Deutsches Diabetes-Zentrum

Leibniz Gemeinschaft

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

IMMPACT-XI: Research Design Considerations for Clinical Trials of Pre-Emptive Analgesia and the Prevention of Chronic Pain Arlington, Virginia, June 5-6, 2009

Painful Diabetic Peripheral Neuropathy

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Prevention of Painful Diabetic Neuropathy

Outline

- Risk factors for painful diabetic neuropathy
- Causal treatment of diabetes and prediabetes to prevent neuropathy
- Disease-modifying treatment in diabetic polyneuropathy

Prevention of Painful Diabetic Neuropathy

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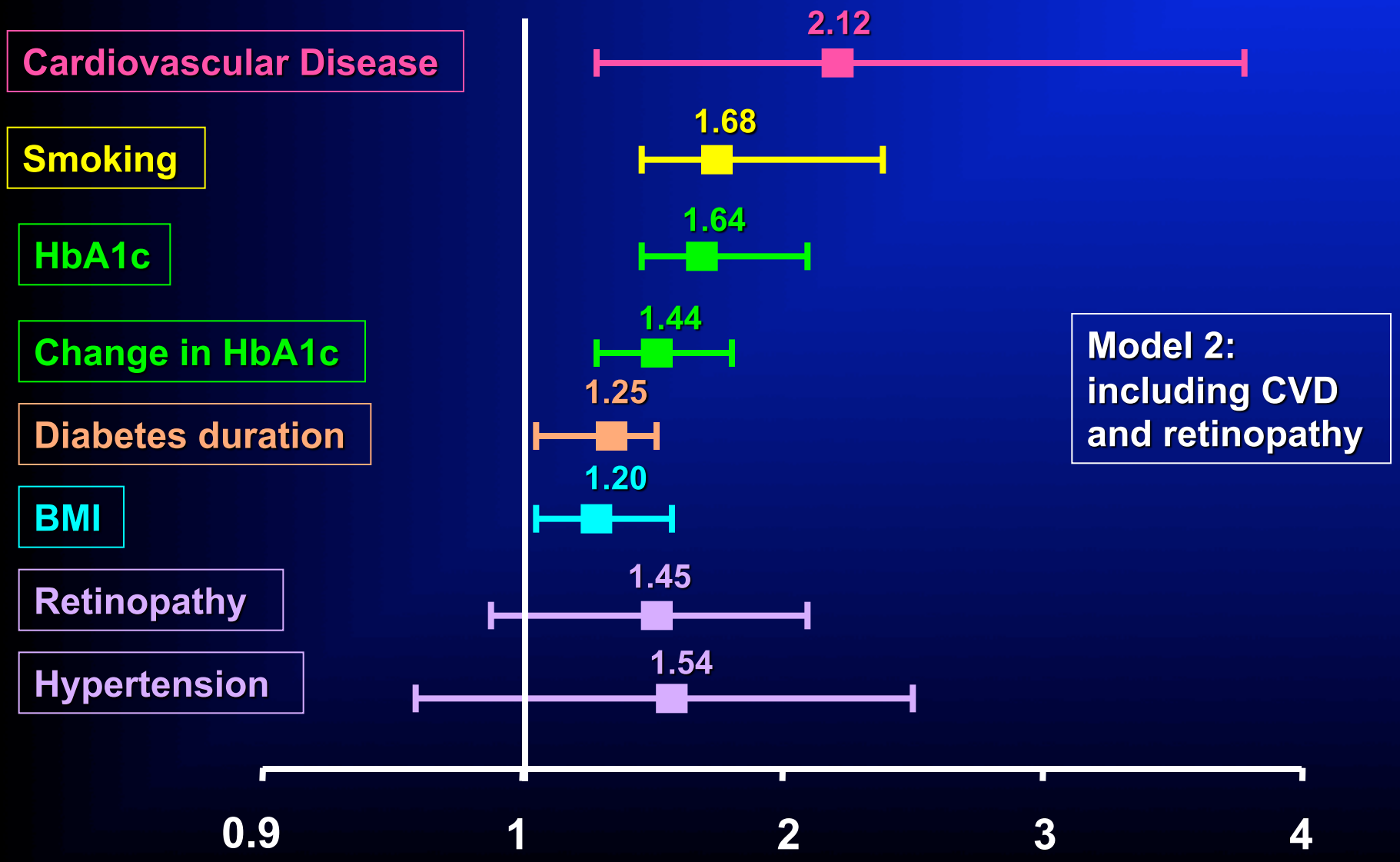
- **Disease-modifying treatment in diabetic polyneuropathy**

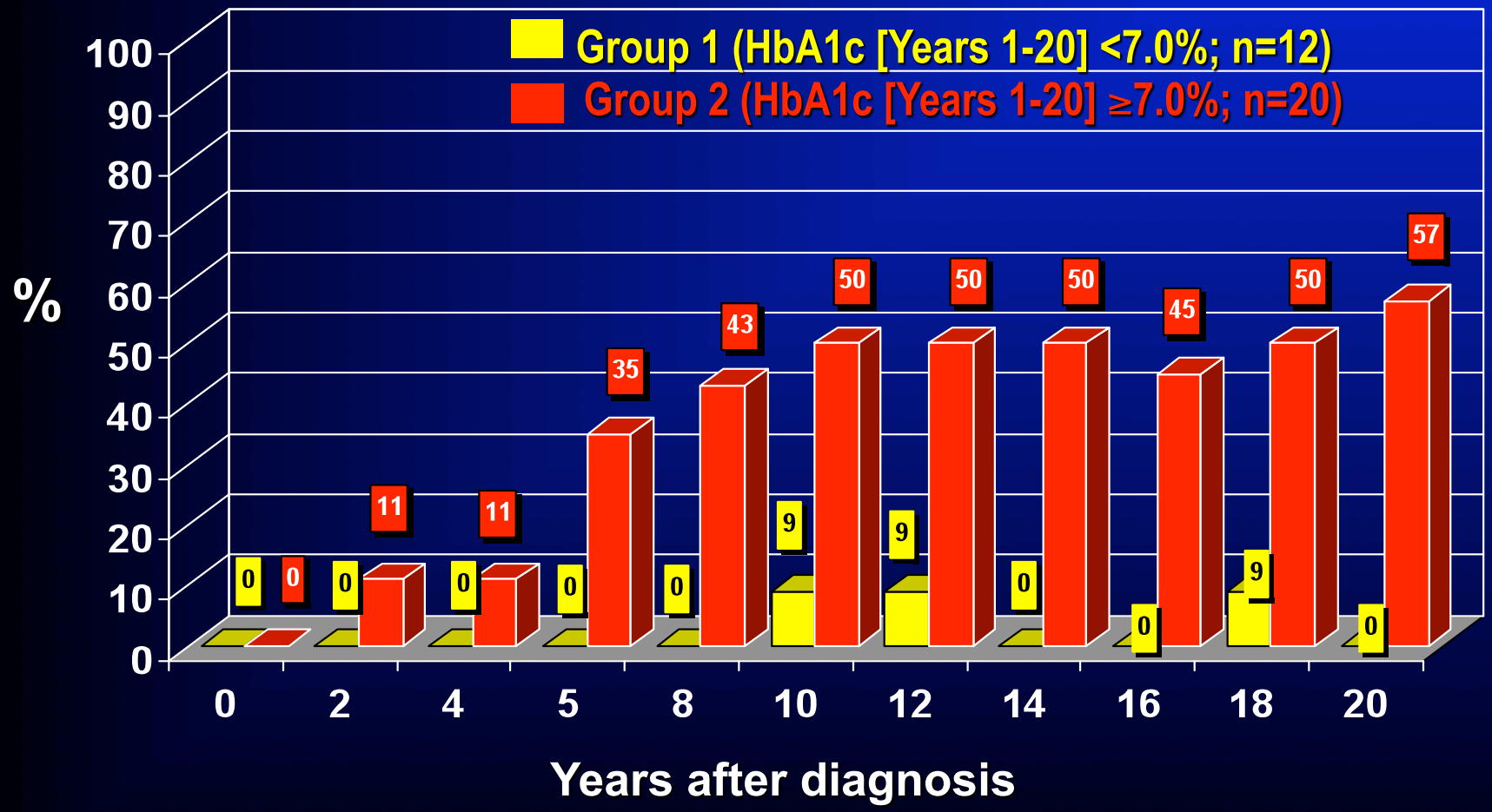
EURODIAB: Risk factors for Incidence of Polyneuropathy

Odds Ratios (95% CI); n=932 with Type 1 Diabetes; Follow-Up: 7.3±0.6 years



Tesfaye et al., N Engl J Med 2005; 352: 341-50

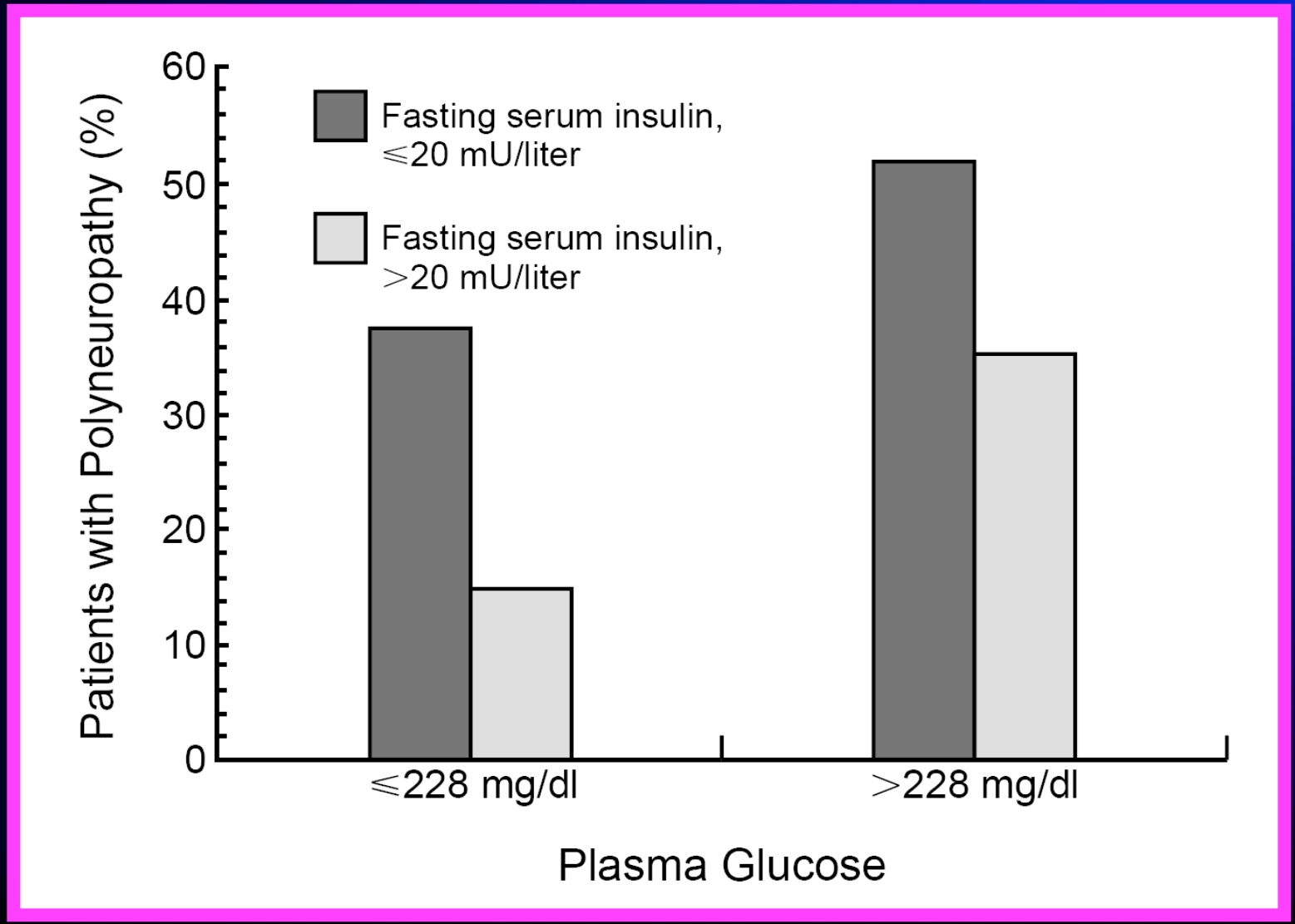
Prevention of Polyneuropathy by Near-Normoglycemia over 20 Years after Diagnosis of Type 1 Diabetes



Ziegler et al., 2007

Prevalence of DPN in Type 2 Diabetic Patients after 10 Jahren Is Associated with Initial Fasting Serum Insulin and Blood Glucose (0-5-10 Years)

Hypoinsulinemia and Hyperglycemia Are Predictors of Diabetic Polyneuropathy (DPN)



Partanen et al., N Engl J Med 1995; 333:89-94

Risk Factors and Comorbidities of Painful Diabetic Neuropathy

MONICA/KORA Augsburg Surveys S2+S3

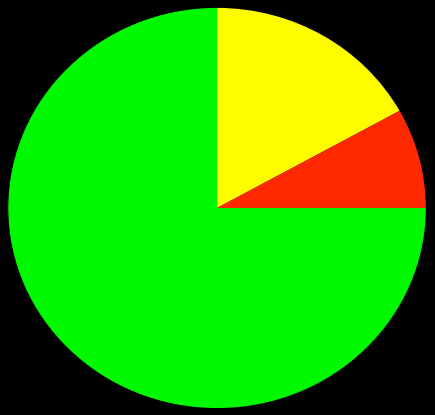
Diabetic (n=195)	OR (95% CI)	P Value
Age (years)	1.08 (1.00-1.16)	0.0389
Weight (kg)	1.03 (1.00-1.06)	0.0539
PAD (ABI<0.9)	9.27 (3.44-25.0)	<0.0001

Augsburg Myocardial Infarction Registry

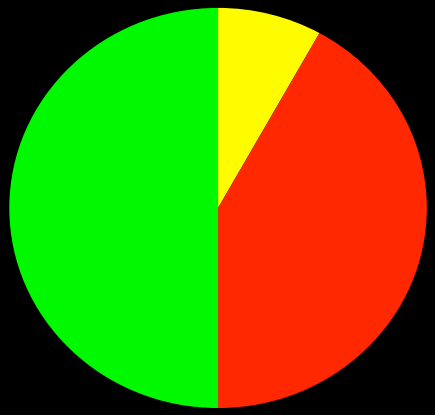
Diabetic (n=214)	OR (95% CI)	P Value
Waist circumference(cm)	1.05 (1.01-1.09)	0.0054
Physical activity	0.31 (0.10-0.99)	0.0484
PAD (ABI<0.9)	5.61 (2.43-12.96)	<0.0001

PAD = peripheral arterial disease, ABI = ankle-brachial index

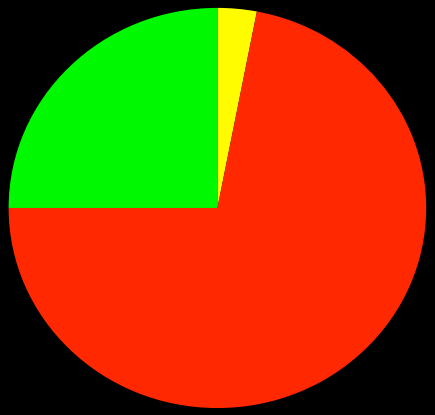
Ziegler et al., Pain Med 2009, 10: 393-400; Eur J Pain 2008, Sep 7 [Epub ahead of print]



