Preservation of Beta Cell Function in Type 1 Diabetes

Intervention Studies:

Azathioprine/Steroids

Cyclosporin

Anti-CD3

DiaPep 277

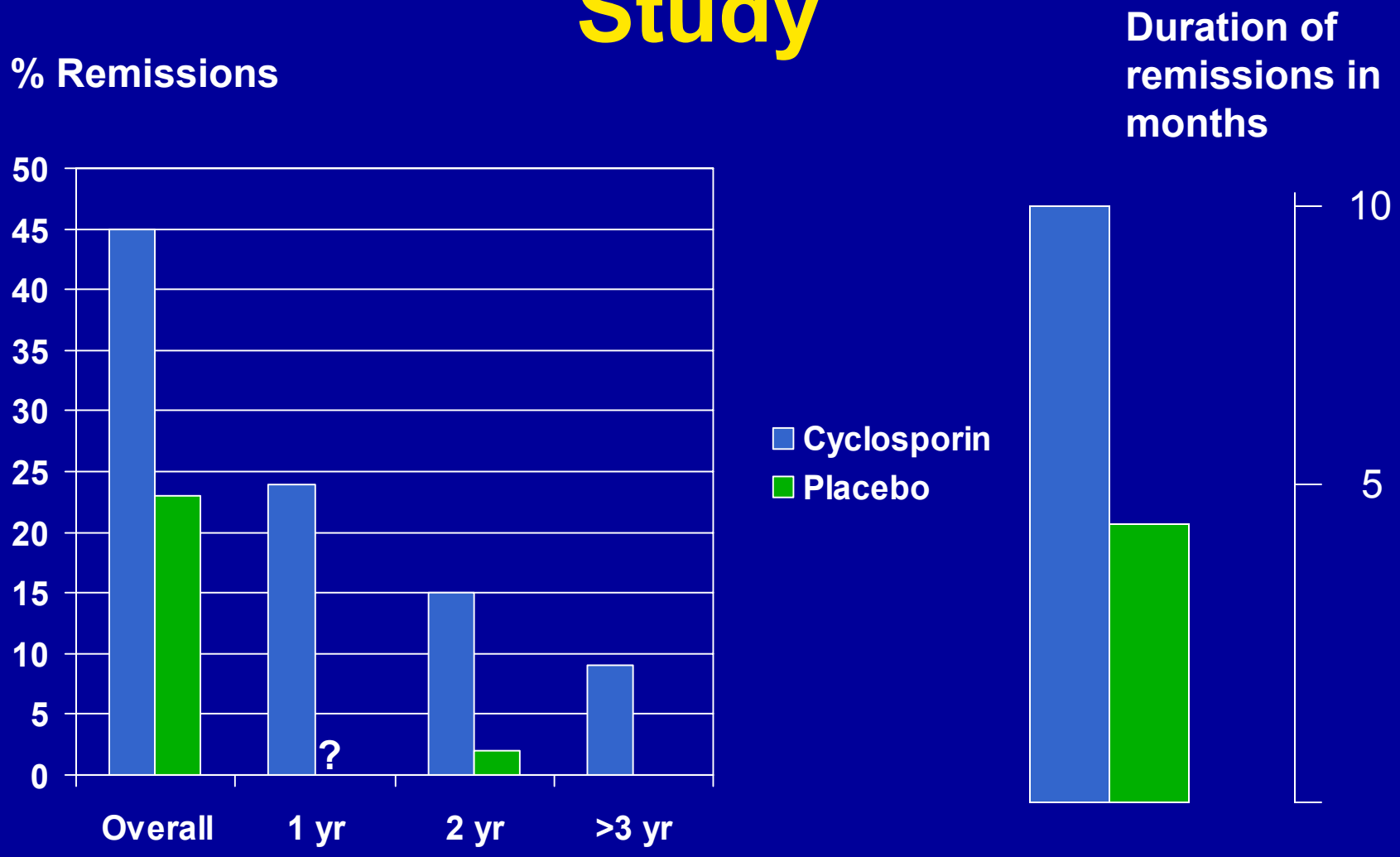
TrialNet
- MMF/DZB
- Anti CD-20 (Rituximab)

Canadian-Diabetes-France (Plus) Study

1) Newly diagnosed IDDM
   - **90 Placebo**
   - **129 Cyclosporin**
2) Intensive insulin therapy
3) Cyclosporin- A
   - **5-10 mg/kg/day**
   - **Discontinued if no remission in 6 mo.**
   - **or remission → relapse**
   - **Continued for duration of remission**

Diabetes 36:768-774, 1990

Cyclosporin-A: Diabetes-France Study



Diabetes 39: 768-774, 1990

Preservation of Beta Cell Function in Type 1 Diabetes

Prevention Studies:

Parenteral Insulin

Oral Insulin

Nicotinamide

TRIGR

TrialNet

- Omega-3 FA
- GLP-1


Type 1
Diabetes
TrialNet

TrialNet Goals

- Alter T1DM disease process in:
  - New-onset Type 1 Diabetes
  - Relatives “at risk” of Type 1 Diabetes
  - High genetic risk individuals
- Further define epidemiology, natural history, and risk factors of Type 1 Diabetes

TrialNet

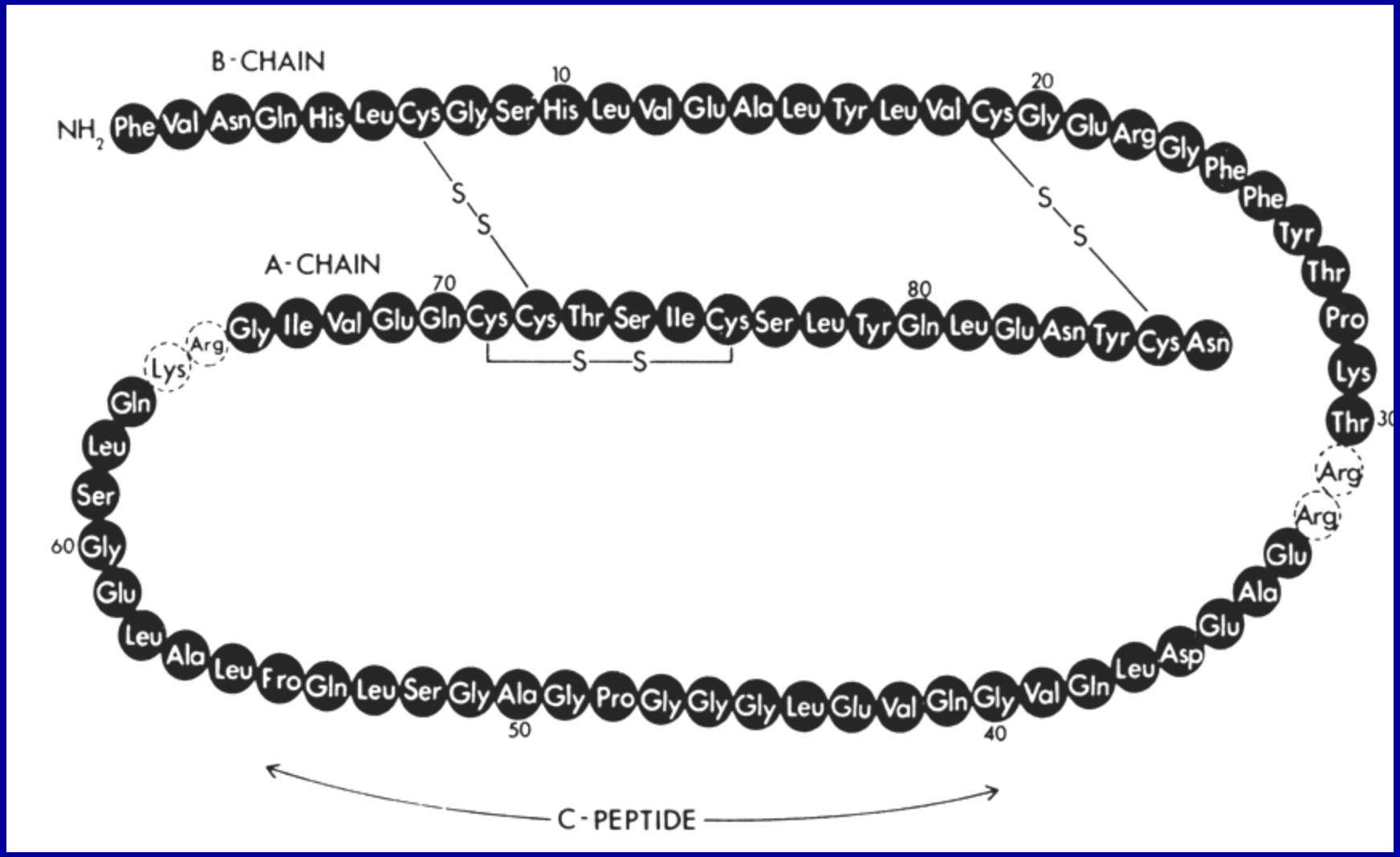
18 Clinical Centers:

USA, Canada, Europe, Australia

Core Laboratories:

Genetic, Immunologic, Metabolic, Biochemical, Viral

Coordination/Statistical Center


B-CHAIN
NH2
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr
10
20
S S
S S
A-CHAIN
Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
70
80
S S
Arg
Lys
Gln
Leu
Ser
60 Gly
Glu
Leu
Ala
Leu
Pro
Gln
Leu
Ser
Gly
Ala
Gly
Pro
Gly
Gly
Gly
Leu
Glu
Val
Gln
Gly
Val
Gln
Leu
Asp
Glu
Ala
Glu
Arg
Arg
50
40
C-PEPTIDE

C-Peptide Basic Information

- Secreted in 1 to 1 molar ratio with insulin
- Negligible first pass hepatic extraction
- High quality, specific assays that accurately measure the low levels of type 1 diabetes
- 1 ng/ml = 0.331 nmol/l
- Detection limit ≈ 0.1 ng/ml or 0.03 nmol/l
- T ½ for insulin and c-peptide are different Insulin ≈ 3 min., c-peptide ≈ 35 min.

Factors Affecting Residual β-Cell Function in Type 1 Diabetes

- Age at diagnosis
- Duration of diabetes
- Metabolic control
- Marked inter-individual variation

C-Peptide After Diagnosis of Type 1 Diabetes

Data Contributions:

Control Patients from Intervention Studies
- BCG
- Canadian/European Cyclosporine Study
- Miami Cyclosporine Study

Neil White

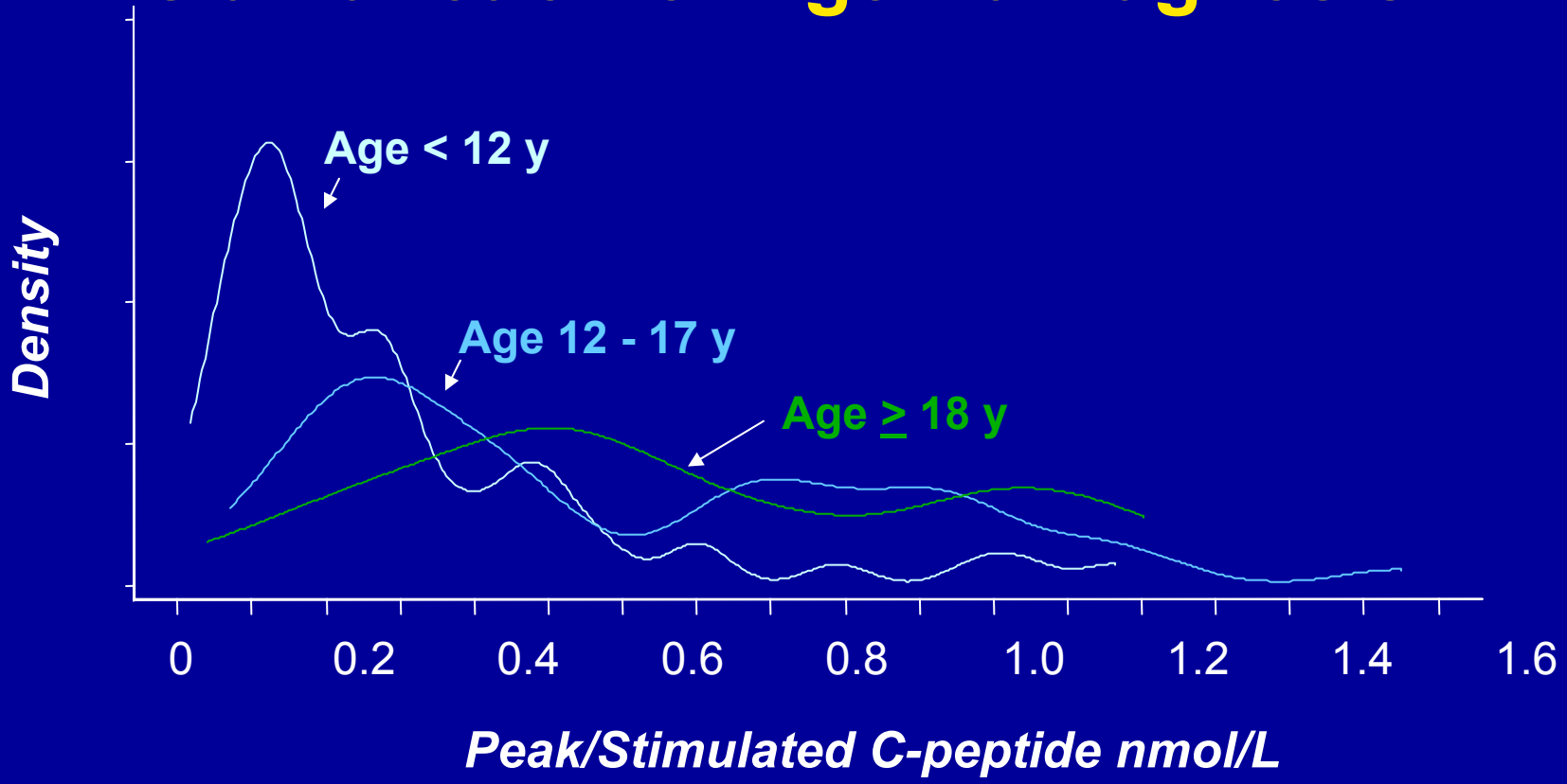
Kevan Herold

Dorothy Becker

Paulo Pozzilli

Johnny Ludviggson

DESIGN OF STUDIES OF β-CELL PRESERVATION
Distribution of 2 h Peak Value From MMTT As a Function of Age At Diagnosis



