Type 2 Diabetes: A Comprehensive Review for the Practicing Clinician

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MGH/HMS Internal Medicine Course

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Conflict(s) of Interest

Dr. Nathan has no conflicts of interest regarding this presentation.

Learning Objectives

- **To understand the prevalence, complications, modifiable risk factors, and the treatment goals and their rationale for type 2 diabetes.**

- **To recognize the means of preventing diabetes that have been proved in clinical trials.**

- **To understand the strategies and specific medications proved effective in achieving the accepted metabolic goals.**

- **To be able to identify the relative benefits and risks of the commonly used diabetes medications.**

Prevalence of Diabetes in the U.S.

2020 National Diabetes Statistics Report (2016-18 data)		
Prevalence of all diabetes	34.2	million (10.5%)
Type 1	1+	million (0.4%)
Type 2	32	million
Diagnosed	25	million
Undiagnosed	7	million
GDM	>150,000	(~10% of pregnancies)
Prediabetes	88	million (34.5% of $\geq$ 18 yo)

>120,000,000 with diabetes and pre-diabetes

Prevalence of Diabetes in the U.S.

2020 National Diabetes Statistics Report (2016-18 data)

Prevale

Type

Type
Diag
Und

GDM   egnancies)
Predia   of ≥ 18 yo)

- Most common cause of ESRD in adults
- Most common cause of blindness
- Most common cause of amputations
- 2-5 fold increased risk for CVD

Pathogenesis of Type 2 Diabetes

Insulin resistance

Genetics

Obesity — **"Environmental" factors**

Age

Sedentary — **responsible for epidemic**

Prevention methods are largely directed at reversing the identified risk factors
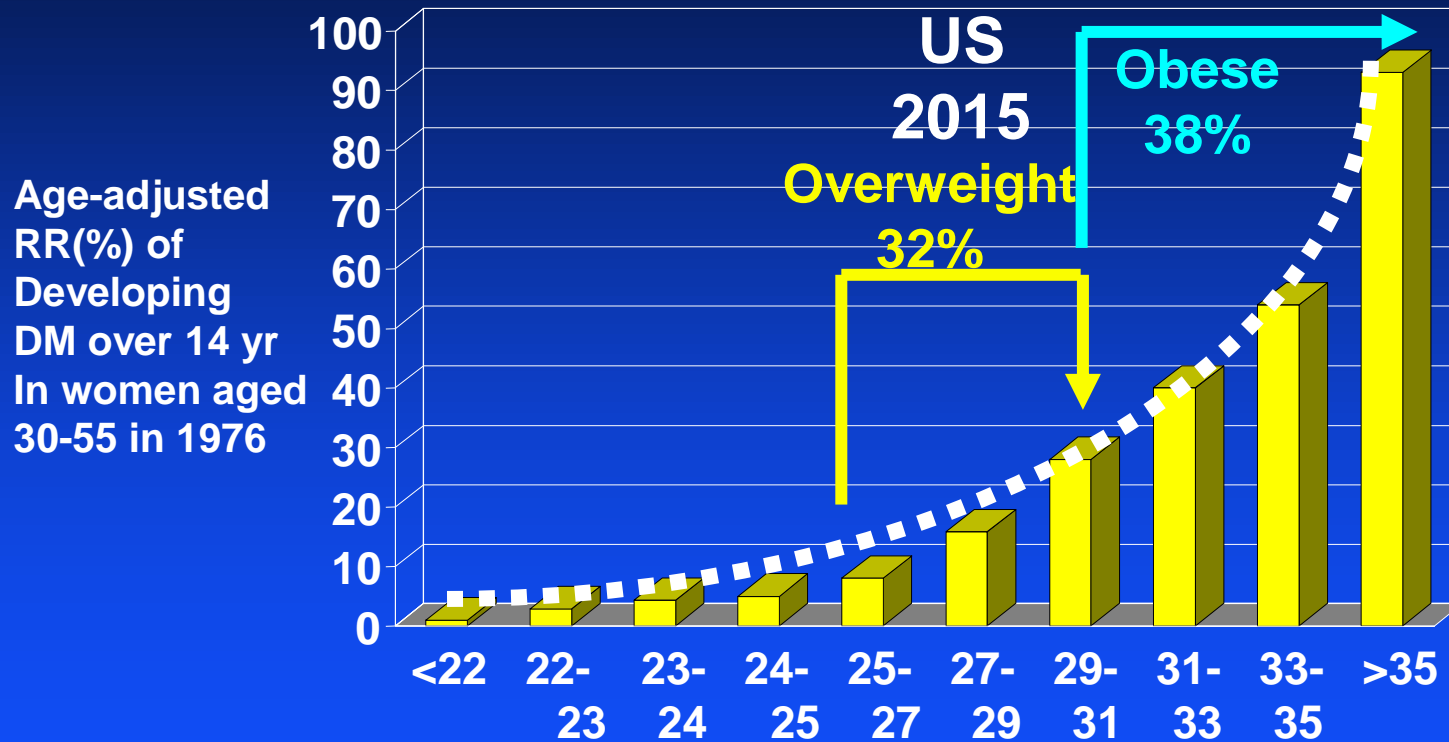
Decreased insulin secretion