75% Normal Function



50% Normal Function



25% Normal Function

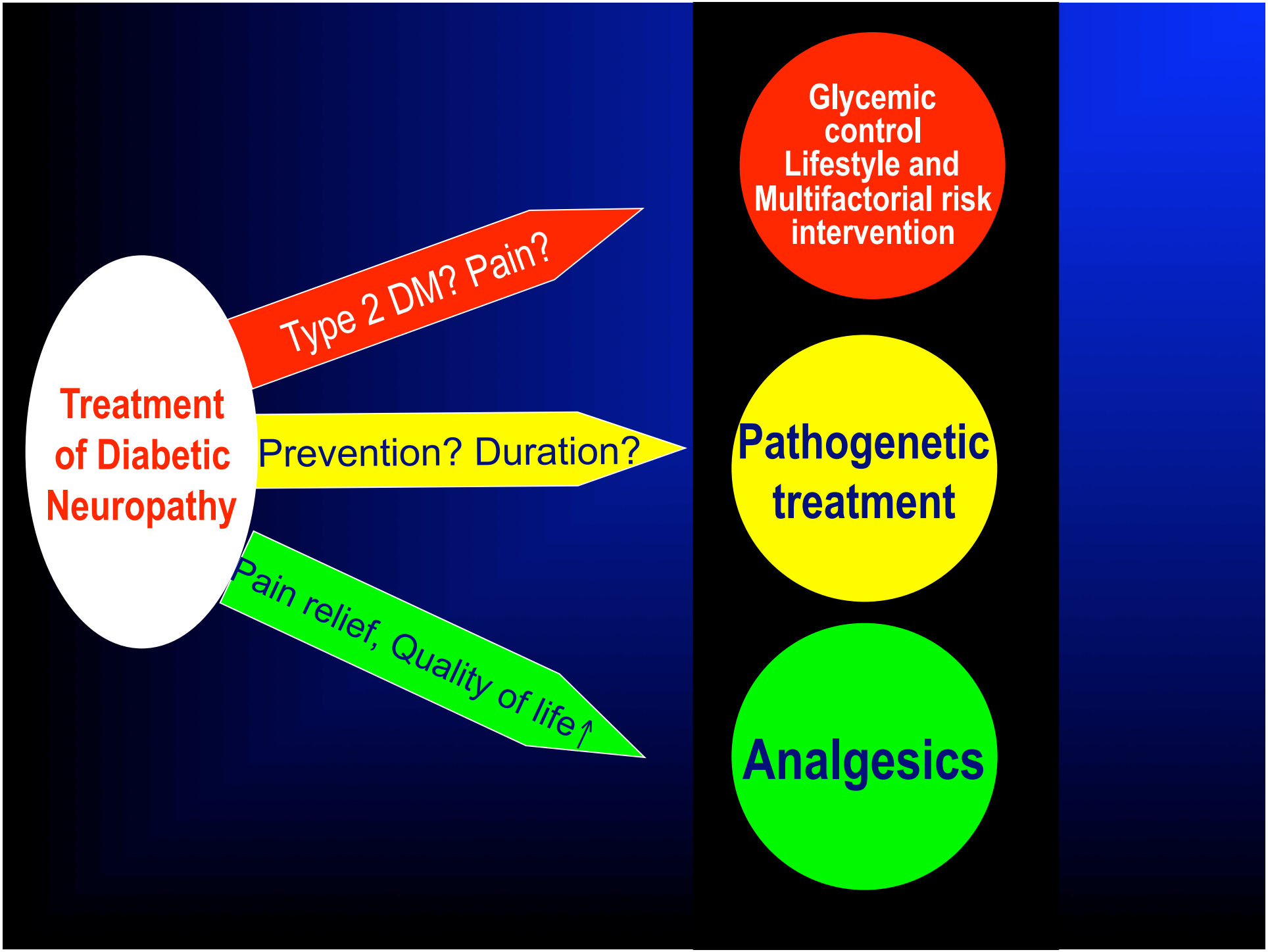
Duration of Diabetes

Irreversible Component of Abnormality

Reversible Component of Abnormality

Normal

Modified from Pfeifer & Schumer, Diabetes, 1995


Treatment of Diabetic Neuropathy
Type 2 DM? Pain?
Prevention? Duration?
Pain relief, Quality of life↑
Glycemic control Lifestyle and Multifactorial risk intervention
Pathogenetic treatment
Analgesics

Prevention of Painful Diabetic Neuropathy

Outline

- Risk factors for painful diabetic neuropathy
- **Causal treatment of diabetes and prediabetes to prevent neuropathy**
- Disease-modifying treatment in diabetic polyneuropathy

Prevention of Diabetic Neuropathy

Randomized Controlled Clinical Trials of Intensive vs Conventional Diabetes Therapy

Type 1 Diabetes

- Diabetes Control and Complications Trial (DCCT)
  Epidemiology of Diabetes Intervention and Complications Study (EDIC)
- Stockholm Diabetes Intervention Study (SDIS)
- Oslo study

Type 2 Diabetes

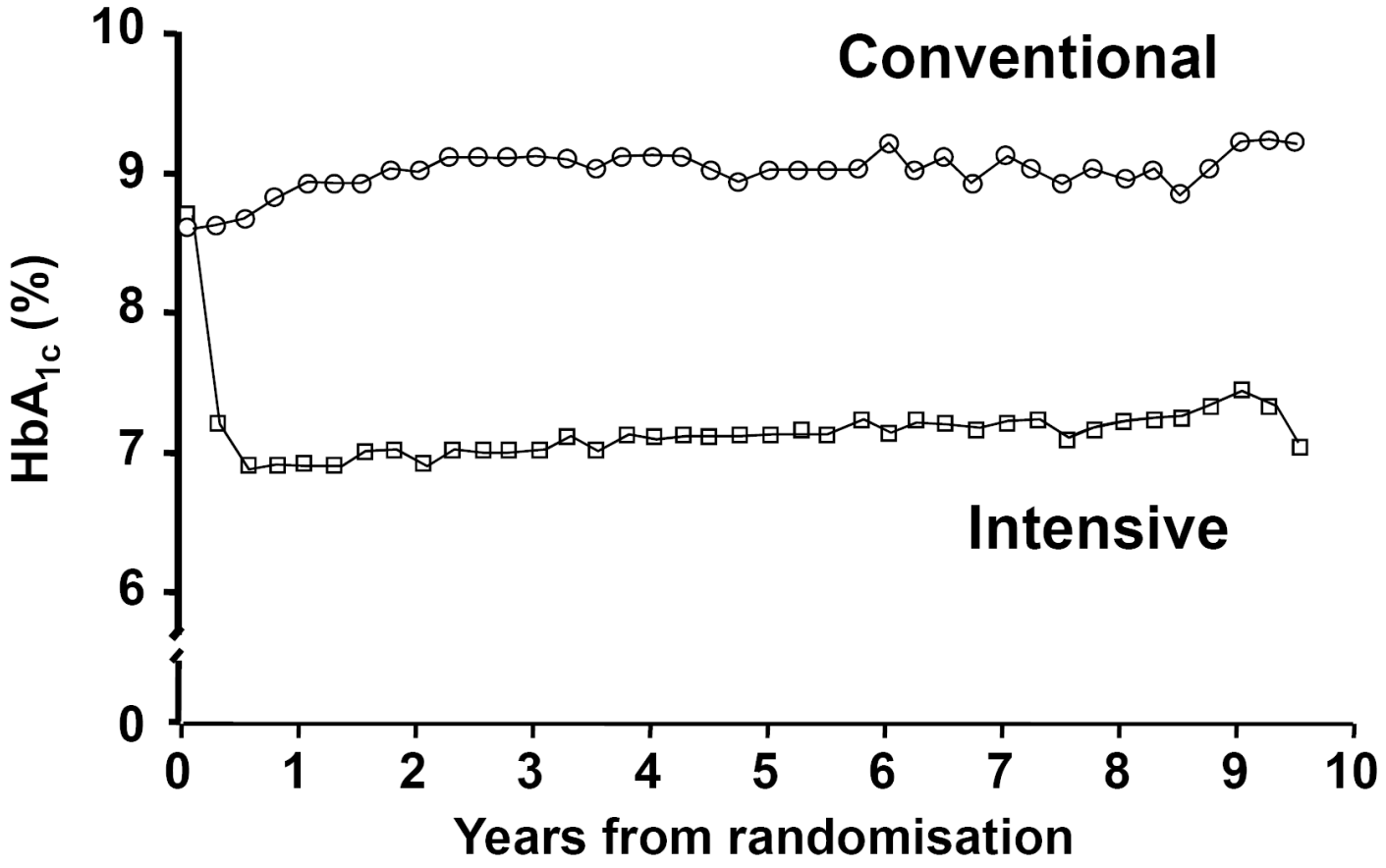
- United Kingdom Prospective Diabetes Study (UKPDS)
- Kumamoto study
- Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study
- Veterans Affairs Diabetes Trial (VADT)
- Steno Type 2 study (multifactorial risk intervention)

Prediabetes (IGT/IFG)

- Diabetes Prevention Program (DPP)

Diabetes Control and Complications Trial (DCCT)

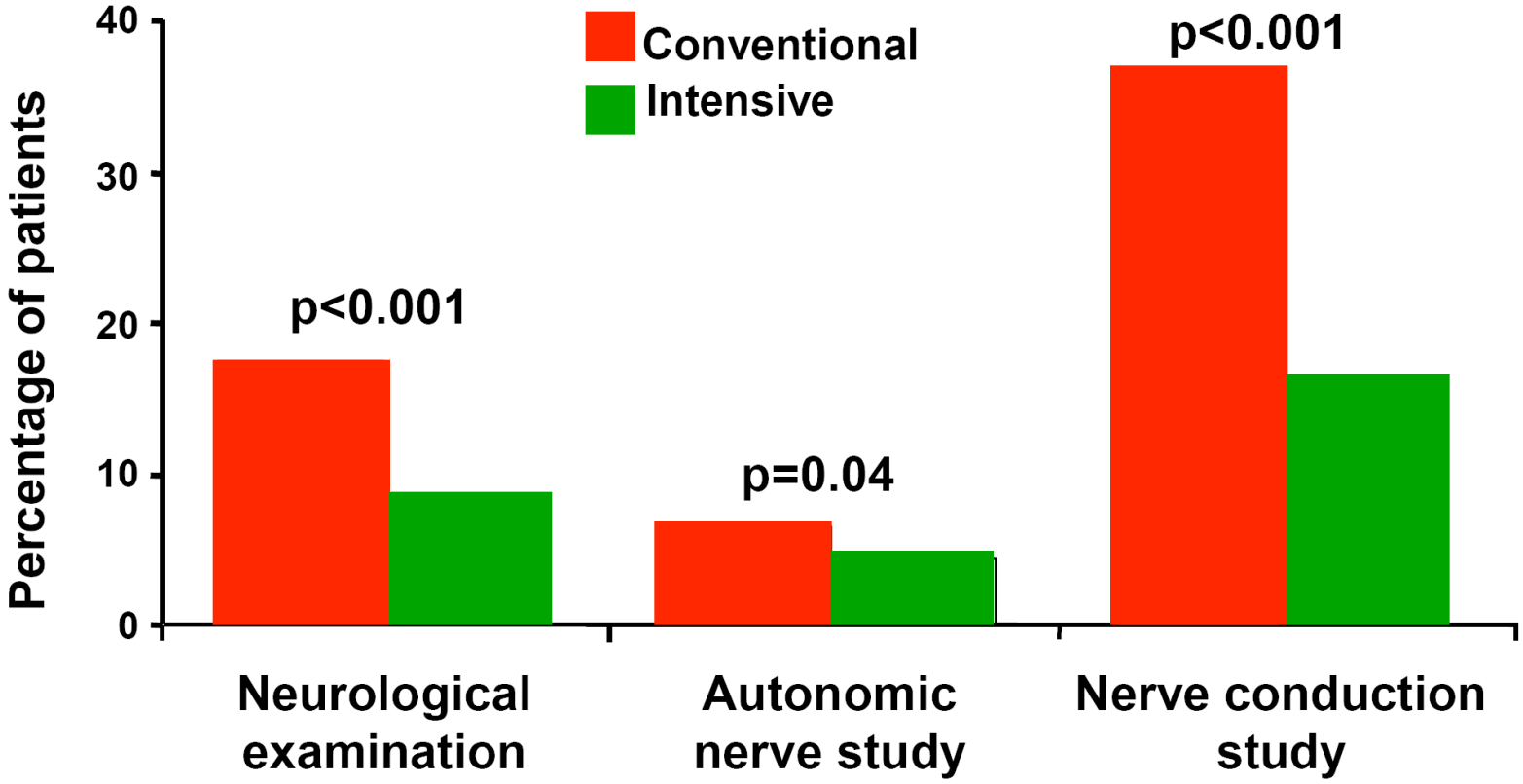
Effects of management on HbA1c



DCCT Research Group, NEJM 1993; 329:977–986

Diabetes Control and Complications Trial (DCCT)

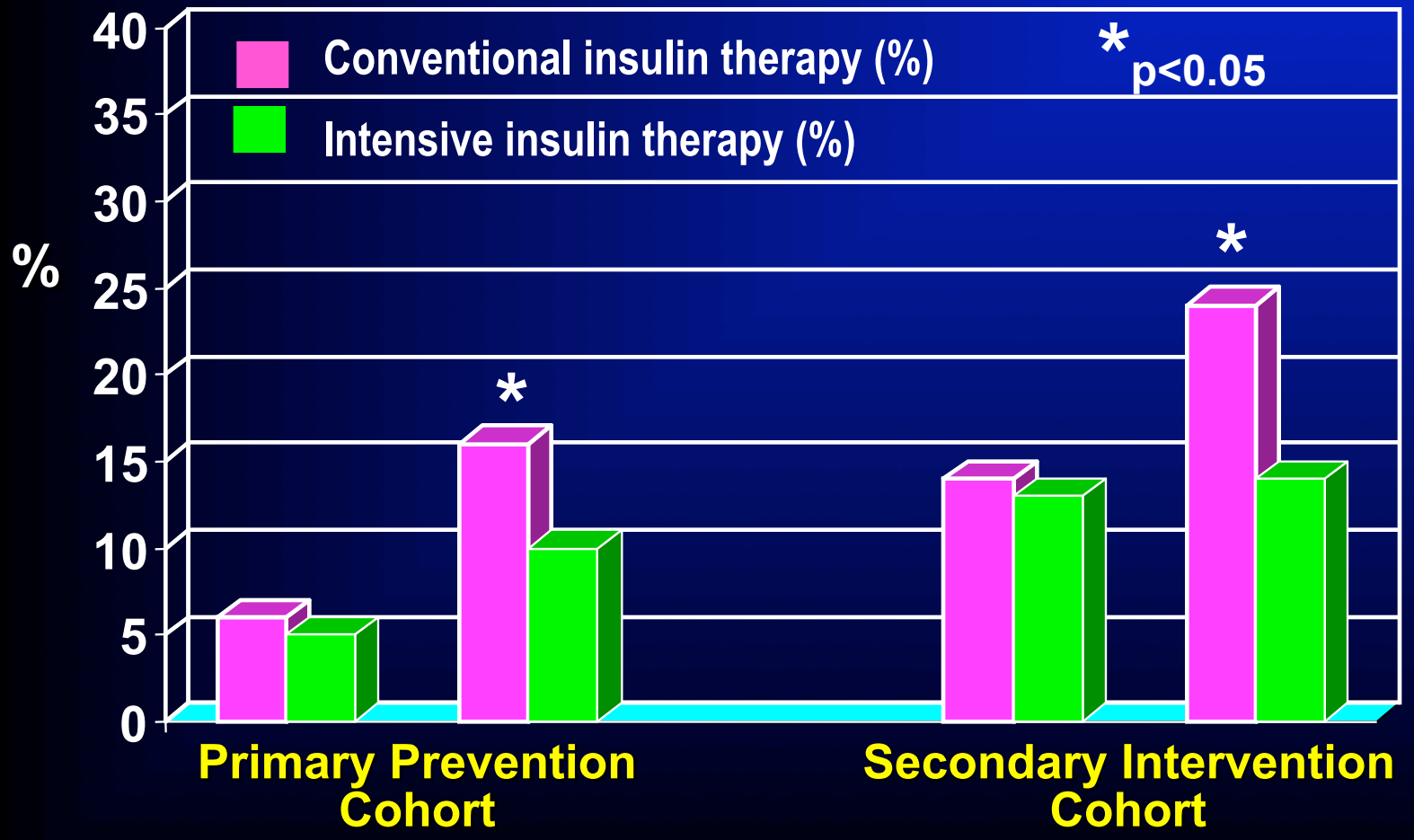
Intensive insulin therapy decreased the incidence of clinically meaningful neuropathy by 60%