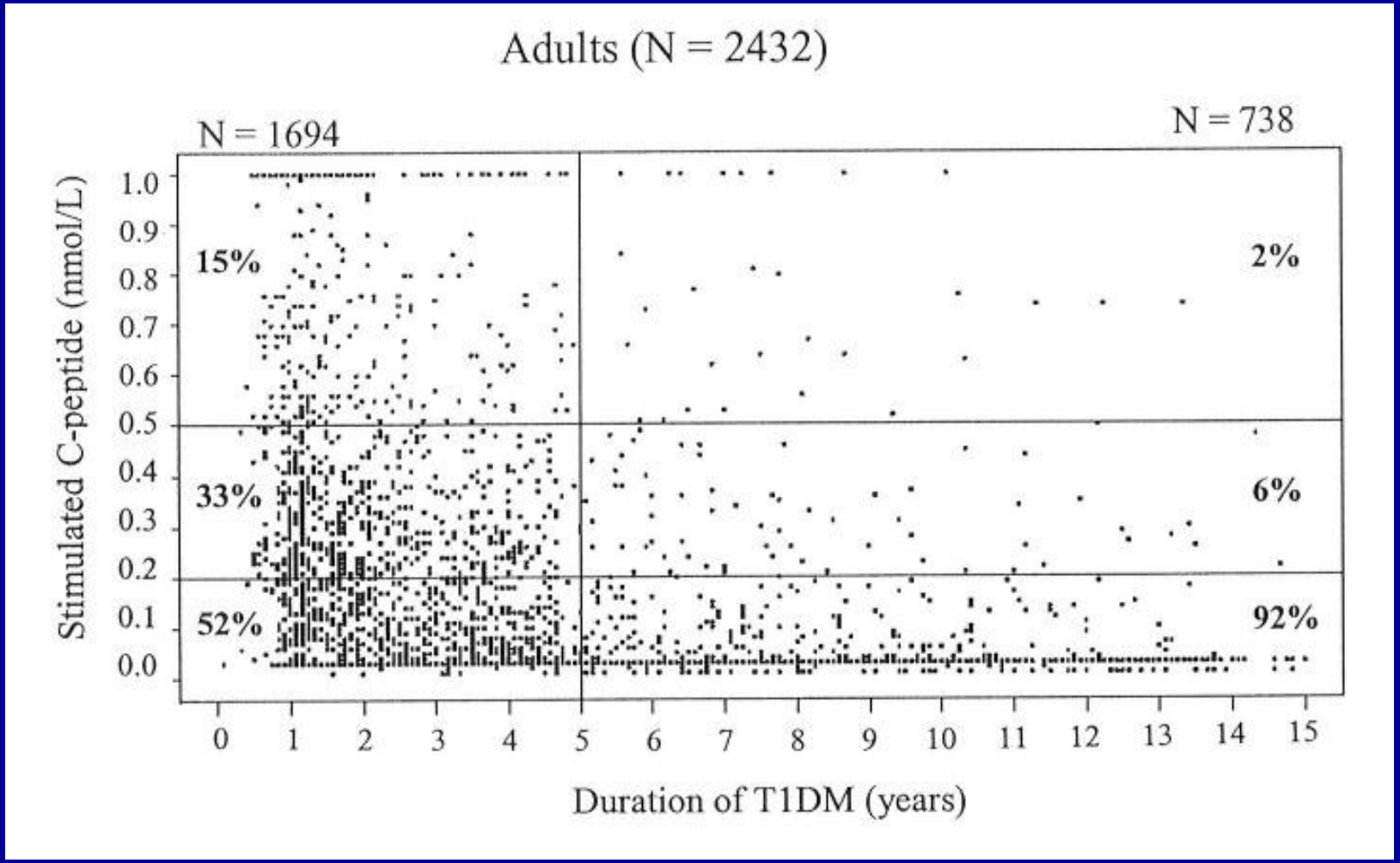
Diabetes 53: 250-264, 2004

TrialNet

C-Peptide in DCCT

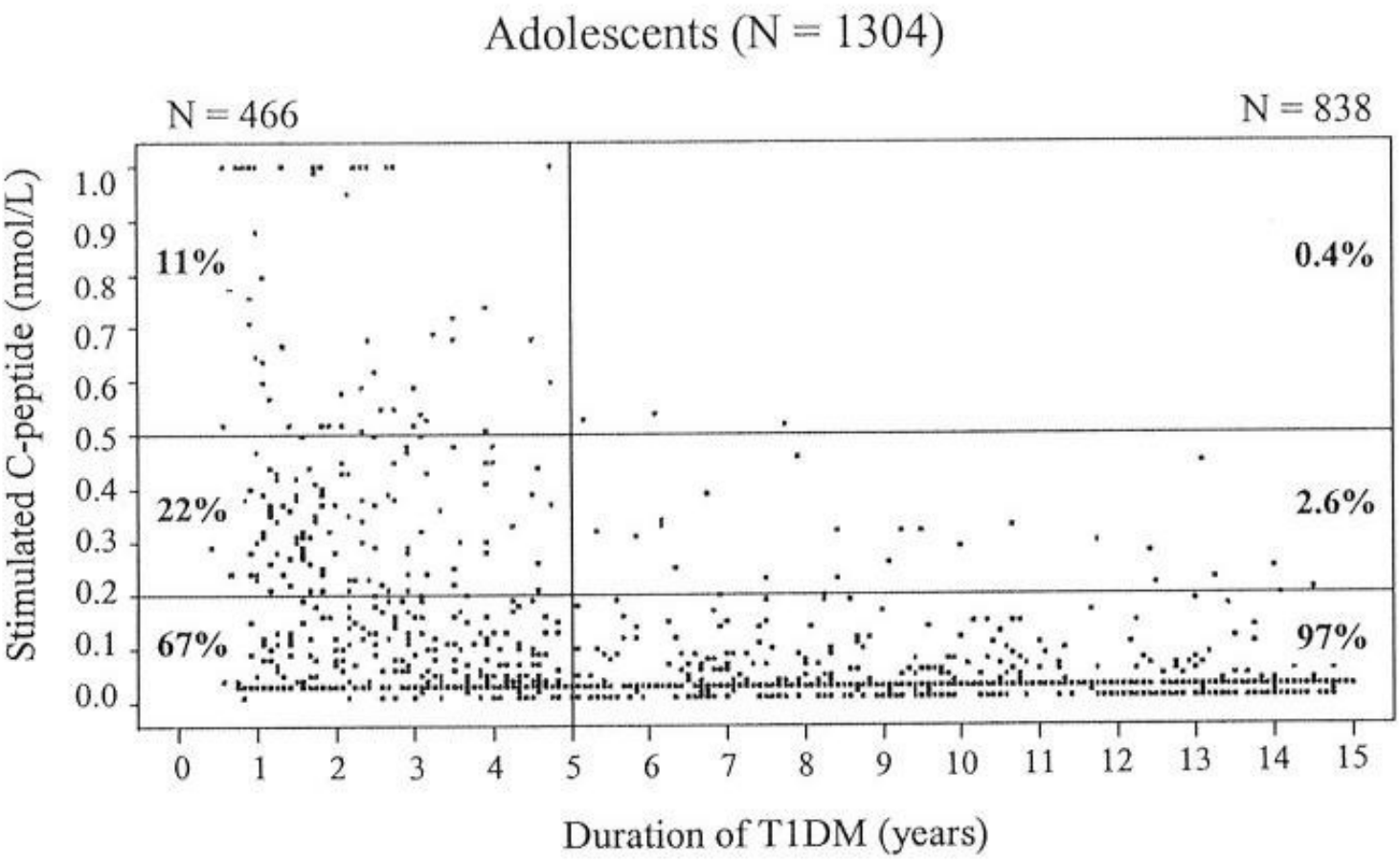
MMTT stimulation of 3736 T1DM patients, age 13-39 y.o., with diabetes of 1-15 years duration.

