Diabetes Mellitus 2004: Biomarkers and the Development of New Therapeutics and Diagnostics

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FDA/NIH Joint Symposium

May 13, 2004

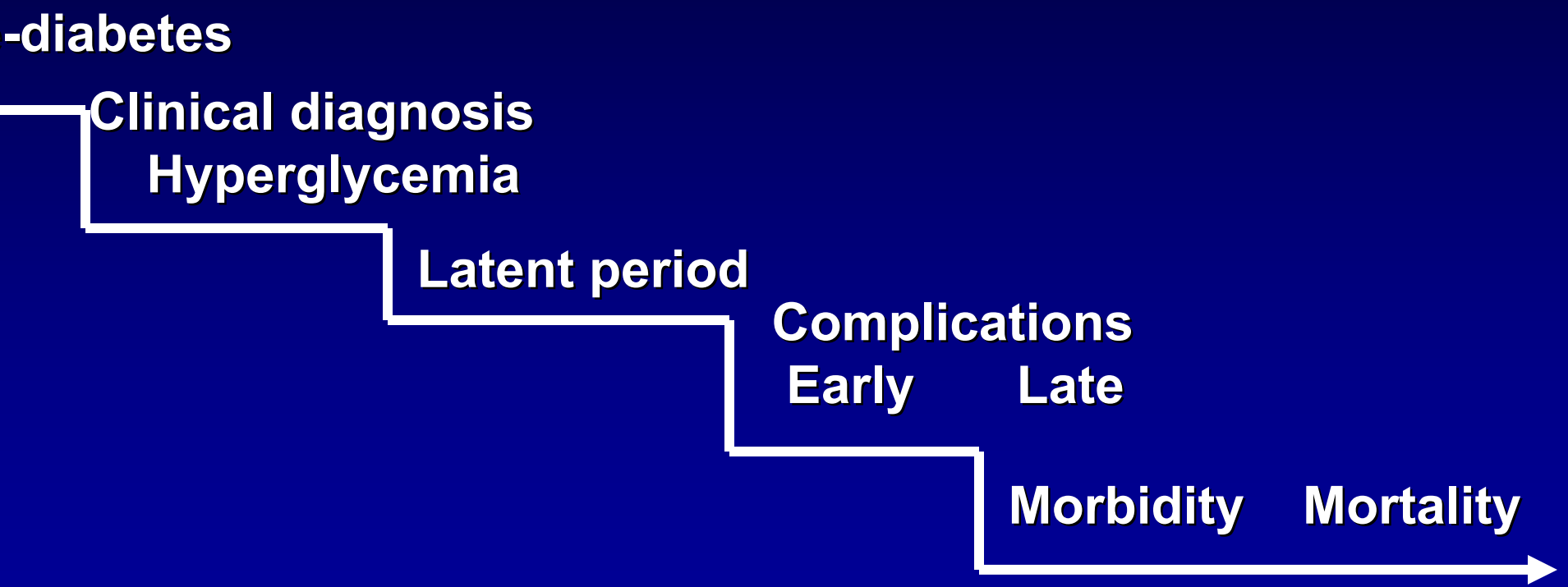
Nosology

- **Diabetes mellitus is a chronic disease characterized by abnormal metabolism of *glucose* (blood sugar) as well as other nutrients such as protein and fat, and accompanied by the risk of long-term complications specific to diabetes that affect the eye, kidney and nervous system.**

World Book Encyclopedia, 2000

Clinical Course of Diabetes

Implications for Development of New Therapies using Surrogate Outcomes



Surrogates and Biomarkers

- surrogate *n* something that serves as a substitute

  Merriam Webster

- biomarker *n*

Biomarkers

- Pubmed lists 276,549 citations with "biomarker" (3283 since 1/1/04)
- Medline lists only 10 citations in 2004 cross-indexed by "biomarker" and "diabetes"
  - Coronary calcification and CVD
  - Inflammatory markers -risk for Type 2
  - Oxidant stress, inflammation
  - Proteomics
  - Periodontal disease and CVD risk
  - Urinary isoprostanes- risk for Type 1

Surrogates and Biomarkers

- surrogate *n* something that serves as a substitute

Merriam Webster

- biomarker *n* a biological process or biochemical indicator that precedes the development of disease and is usually indicative of the future development or progression of the disease. May be used to measure the effects of treatment.

David M. Nathan

Primary Prevention

Clinical Course of Diabetes

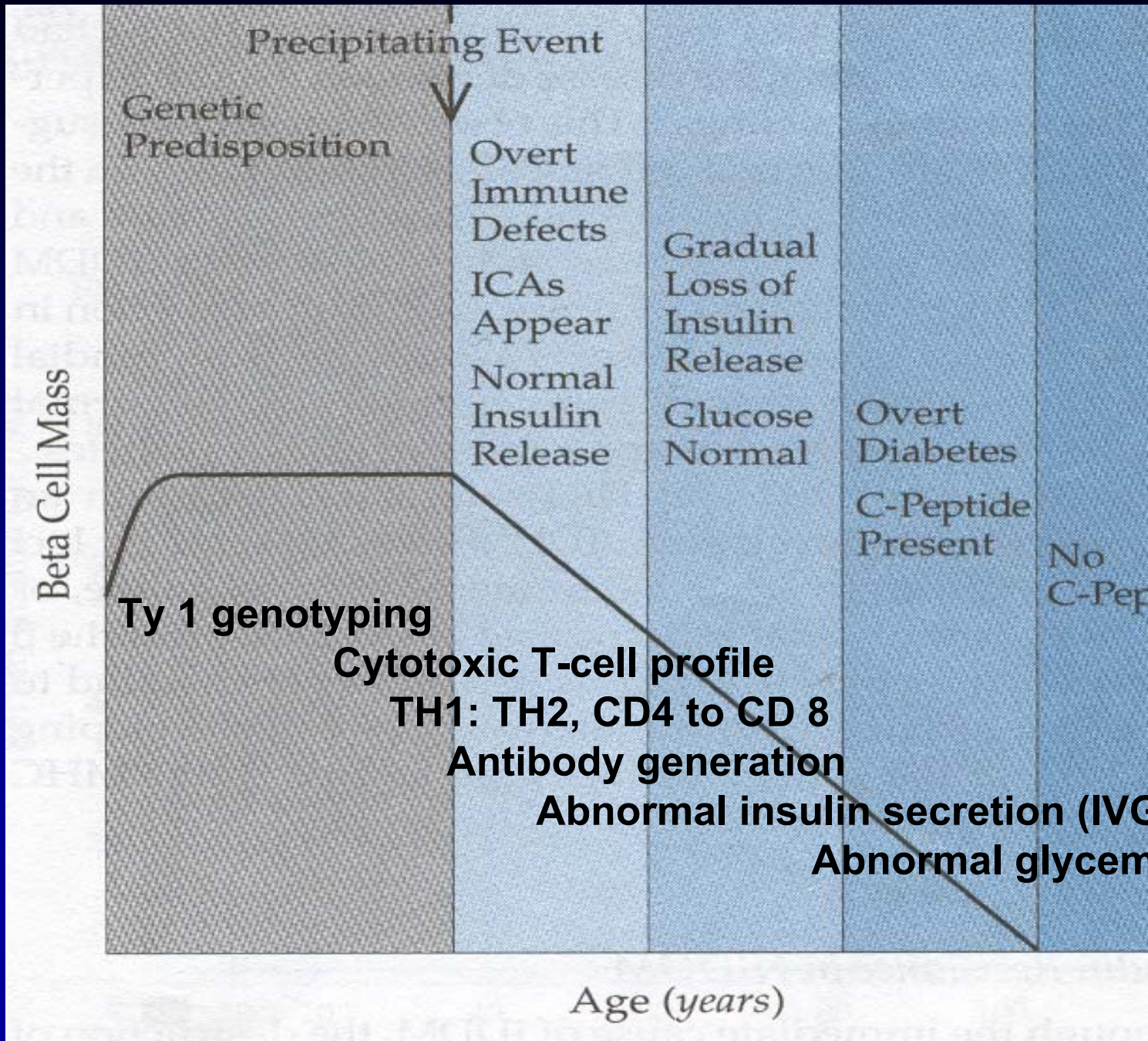
Implications for Development of New Therapies using Surrogate Outcomes

re-diabetes | Clinical diagnosis Hyperglycemia | Latent period | Complications Early | Complications Late | Morbidity | Mortality

