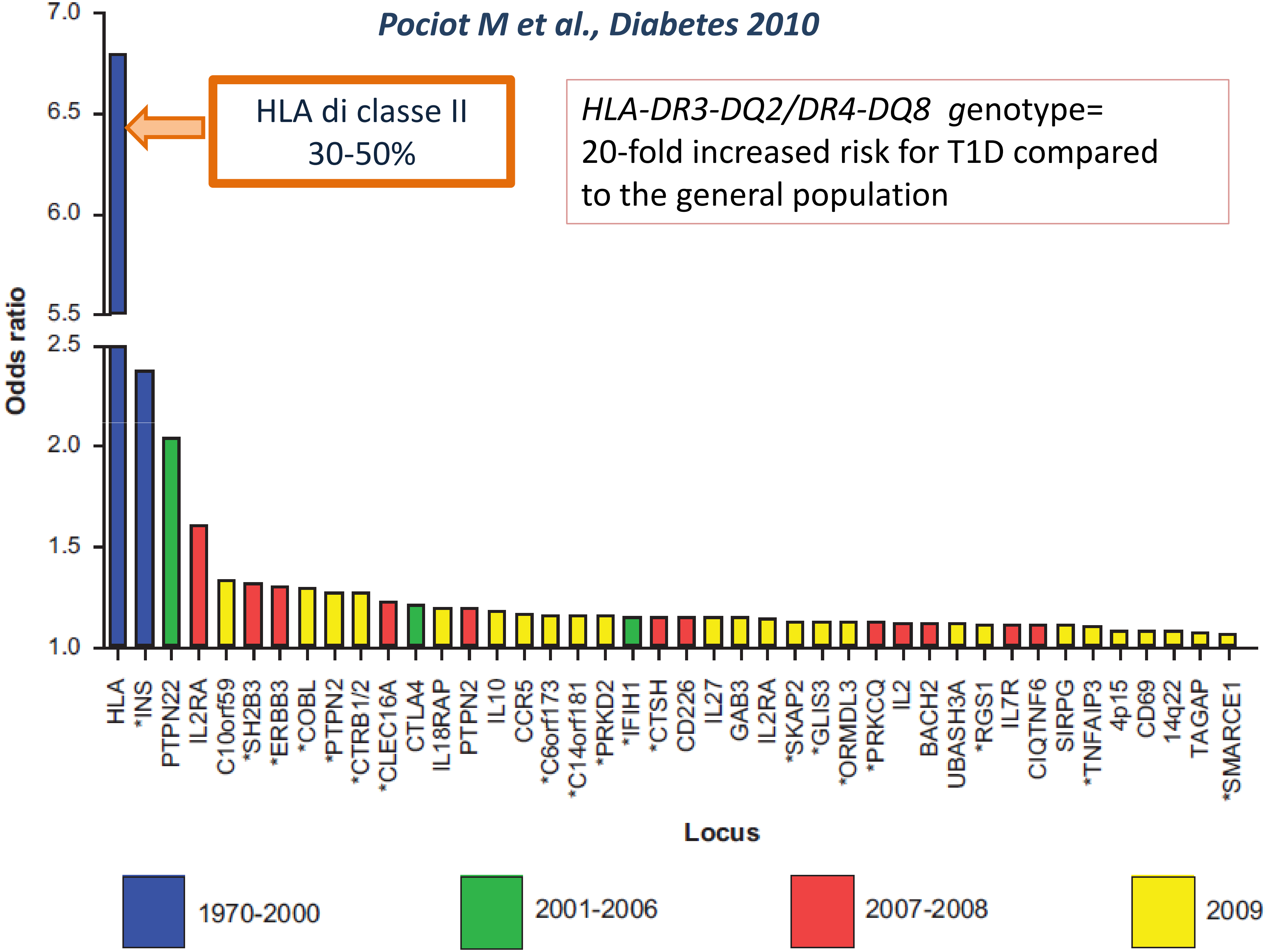


Natural history of T1D



Genetics of T1D

Pociot M et al., Diabetes 2010



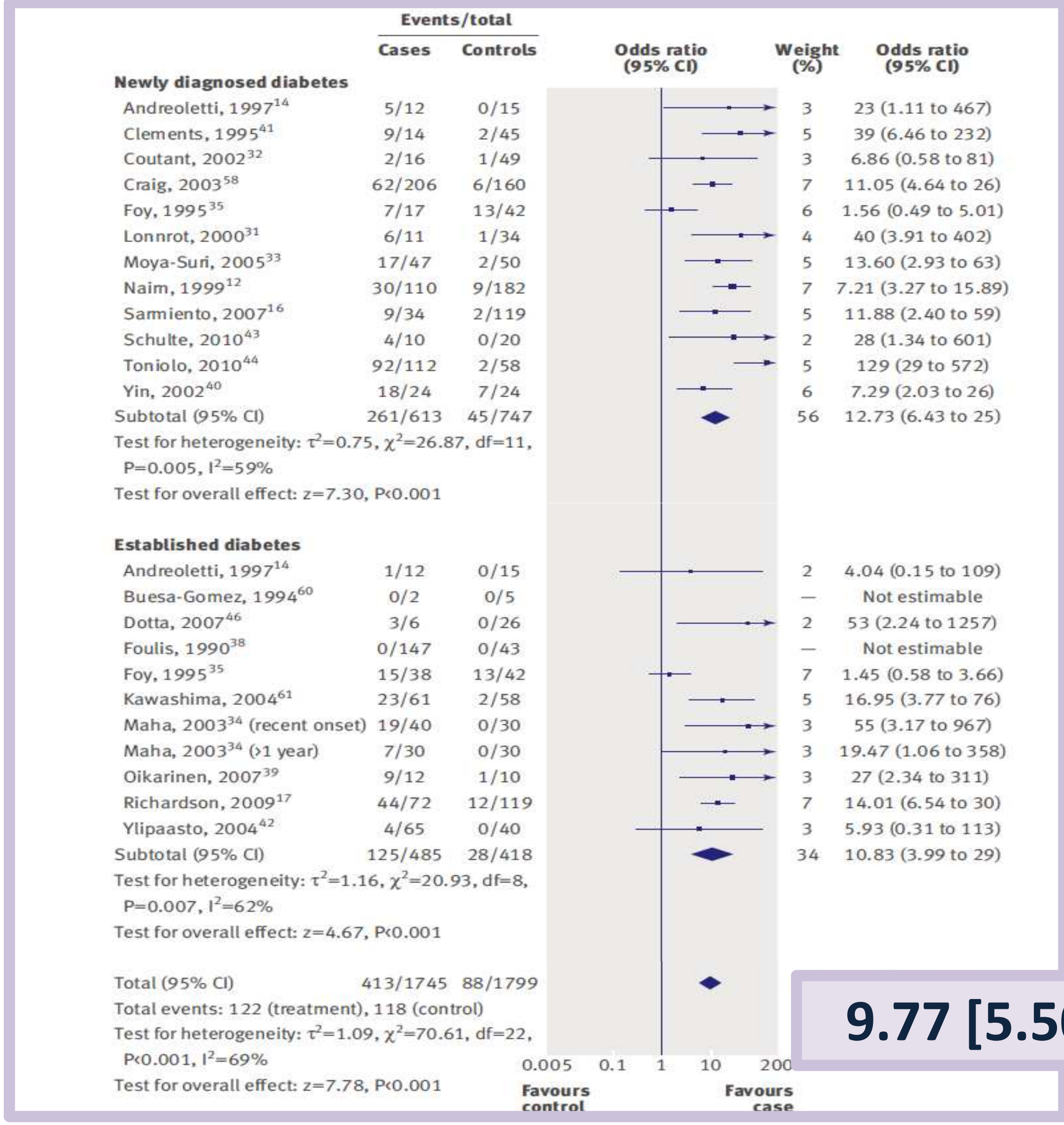
HLA-DR3-DQ2/DR4-DQ8 genotype=
20-fold increased risk for T1D compared to the general population

Factors implicated in T1D pathogenesis

Environmental factors	Hypothesis
Viral infections (e.g. enteroviruses)	Viral hypothesis

Pozzilli P et al., Diabet Med 2008

Role of Enterovirus in T1D pathogenesis

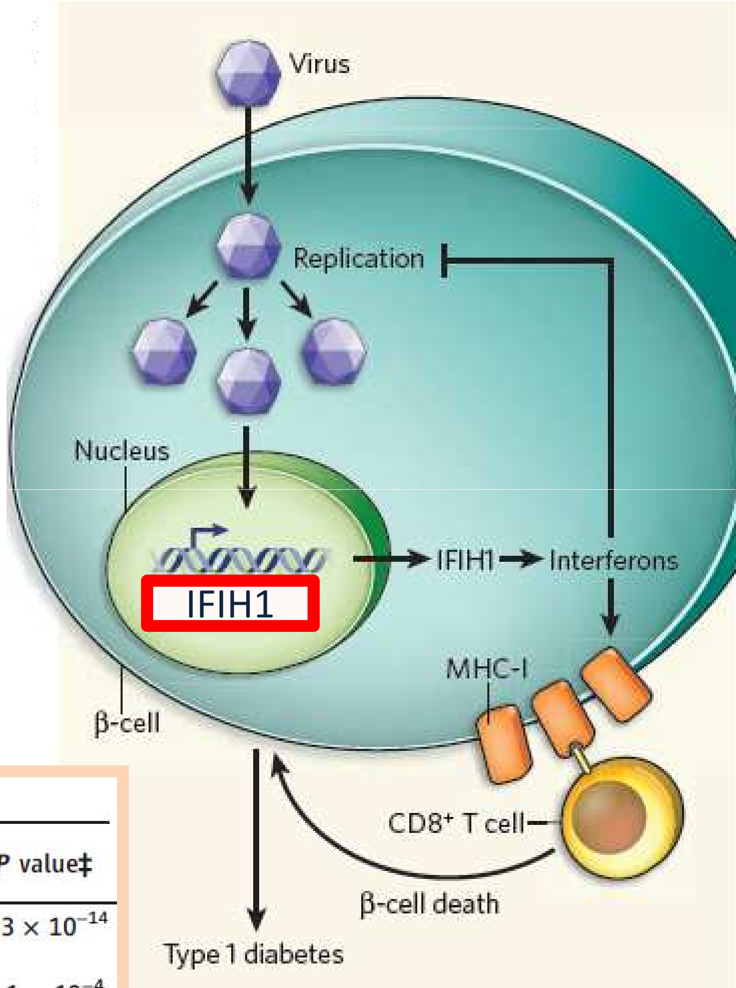


9.77 [5.50 to 17.35]