Genes, fetal environment

Fasting Hyperglycemia

Type 2 Diabetes

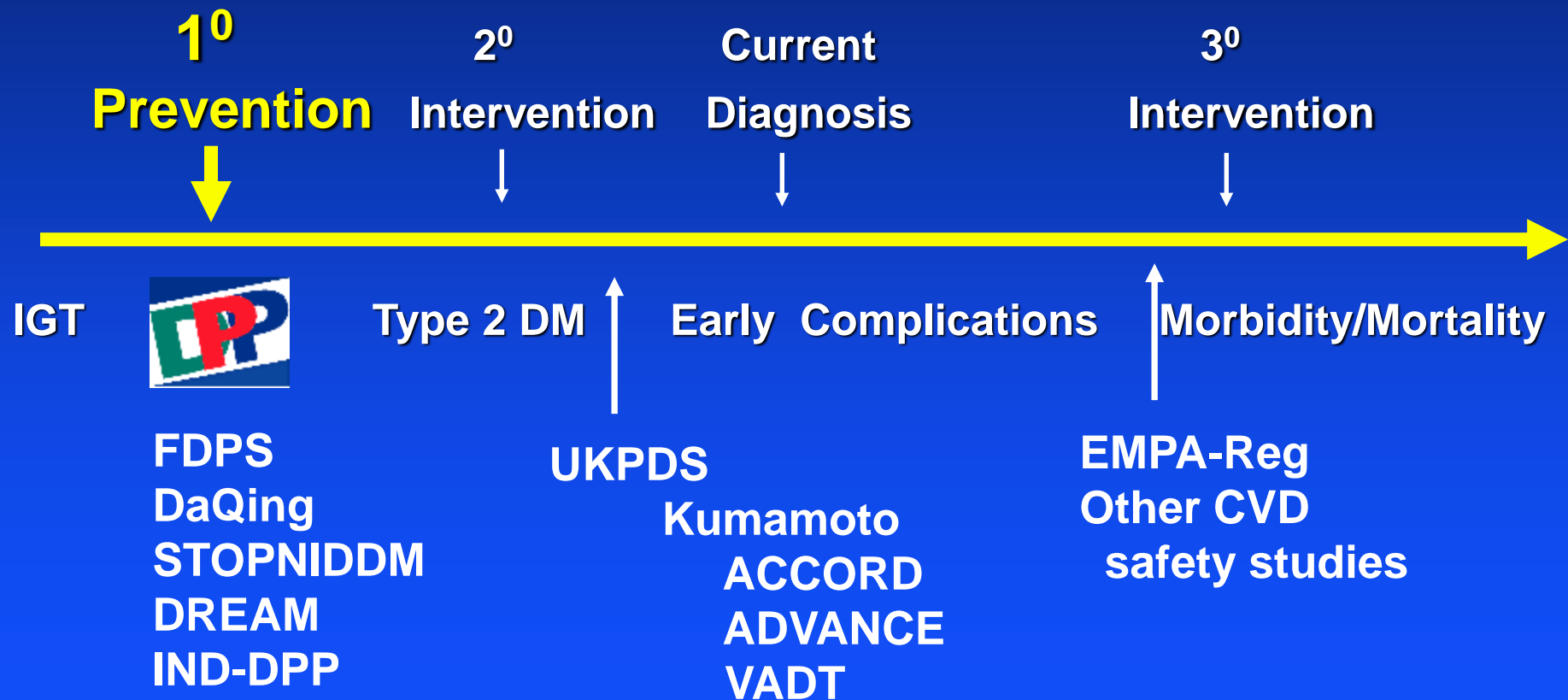# Risk for Development of Type 2 Diabetes