C-PEPTIDE IN DCCT SCREENED SUBJECTS



Diabetes 53: 250-264, 2004

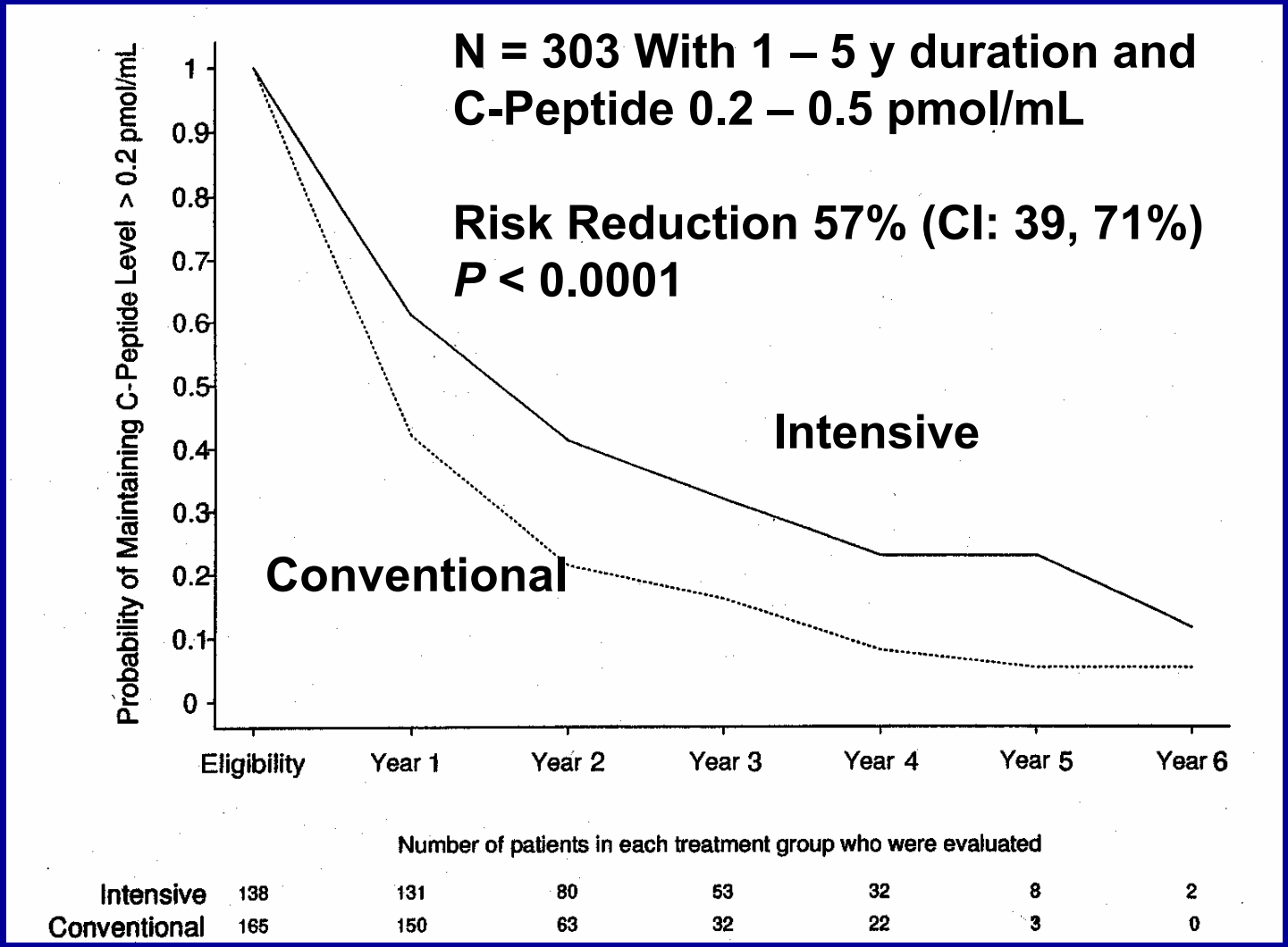
C-PEPTIDE IN DCCT SCREENED SUBJECTS



Diabetes 53: 250-264, 2004

Effect of Intensive vs Conventional Therapy on β-Cell Function

Ann Int Med 128: 517-523, 1998



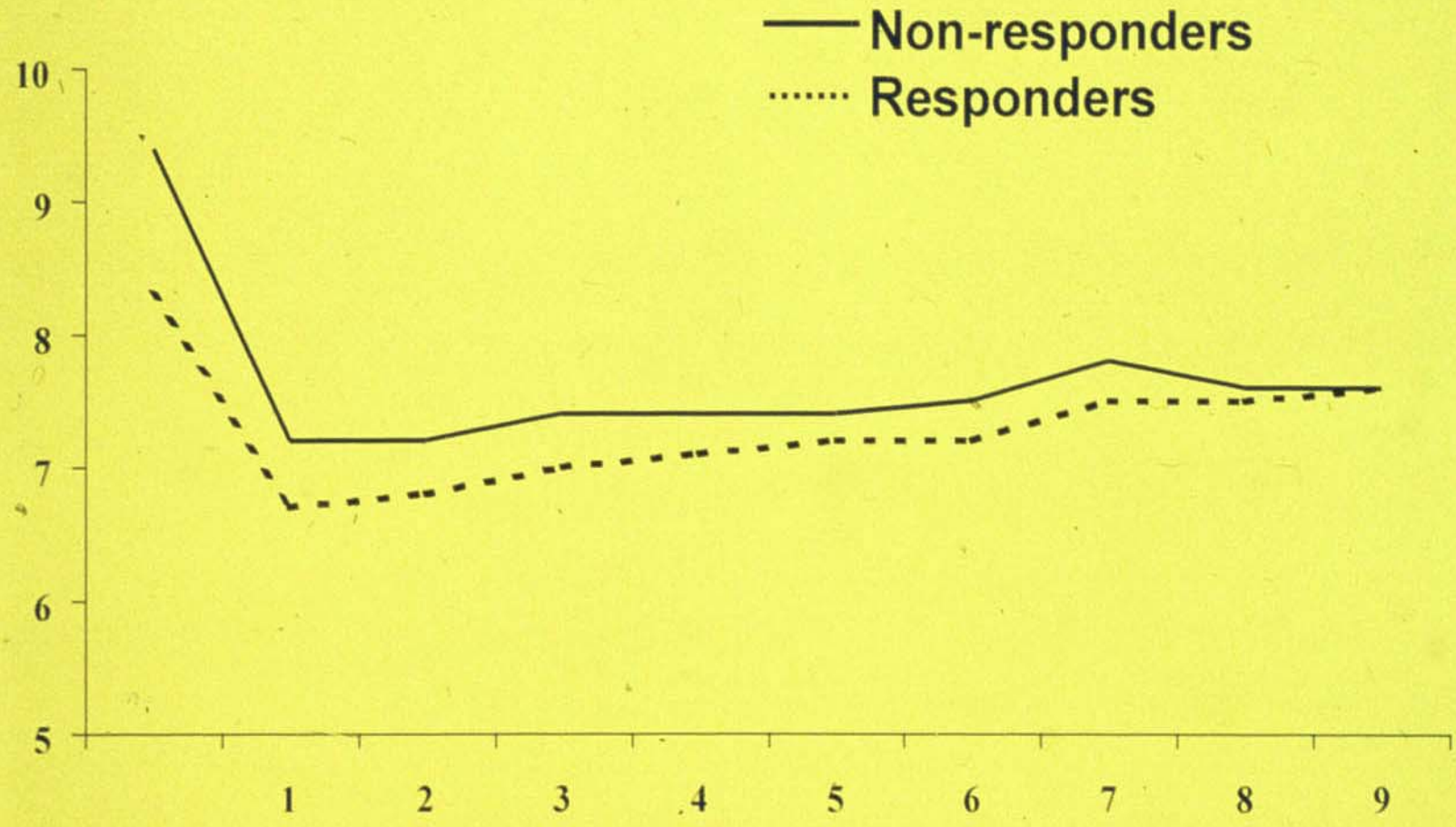
Relationship of Stimulated C-peptide to Fasting Glucose, HbA_1C and Insulin Dose