Yueng WC et al., BMJ 2011

A virus-gene interaction in the pathogenesis of T1D

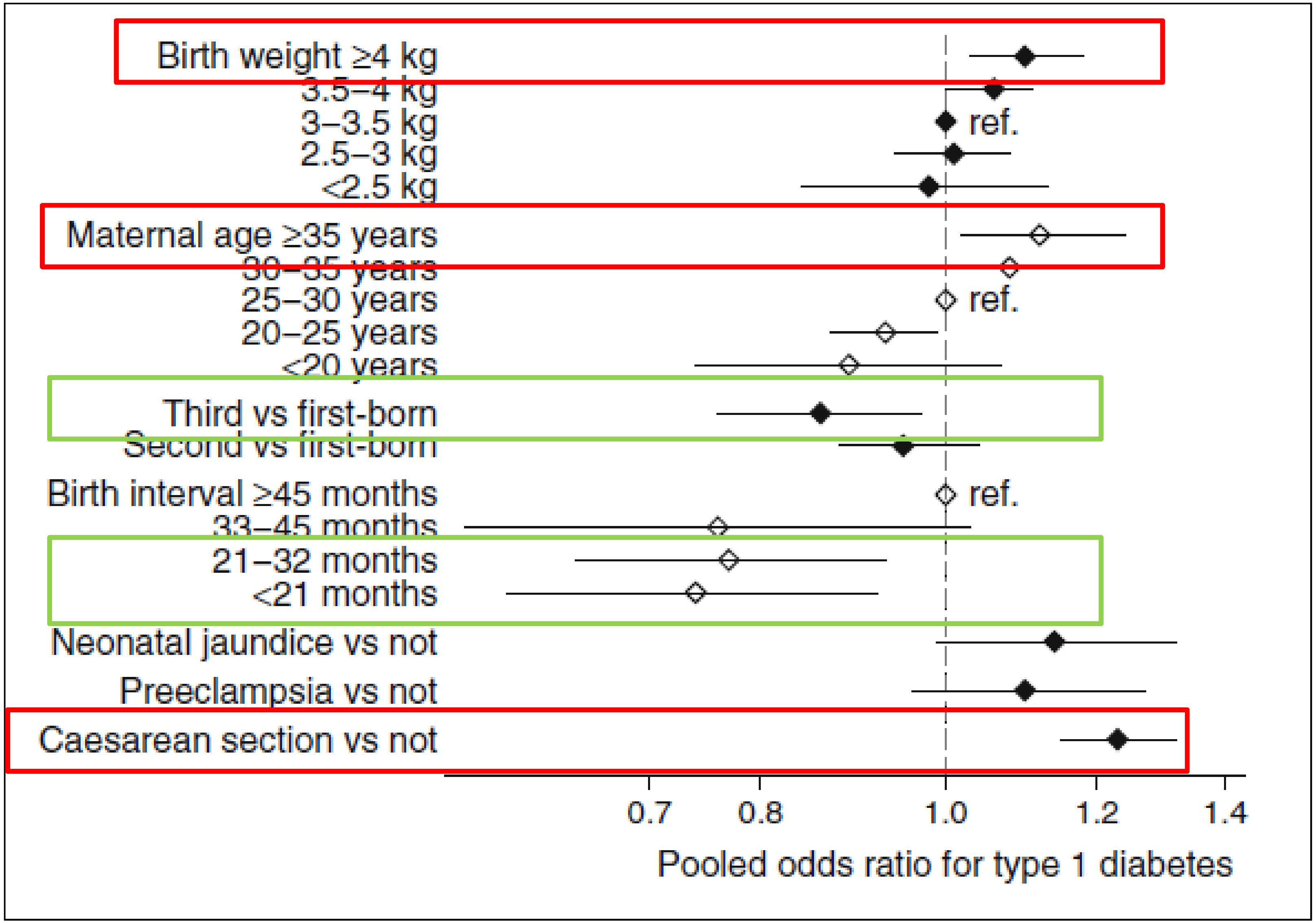
- **IFIH1: interferon-induced helicase**
- One of a family of intracellular proteins known to recognise viral RNA and mediate the innate immune response
- IFIH1 is causal in T1D based on the protective associations of four rare variants, where the derived alleles are predicted to reduce gene expression or function



	Allele* 1 > 2		Case–control study								
			11	(%)	12	(%)	22	(%)	MAF (%)	OR (95% CI)†	*P* value‡
rs35667974/I923V Exon 14	A > G	T1D	7853	(97.8)	172	(2.1)	3	(0.04)	1.1	0.51	1.3×10^{-14}
		controls	9166	(95.7)	404	(4.2)	4	(0.04)	2.2	(0.43 – 0.61)	
rs35337543/IVS8+1 Intron 8, splice site	G > C	T1D	7945	(98.0)	163	(2.0)	0	(0.0)	1.0	0.68	1.1×10^{-4}
		controls	9330	(97.1)	280	(2.9)	0	(0.0)	1.5	(0.56 – 0.83)	
rs35744605/E627X Exon10	G > T	T1D	8109	(99.1)	76	(0.9)	0	(0.0)	0.46	0.69	9.0×10^{-3}
		controls	9621	(98.7)	131	(1.3)	0	(0.0)	0.67	(0.52 – 0.91)	
rs35732034/IVS14+1 Intron 14, splice site	G > A	T1D	8047	(98.6)	109	(1.3)	2	(0.03)	0.69	0.74	1.2×10^{-2}
		controls	9552	(98.1)	180	(1.9)	1	(0.01)	0.93	(0.59 – 0.94)	

Nejentsev S et al., Science 2009
Downes K et al., PloS One 2011

Perinatal factors



Steele LC et al., Diabetologia 2013

Postnatal risk factors for T1D

- Gut microbiome
- Rapid postnatal growth
- Low vitamin D levels
- Feeding patterns in infancy

Vehik K et al., Diabetes Metab Res Rev 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dietary Intervention in Infancy and Later Signs of Beta-Cell Autoimmunity

230 newborn infants with a first degree relative with T1D

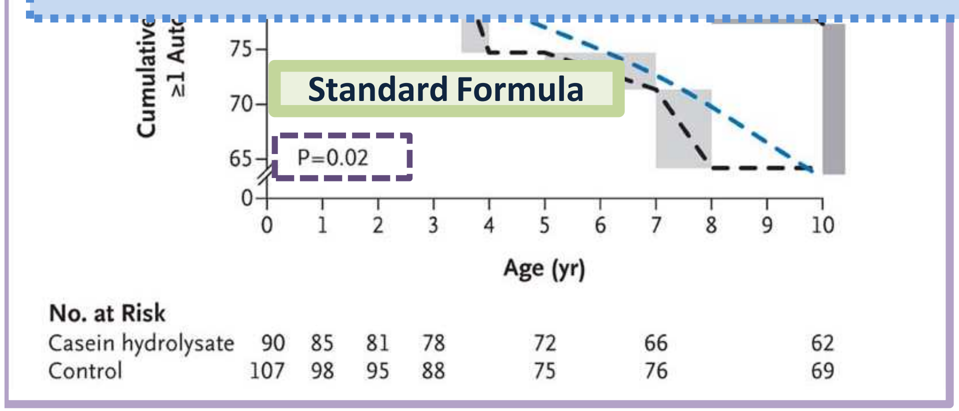
113 were assigned to be weaned to a highly hydrolyzed casein-based formula (Nutramigen)

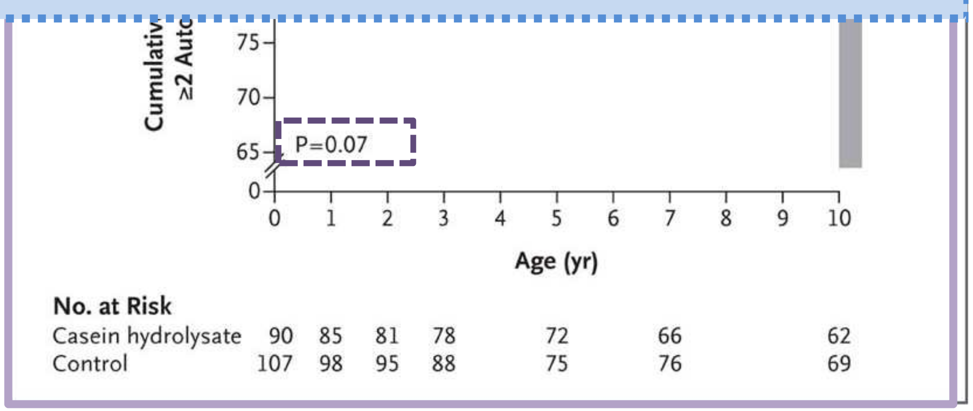
117 were assigned to be weaned to a regular cow's milk based formula

Knip M et al., N Engl J Med 2010

Cumulative incidence of developing one or more T1D autoantibodies

Nutritional intervention during infancy, such as that provided in this study, may be an attractive strategy to reduce T1D risk, since it could be implemented relatively easily as a public health measure.