DCCT Research Group, NEJM 1993; 329:977–986

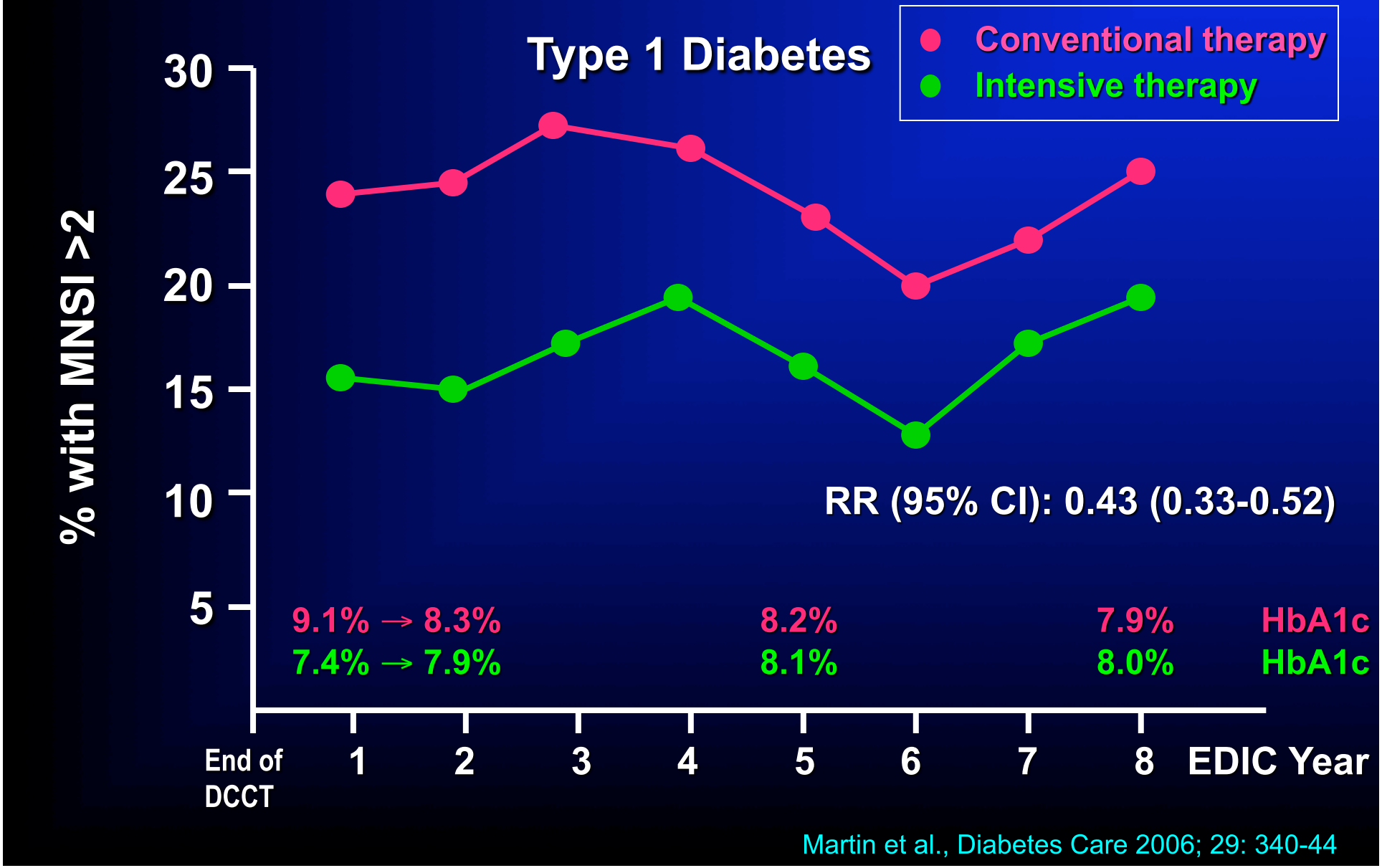
Diabetes Control and Complications Trial (DCCT)

Patients with clinically defined polyneuropathy (%)



DCCT Research Group, Ann Neurol, 1995

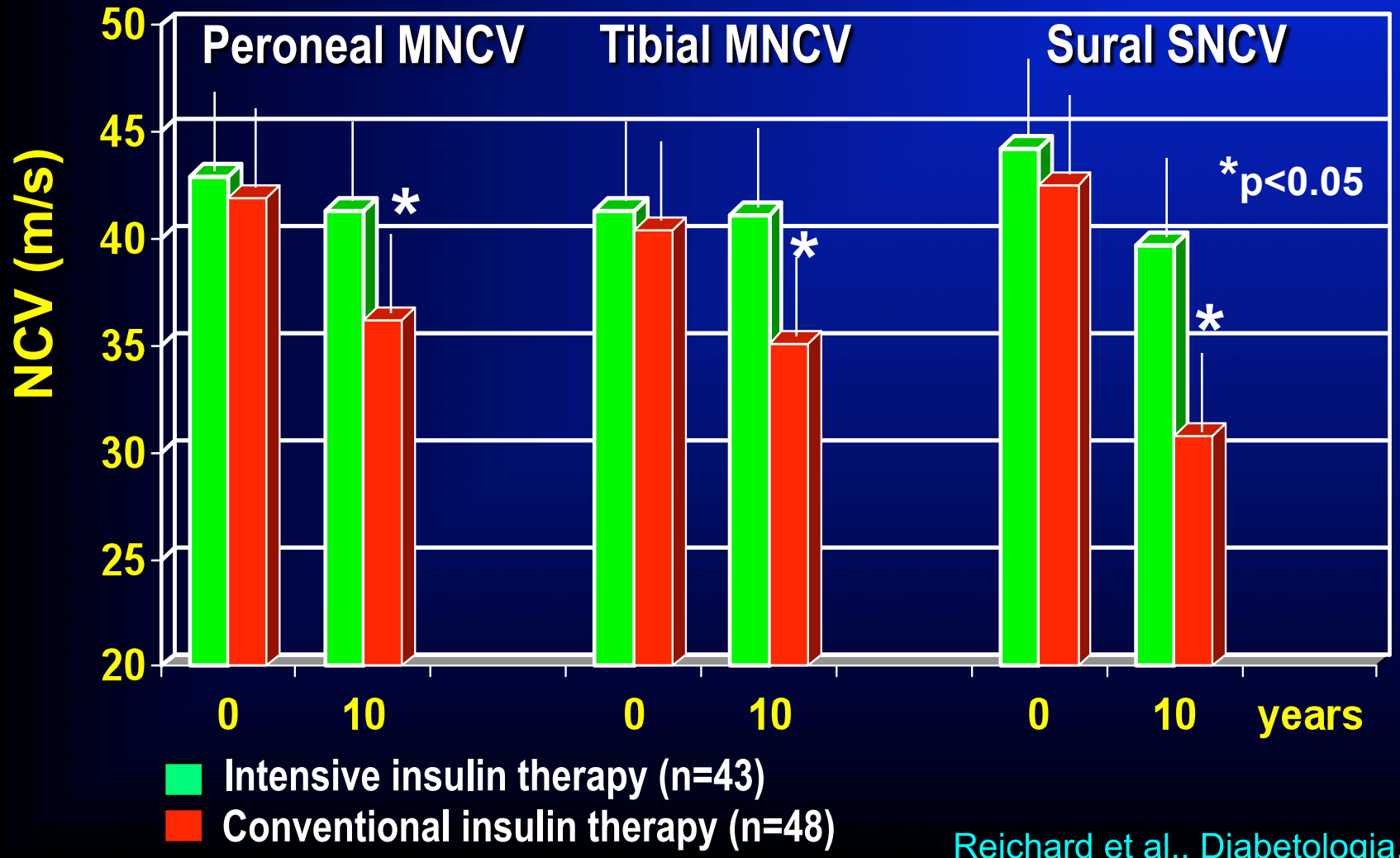
Epidemiology of Diabetes Intervention and Complications (EDIC) Study
8-Year Follow-Up of Polyneuropathy (MNSI >2) after DCCT Completion



Martin et al., Diabetes Care 2006; 29: 340-44

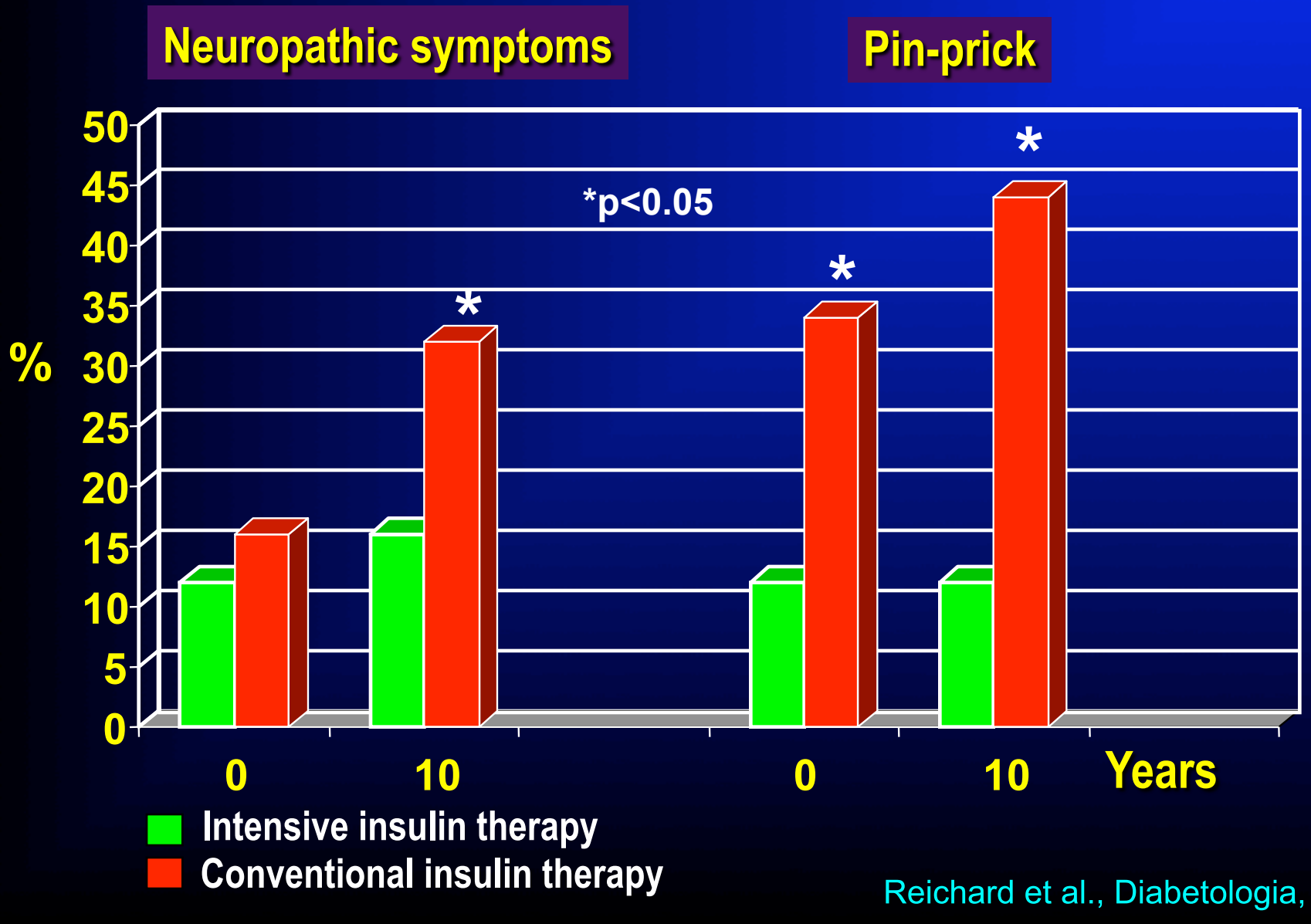
Stockholm Diabetes Intervention Study

Nerve conduction velocity (NCV) after 10 years



Reichard et al., Diabetologia, 1996

Stockholm Diabetes Intervention Study



Reichard et al., Diabetologia, 1996

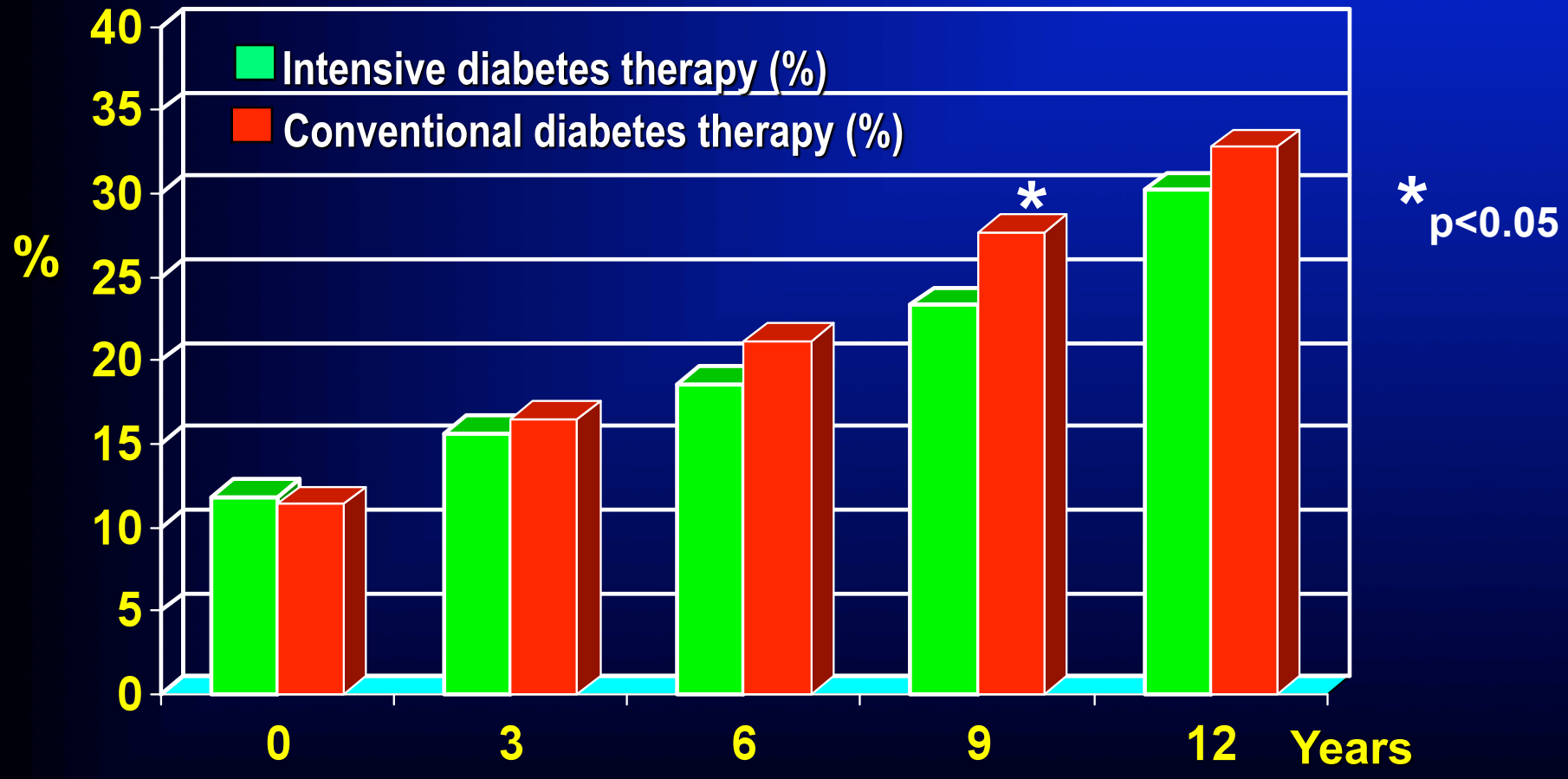
UK Prospective Diabetes Study (UKPDS)