JCEM 65:30-36, 1987

	MMTT Stimulated C-peptide (nmol/l)			
	≥ 0.05	0.05-0.10	0.1-0.2	>0.2
Fasting Glucose (mg/dl)	222 ± 6	206 ± 12	217 ± 11	117 ± 6*
HbA_1C (%)	9.3 ± 0.1	9.8 ± 0.3	9.2 ± 0.2	8.4 ± 0.2*
Insulin Dose(u/kg)	0.78 ± 0.02	0.75 ± 0.04	0.64 ± 0.02*	0.52 ± 0.02*

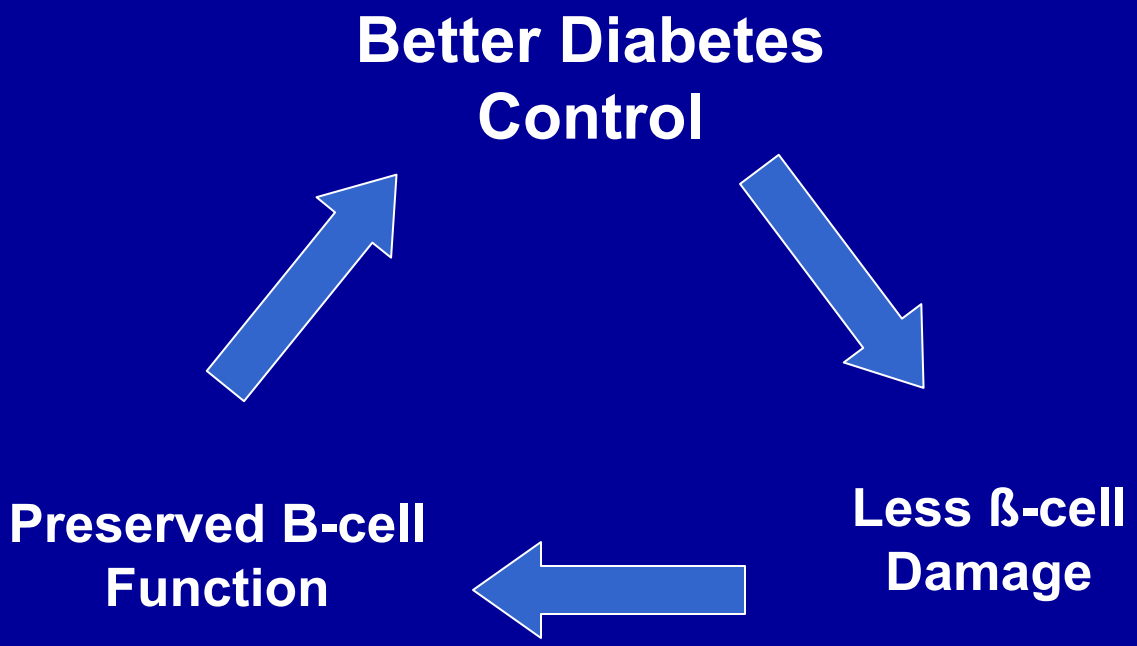
* = $p < 0.05$

HbA_{IC} in Intensive Rx DCCT Patients



Ann Intern Med 128:517-23, 1998

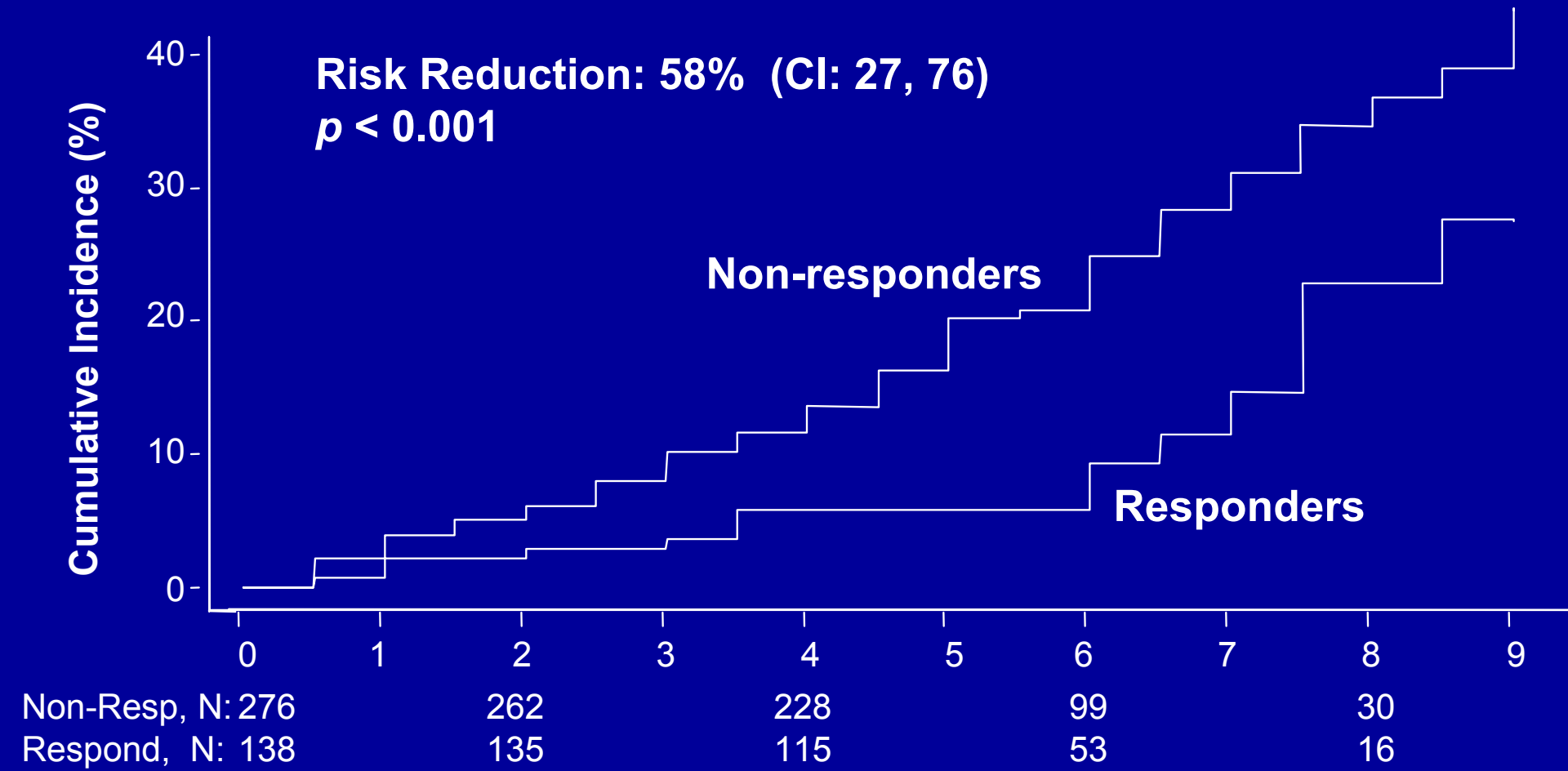
Virtuous Cycle



BENEFITS OF β-CELL PRESERVATION

DCCT Intensive Therapy Group