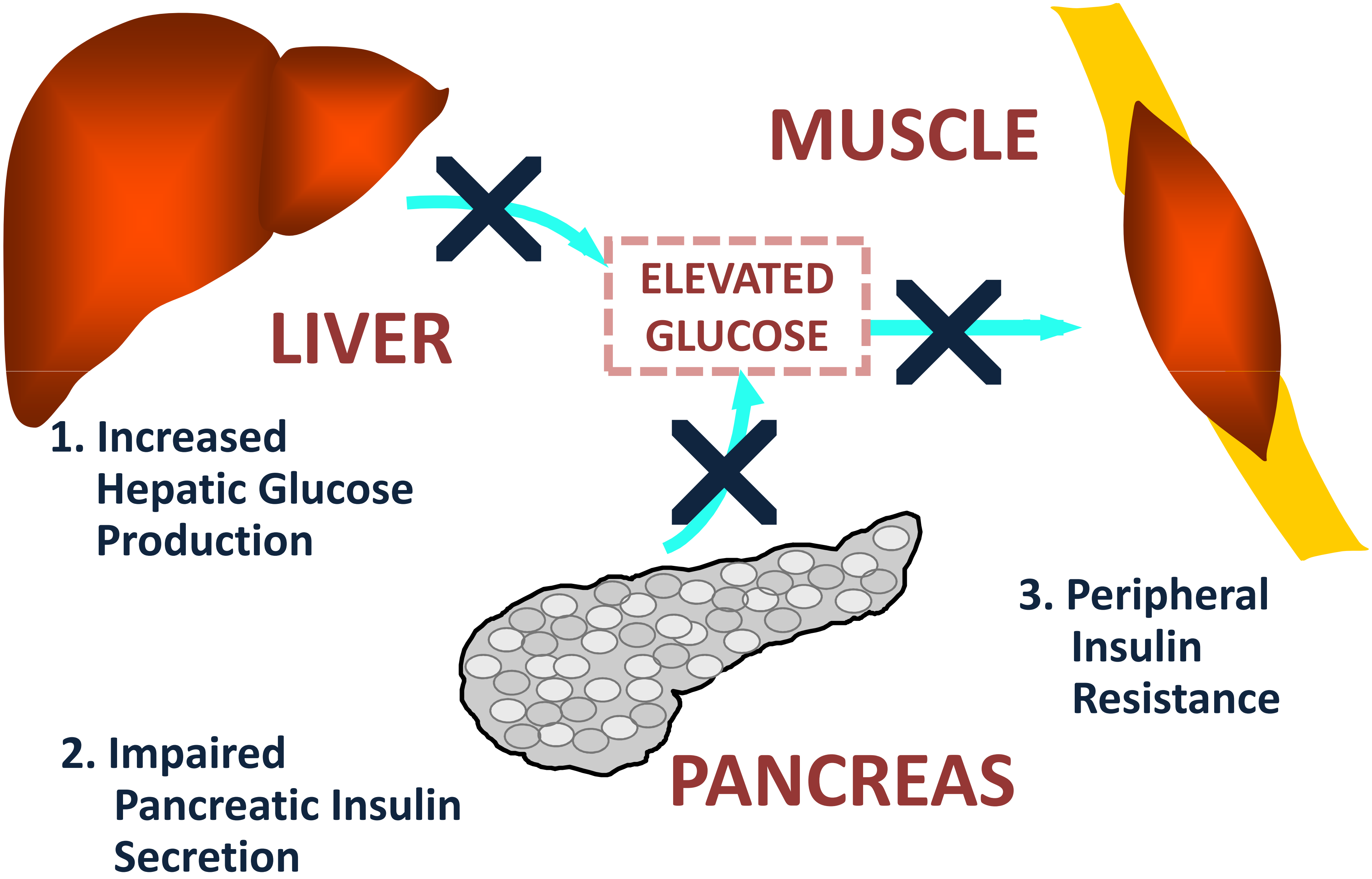
N= 17 (17%) *vs* **N= 33 (30%)**

N= 8 (8%) *vs* **N= 17 (16%)**

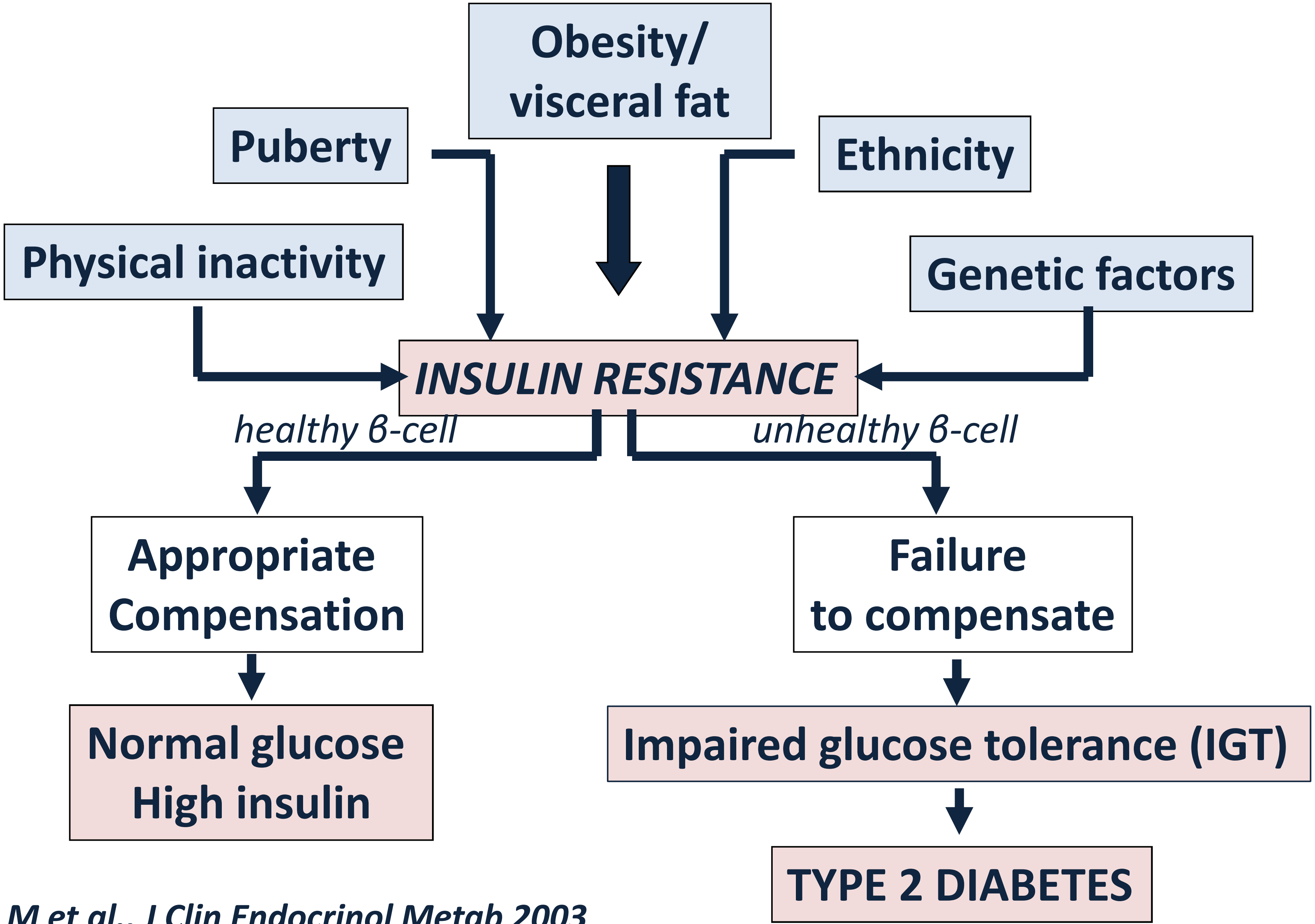
Knip M et al., N Engl J Med 2010

An update on the pathogenesis of Type 2 diabetes

Pathogenesis of Type 2 Diabetes

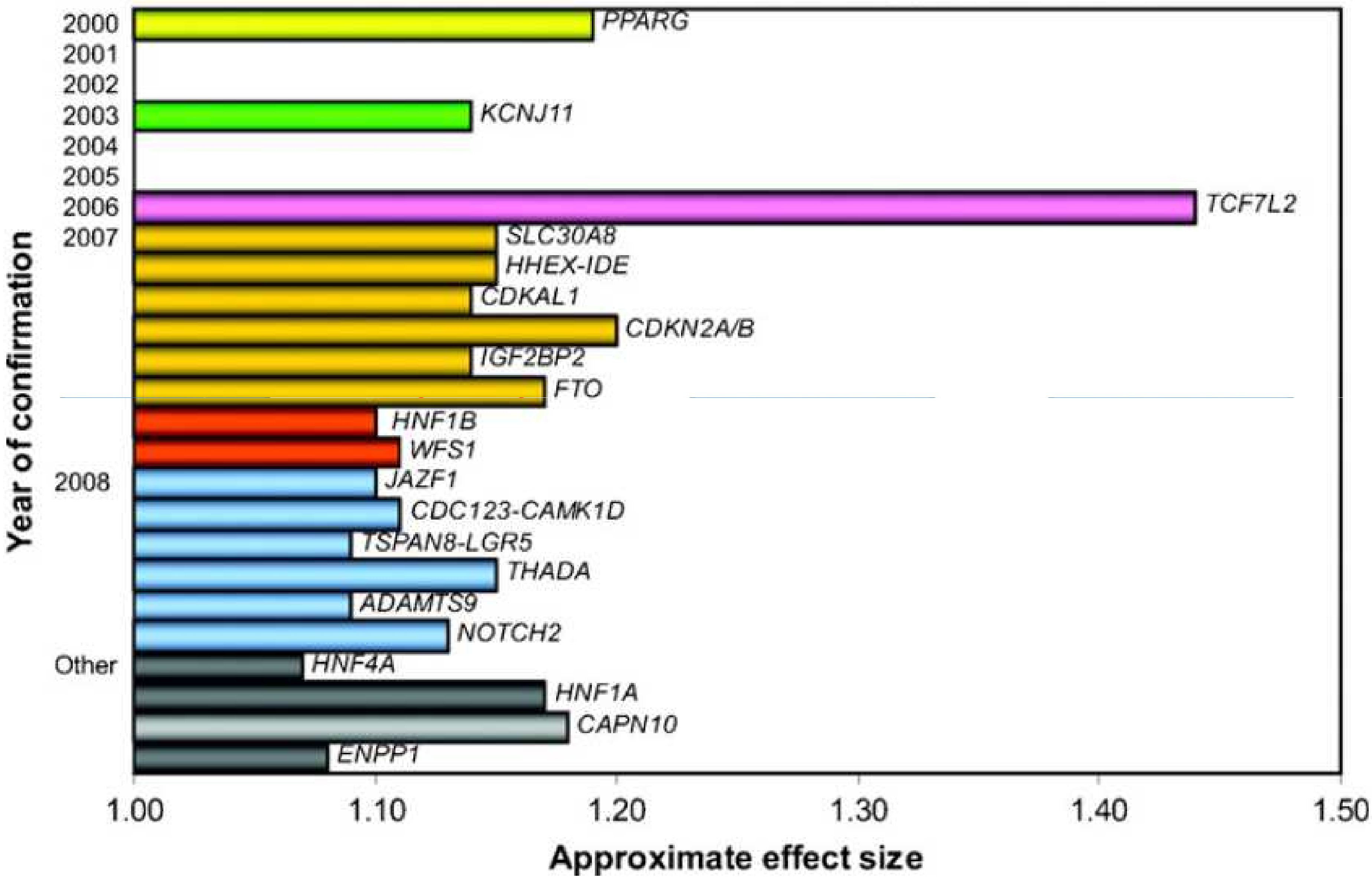


Type 2 diabetes mellitus: risk factors



Goran M et al., J Clin Endocrinol Metab 2003

Genetic loci associated with T2D

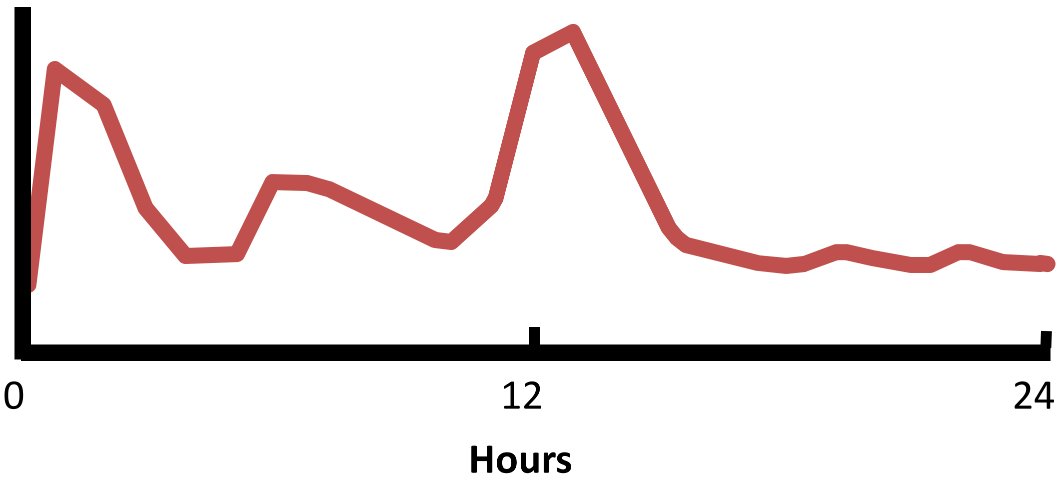


McCarthy MI et al., Diabetes 2008; Florez JC et al., J Clin Endocrinol Metab 2008