HbA1c: Median values

UKPDS Group, Lancet, 1998

UK Prospective Diabetes Study (UKPDS)

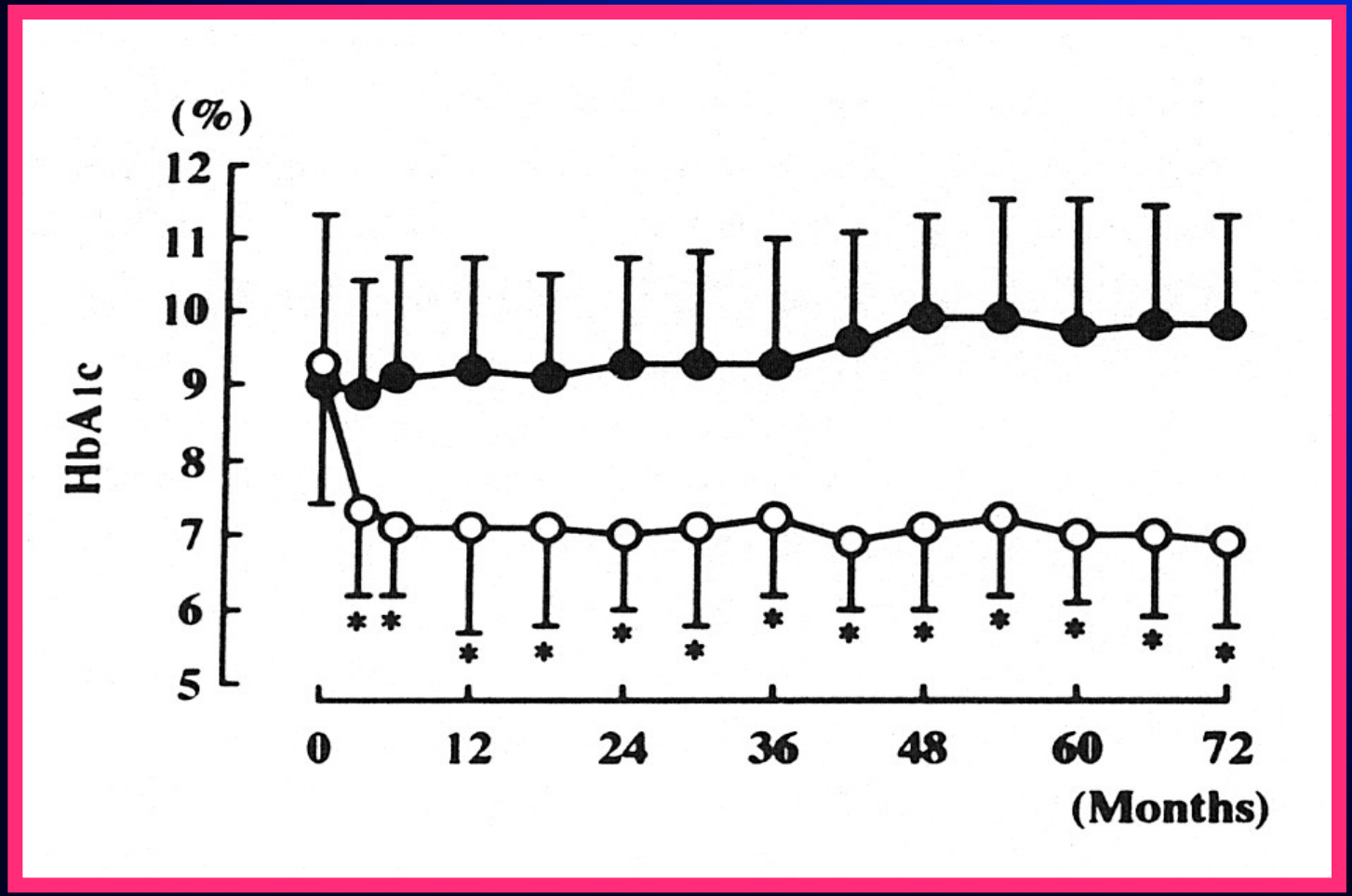
Elevated Vibration Perception Threshold (Biothesiometer >25 V)



UKPDS Group, Lancet, 1998

Kumamoto Study

HbA1c in patients receiving intensive (○) and conventional (●) insulin therapy



Ohkubo et al., Diabetes Res Clin Pract, 28, 1995

Kumamoto Study

10-Year Follow-Up

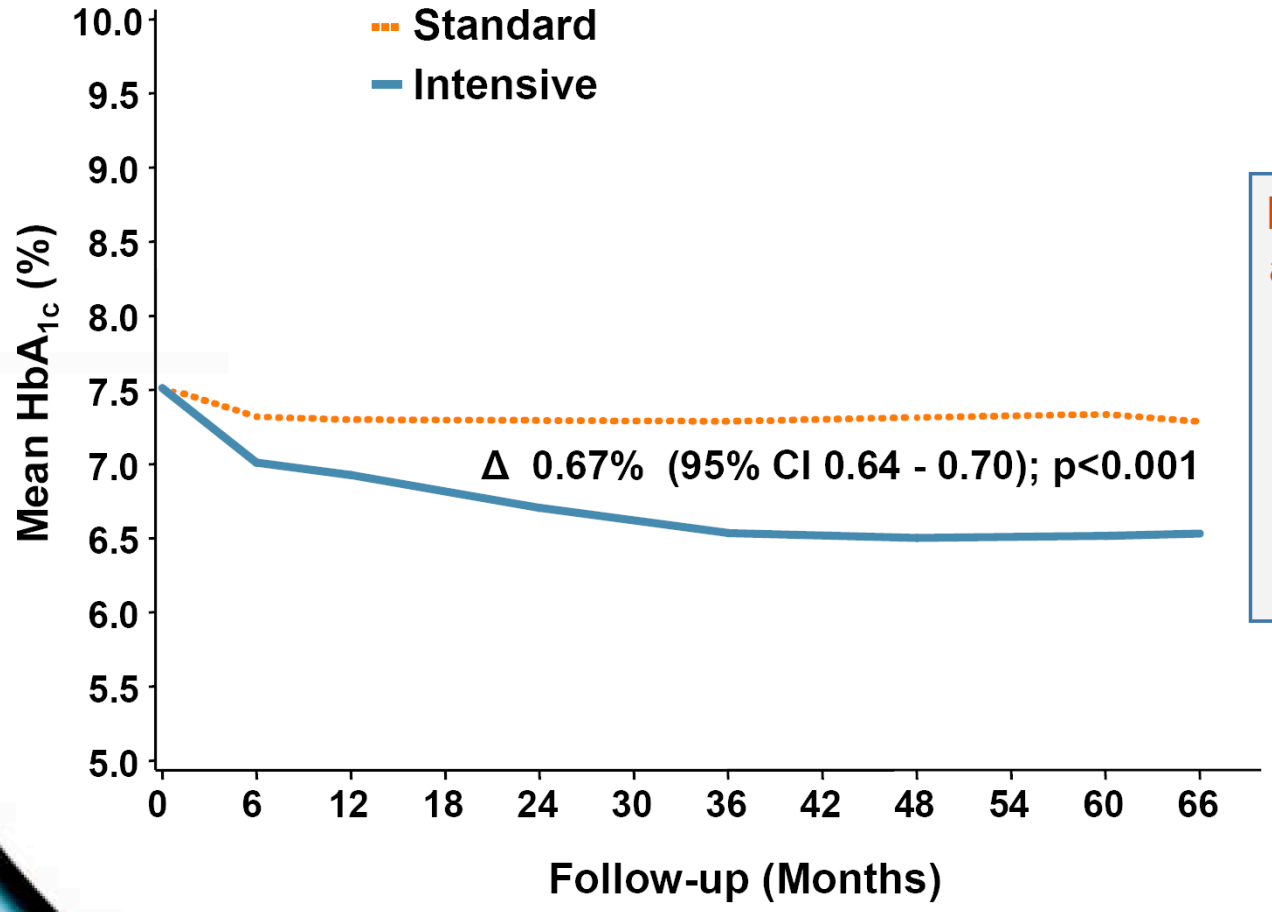
Intensive (n=55) vs. conventional (n=55) insulin therapy

- **Neuropathy (NCV+VPT↓ or AFT↓):**
  → Risk reduction by 64%
- **Neuropathy-free interval:**
  → Prolonged by 2.2 years

NCV = Nerve conduction velocity
VPT = Vibration perception threshold
AFT = Autonomic function tests

Wake et al., Diabetes Res Clin Pract, 2000

Hemoglobin A_{1c}

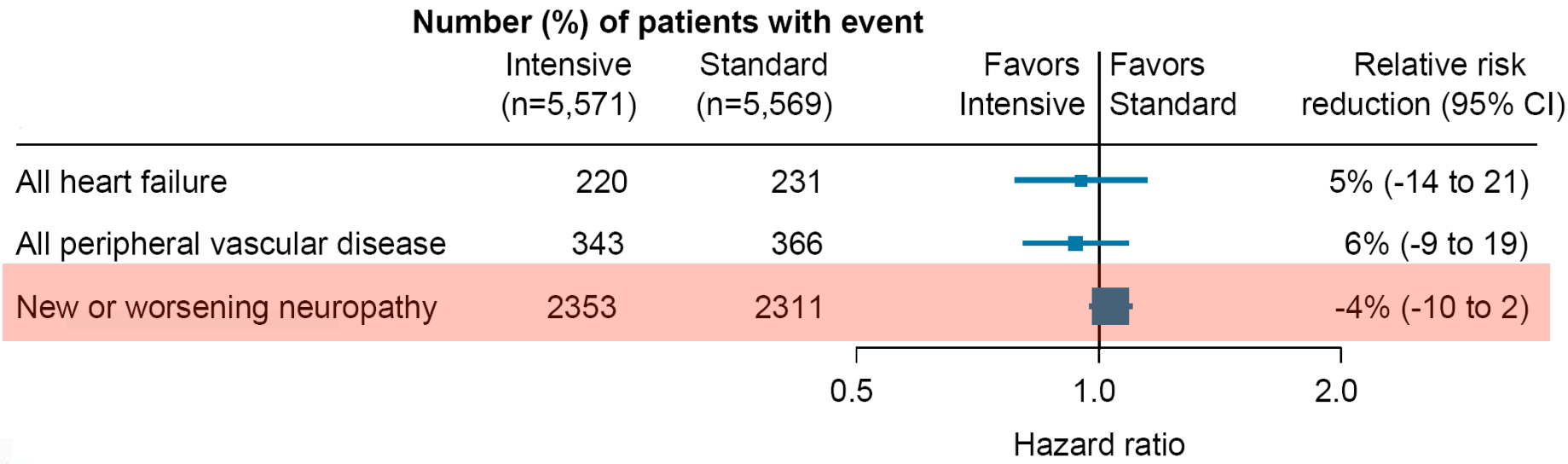


Mean HbA_{1c} at final visit	
7.3 %	
6.5%	

The George Institute for International Health

The ADVANCE Collaborative Group, N Engl J Med 2008; 358: 2560-72

Heart failure, PVD and neuropathy

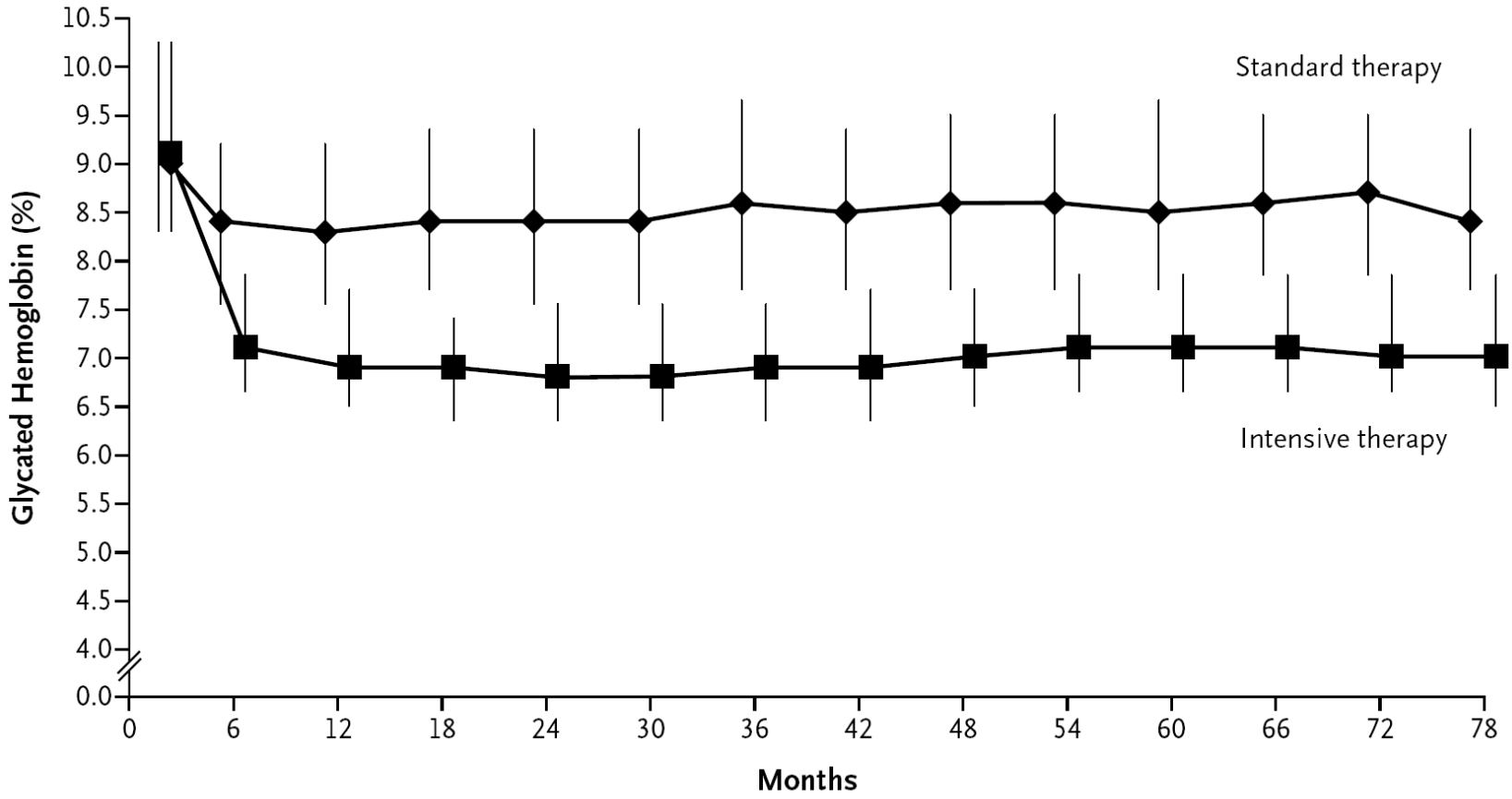


No effect of intensive diabetes treatment on the progression of polyneuropathy in type 2 diabetes