Effect of BMI in Women

Age-adjusted RR(%) of Developing DM over 14 yr In women aged 30-55 in 1976

US 2015
Overweight 32%
Obese 38%

Attained BMI

NHS. *Ann Int Med* 1995;122:481
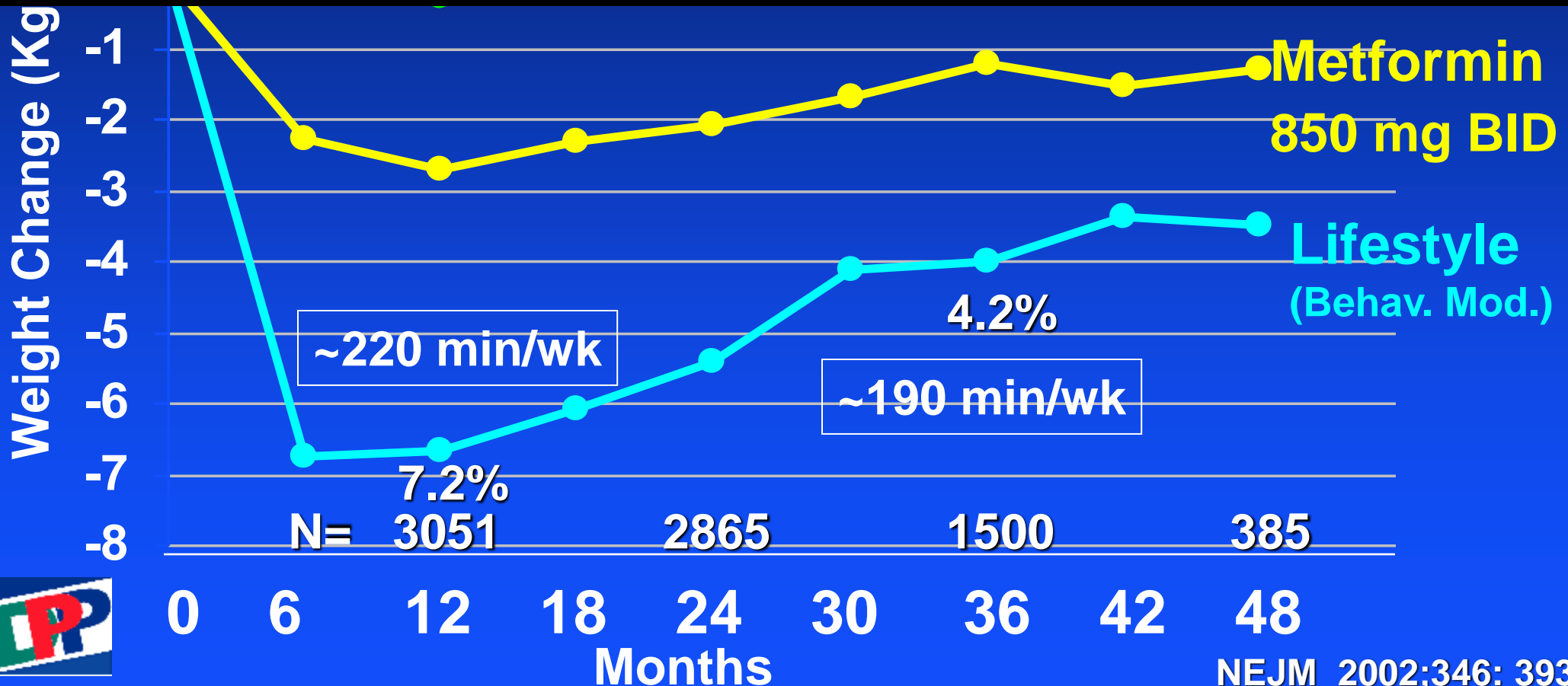
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Beyond Associations

Strong support for a causal role of obesity in type 2 diabetes is derived from bariatric surgery studies in which loss of 35-50% of excess weight ameliorates the majority of diabetes, including remissions in 30-65%, and from preventions studies.