An update on T1D treatment

Goals of Intensive Diabetes Therapy

- Maintain near normal glycaemia
- Avoid short-term crisis
- Minimize long-term complications
- Improve the quality of life



The Miracle of Insulin

Patient J.L., December 15, 1922

February 15, 1923

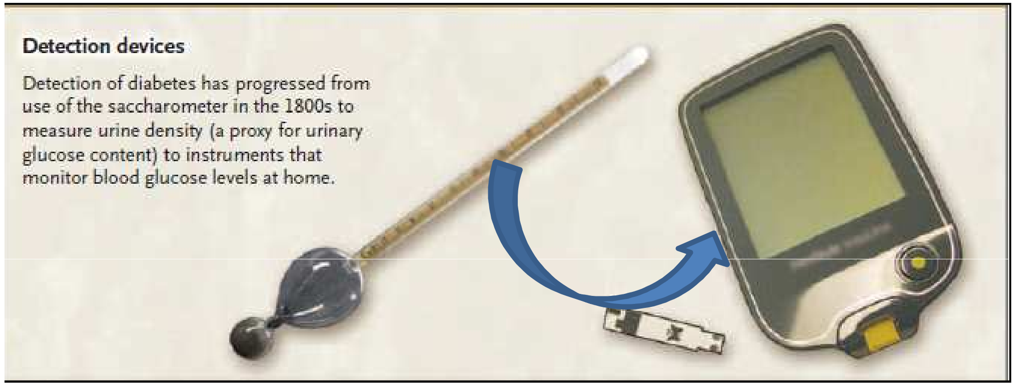
Before insulin was discovered in 1921, everyone with type 1 diabetes died within weeks to years of its onset

The NEW ENGLAND JOURNAL of MEDICINE

200 NEJM ANNIVERSARY ARTICLE

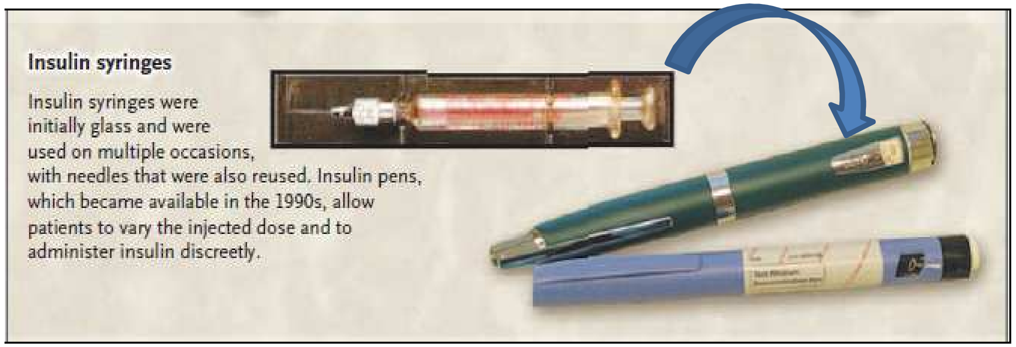
The Past 200 Years in Diabetes

Detection devices



Insulin preparations

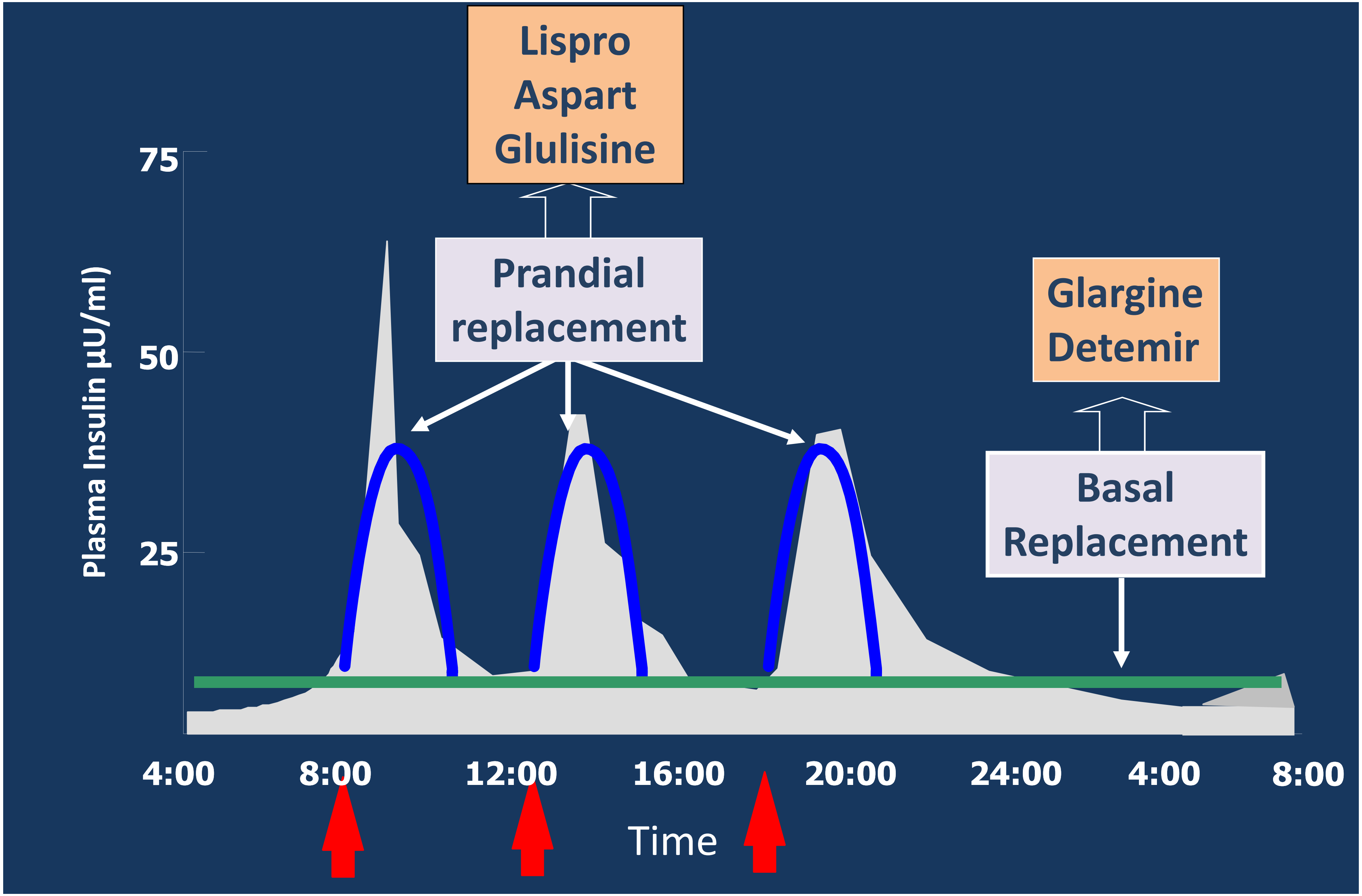
Insulin syringes



Insulin pumps

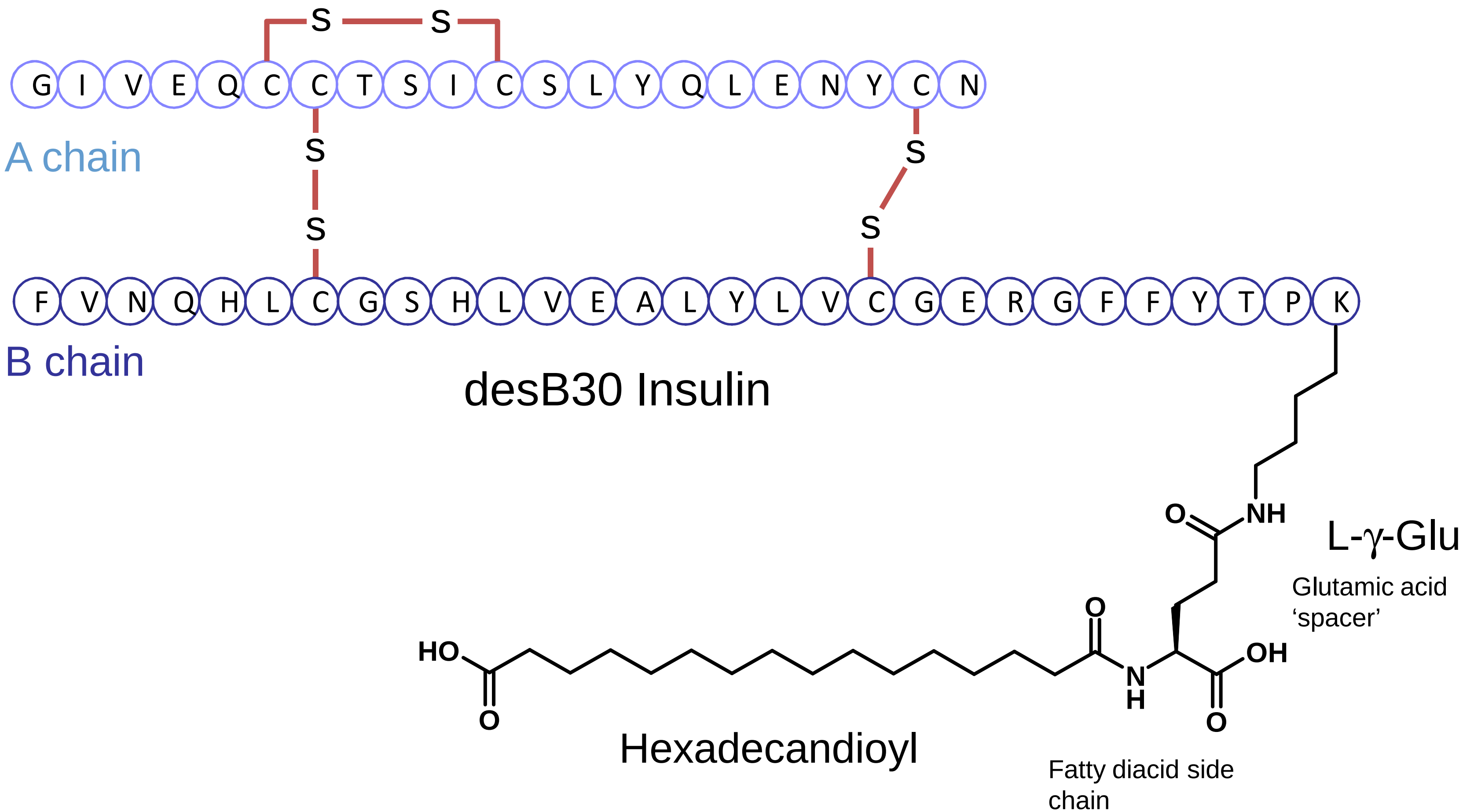
Polomsky KS, N Engl J Med 2012;367:1332-40

Insulin Analogues



Insulin degludec: A new long-acting analog

LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin



Insulin degludec is a new basal insulin that forms soluble multihexamer assemblies after subcutaneous injection, resulting in an ultra-long action profile.
The amino acid sequence is identical to human insulin except for removal of threonine at B30.
At B29, a glutamic acid spacer is attached that bridges to a 16-carbon diacid.