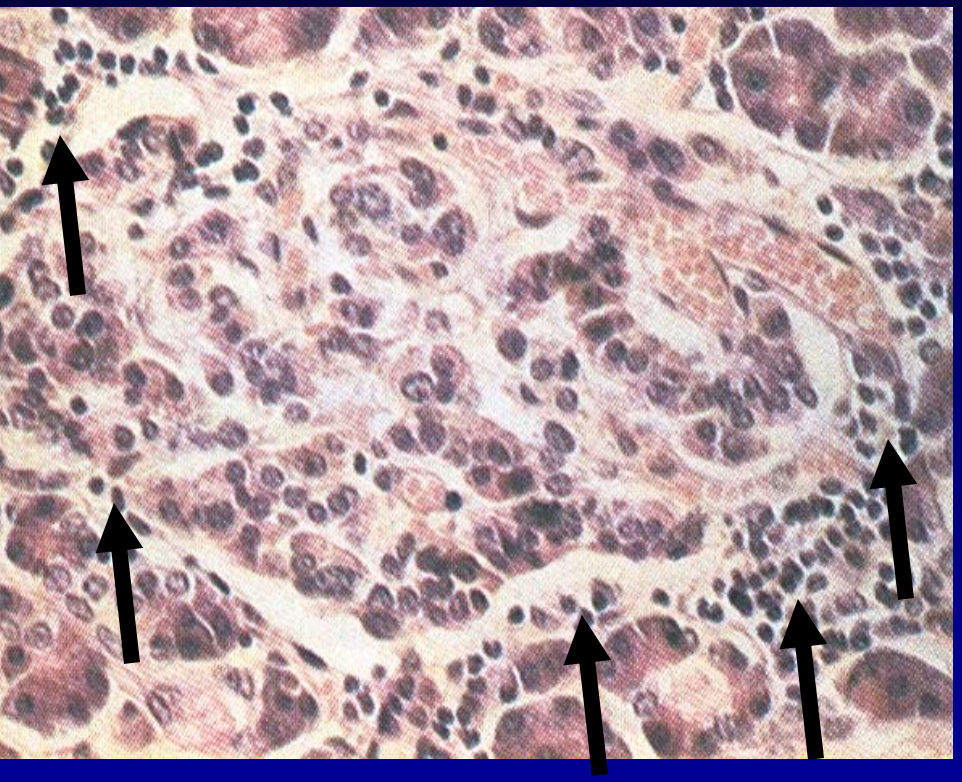
rimary
prevention

DPT 1
DPP

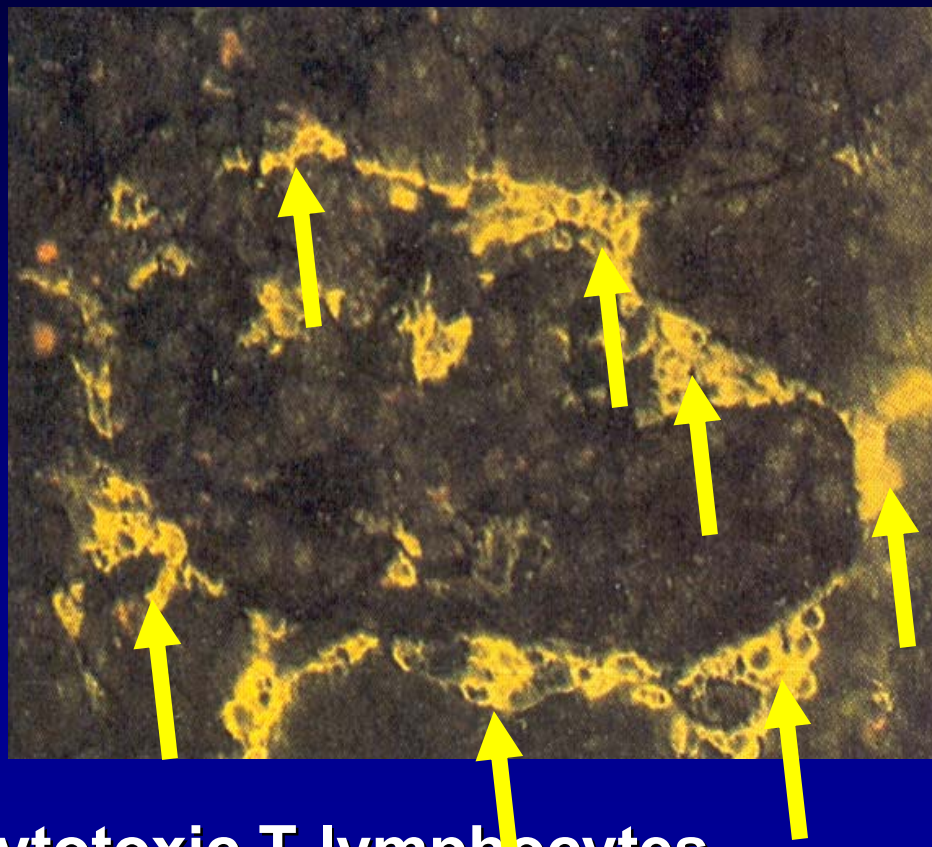
Course of utoimmune Type 1 Diabetes



Islet in New Onset Type 1 Diabetes



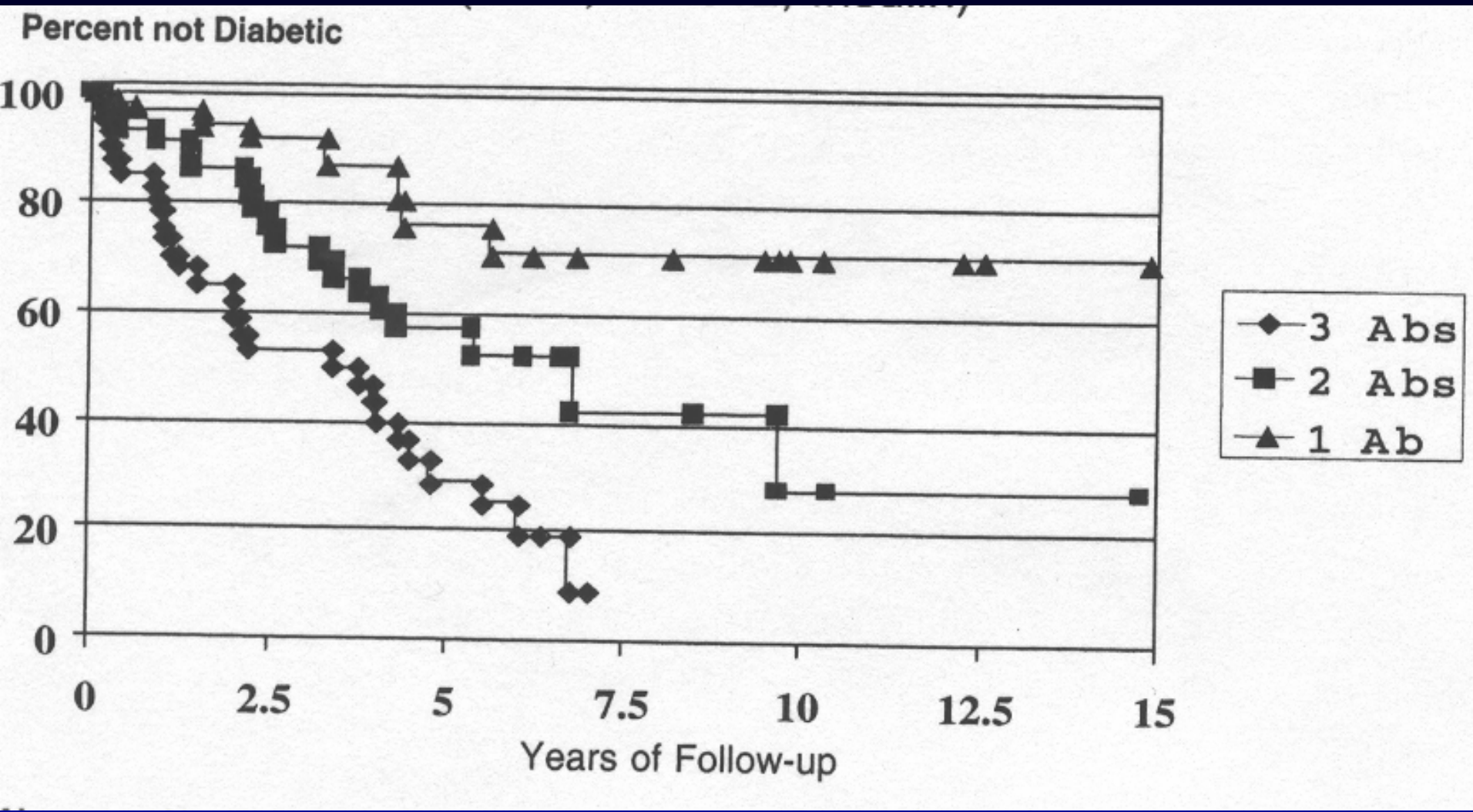
H & E



Cytotoxic T-lymphocytes

Bottazzo NEJM 1985;313:353

utoantibodies and the Development of Type 1 Diabetes



From Eisenbarth

Prevention of Type 1 Diabetes

DPT 1

- Outcome was hyperglycemia- detected most often with OGTT
- Able to predict development of diabetes with a high degree of accuracy
- Could other outcomes earlier in the course of diabetes development be employed as an (the) outcome in prevention studies?