The ADVANCE Collaborative Group, N Engl J Med 2008; 358: 2560-72

Veterans Affairs Diabetes Trial (VADT)

Changes in Median Glycated Hemoglobin Levels from Baseline through 78 Months



No. at Risk													
Standard therapy	899	811	812	759	760	727	727	707	688	667	644	472	329	225
Intensive therapy	892	801	805	763	754	729	706	692	668	661	639	489	340	223

Duckworth et al., NEJM, 2008

Veterans Affairs Diabetes Trial (VADT)

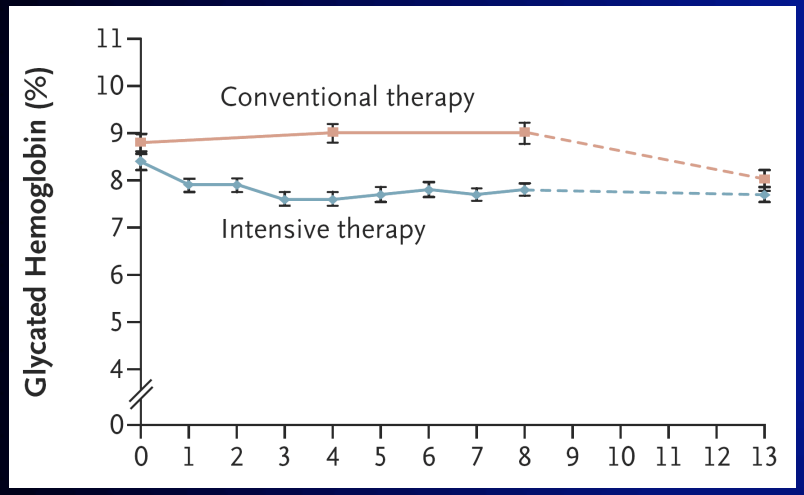
Outcome	Standard Therapy (N=899)	Intensive Therapy (N=892)	P Value†
	no./total no. (%)		
New neuropathy			
Any	218/498 (43.8)	202/464 (43.5)	0.94
Mononeuropathy	20/498 (4.0)	22/464 (4.7)	0.58
Peripheral	199/498 (40.0)	178/464 (38.4)	0.61
Autonomic	26/498 (5.2)	38/464 (8.2)	0.07

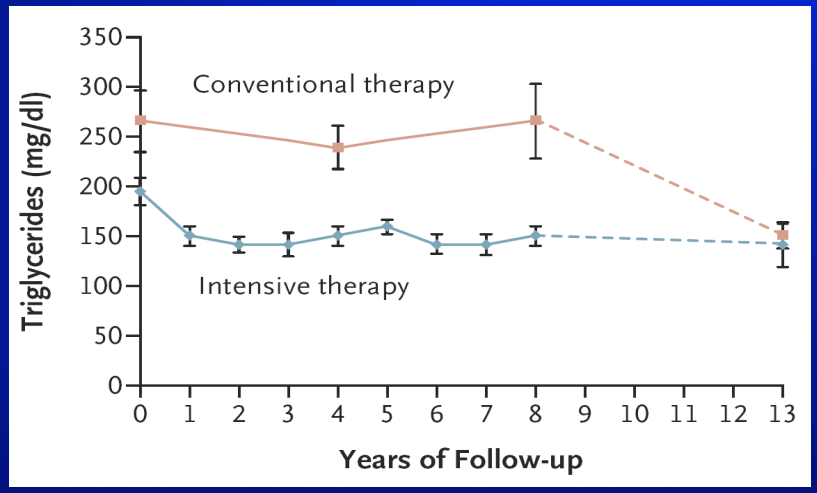
No effect of intensive diabetes treatment on the progression of neuropathy in type 2 diabetes

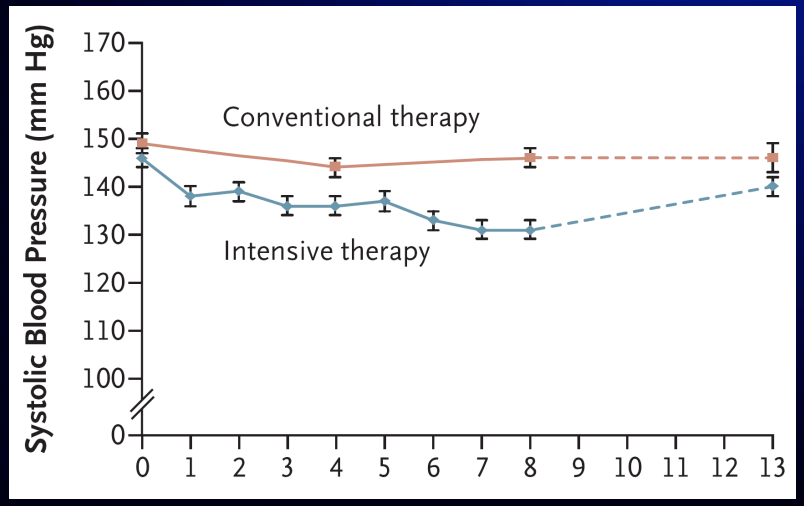
Duckworth et al., NEJM, 2008

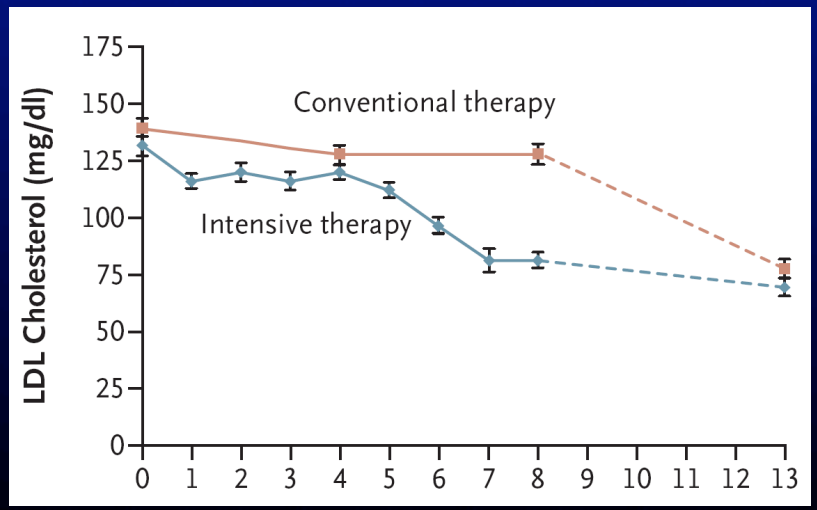
Steno Type 2 Study: Follow-Up after 13 Years

HbA1c, systolic BP, and lipids during the interventional part of the study for all patients (solid lines) and during the follow-up period (dashed lines)





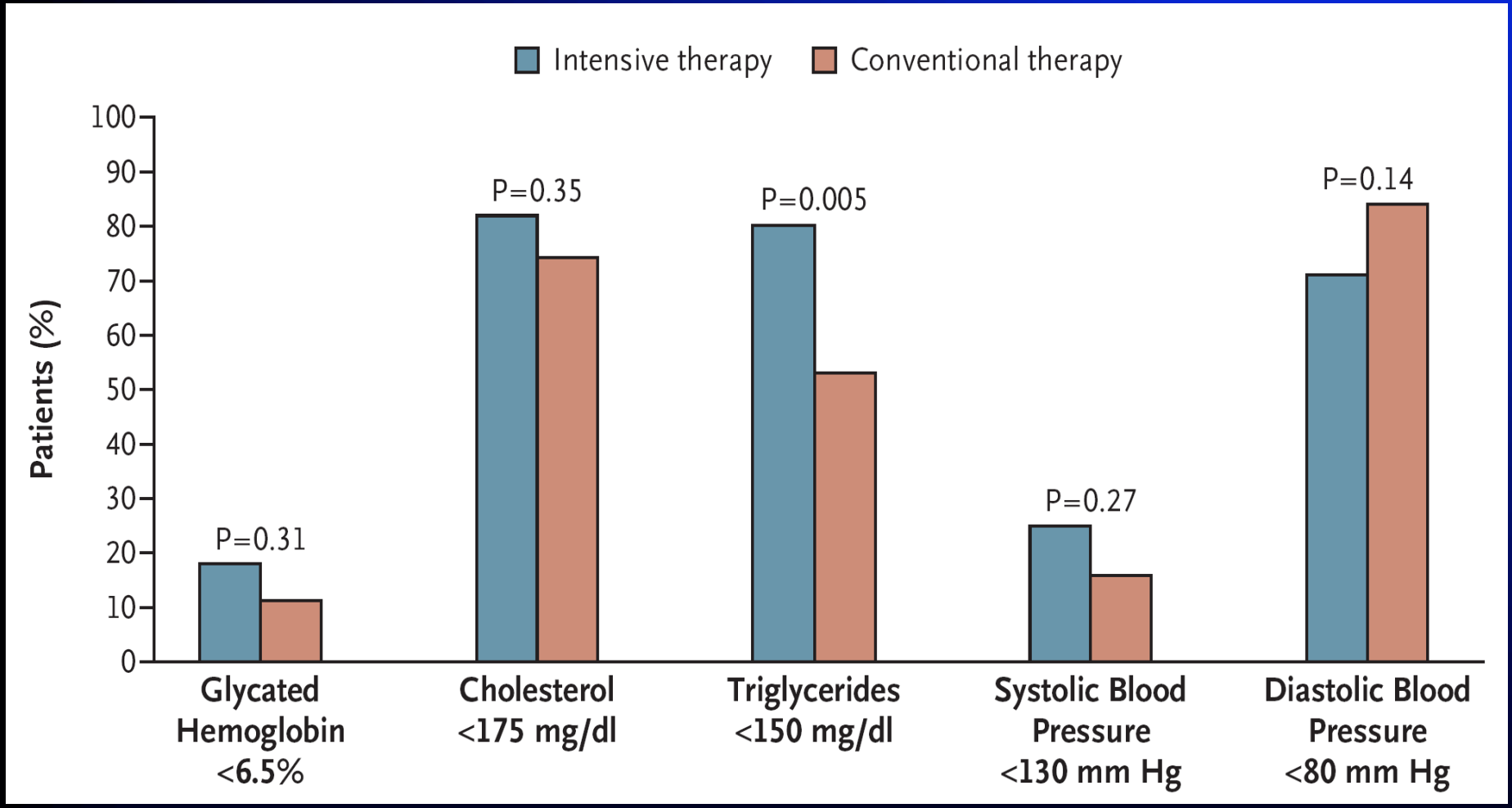




Gæde et al., *N Engl J Med* 2008; 358: 580-591

Steno Type 2 Study: Follow-Up after 13 Years

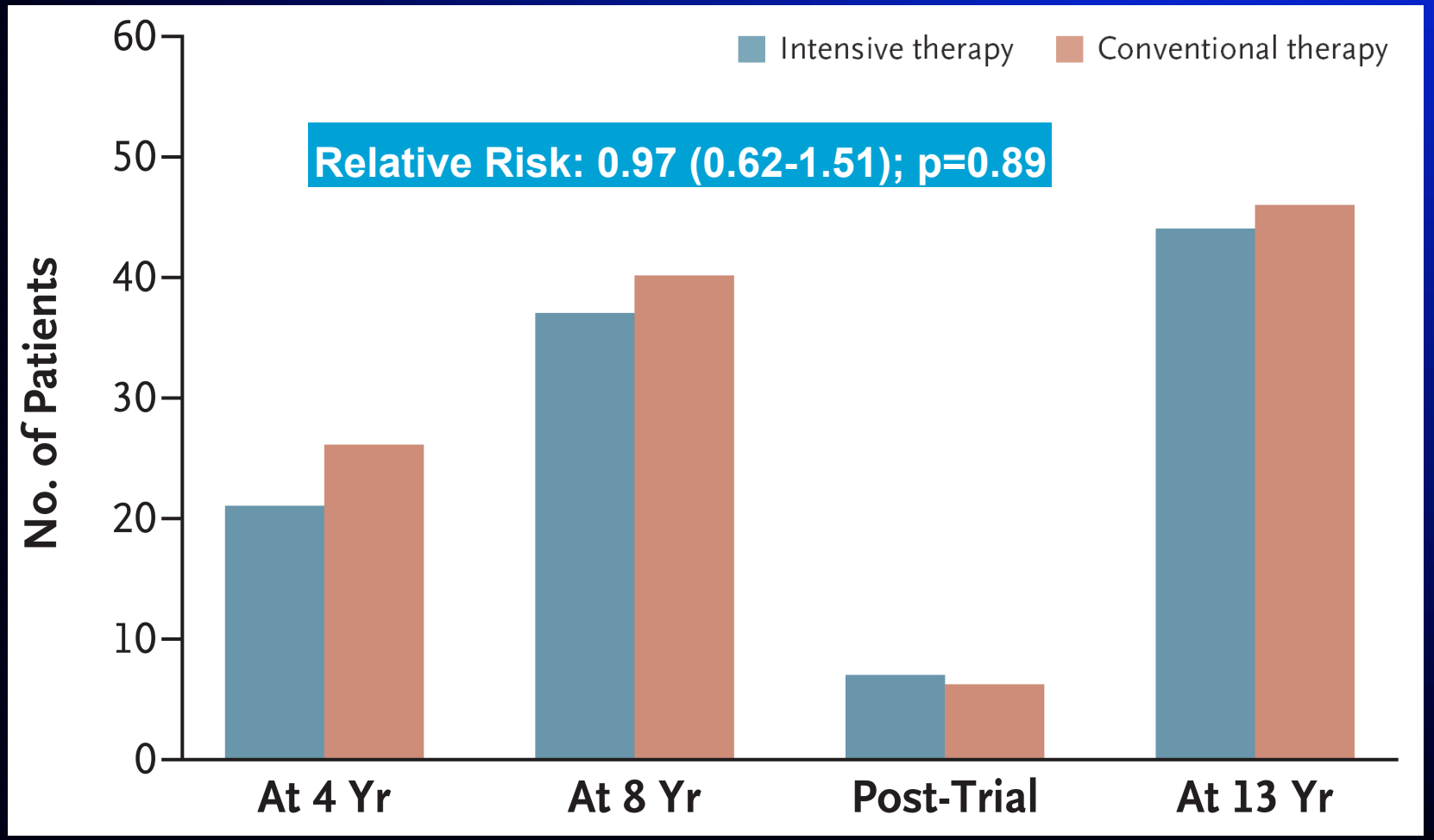
Percentages of patients who achieved the goals of intensive therapy



Gæde et al., *N Engl J Med* 2008; 358: 580-591

Steno Type 2 Study: Follow-Up after 13 Years

No effect of multifactorial intervention on the progression of peripheral neuropathy



Gæde et al., *N Engl J Med* 2008; 358: 580-591

Effects of randomized clinical trials of intensive diabetes therapy in prevention of diabetic polyneuropathy

Trial	*n*	Duration [years]	HbA_{1c} [%] CT vs IT	Neuropathy Outcome			
				Clinical	NCV	VPT	HRV
Type 1 Diabetes							
• DCCT	1441	up to 9	9.1 vs 7.2	+	+		+
• Stockholm Study	91	10	8.3 vs 7.2	+	+		
• Oslo Study	45	8	n.a.		+		
Type 2 Diabetes							
• UKPDS	3867	up to 15	7.9 vs 7.0	--		--/+ (*)	--
• Kumamoto Study	110	6	9.4 vs 7.1		+ (§)	+ (**)	--
• VADT	153	2	9.5 vs 7.4	--		--	--
• ADVANCE Study	11140	5	7.3 vs 6.5	--			
• Steno Type 2 Study	160	7.8	9.0 vs 7.7			--	+(§§)