An ultra-long glucose-lowering effect of beyond 40 hours

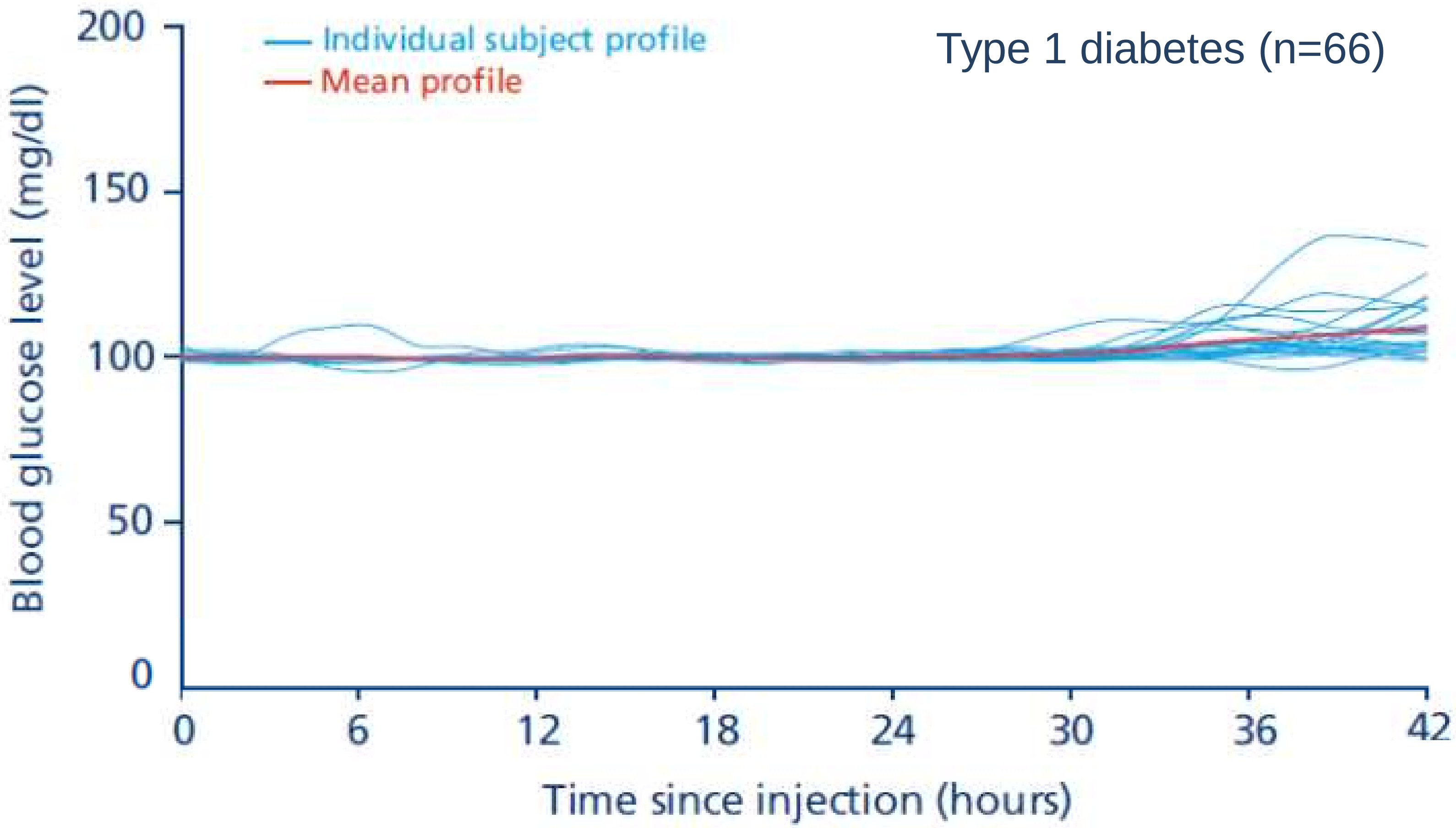
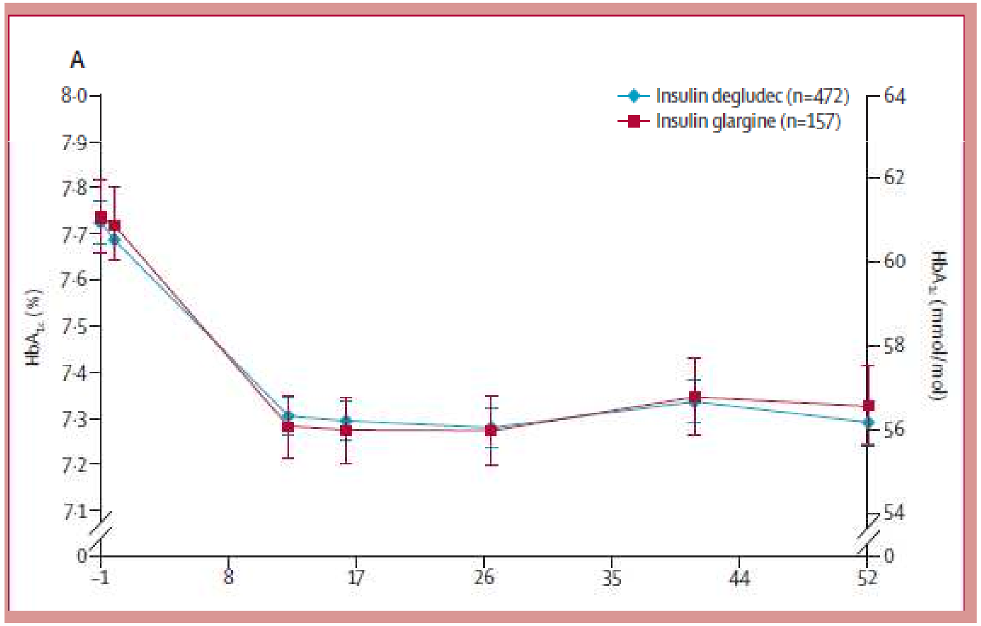


Figure shows mean and individual blood glucose profiles following once-daily s.c. dosing of IDeg (0.6 U/kg) for 8 days

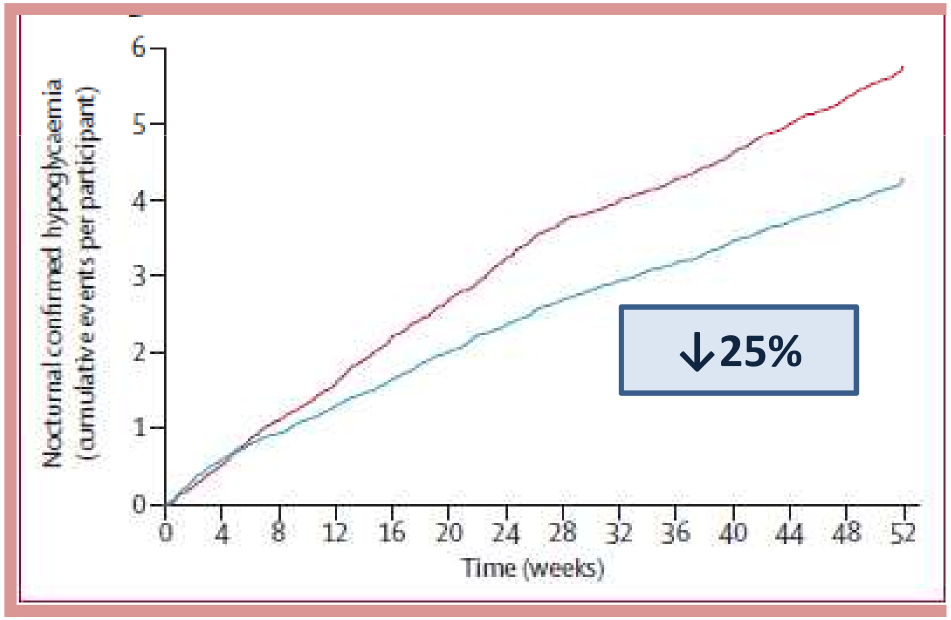
Kurtzhals P et al., Diabetes 2011

Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial

HbA1c



Nocturnal hypoglycaemia



Heller S et al., Lancet 2012

Insulin Degludec in children with Type 1 Diabetes

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Trial Information

A Trial Investigating the Efficacy and Safety of Insulin Degludec in Children and Adolescents With Type 1 Diabetes Mellitus

Official Title: A 26-week, Multinational, Multi-centre, Open-Labelled, Randomised, Parallel, Efficacy and Safety Comparison of Insulin Degludec and Insulin Detemir in Children and Adolescents 1 to Less Than 18 Years With Type 1 Diabetes Mellitus on a Basal-bolus Regimen With Insulin Aspart as Bolus Insulin (BEGIN™: Young 1)