3+ Step Retinopathy Progression



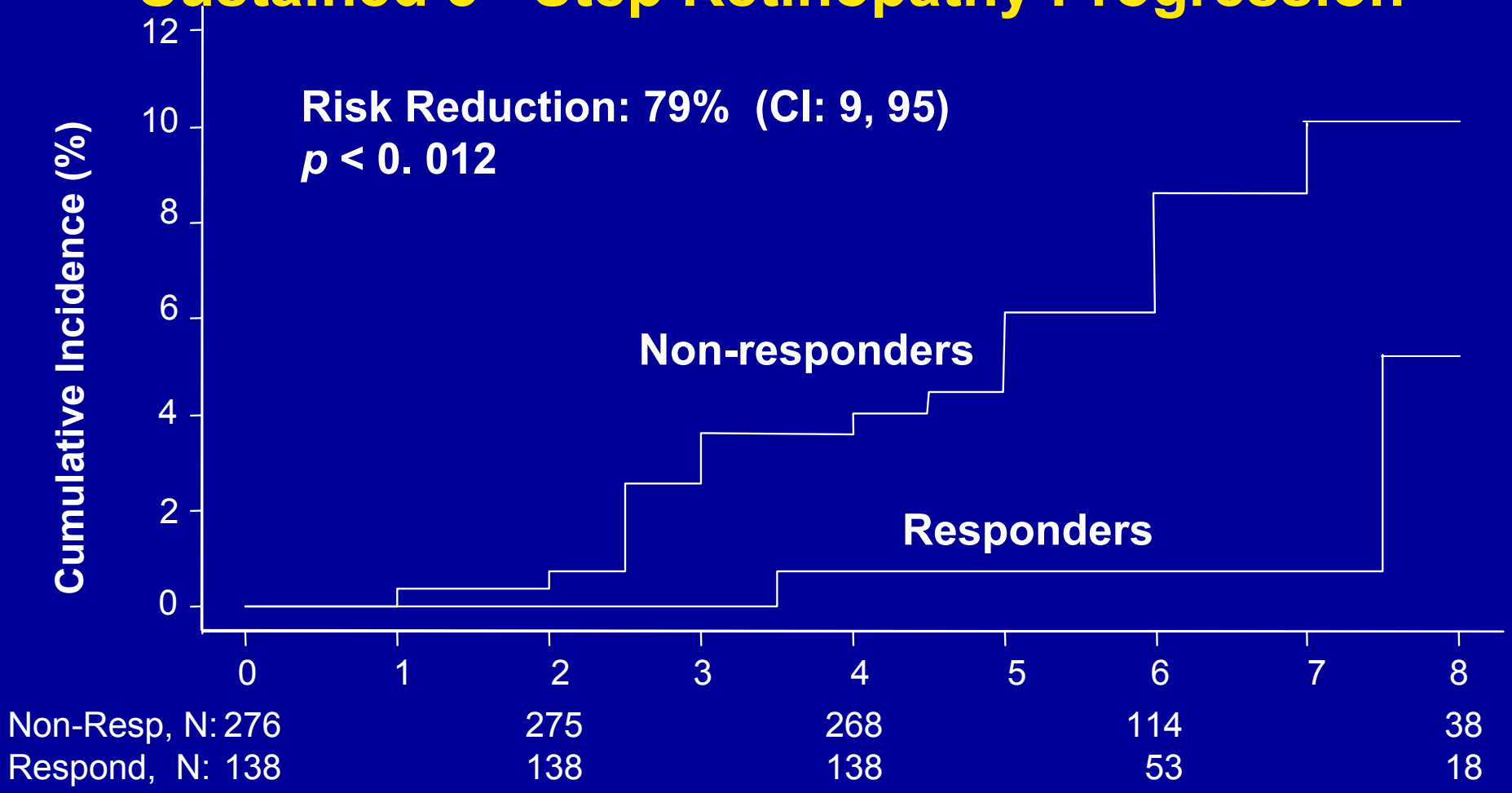
Diabetes 53: 250-264, 2004

TrialNet

BENEFITS OF β-CELL PRESERVATION

DCCT Intensive Therapy Group

Sustained 3+ Step Retinopathy Progression



Diabetes 53: 550-264, 2004

TrialNet

Retinopathy and Nephropathy After 6 Years of DCCT Intensive Therapy Based upon Entry C-Peptide

Stimulated C-peptide (nmol/l)			
Undetectable	**Minimal**	**Baseline only**	**Sustained**
≤ 0.03	**0.04 – 0.2**	**0.21 – 0.5 and ≤ 0.2 at 1 yr**	**0.21 – 0.5 at entry and 1 year**