+ = benefit; -- = no effect; (*) = only n=217 patients available after 15 years out of n=3.836 at baseline; (**)=Significant difference between CT and IT for VPT on the hand but not foot;
(§)= only NCV in the upper but not lower limbs available; (§§)= effects of ACE inhibitors, antioxidants, and statins not discernible from those of glycemic control; CT = conventional treatment; IT = intensive treatment; NCV = nerve conduction velocity; VPT = vibration perception threshold; HRV = heart rate variability

Lifestyle intervention in prediabetes

Lifestyle Intervention after 3 years in IGT (n=72)

Progression of neuropathy despite diet and exercise counseling (DPP)

	1 year	2 years	3 years
Weight	↓ (4.3%)	↔	↔
LDL cholesterol	↓	↓	↓
Weekly exercise	↑	↔	↔
2h BG in OGTT	↔	↓	↔
IENFD	↑	↔	(↓)
QSART	↑	↔	(↓)
LDF	↑	↔	(↓)
UENS		↔	↓

IENFD = Intraepidermal nerve fiber density
QSART = Quantitative sudomotor axon reflex test
LDF = Laser Doppler flow
UENS = Utah Early Neuropathy Scale

↑ **Increased**
↓ **Decreased**
↔ **Unchanged**

Singleton et al., Neurology 2007 (abstract)

Disease-modifying treatment of diabetic neuropathy based on the putative pathogenetic mechanisms

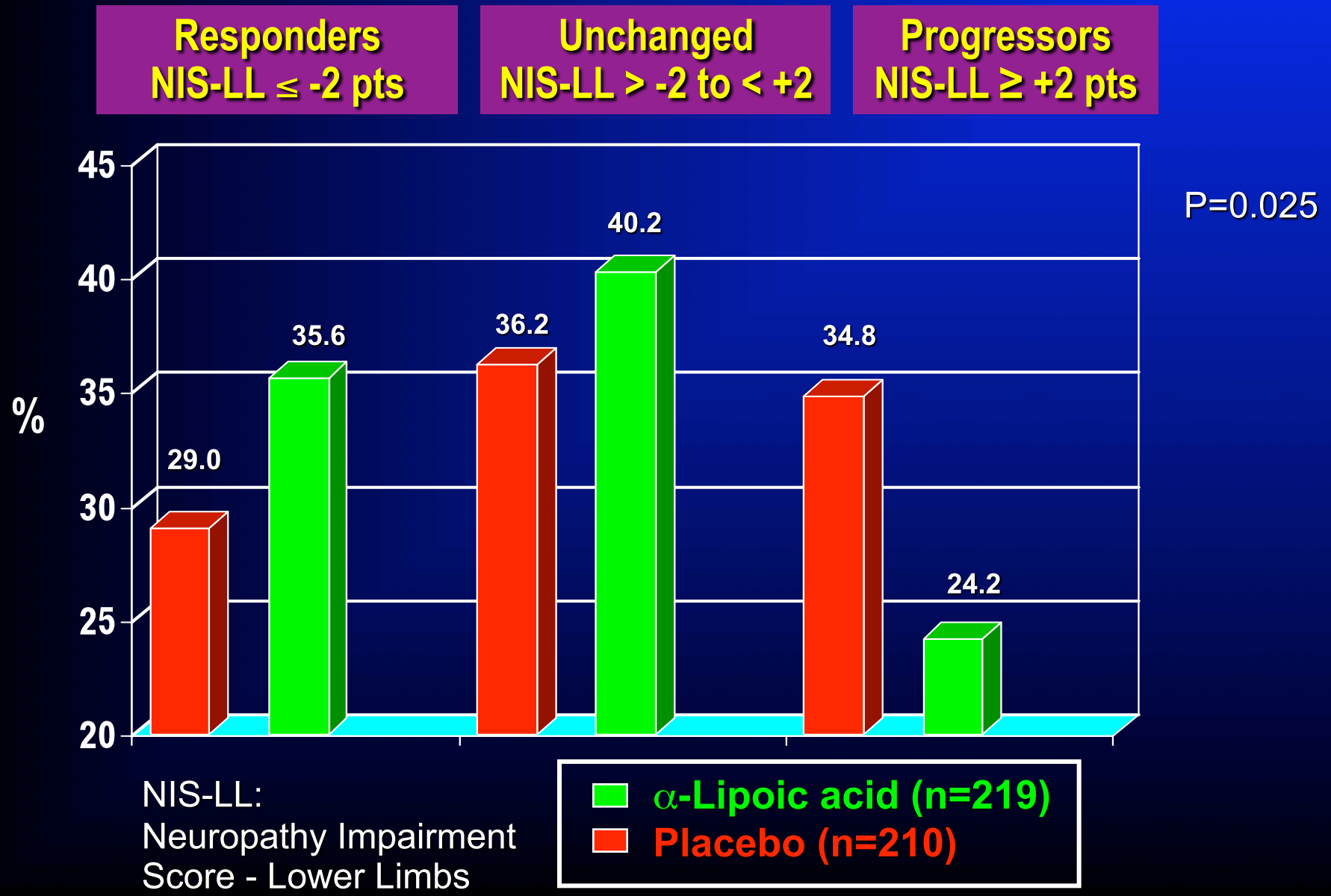
Abnormality	Compound	Aim of treatment	Status of RCTs
Polyol pathway ↑	Aldose reductase inhibitors	Nerve sorbitol ↓	
	Sorbinil		Withdrawn (AE)
	Tolrestat		Withdrawn (AE)
	Ponalrestat		Ineffective
	Zopolrestat		Withdrawn (marginal effects)
	Zenarestat		Withdrawn (AE)
	Lidorestat		Withdrawn (AE)
	Fidarestat		Effective in RCTs, trials ongoing
	AS-3201		Effective in RCTs, trials ongoing
	Epalrestat		Marketed in Japan
Myo-inositol ↓	*Myo*-inositol	Nerve *myo*-inositol ↑	Equivocal
Oxidative stress ↑	α-Lipoic acid	Oxygen free radicals ↓	Effective in RCTs, trials ongoing
Nerve hypoxia ↑	Vasodilators	NBF ↑	
	ACE inhibitors		Effective in one RCT
	Prostaglandin analogs		Effective in one RCT
	phVEGF$_{165}$ gene transfer	Angiogenesis ↑	RCTs ongoing
Protein kinase C ↑	Protein kinase C-β inhibitor (ruboxistaurin)	NBF ↑	RCTs ongoing
C-peptide ↓	C-peptide	NBF ↑	Studies ongoing
Neurotrophism ↓	Nerve growth factor (NGF)	Nerve regeneration, growth ↑	Ineffective
	BDNF	Nerve regeneration, growth ↑	Ineffective
LCFA metabolism ↓	Acetyl-L-carnitine	LCFA accumulation ↓	Ineffective
GLA synthesis ↓	γ-Linolenic acid (GLA)	EFA metabolism ↑	Withdrawn
NEG ↑	Aminoguanidine	AGE accumulation ↓	Withdrawn

AE, adverse event; AGE: advanced glycation end product; BDNF, brain-derived neurotrophic factor; EFA: essential fatty acid; LCFA, long-chain fatty acid; NBF, nerve blood flow; NEG, nonenzymatic glycation; RCT, randomized clinical trial.

Ziegler, Diabetes Care 2008

NATHAN 1 Study

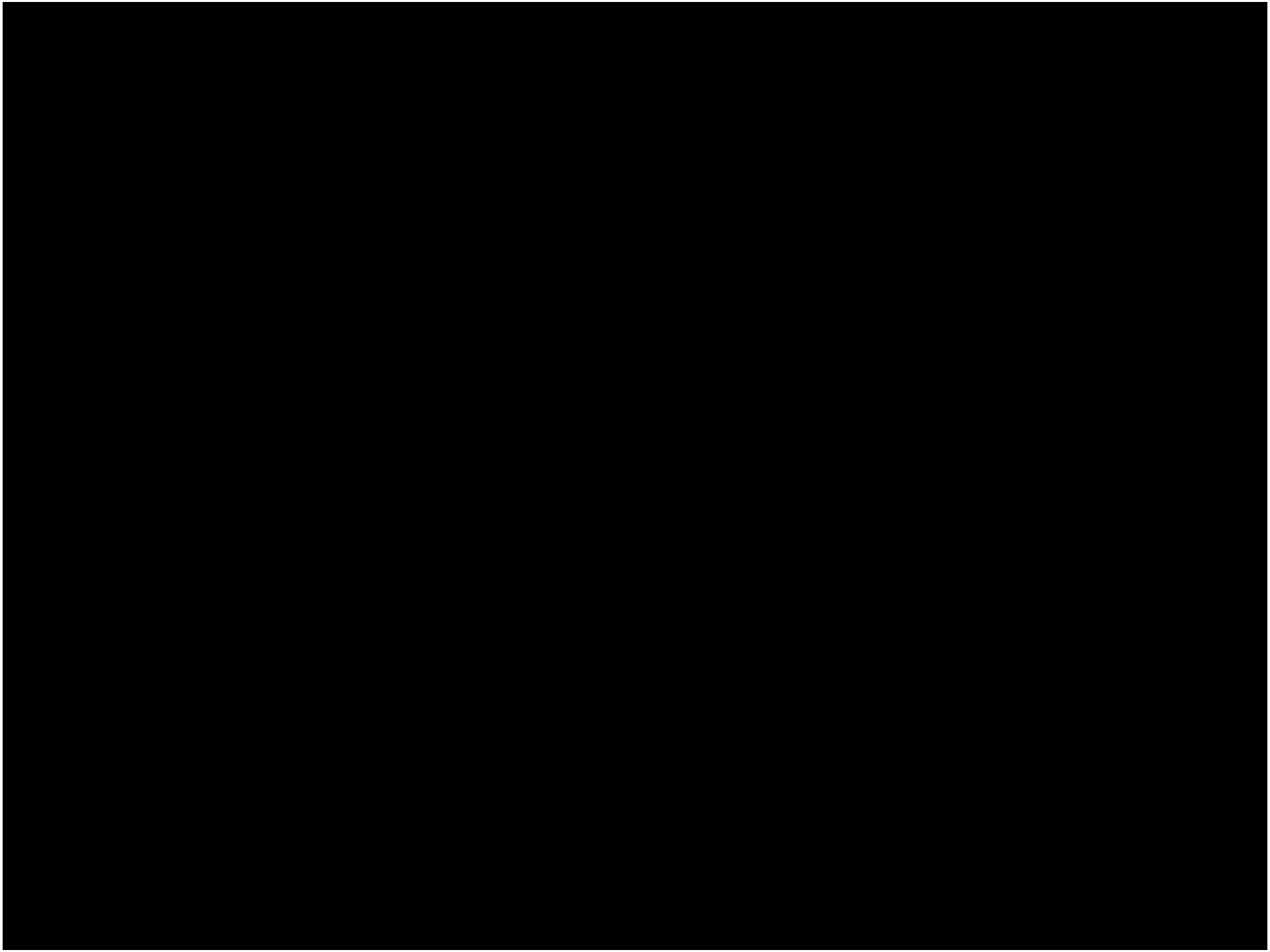
NIS-LL Responders vs NIS-LL Progressors after 4 Years



Ziegler et al., 2007

Conclusions

- Cardiovascular risk factors may represent targets for strategies to prevent (painful) diabetic polyneuropathy.
- Intensive diabetes therapy aimed at normo-glycemia prevents the development/progression of polyneuropathy in type 1 diabetes, but there is no such a clear evidence in type 2 diabetes and prediabetes.
- No controlled prevention studies are available in painful diabetic neuropathy.



KORA A Study: MONICA/KORA Augsburg Surveys S2+S3
Augsburg Myocardial Infarction Registry

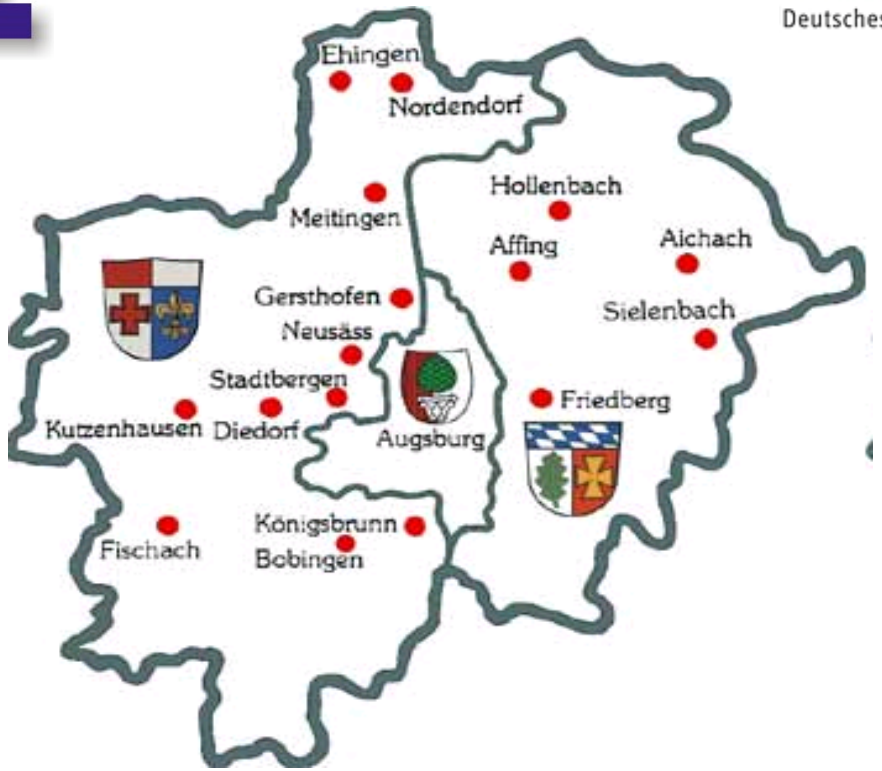
Leibniz Gemeinschaft

KOOPERATIVE GESUNDHEITSFORSCHUNG IN DER REGION AUGSBURG
KORA

HELMHOLTZ GEMEINSCHAFT

DDZ

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt



Definition of Painful Neuropathy

Pain in the lower legs/feet

+

MNSI Score >2 points

Michigan Neuropathy Screening Instrument (MNSI)

Clinical examination

1. Appearance of feet

	Right	Left
a. Normal	☐ 0 Yes ☐ 1 No	☐ 0 Yes ☐ 1 No
b. If no, check all that apply:		
Deformities	☐	☐
Dry skin, callus	☐	☐
Infection	☐	☐
Fissure	☐	☐
Other	☐	☐
specify:	_____	_____