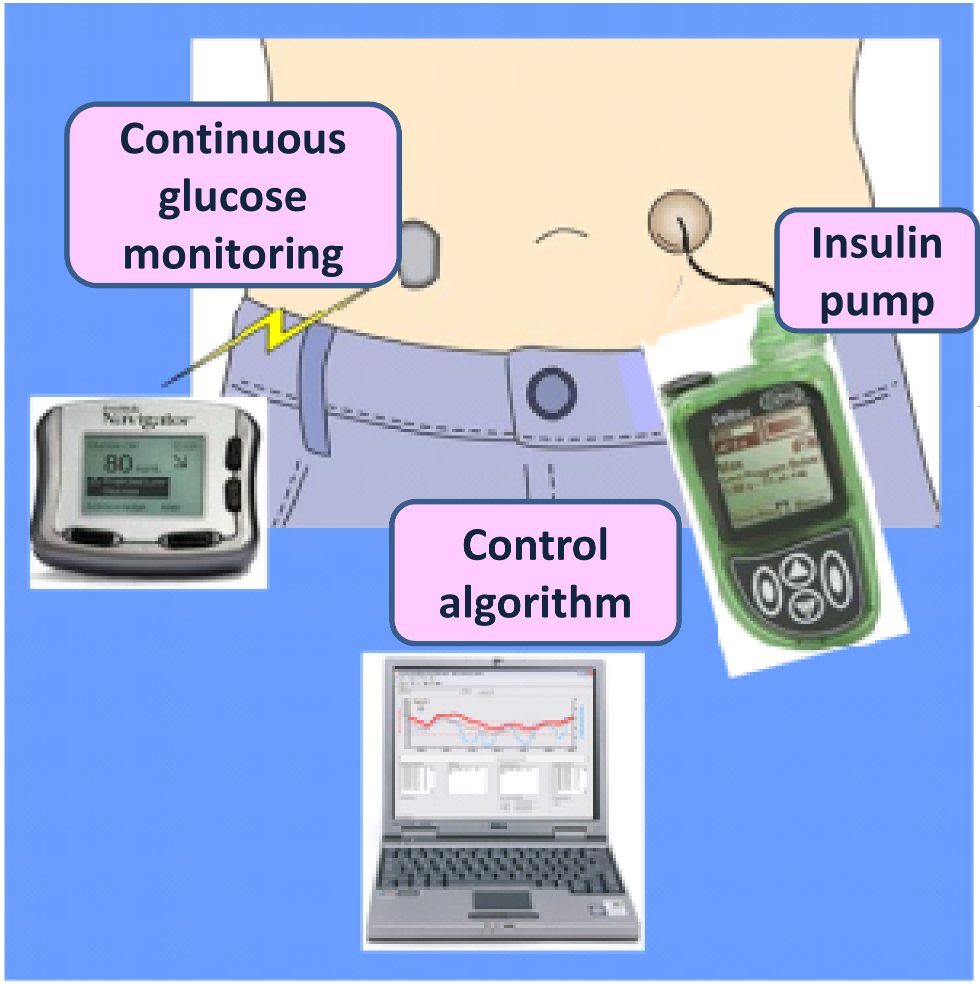
Summary

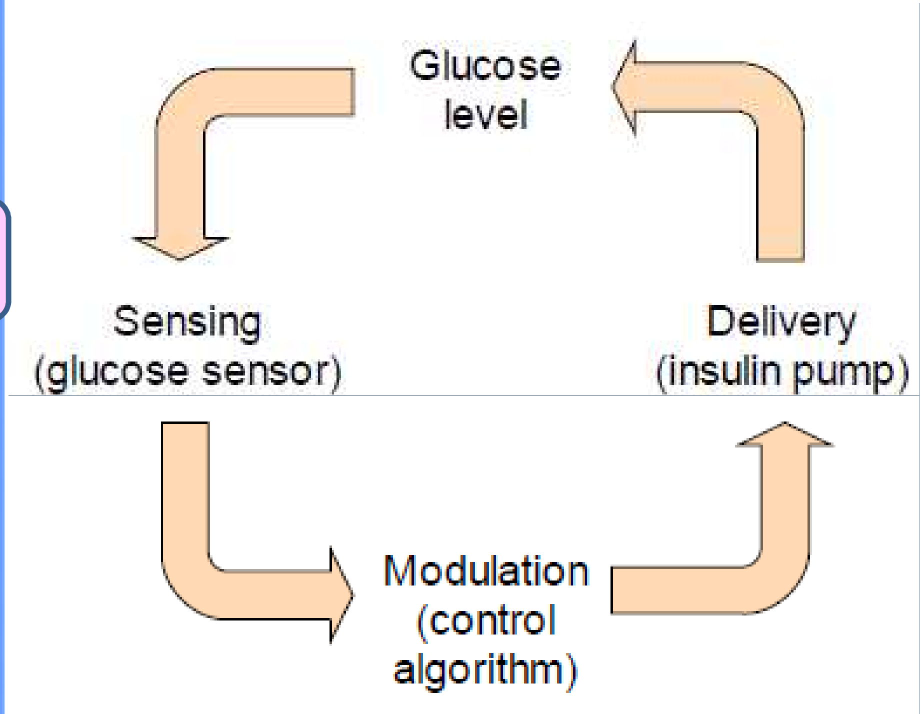
This trial is conducted in Africa, Asia, Europe and the United States of America (USA). The aim of this trial is to investigate the efficacy and safety of insulin degludec in children and adolescents with type 1 diabetes mellitus.

Phase: Phase 3

Sponsor: Novo Nordisk

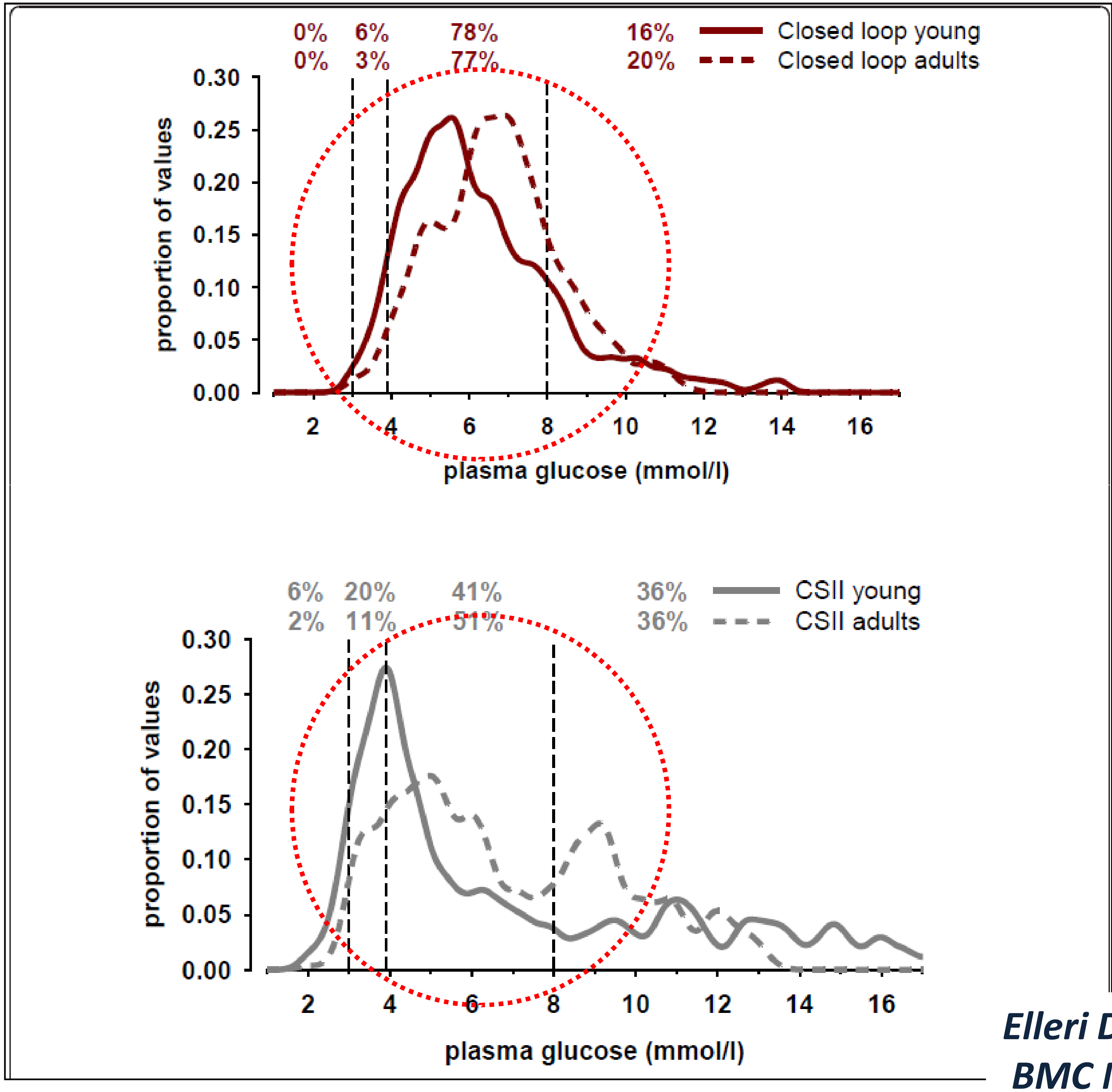
Artificial Pancreas or Closed Loop system





Cobelli C et al., Diabetes 2011

Overnight closed loop



Elleri D et al., BMC Medicine 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

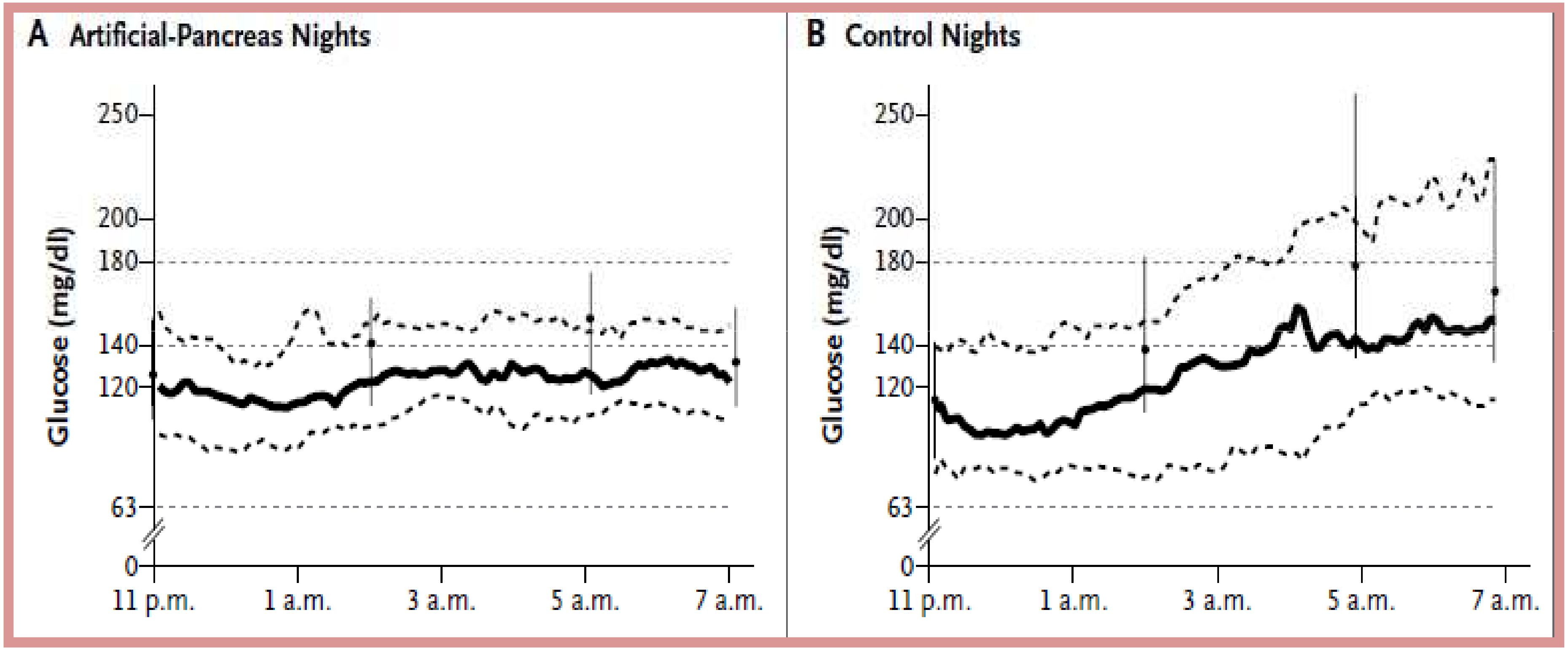
N Engl J Med 2013;368:824-33

Nocturnal Glucose Control with an Artificial Pancreas at a Diabetes Camp

Moshe Phillip, M.D., Tadej Battelino, M.D., Eran Atlas, M.Sc., Olga Kordonouri, M.D., Natasa Bratina, M.D., Shahar Miller, B.Sc., Torben Biester, M.D., Magdalena Avbelj Stefanija, M.D., Ido Muller, B.Sc., Revital Nimri, M.D., and Thomas Danne, M.D.