Prevention of Type 1 Diabetes

Use of Biomarkers

- Several studies have used biomarkers, e.g. c-peptide secretion; most have considered these not reliable enough
- Further refinements in biomarkers may result in alternative outcomes in prevention studies

  "…understanding the course of development of diabetes may refine predictive markers, facilitating the design of future intervention studies" DPT 1

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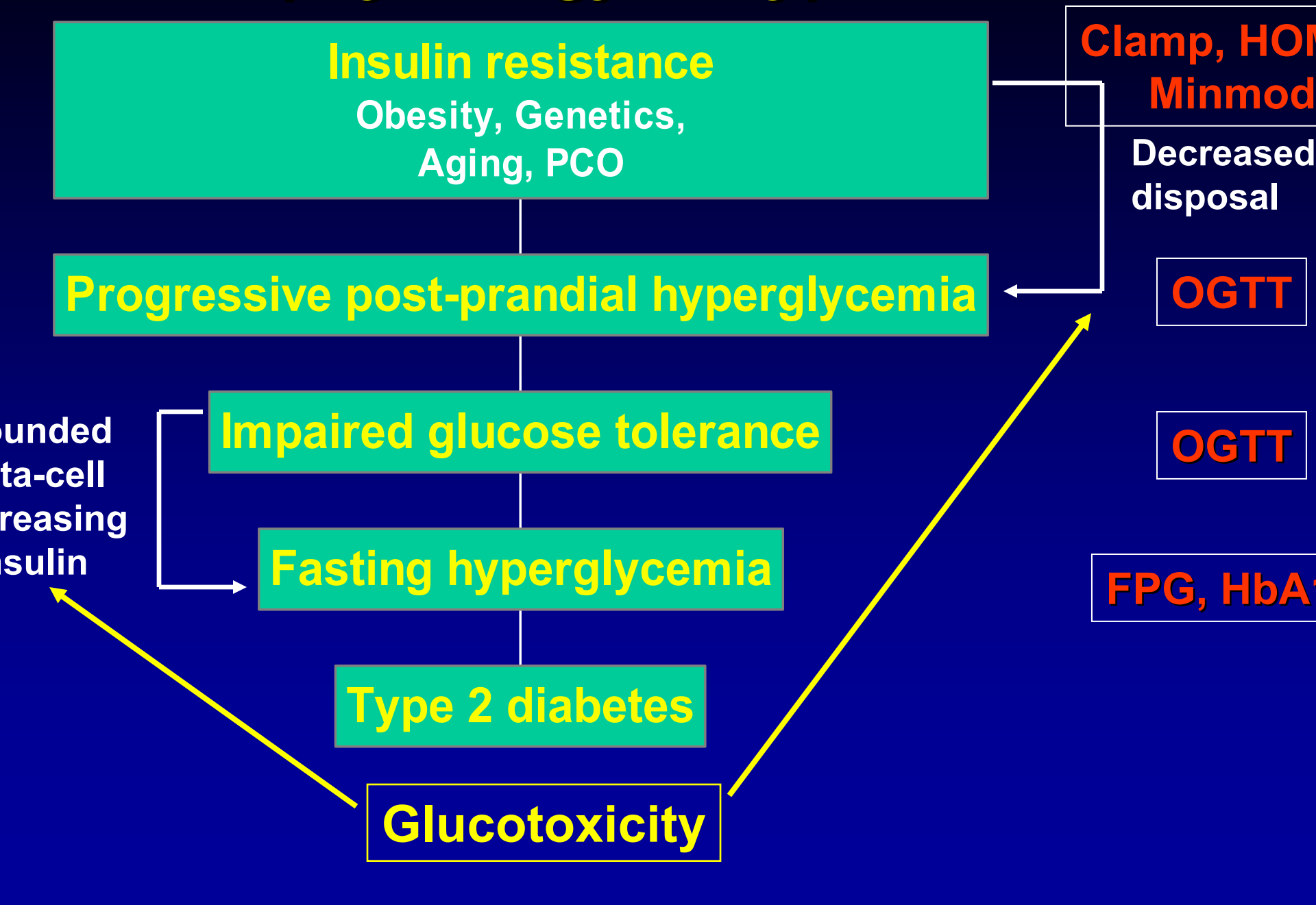
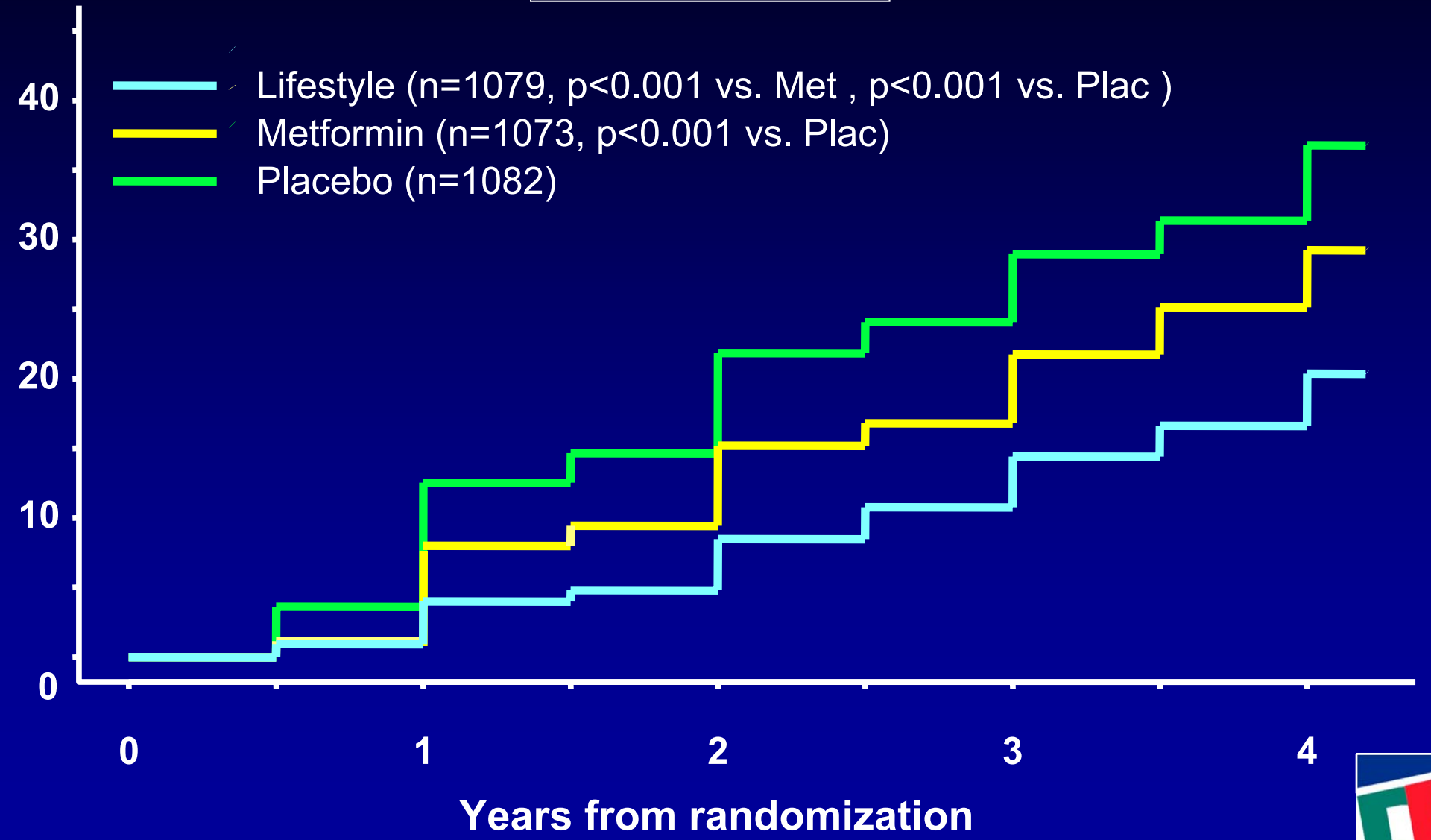
Pathophysiology of Type 2 Diabetes