Response to an Epidemic

1^0
Prevention

2^0
Intervention

Current
Diagnosis

3^0
Intervention

IGT

Type 2 DM

Early Complications

Morbidity/Mortality

FDPS
DaQing
STOPNIDDM
DREAM
IND-DPP

UKPDS
Kumamoto
ACCORD
ADVANCE
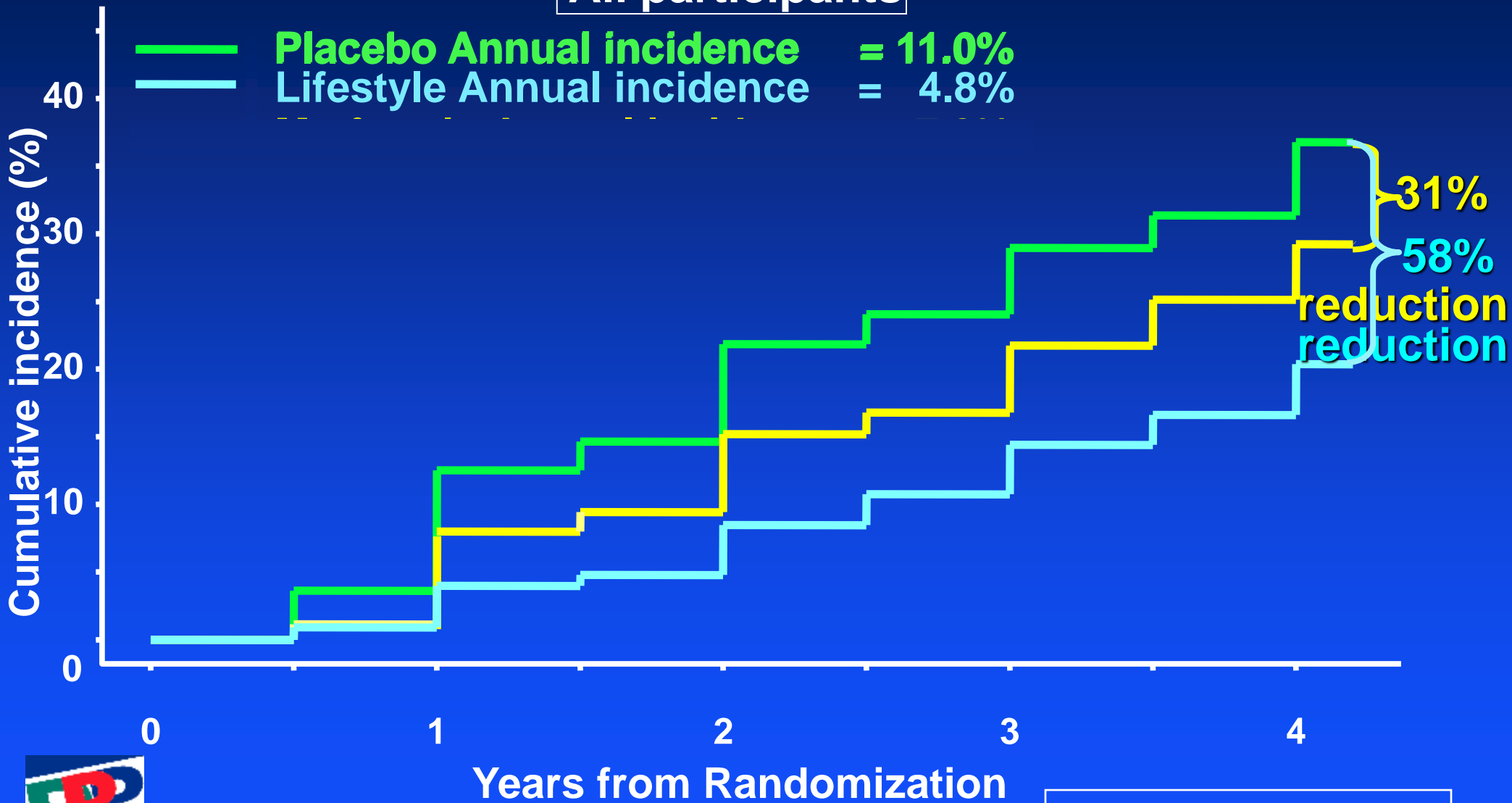VADT

EMPA-Reg
Other CVD
 safety studies

Mean Weight Change from Baseline

DPP tested a behavioral lifestyle intervention that achieved a 7% weight loss (~15 lb) or metformin to prevent diabetes in a high risk population with pre-diabetes
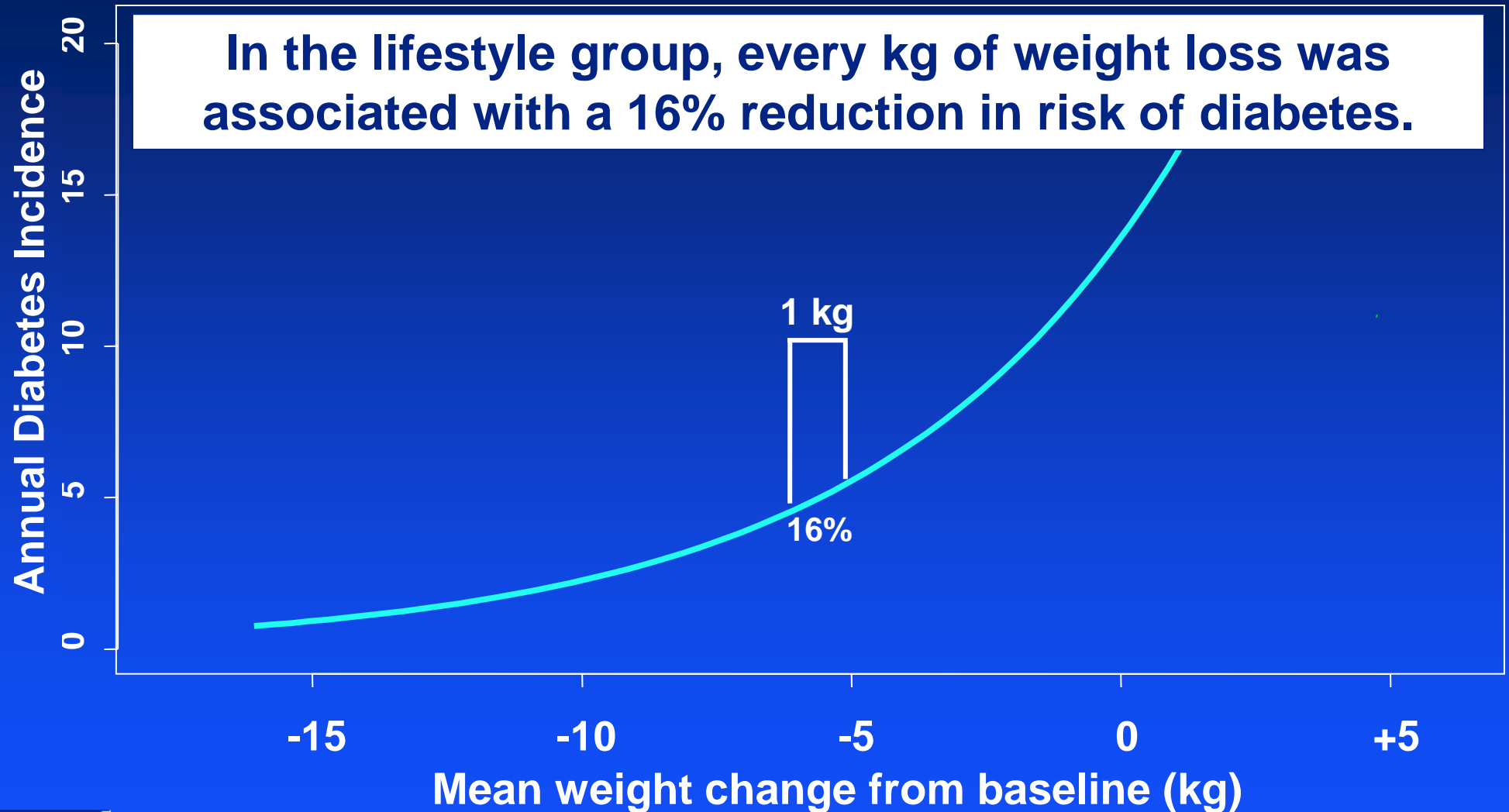
Weight Change (Kg)

-1
-2
-3
-4
-5
-6
-7
-8

Metformin
850 mg BID

Lifestyle
(Behav. Mod.)

~220 min/wk

~190 min/wk

4.2%

7.2%

N=   3051   2865   1500   385

0   6   12   18   24   30   36   42   48

Months

Percent Developing Diabetes

All participants

Placebo Annual incidence = 11.0%
Lifestyle Annual incidence = 4.8%

31% reduction
58% reduction

Cumulative incidence (%)

Years from Randomization

NEJM 2002;346: 393-403

Effect of Weight Loss on Diabetes Prevention

In the lifestyle group, every kg of weight loss was associated with a 16% reduction in risk of diabetes.

Annual Diabetes Incidence

1 kg

16%

Mean weight change from baseline (kg)

Long-term Diabetes Prevention

Risk Reduction Persisted

	After 2.8 y of DPP	After 10 y DPP/DPPOS	After 15 y DPP/DPPOS
ILS v PLBO	58%	34%	27%
MET v PLBO	31%	18%	18%

NEJM 2002;346:393	*Lancet* 2009;374:1677	*Lancet* D&E 2015;3:866

Other Benefits over Time with ILS
(compared with placebo)

- Lower HbA1c with <u>fewer</u> meds
- Lower BP and lipid levels with <u>fewer</u> meds