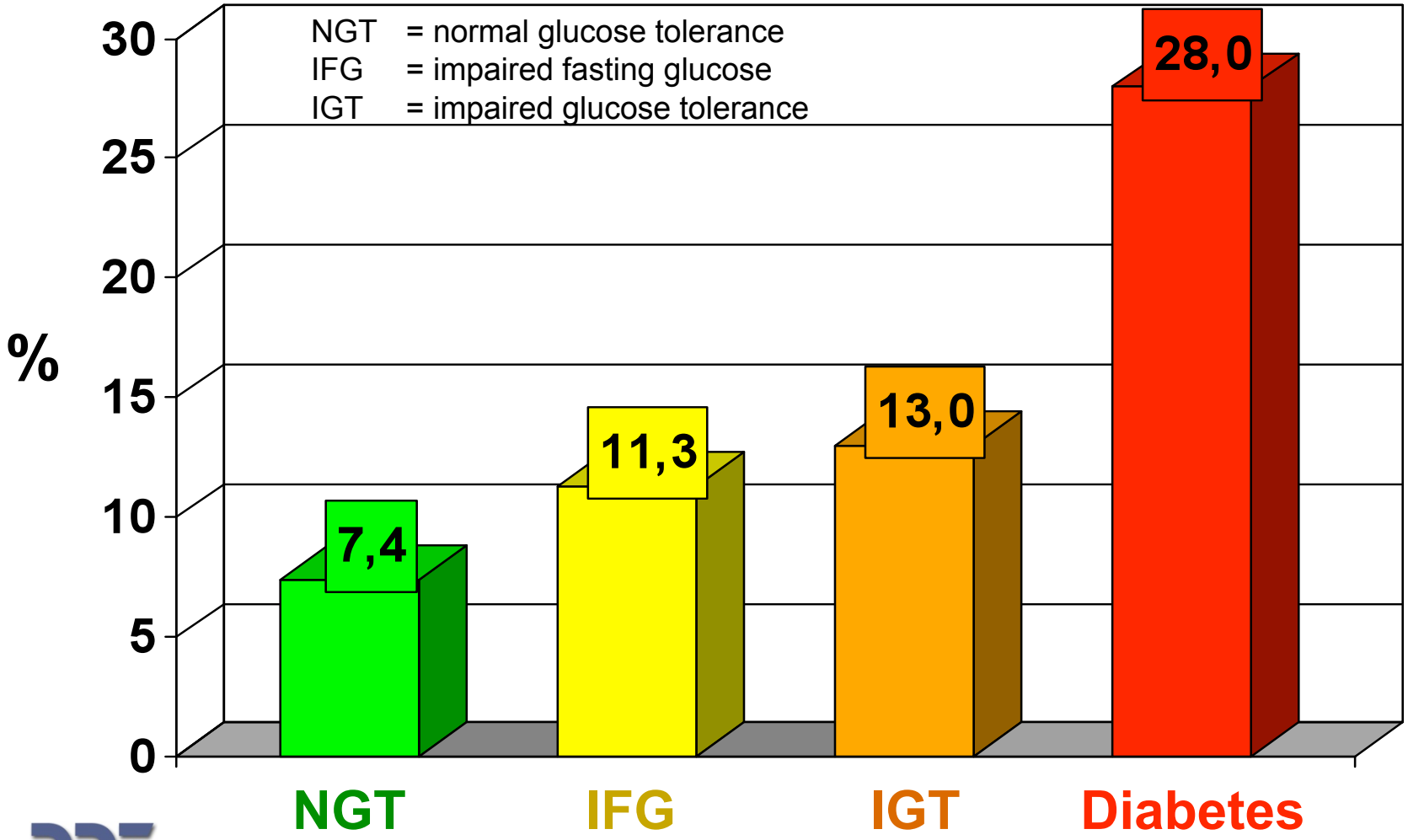
	Right		Left	
2. Ulceration	Absent ☐ 0	Present ☐ 1	Absent ☐ 0	Present ☐ 1

	Right			Left		
3. Ankle reflexes	Present ☐ 0	Present/ Reinforcement ☐ 0.5	Absent ☐ 1	Present ☐ 0	Present/ Reinforcement ☐ 0.5	Absent ☐ 1
4. Vibration perception at great toe	Present ☐ 0	Decreased ☐ 0.5	Absent ☐ 1	Present ☐ 0	Decreased ☐ 0.5	Absent ☐ 1
5. Monofilament	Normal ☐ 0	Reduced ☐ 0.5	Absent ☐ 1	Normal ☐ 0	Reduced ☐ 0.5	Absent ☐ 1

Feldman et al., Diabetes Care 1994; 17: 1281-9

Prevalence of Polyneuropathy in Prediabetes and Diabetes

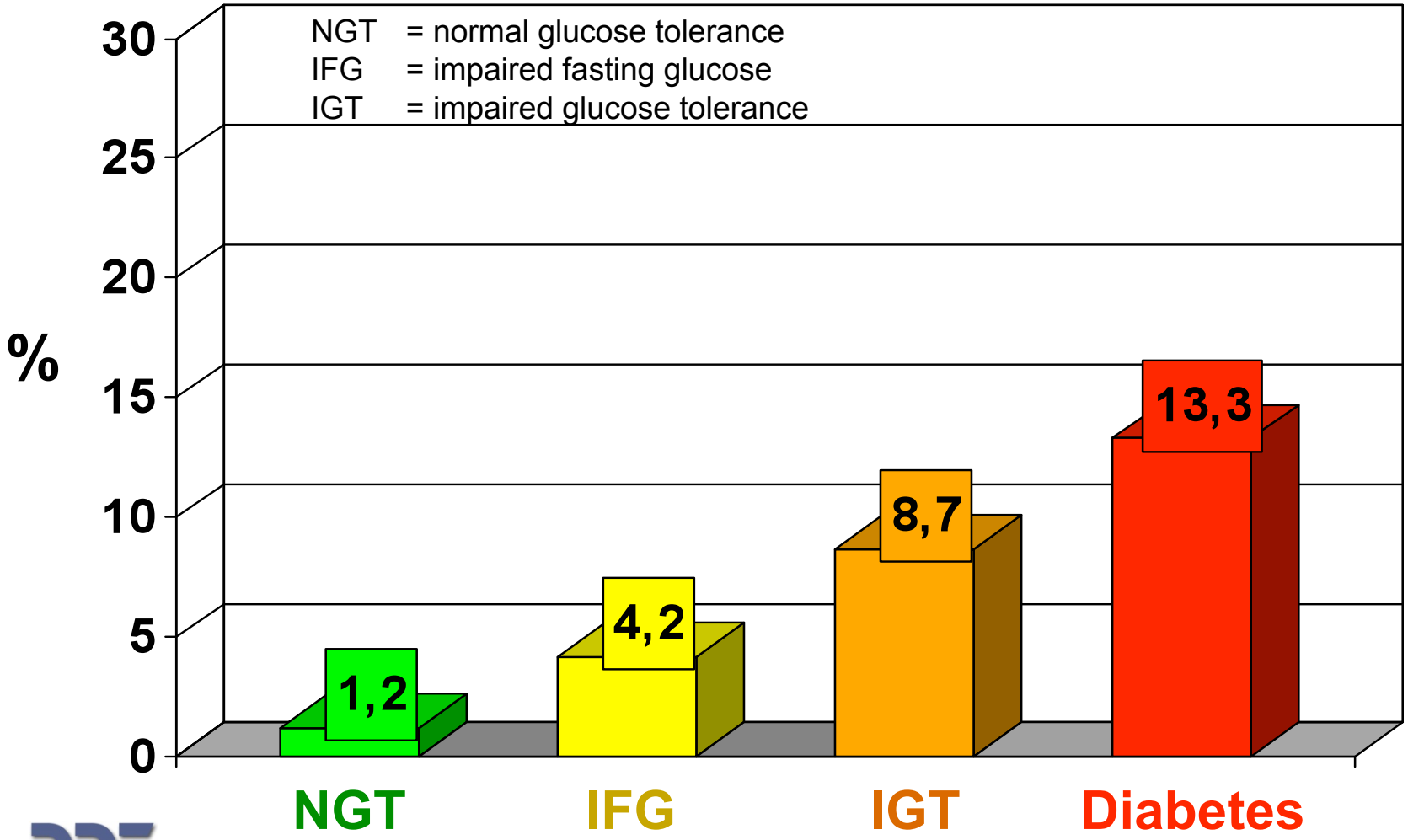
MONICA/KORA Augsburg Surveys S2+S3



Ziegler et al., Diabetes Care 2008; 31: 556-561

Prevalence of Painful Neuropathy in Prediabetes and Diabetes

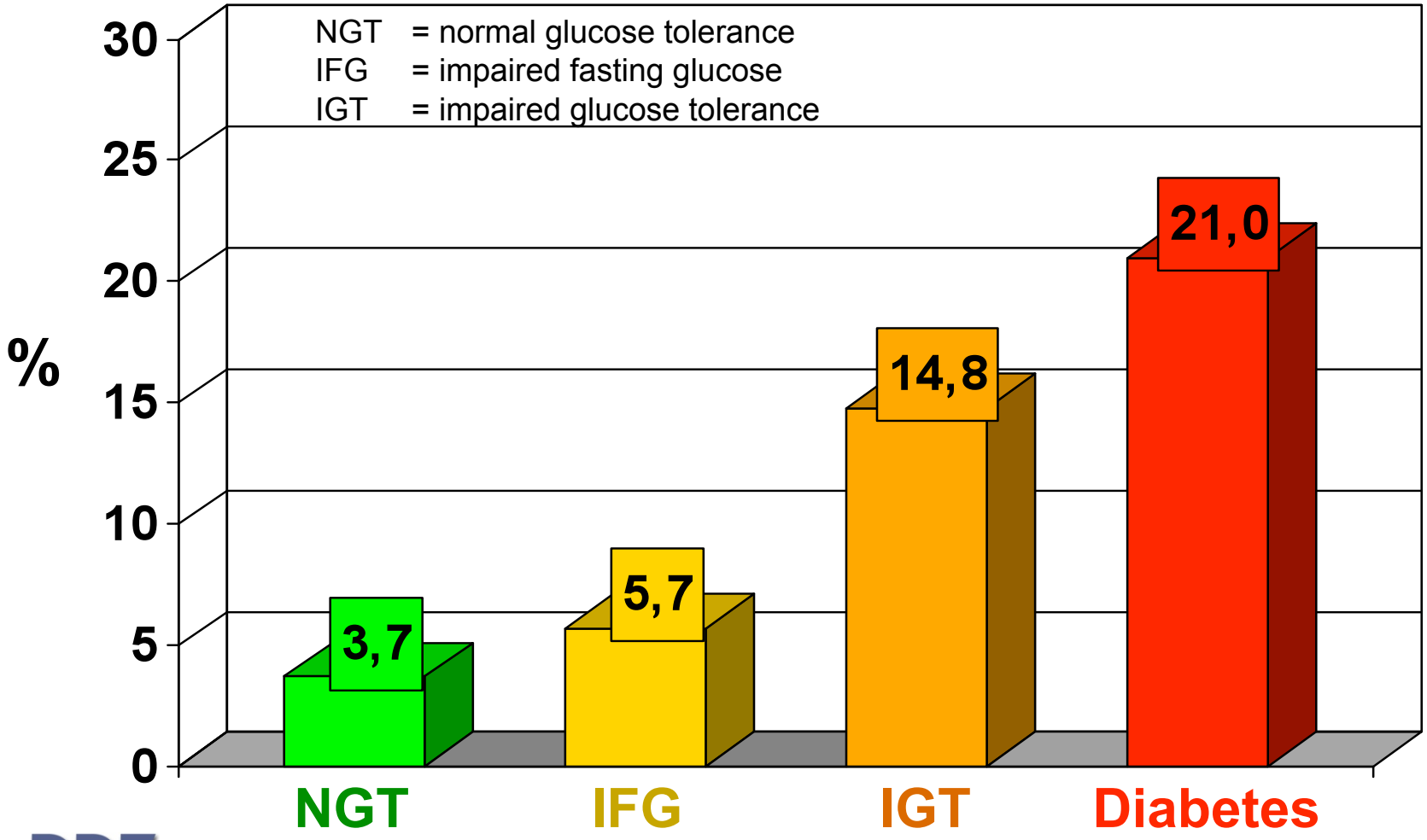
MONICA/KORA Augsburg Surveys S2+S3



Ziegler et al., Pain Med 2009; 10: 393-400

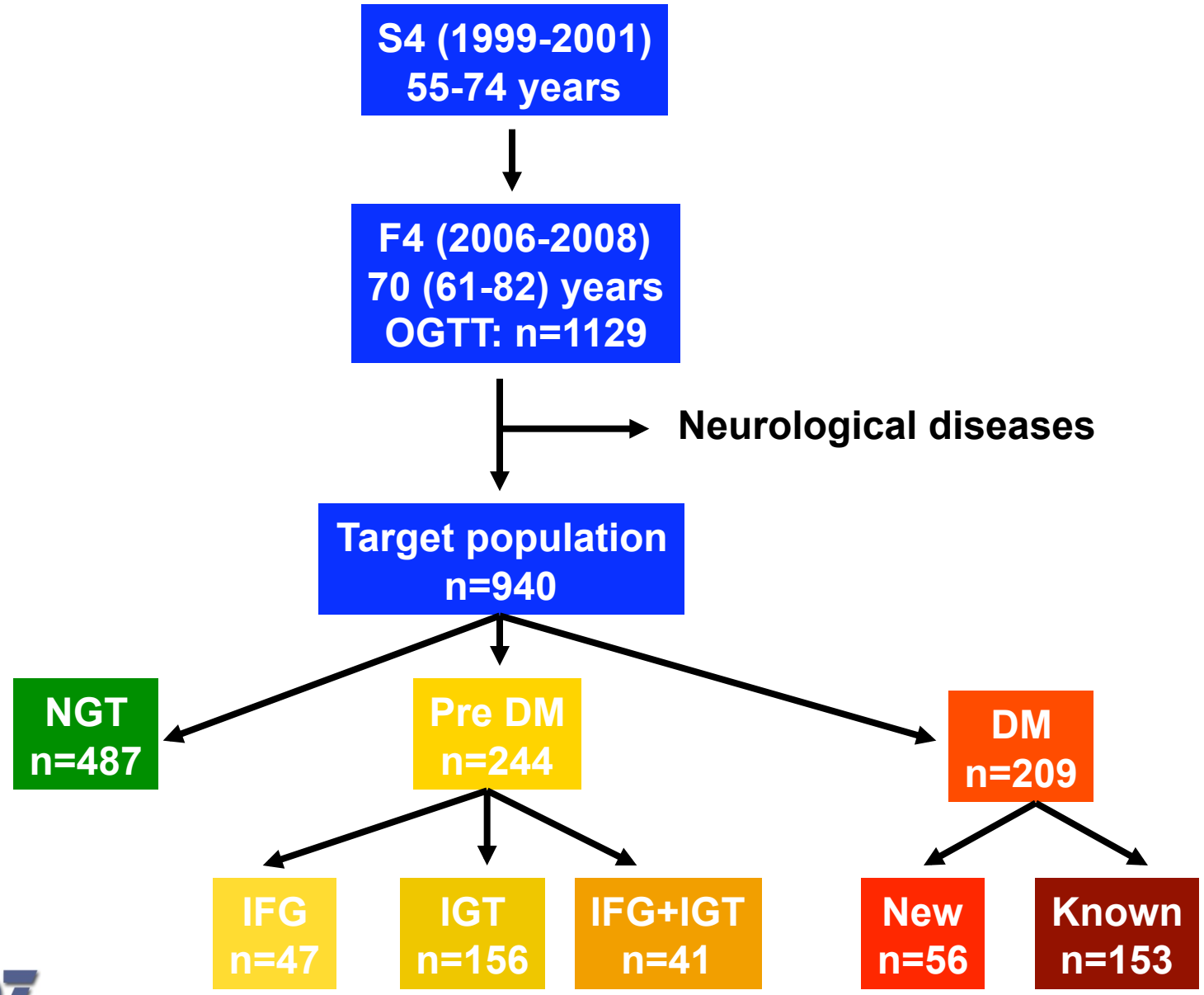
Prevalence of Painful Neuropathy in Prediabetes and Diabetes in Survivors of Myocardial Infarction

Augsburg Myocardial Infarction Registry



Ziegler et al., Eur J Pain 2008, Sep 7 [Epub ahead of print]