Variable	Artificial pancreas	Control	p
Total number of episodes of glucose level <63 mg/dl	7	22	0.003
Overnight glucose level (mg/dl)			
Median	126.4	140.4	n.s.
Interquartile range	115.7-139.1	105.7-167.4	

Glucose control in the two study treatments



Night glucose control with MD-Logic artificial pancreas in home setting: a single blind, randomized crossover trial – interim analysis

Table 1. Baseline patient characteristics

	Adults (n = 5)	Adolescents (n = 10)	All (n = 15)
Age (yr)	30.3 ± 11.3	13.3 ± 2.5	19.0 ± 10.4
Body mass index (kg/m^2)	27.1 ± 2.6	20.6 ± 2.7	22.8 ± 4.1
Body mass index	27.1 ± 2.6	0.5 ± 0.9*	—
A1c (%)	7.5 ± 0.5	7.6 ± 0.6	7.5 ± 0.5
A1c (mmol/mol, IFCC)	58.4 ± 5.4	59.1 ± 6.3	58.6 ± 5.9
Diabetes duration (yr)	18.6 ± 11.6	5.2 ± 3.8	9.9 ± 8.2
Pump therapy duration (yr)	10 ± 6.2	3.4 ± 2.7	5.2 ± 4.7
Daily insulin dose (total units)	56.3 ± 27	49 ± 22.2	51.4 ± 23.2
Daily insulin dose (units/kg)	0.7 ± 0.3	0.9 ± 0.3	0.9 ± 0.3

*BMI-SD score.

Table 2. Primary endpoints analysis, N = 15

Variable	Closed-loop*	Control*	p Value
Time glucose level spent below 70 mg/dL (min)	3.8 (0, 11.6)†	48.7 (0.6, 67.9)†	0.0034
Percent of nights in which mean glucose levels were within 90–140 (mg/dl)‡	67.0 (30.0, 88.0)	50.0 (25.0, 75.0)	0.5692

Nimri R et al., Pediatr Diabetes 2013

An update on T2D treatment

T2D: Treatment Strategies

- Aggressive weight management and lifestyle modification
- Diet and exercise first line therapy
- Pharmacological therapy: Oral agents (Metformin) and insulin
- Treat concomitant co-morbities: hypertension, hyperlipidemia

Flint A et al., Diabetes Care 2011

Effect of Metformin in Pediatric Patients With Type 2 Diabetes

Jones KL et al., Diabetes Care 2002

A randomized controlled trial

Variable	Metformin	Placebo	Difference (metformin – placebo)
Baseline mean FPG (mmol/l)	9.0 ± 2.7	10.7 ± 2.7	
Last double-blind visit mean FPG (mmol/l)	7.0 ± 2.2	11.5 ± 4.5	
Adjusted mean* FPG change from baseline (mmol/l)	−2.4 ± 0.5	1.2 ± 0.5	−3.6 ± 0.8
95% CI	−3.5 to −1.3	0.1 to 2.3	5.1 to −2.0
P†			<0.001‡
Baseline mean HbA_{1c} (%)	8.2 ± 1.3	8.9 ± 1.4	
Last double-blind visit mean HbA_{1c} (%)	7.2 ± 1.2	8.9 ± 1.6	
Adjusted mean* HbA_{1c} (%)	7.5 ± 0.2	8.6 ± 0.2	−1.2 ± 0.2
95% CI	(7.2–7.8)	(8.3–9.0)	(−1.6–−0.7)
P§			<0.001

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

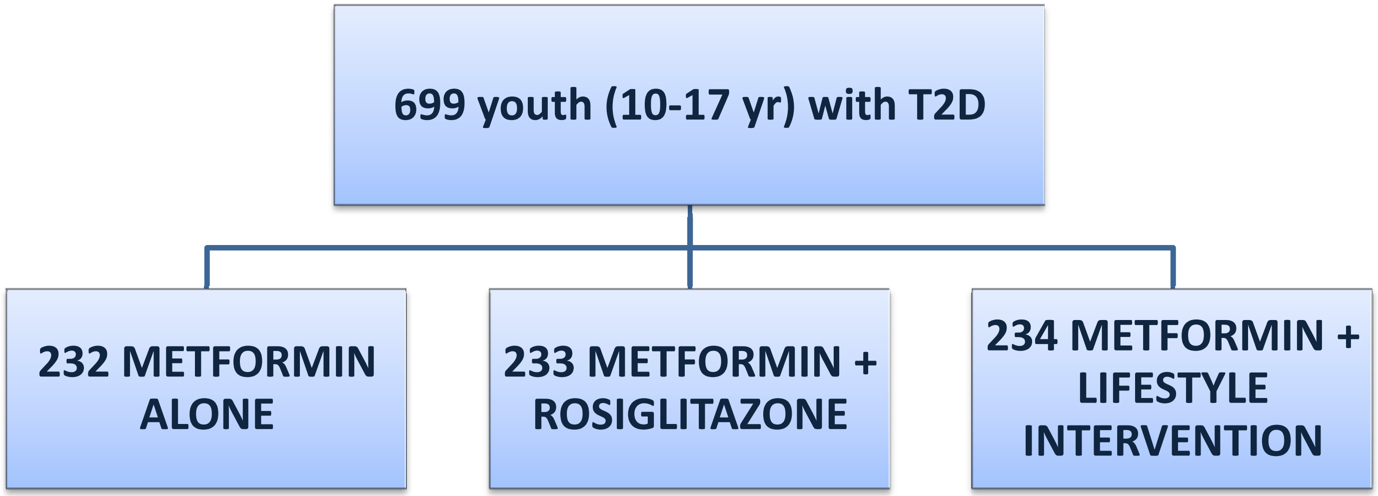
A Clinical Trial to Maintain Glycemic Control in Youth with Type 2 Diabetes

TODAY Study Group*

N Engl J Med 2012

TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth)

TODAY study: a multicenter, randomized clinical trial funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

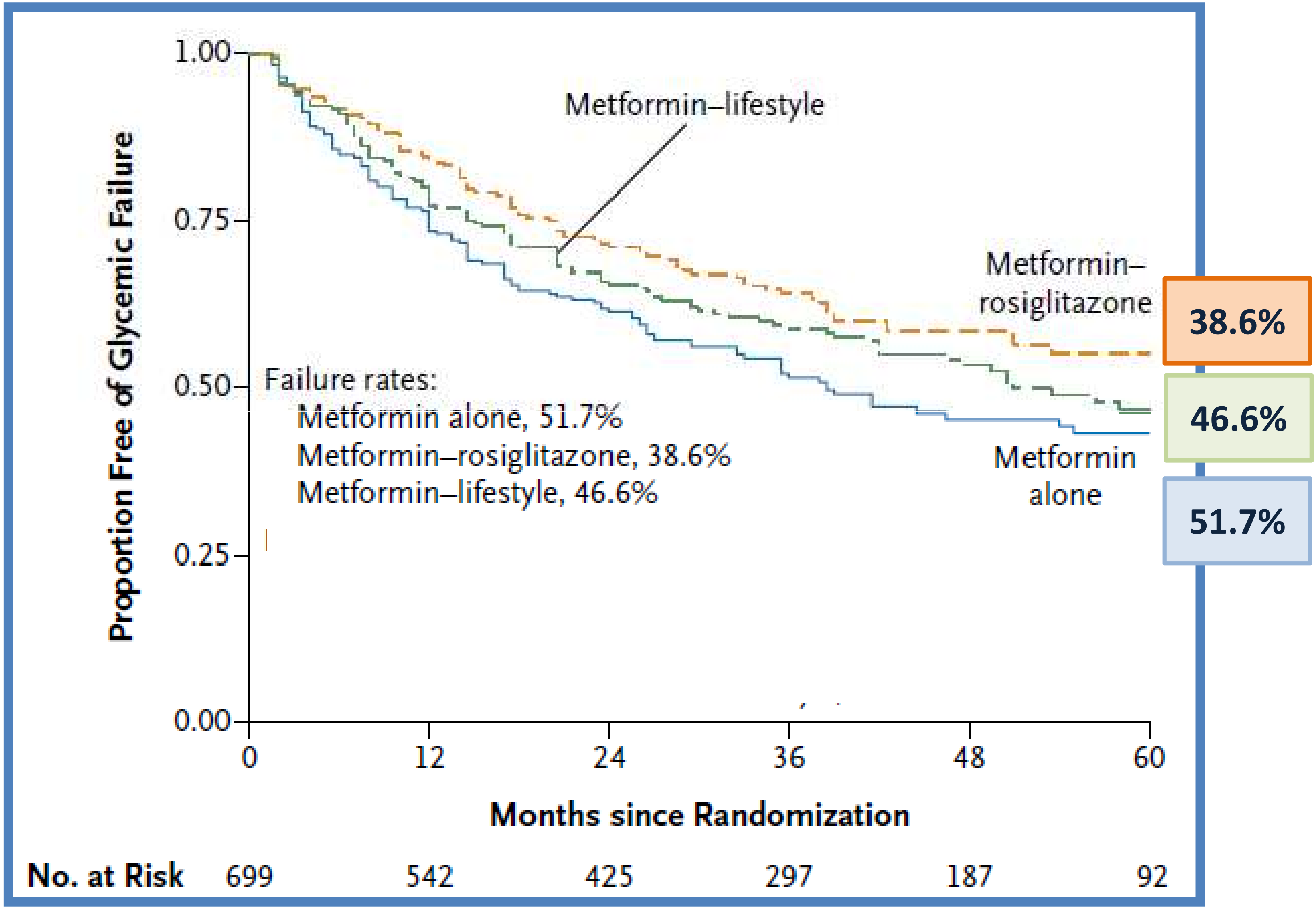


Study aim

To compare the efficacy of three treatment regimens to achieve durable glycemic control in children and adolescents with recent-onset type 2 diabetes.