Response to an Epidemic

1^0

Prevention

2^0

Intervention

Current

Diagnosis

3^0

Intervention

IGT   Type 2 DM   Early Complications   Morbidity/Mortality

**FDPS
DaQing
STOPNIDDM
DREAM
IND-DPP**

**UKPDS
Kumamoto
ACCORD
ADVANCE
VADT**

**EMPA-Reg
LEADER
Other CVD
safety studies**

Pathogenesis of Type 2 Diabetes

G
I
T
Y

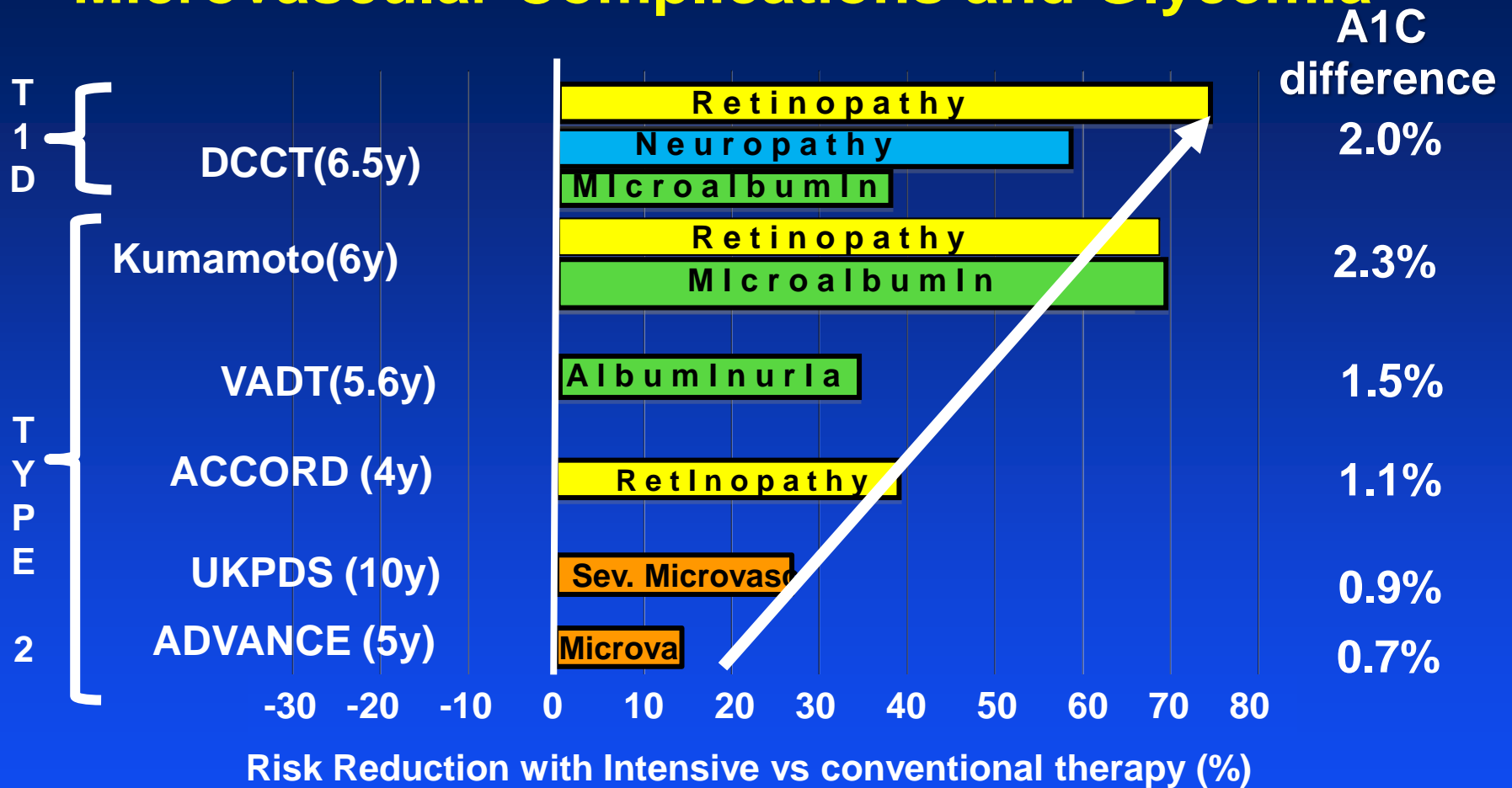→ **Insulin resistance**

Genetics

The current-day care of type 2 DM is largely directed at lowering glucotoxicity, allowing beta-cells to function better and more effectively.
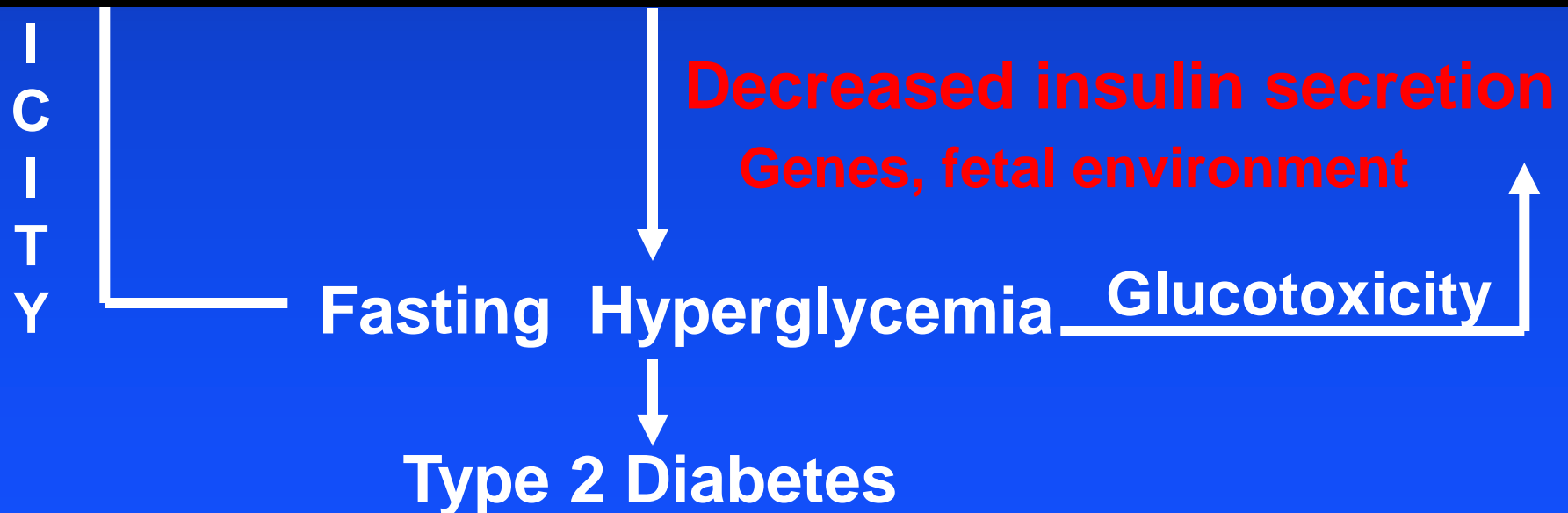