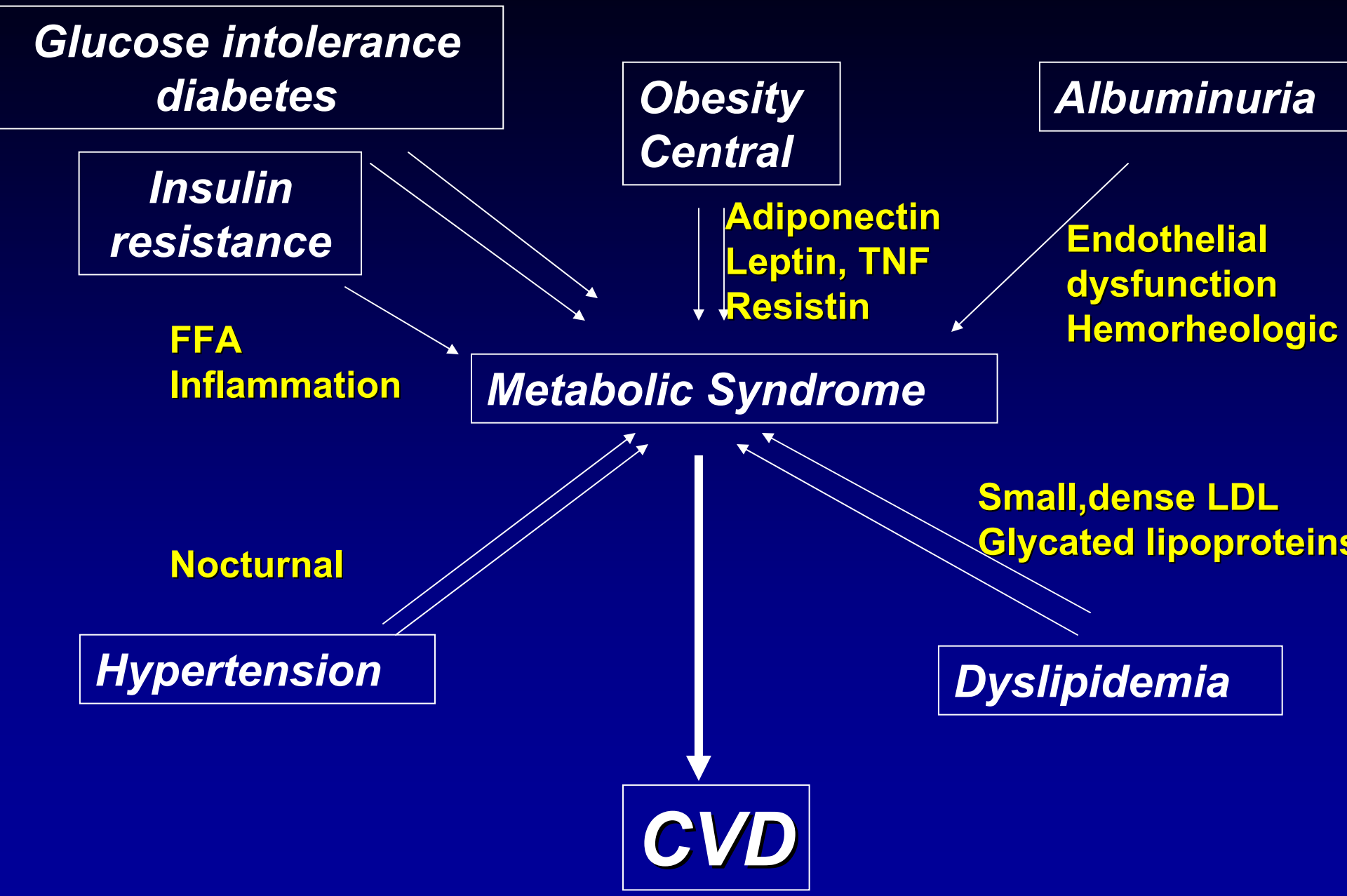
Percent developing diabetes

All participants



Biomarkers for Development of Type 2 Diabetes

- All previous studies have used development of diabetes based on fasting or glucose tolerance testing
- Potential biomarkers include:
  - Lesser degrees of glucose intolerance
  - Insulin resistance
  - Other metabolic changes, e.g FFA


Glucose intolerance
diabetes
Obesity
Central
Albuminuria
Insulin
resistance
Adiponectin
Leptin, TNF
Resistin
Endothelial
dysfunction
Hemorheologic
FFA
Inflammation
Metabolic Syndrome
Small,dense LDL
Glycated lipoproteins
Nocturnal
Hypertension
Dyslipidemia
CVD

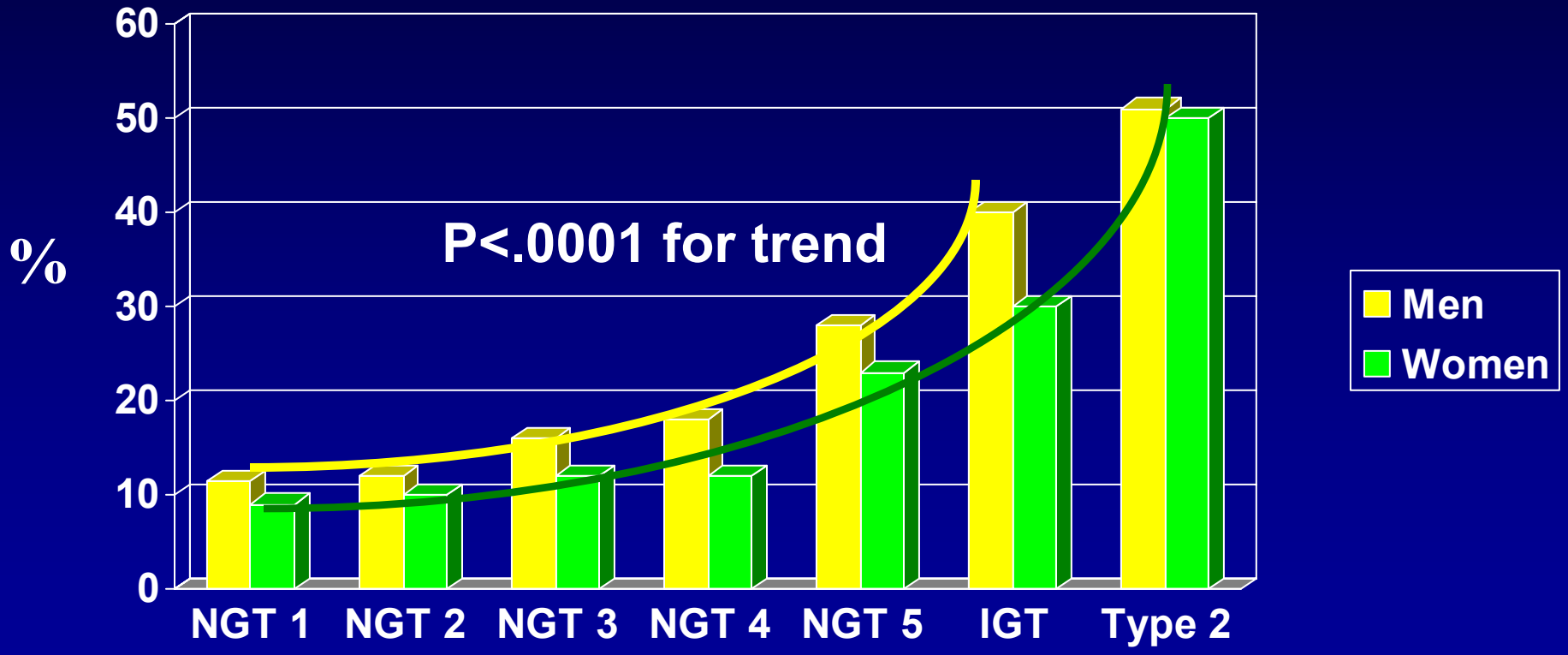
Framingham Offspring Study

Population-based Cohort- children of original Framingham Heart Study population: OGTT at 4th four year cycle exam

	FPG (mg/dL)	HbA1c (%)	Number
NGT 1	60-85	5.1	418
NGT 2	86-90	5.2	541
NGT 3	91-95	5.2	635
NGT 4	96-100	5.3	502
NGT 5	101-139	5.4	559
IGT	76-140	5.5	329
DM	89-298	6.8	125

CVD Risk Associated with Glycemia

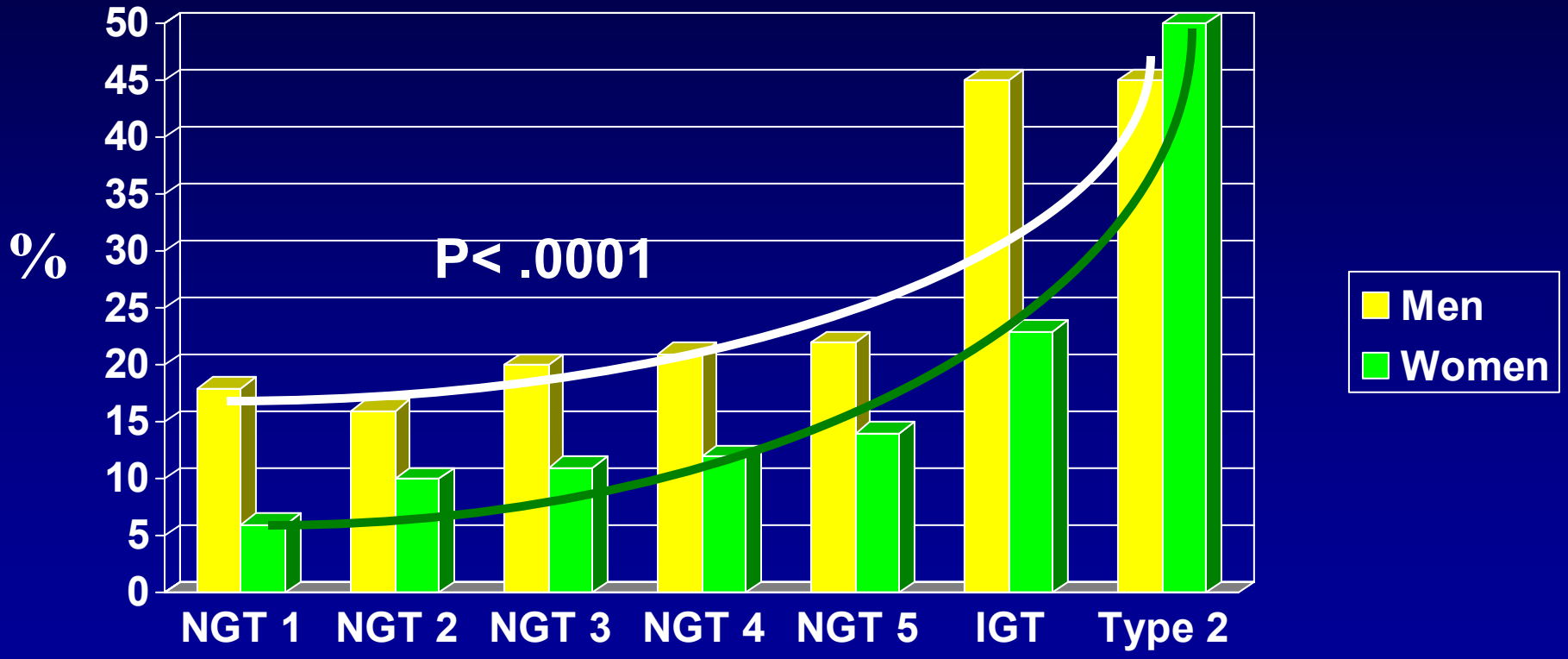
Prevalence of Hypertension: Diastolic > 95, Systolic > 160, or Treatment