4.6 times

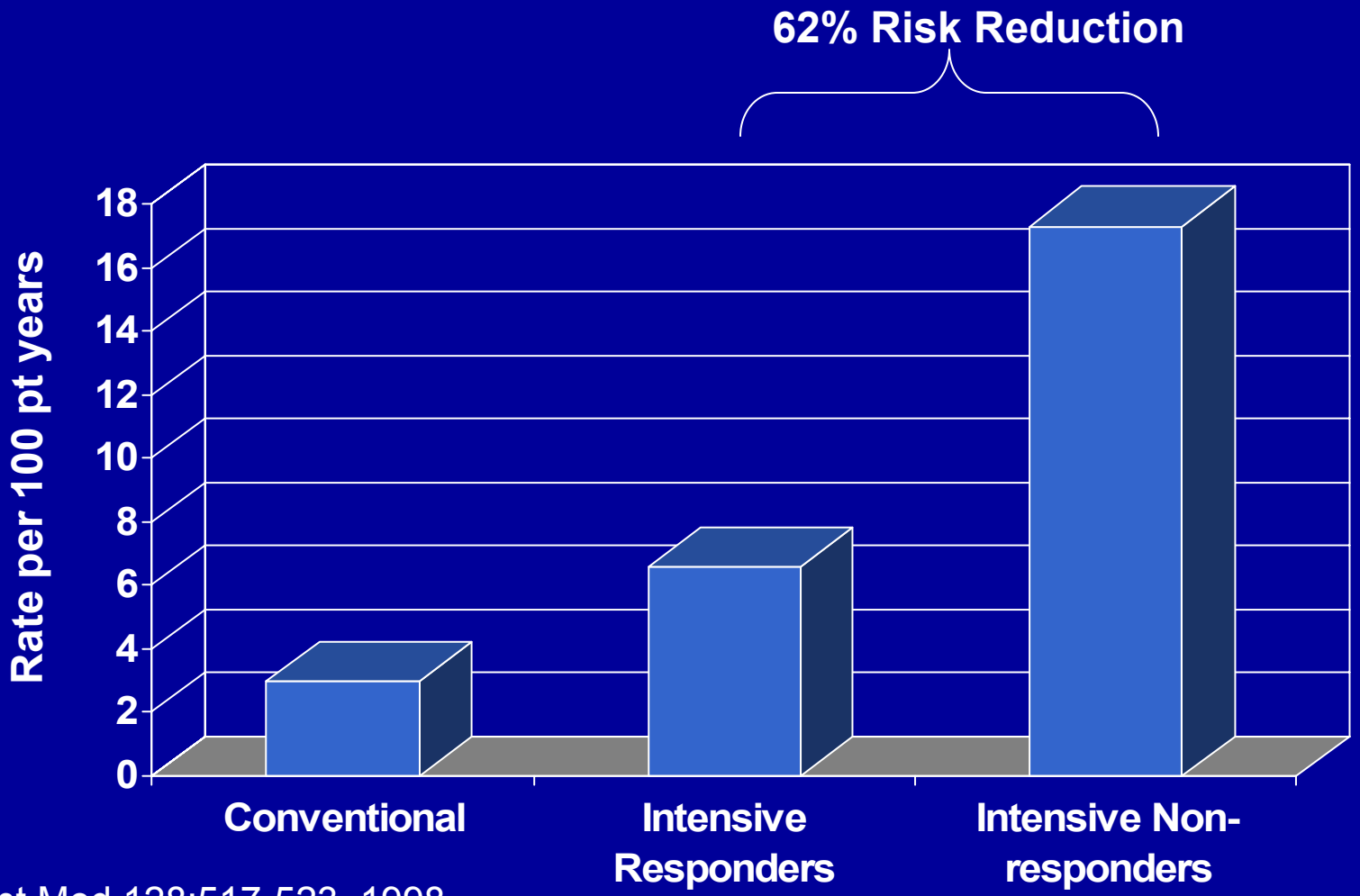
Retinopathy progression ≥ 3 step

4.4 times

Albuminuria

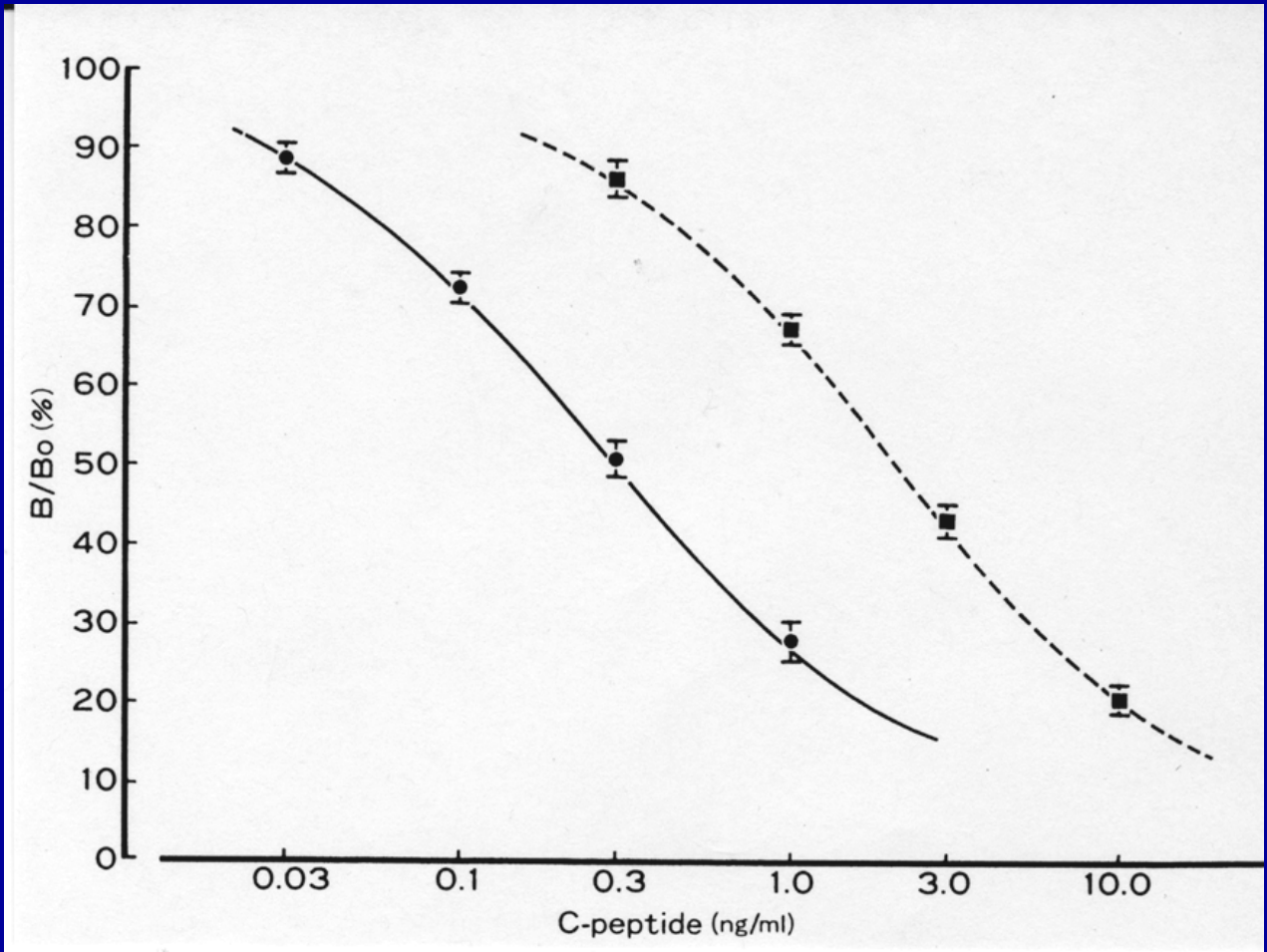
Diabetes Care 26:832-836, 2003

Benefits of β-Cell Preservation in DCCT Hypoglycemia with Coma/Seizure



Ann Int Med 128:517-523, 1998
Diabetes 53:250-264, 2004

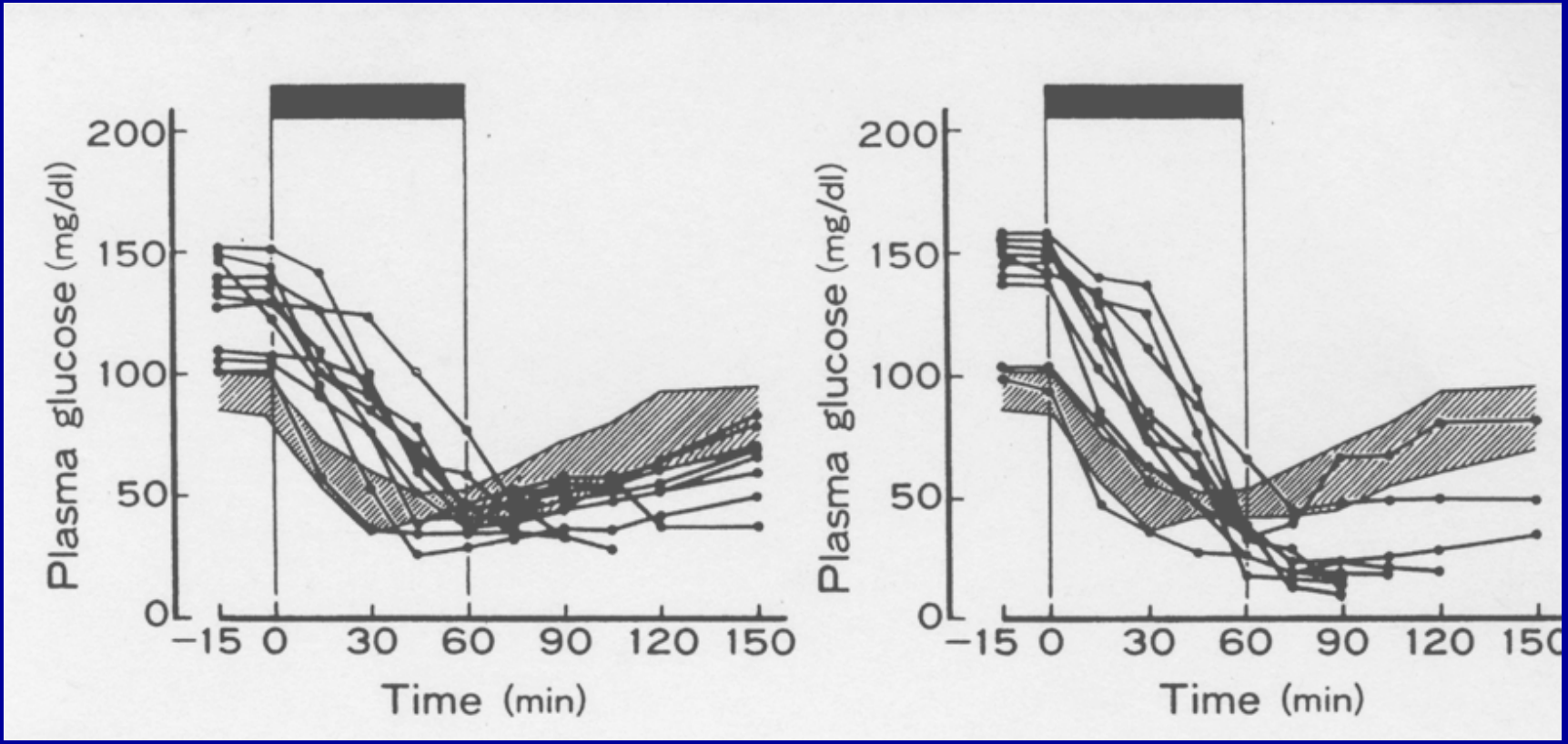
Standard Curves of Standard and Highly Sensitive C-Peptide Assays



Diabetes 37:81-88, 1988

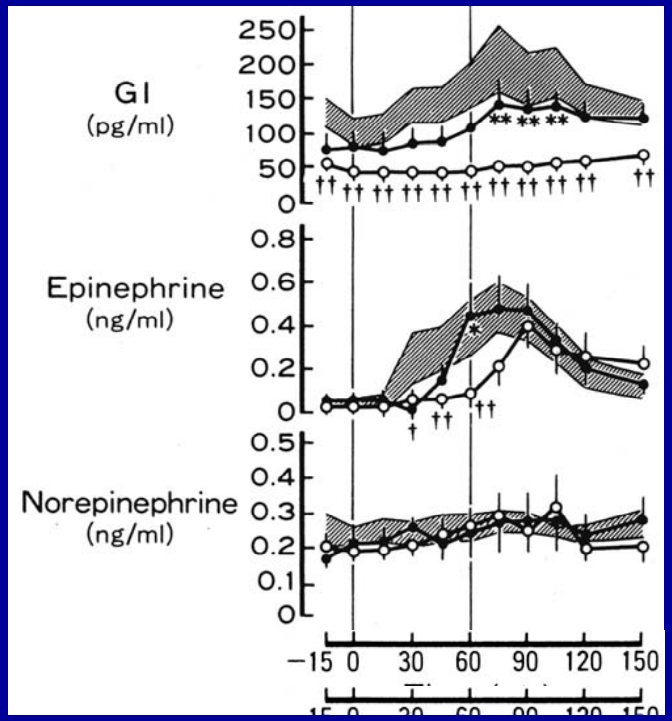
Insulin Induced Hypoglycemia

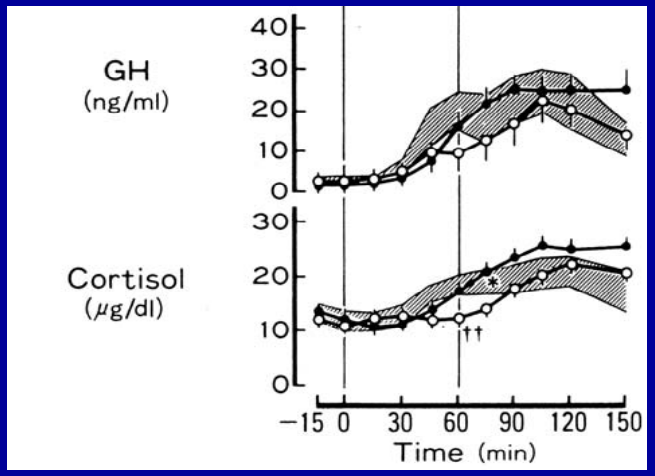
C-Peptide Responders **C-Peptide Non Responders**



Diabetes 37:81-88, 1988

Insulin Induced Hypoglycemia Counter Regulatory Responses in C-Peptide Responders and Non Responders.





Diabetes 37:81-88, 1988

Possible Direct Effects of C-Peptide

Decreased diabetes induced increaed blood flow

Decreases microalbuminuria

Improves nerve conduction velocity

Improves autonomic function

Augments glucose utilization

J of Int Med 240:115-124, 1996
Science 277: 563-66, 1997
Diabetologia 37(Suppl 2): S99-S107, 1994
Diabetes 52:536-41,2003
Diabetes 51:3077-82,2002
Diabet Med 17: 181-189, 2000
J Clin Endo Met 77: 976-981, 1993
Diabet Med 14: 655-659, 1997
Diab. Met. Res. Rev.19:345-7,2003
Diabet Med 21:428-33,2004

C-Peptide Take Home Messages

- Excellent Assays Available
- C-Peptide levels are higher than commonly assumed many years after diagnosis of T1DM
- Glycemic control preserves c-peptide
- Preserved c-peptide results in improved glycemic control
- Higher c-peptide results in less retinopathy and nephropathy
- Higher c-peptide results in less hypoglycemia
- Possible direct beneficial effects

C-Peptide as the Primary Outcome Measure for Type 1 Diabetes Clinical Trials to Preserve β-Cell Function

Activities

IDS Recommendations Diabetes 52: 1059-1065, 2003

ADA Workshop Report Diabetes 53: 250-264, 2004

Wet Workshop – University of Missouri
- optimal assay format
- standardization

International MMTT/GST Comparison