I
C
I
T
Y

Decreased insulin secretion

Genes, fetal environment

Fasting Hyperglycemia — **Glucotoxicity**

Type 2 Diabetes

Setting Metabolic Goals:
Microvascular Complications and Glycemia

Risk Reduction with Intensive vs conventional therapy (%)

Study	A1C difference
T1D — DCCT(6.5y): Retinopathy, Neuropathy, Microalbumin	2.0%
Kumamoto(6y): Retinopathy, Microalbumin	2.3%
VADT(5.6y): Albuminuria	1.5%
ACCORD (4y): Retinopathy	1.1%
UKPDS (10y): Sev. Microvasc	0.9%
ADVANCE (5y): Microva	0.7%

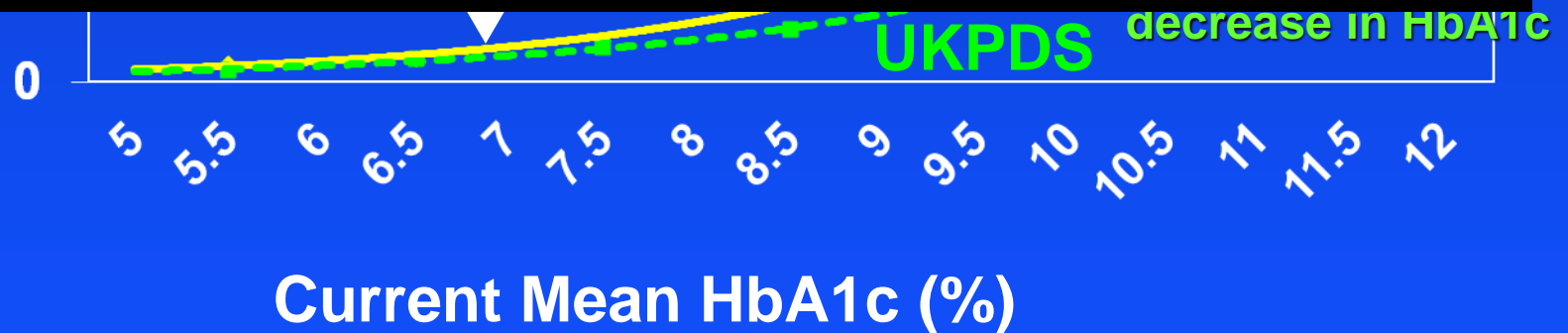x-axis: -30 -20 -10 0 10 20 30 40 50 60 70 80