Framingham Offspring Study

CVD Risk Associated with Glycemia

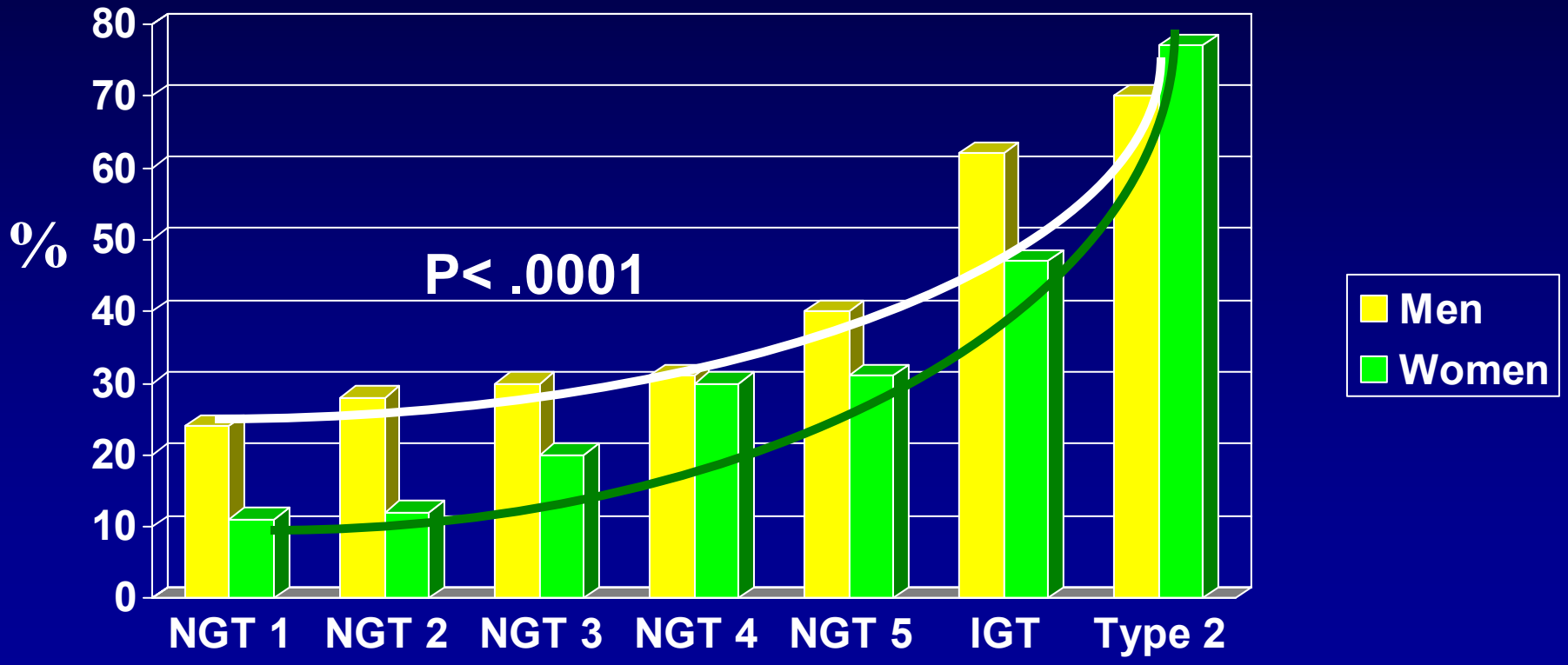
Prevalence of Hyperlipidemia: Triglyceride > 200 mg/dL



Framingham Offspring Study

CVD Risk Associated with Glycemia

Prevalence of Metabolic Score ≥ 2



Framingham Offspring Study

Distribution of Hemostatic Factors

	Q1	Q2	Q3	Q4	Q5	IGT	NIDDM	P
Fibrinogen	285	289	292	298	302	302	315	*
Factor VII	95	95	97	97	98	101	101	*
PAI-1	17	18	20	22	24	30	35	*
t-PA	7.6	7.7	8.5	8.7	9.7	10.9	11.8	*
vW factor	125	124	126	127	128	133	140	+

* <.0001 for trend; + < .05

Framingham Offspring Study

Secondary Intervention

Clinical Course of Diabetes

Implications for Development of New Therapies using Surrogate Outcomes

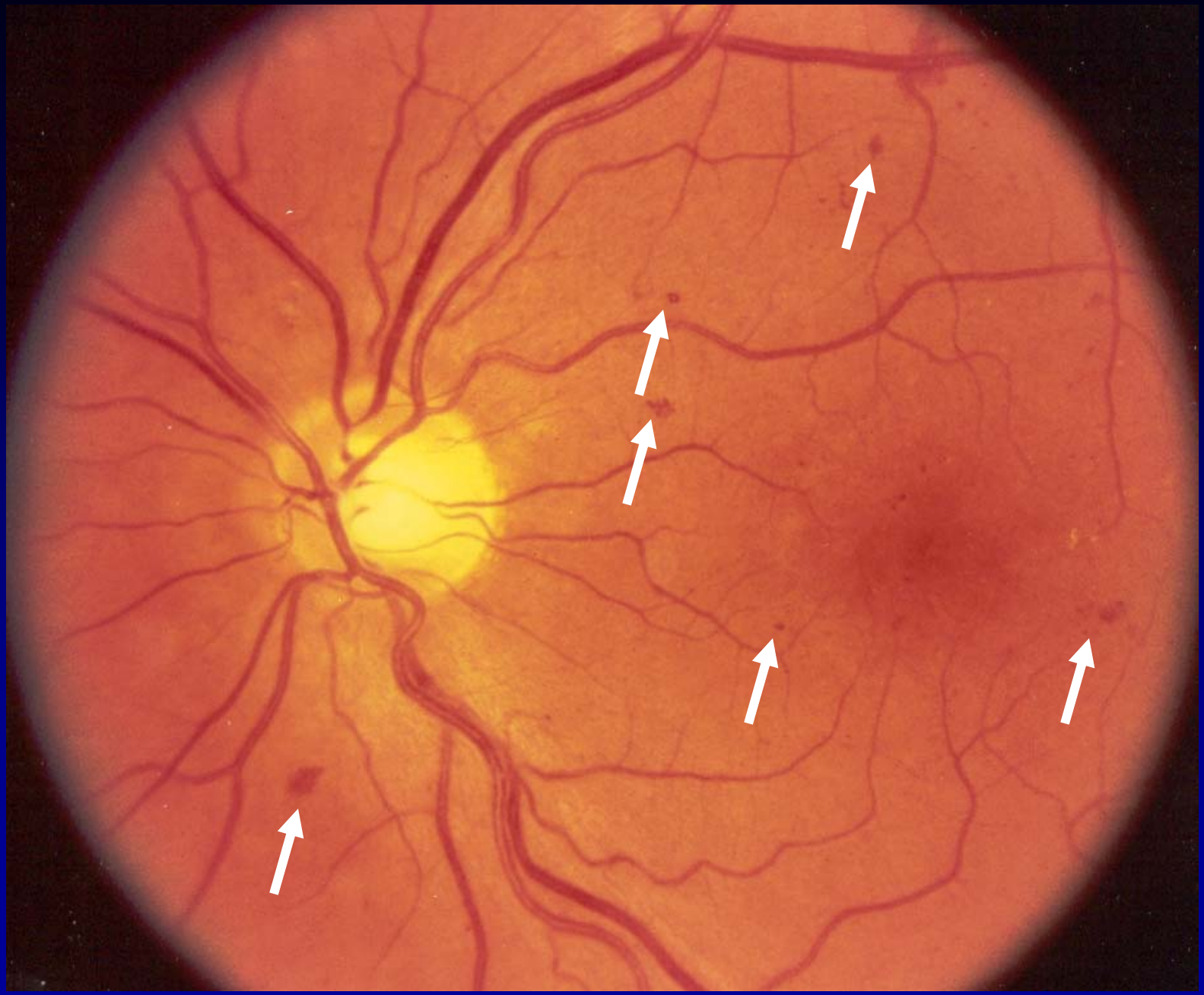
re-diabetes | Clinical diagnosis Hyperglycemia | Latent period | Complications Early | Complications Late | Morbidity | Mortality