TODAY Study Group, N Engl J Med 2012

Primary outcome: freedom from glycemic failure



TODAY Study Group, N Engl J Med 2012

Lessons from the TODAY study

Single drug monotherapy with metformin was ineffective in maintaining glycemic control for ~50 % of the cohort within approximately 1 year of treatment

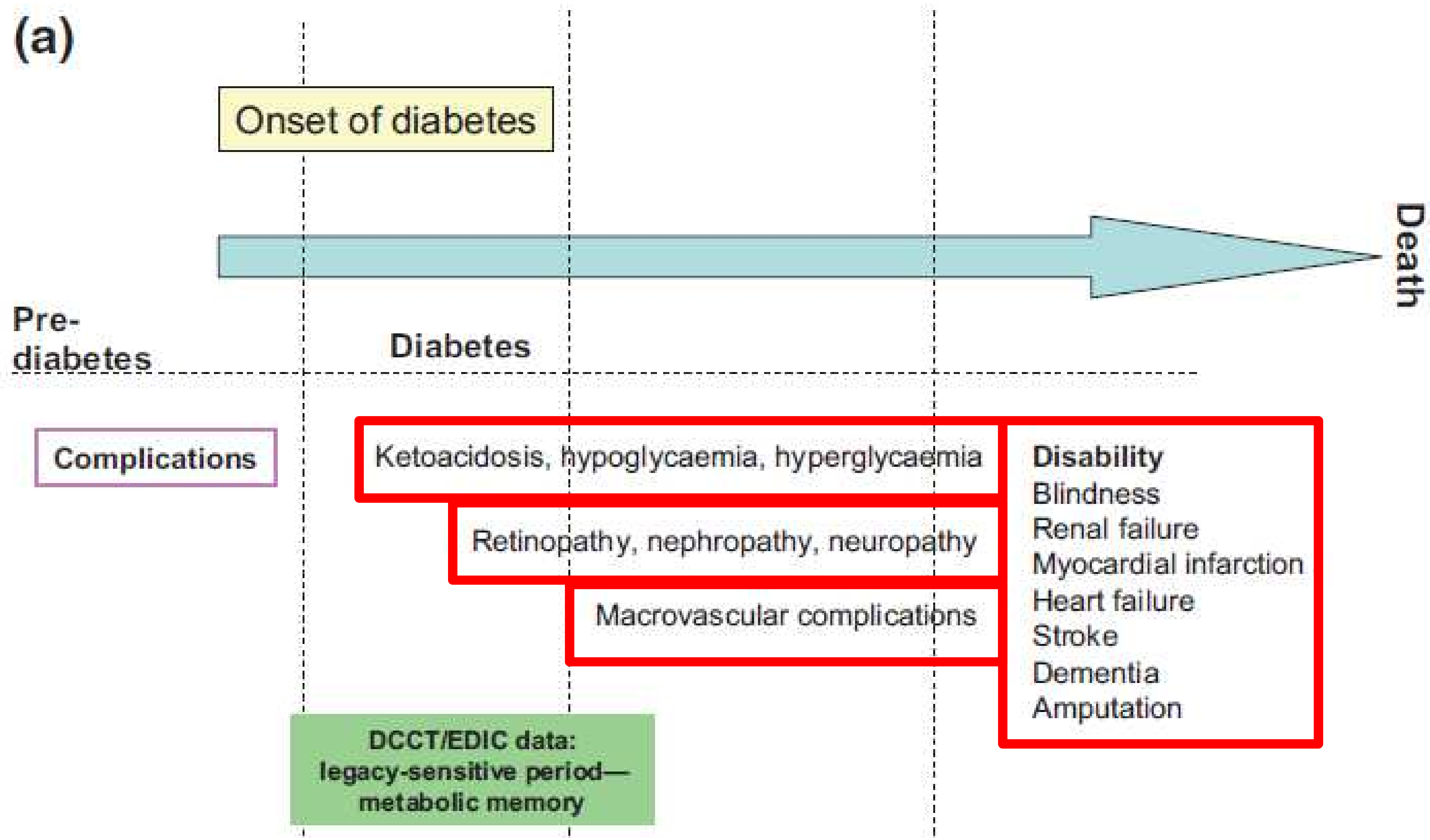
Lifestyle changes are exceedingly difficult to effect in youth with T2D.

Early and aggressive intensification of therapy is essential in many patients.

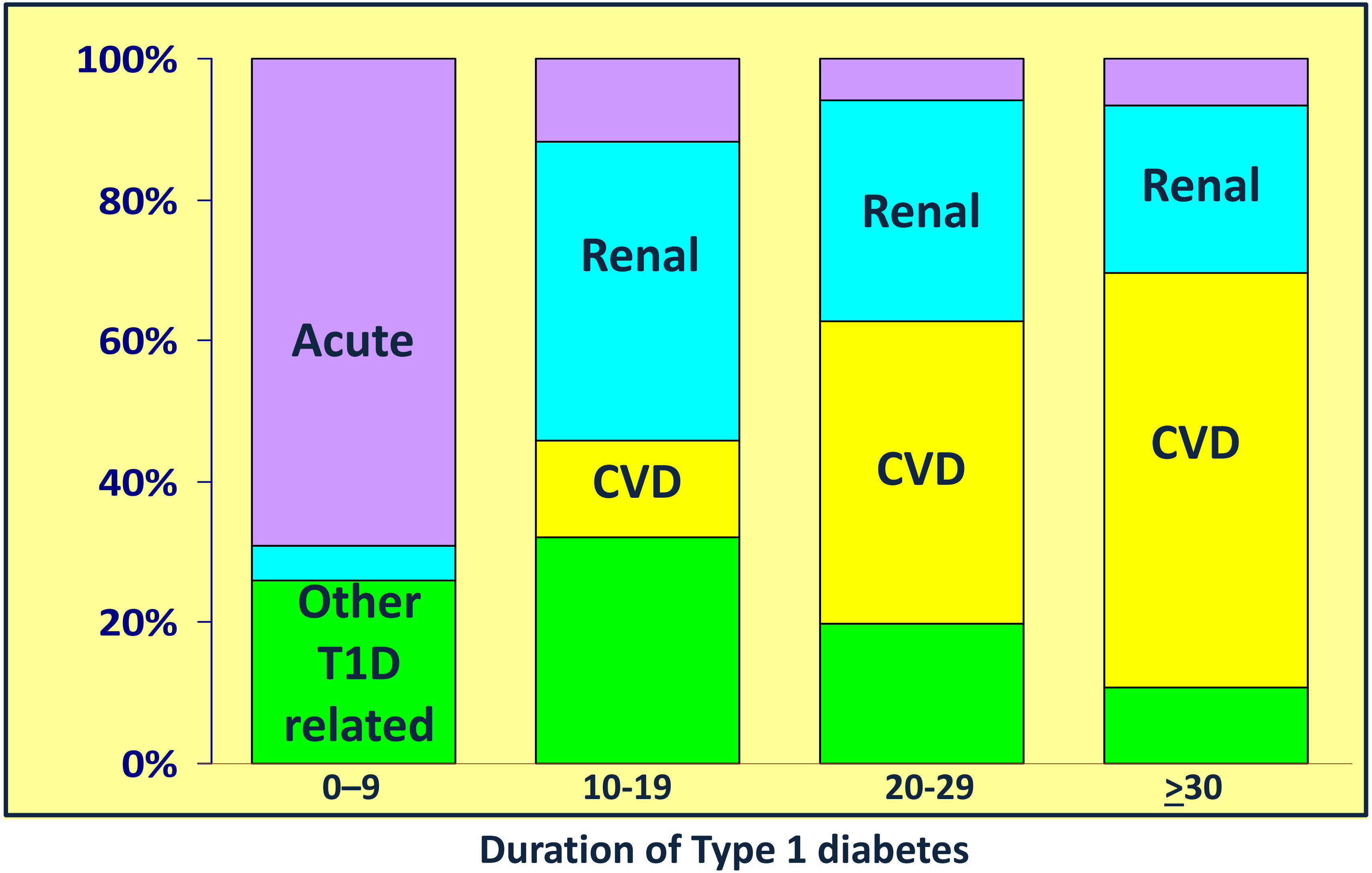
George MM et al., Curr Diab Rep 2013

Diabetes complications

Complicantions



Causes of mortality associated with T1D



Orchard TJ et al., Diabetes 2010

Complications in youth with T2D

	Site or population	Patients (n)	Age of onset (years)*	At presentation	Duration <5 years†	Duration 5–10 years†
Pre-hypertension						
Upchurch et al (2003)[23]	Houston, TX	98	13·6 (SD 2·3) (8·7–18·4)	Systolic, 55% Diastolic, 19%	..	..
Hypertension						
Zdravkovic et al (2004)[22]	Toronto, ON	41	13·5 (SD 2·2) (8·8–17·5)	10%	..	..
Fagot-Campagna et al (1998)[24]	Pima Indians	100	15–19	18%	..	..
Scott et al (1997)[9]	Arkansas	50	13·9 (0·4)	32%	..	..
Hotu et al (2004)[37]	New Zealand	18	15 (11–19)	..	28% (4 years)	..
Upchurch et al (2003)[23]	Houston, TX	98	13·6 (SD 2·3) (8·7–18·4)	Systolic, 49% Diastolic, 17%	..	..
Microalbuminuria						
Fagot-Campagna et al (1998)[24]	Pima Indians	36	15–19	22%	..	60% (10 years
McGrath et al (1999)[25]	Maori	28	19·5 (5–29·5)	14%	..	62%
Hotu et al (2004)[37]	New Zealand	18	15 (11–19)	..	42% (4 years)	..
Ettinger et al (2005)[26]	New York	26	15 (SD 1·9) (11·8–18·1)	..	40%	..
Yokoyama et al (1998)[27]	Japan	426	22·6 (SD 5·6)	..	..	9·6% (6·8 ye
Eppens et al (2006)[30]	Australia	68	13·2 (11·6–15)‡	7%	28% (0·6–3 years)	..
Macroalbuminuria						
Fagot-Campagna et al (1998)[24]	Pima Indians	36	15–19	0	..	17%
Background retinopathy						
Yokoyama et al (1997)[33]	Japan	91/1065	..	9·3%	..	..
Okudaira et al (2000)[34]	Japan	322	22·6 (SD 5·6)	..	18·3% (4·4 [SD 6·0] years)	27% (5·7 year

Pinhas-Hamiel O et al., Lancet 2007

Higher complication rate in youth with T2D compared to youth with T1D

	T1D (N 1011)	T2D (N 341)
Age (years)	15.1 ± 3.2	16.5 ± 2.3
BMI z-scores	0.66 ± 0.8	1.8 ± 0.7
Total cholesterol (mmol/L)	4.3 ± 1.0	4.6 ± 1.0
LDL-C (mmol/L)	2.9 ± 2.2	2.8 ± 0.8
HDL-C (mmol/L)	1.5 ± 0.4	1.3 ± 0.3
Triglycerides (mmol/L)	1.3 ± 0.9	2.2 ± 2.2
Renal complications	27 (2.7) Age: 9.9 ± 6.3	30 (8.9) Age: 7.5 ± 5.7
Renal failure	14 (1.4) Age: 9.3 ± 5.5	23 (6.7) Age: 9.1 ± 6.0
Retinopathy	139 (13.8) 7.9 ± 5.8	40 (11.7) 7.4 ± 5.9
Neuropathy	50 (5.0) Age: 9.8 ± 4.9	26 (7.6) Age: 6.5 ± 5.6

Dart AB et al., Diabetes Care 2013

Summary & Conclusions

- Over the last decades there has been an increasing incidence of both T1D and T2D.

- Genetic, molecular and clinical studies have allowed a better understanding of the pathogenesis of T1D and T2D.

- Obesity represents an important 'confounding factor' for the diagnosis of childhood diabetes.

Summary & Conclusions

- Insulin analogues, pump therapy, oral agents have improved the management of childhood diabetes.

- The future?
  - Adjunctive therapies (GLP-1a, DPP-IV)
  - Artificial pancreas
  - Successful transplantations
  - Alternative routes of insulin administration

GRAZIE!