Setting Metabolic Goals:
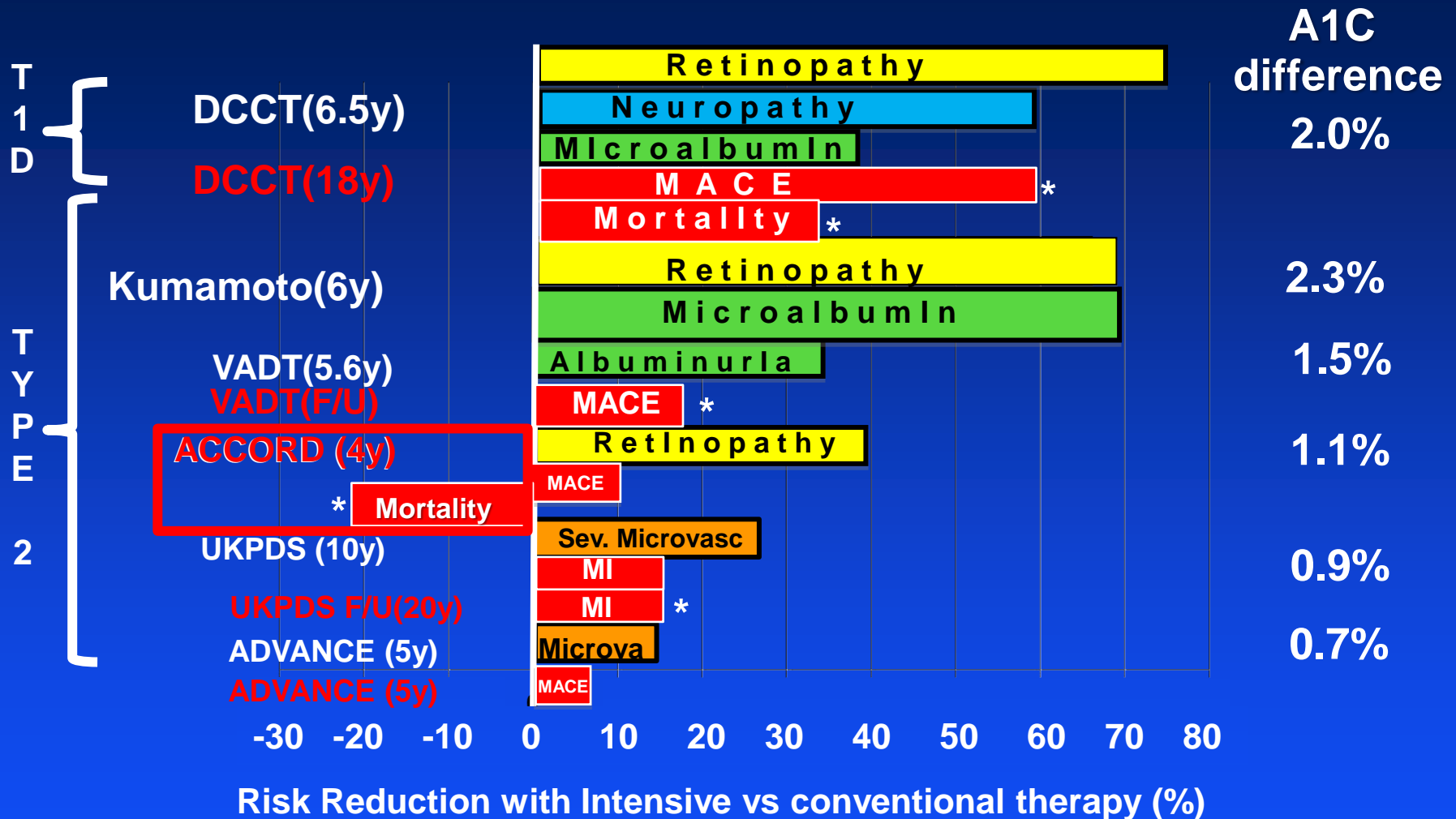## Microvascular Complications and Glycemia

DCCT (Type 1) and UKPDS (Type 2)

**Setting metabolic goals:
Reduction in microvascular complications roughly proportional to A1c reduction.
A1c <7% target set for many, <u>but not all</u>, patients with diabetes.**

Event
Ra...
p...
1000

...sk
decrease in HbA1c

UKPDS

0

5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10 10.5 11 11.5 12

Current Mean HbA1c (%)

Cardiovascular