rimary
prevention

Secondary intervention

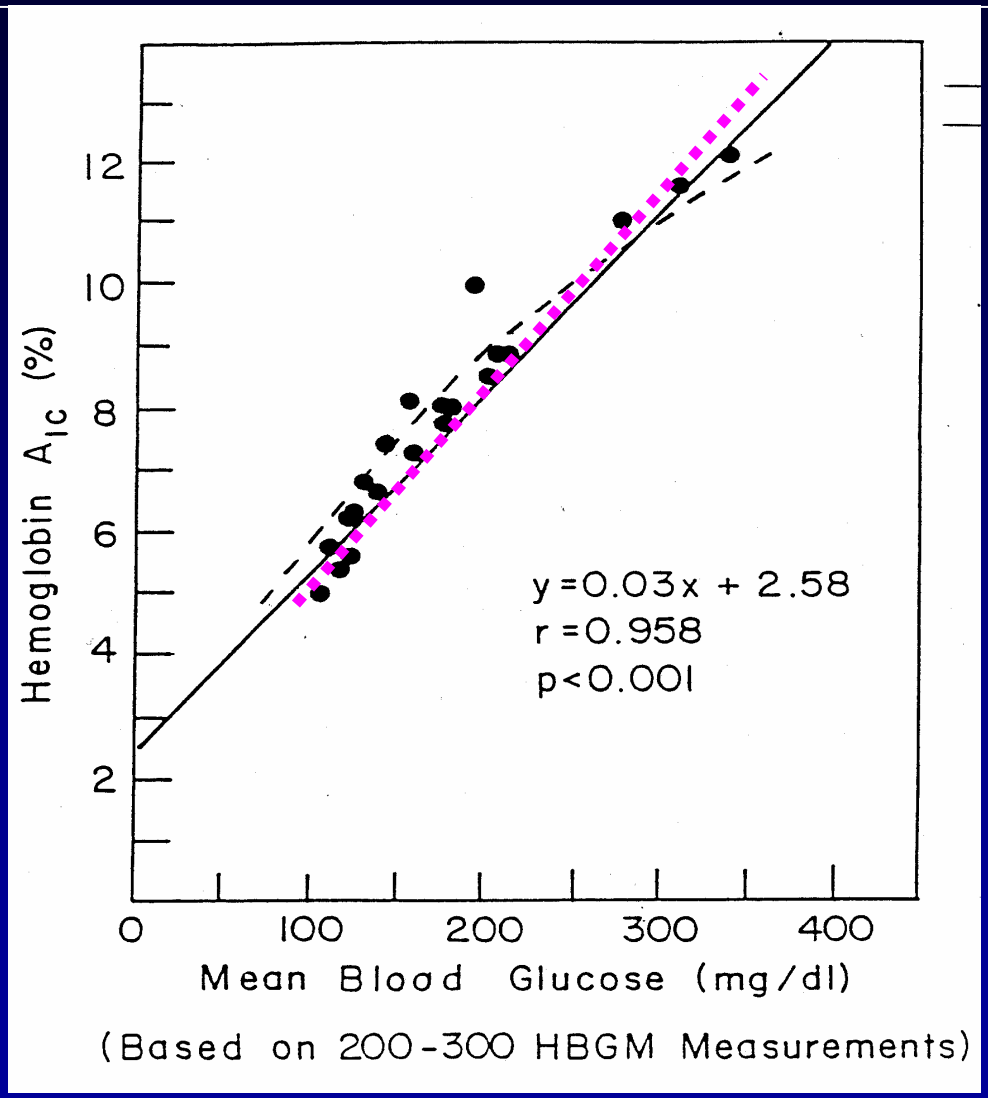
DPT 1
DPP

DCCT
UKPDS



Relationships among measures of glycemia

HbA1c and Mean Capillary Glucose

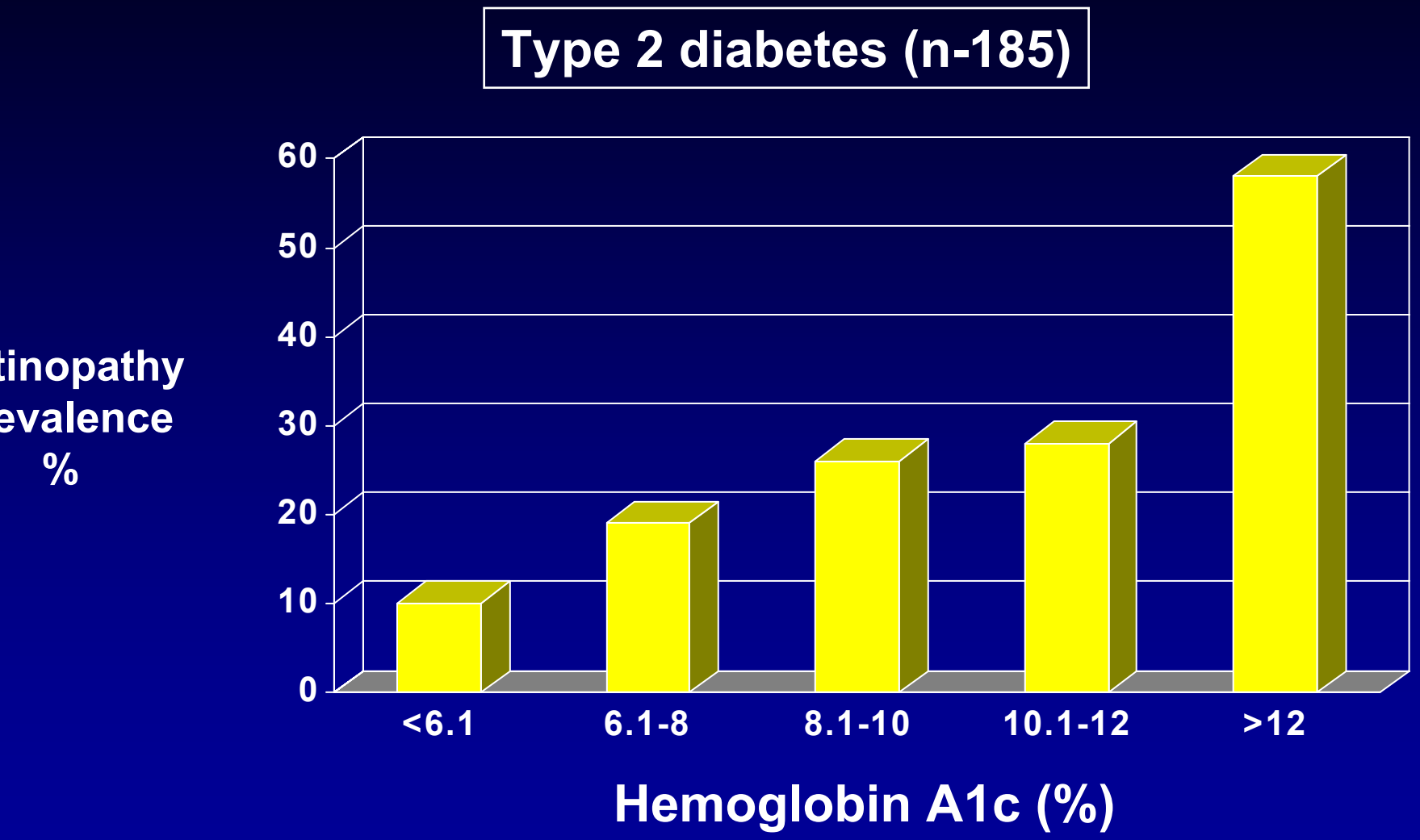


Rohlfing, et al.
Diabetes Care
002;25: 275
= 1439.
6,000 A1cs
ith 7 point
rofiles

Nathan, et al.
N Engl J Med
1984;310:341
n=21, 8-12 wks

Svendson
Diabetologia
1982;23:403
n=15, 5 wks

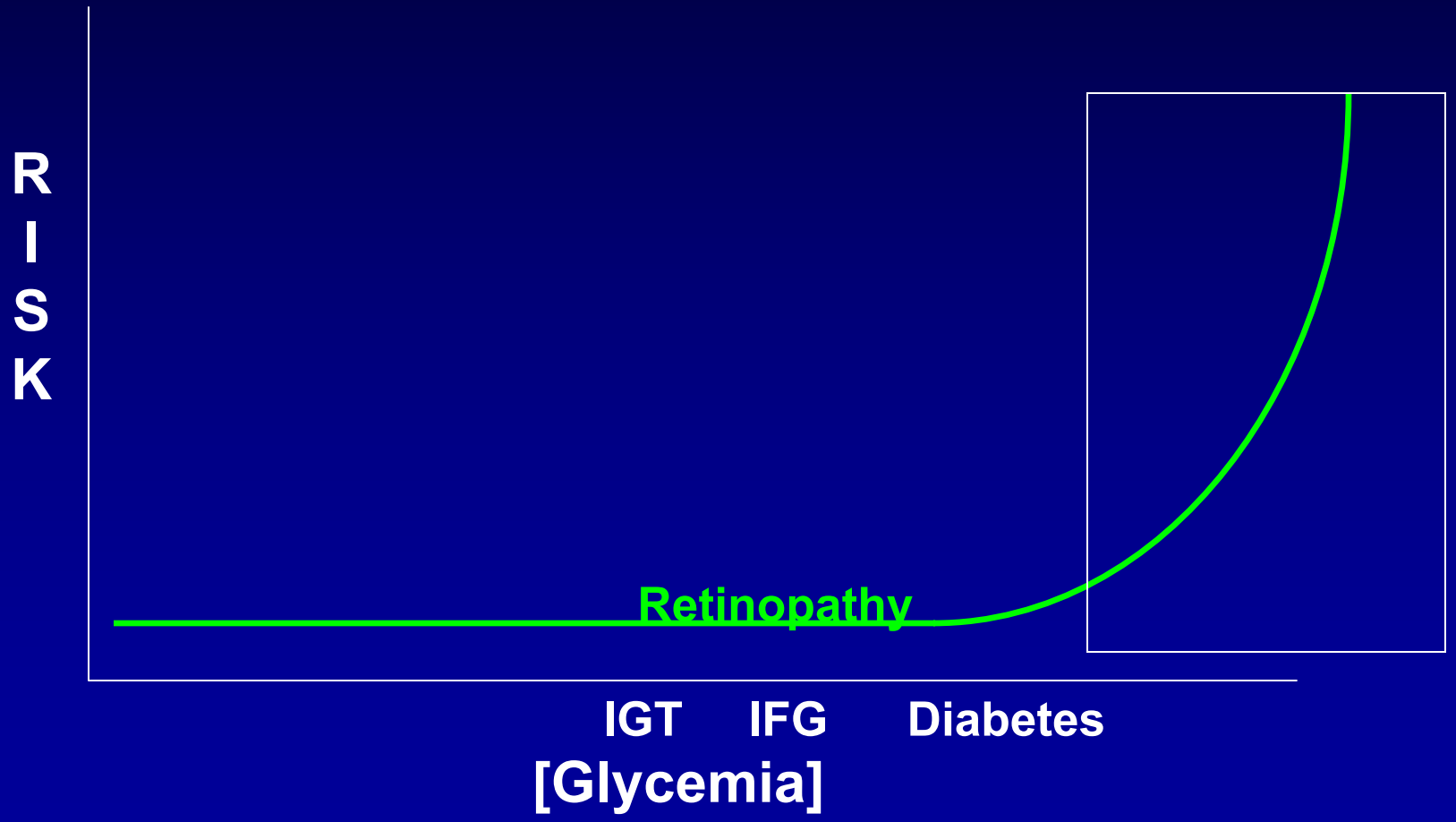
Retinopathy and Glucose Control



P=.002 for trend

Nathan et al.
Diabetes 1986;35:797

Categories and Continuums: Hyperglycemia and its Consequences



MEASURES OF OPHTHALMIC OUTCOME

TEST	FREQUENCY
STEREO FUNDUS PHOTOS	6 MONTHS
EYE EXAMINATION	YEARLY
VISUAL ACUITY	YEARLY

DCCT

RETINOPATHY SCALE

STEPS	LEVEL OF RETINOPATHY	ELIGIBILITY
1	NO RETINOPATHY	1º PREVENTION
2	MICROANEURYSMS ONE EYE	2º INTERVENTION
3	MICROANEURYSMS BOTH EYES	
4 - 5	MILD NPDR	
6 - 9	MODERATE NPDR	
10 - 13	SEVERE NPDR	
14 - 15	MILD PDR	
16 - 17	MODERATE PDR	
18 - 25	HIGH RISK PDR AND WORSE	

DCCT

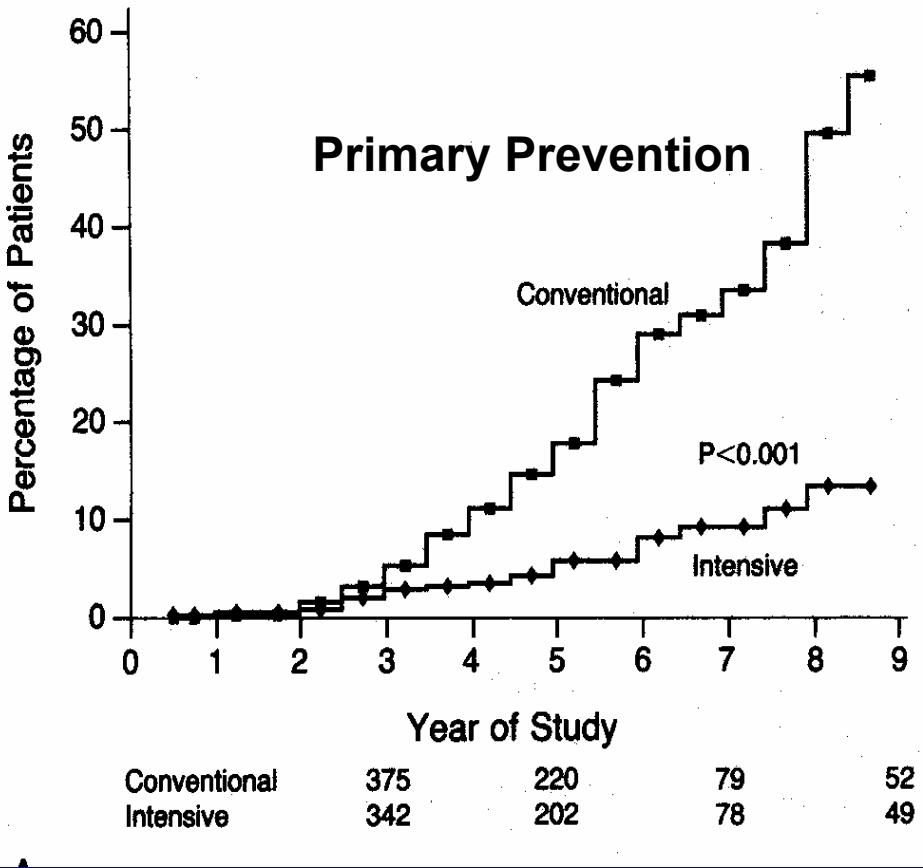
MEASURES OF NEPHROPATHY

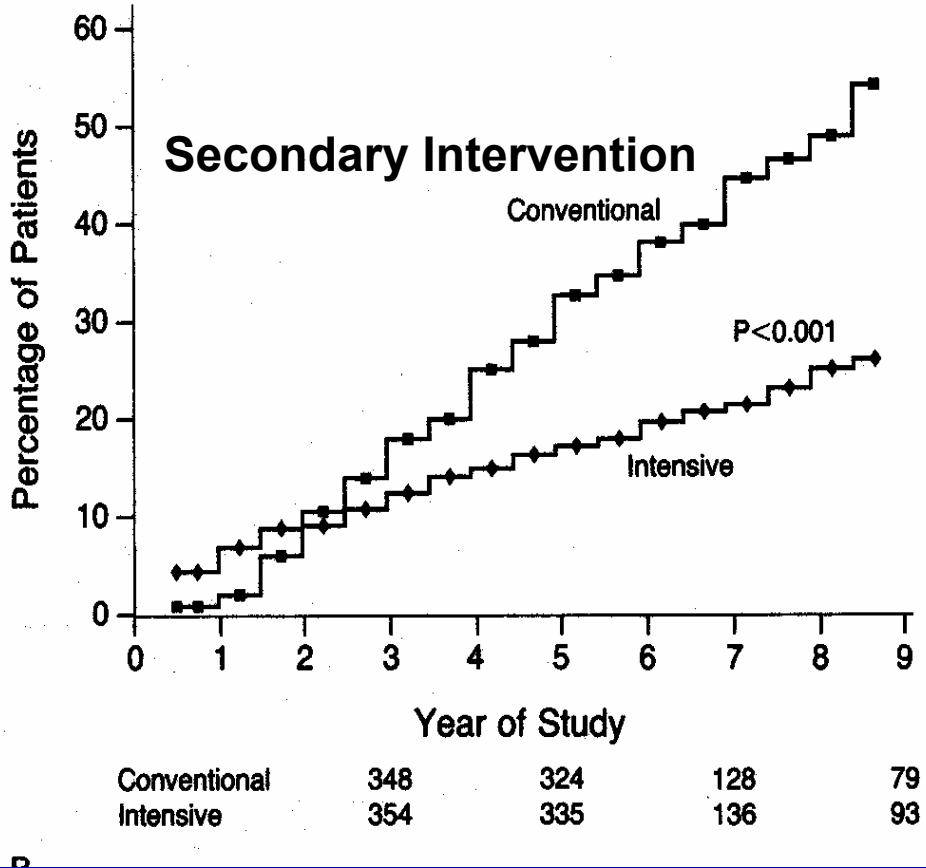
TEST	FREQUENCY
ALBUMIN EXCRETION RATE	YEARLY
SERUM CREATININE	YEARLY
CREATININE CLEARANCE	YEARLY
^{125}I-IOTHALAMATE CLEARANCE	3 Y, END

DCCT

DCCT

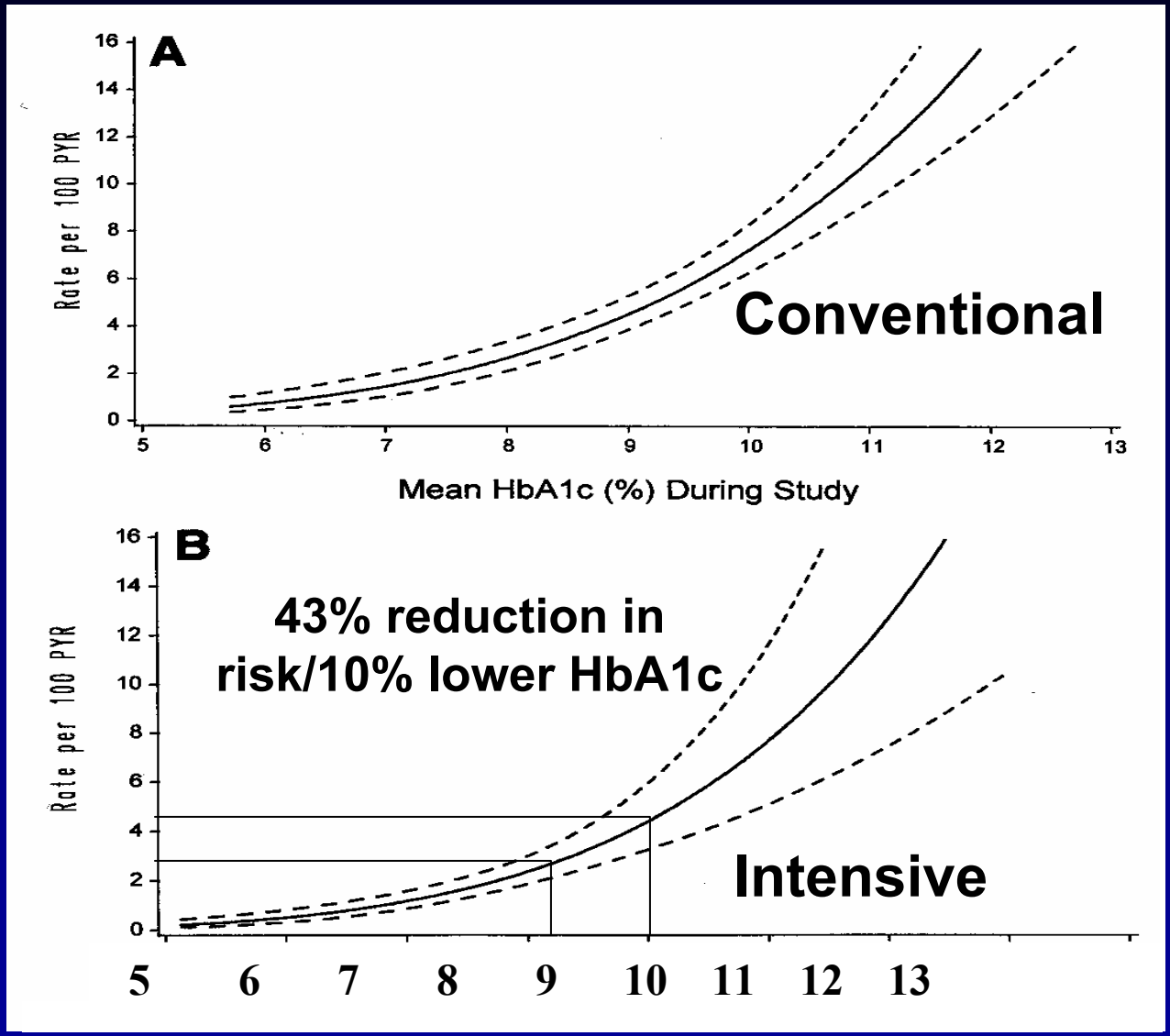
Retinopathy Results





DCCT Research Grou
NEJM 1993;342:381

Association of HbA1c with Risk for Retinopathy



Diabetes
995;44:968

Mean HbA1c(%) During Study

DCCT

Biomarkers in the Secondary Intervention of Type 1 Diabetes

- The DCCT used biomarkers (e.g. 3-step retinopathy progression as the primary outcomes)
- Differences in HbA1c accounted for the vast majority of the differences in outcomes between treatment groups
- Biomarkers, including pre-disease levels of retinopathy or HbA1c, could be used in future clinical trials

FURTHER PROGRESSION OF RETINOPATHY

FROM DCCT CLOSE-OUT TO EDIC YEAR 4

OUTCOME	*DCCT Group*		*% Odds*	
	Conv	*Int*	*Reduction**	*95% C.I.*
≥ 3-Steps Progression	21%	6%	72%	(59, 81)
Severe Non-Proliferative Diabetic Retinopathy	10	2	76	(52, 88)
Clinically Significant Macular Edema	8	1.5	77	(52, 89)
Laser Therapy (Focal or Scatter)	6	1	77	(45, 91)

All P < 0.002

** Adjusted for status at DCCT closeout.*

DCCT/E

MAJOR MACROVASCULAR EVENTS

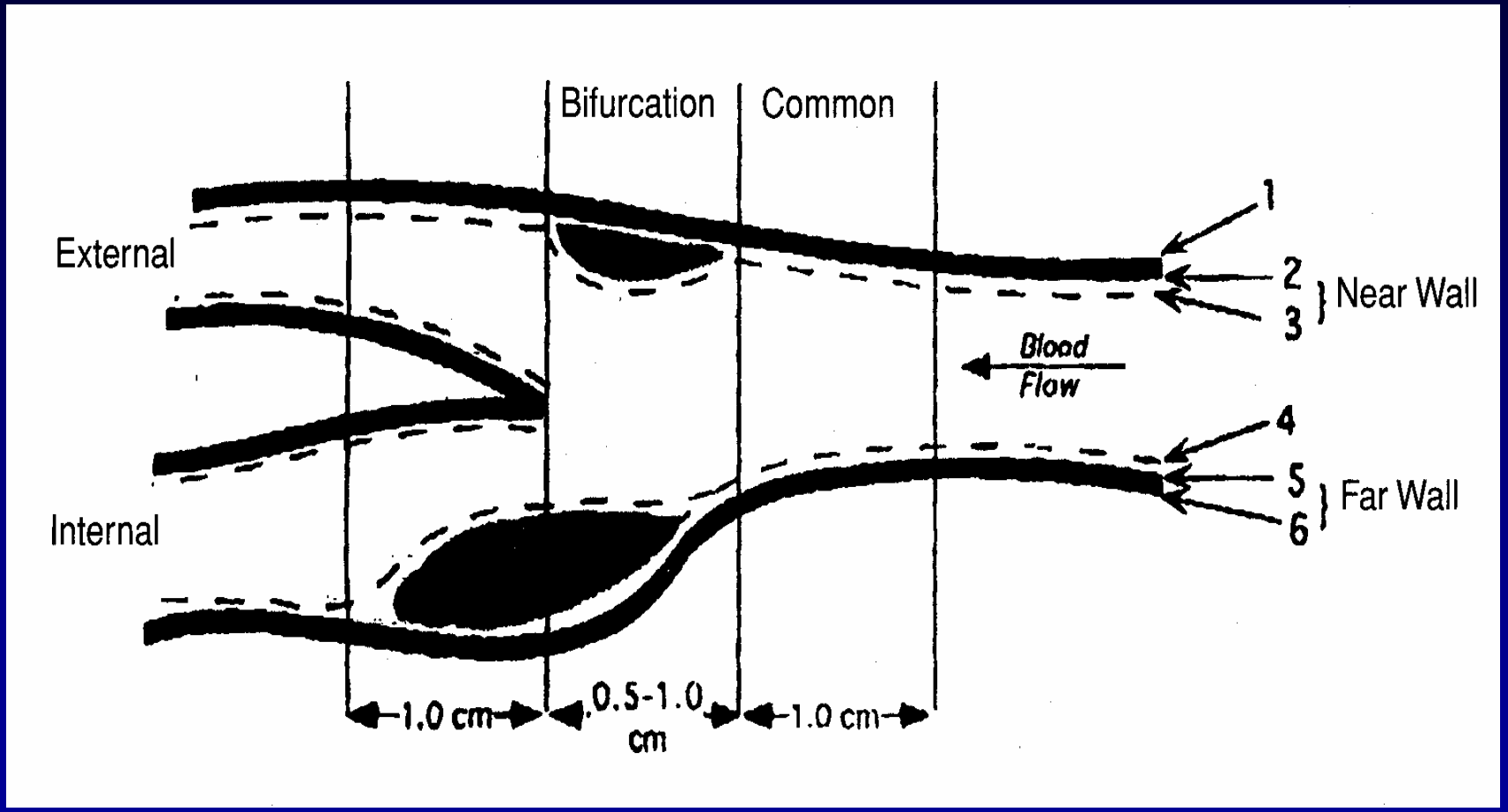
COMBINED COHORT

	INTENSIVE	CONVENTIONAL
CARDIAC	3	14
CEREBRAL	0	0
PERIPHERAL	18	24
TOTAL	21	38

Am J Cardiology
1995;75:894

DCCT

Atherosclerosis measured by Carotid Ultrasonography



Change in Carotid Artery IMT Over 5 Years of EDIC (Year 6 – Year 1)

DCCT Treatment Group	Intensive	Conventional	p
Common Carotid N = 1219	.029 ± .91	.040 .108	.004
Internal Carotid N = 1175	.081 ± .280	.095 ± .275	.049

JM 2003

DCCT/EDIC

Type 1 Diabetes and CVD

- The largest and longest duration study to date of Type 1 diabetes has not yet demonstrated a beneficial effect of glycemic interventions on CVD events
- Biomarkers of CVD (measures of atherosclerosis) have been shown to be sensitive to glycemic intervention
- Further followup may demonstrate a benefit of intensive therapy on CVD events and a correlation between the measures of atherosclerosis and CVD events

Clinical Course of Diabetes

Implications for Development of New Therapies using Surrogate Outcomes

re-diabetes | Clinical diagnosis Hyperglycemia | Latent period | Complications Early | Complications Late | Morbidity Mortality

rimary prevention

Secondary intervention

Tertiary intervention

DPT 1
DPP

DCCT
UKPDS

DRS
ETDRS
ACEI -renal, CVD
Lipids- CVD

Clinical Course of Diabetes

Implications for Development of New Therapies using Surrogate Outcomes