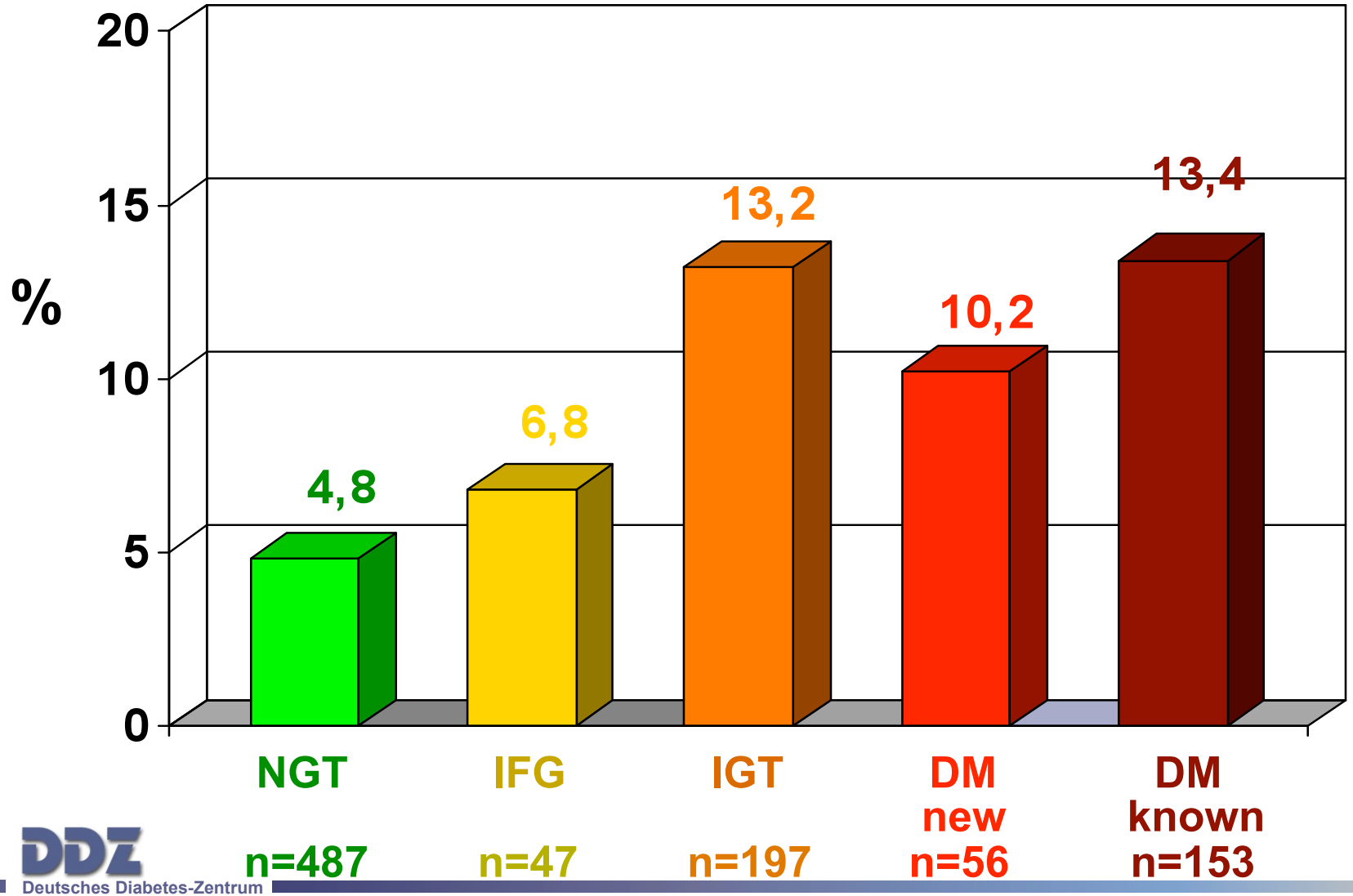
KORA Follow-Up F4



Prevalence of painful neuropathy

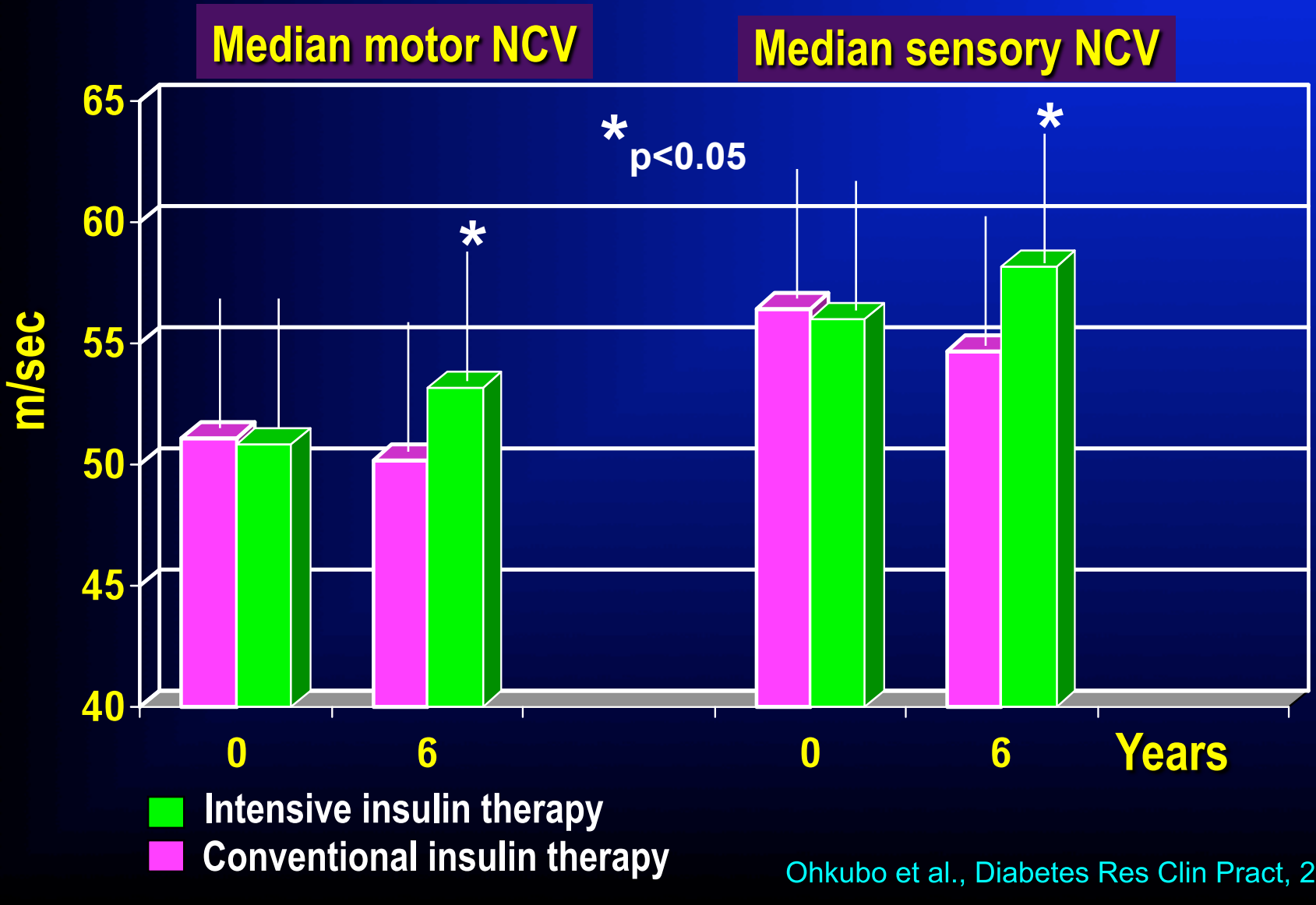
MONICA/KORA Augsburg F4 (Age: 61-82 years)

MNSI>2 (original) + Pain in the feet/distal legs 4 weeks



Kumamoto Study

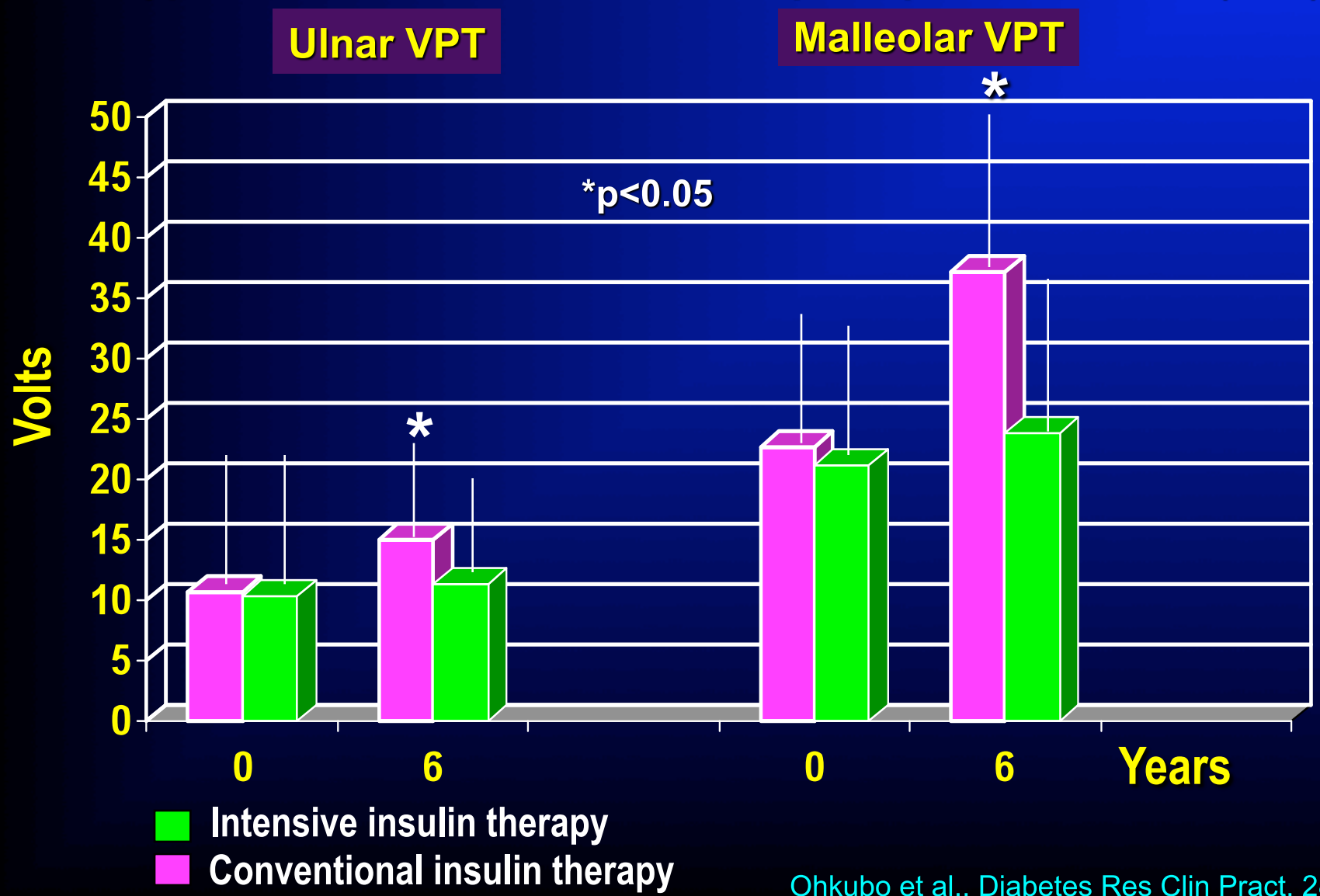
Type 2 Diabetes; n=110; Nerve conduction velocity



Ohkubo et al., Diabetes Res Clin Pract, 28, 1995

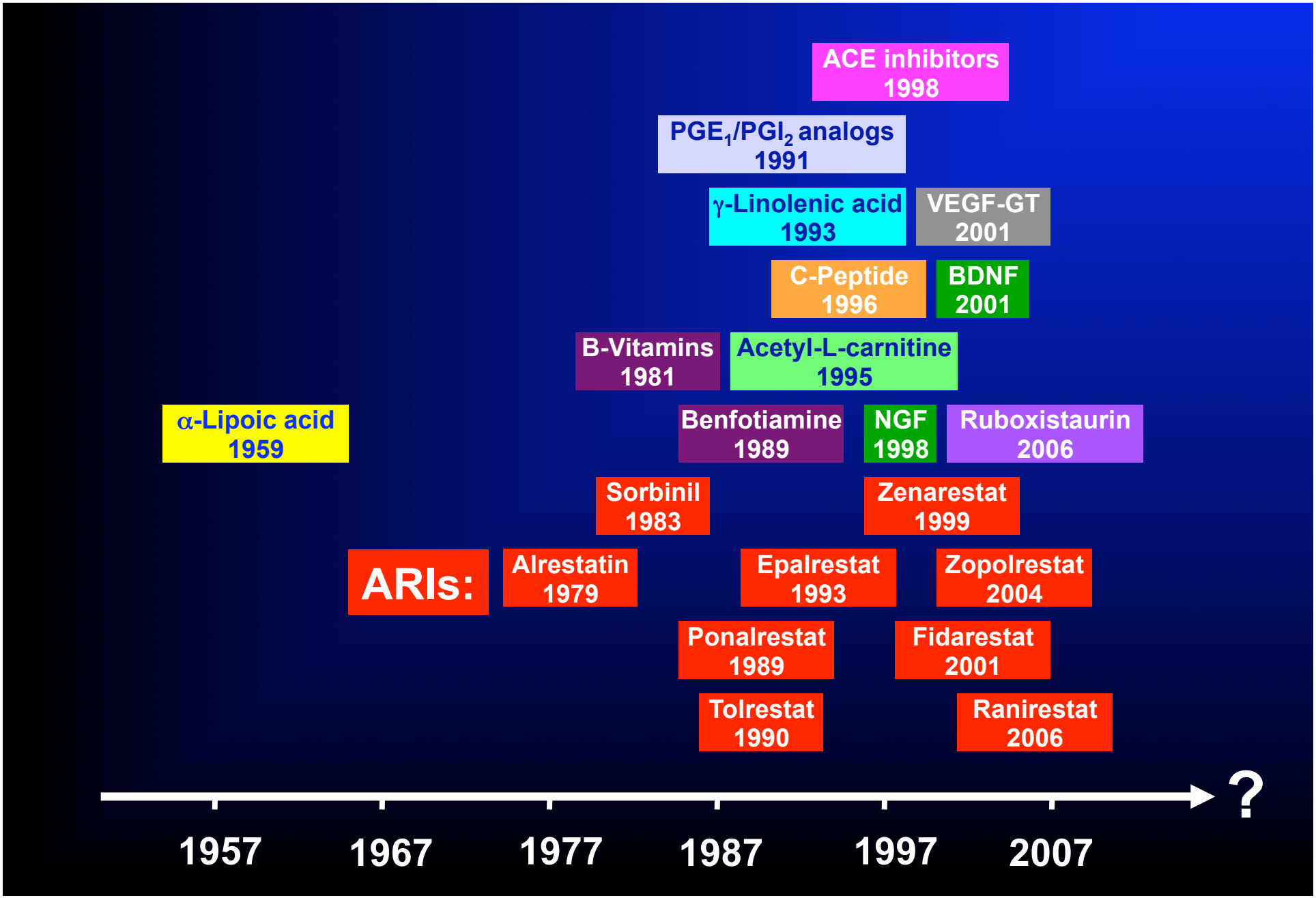
Kumamoto Study

Type 2 Diabetes; n=110; Vibration perception threshold (VPT)



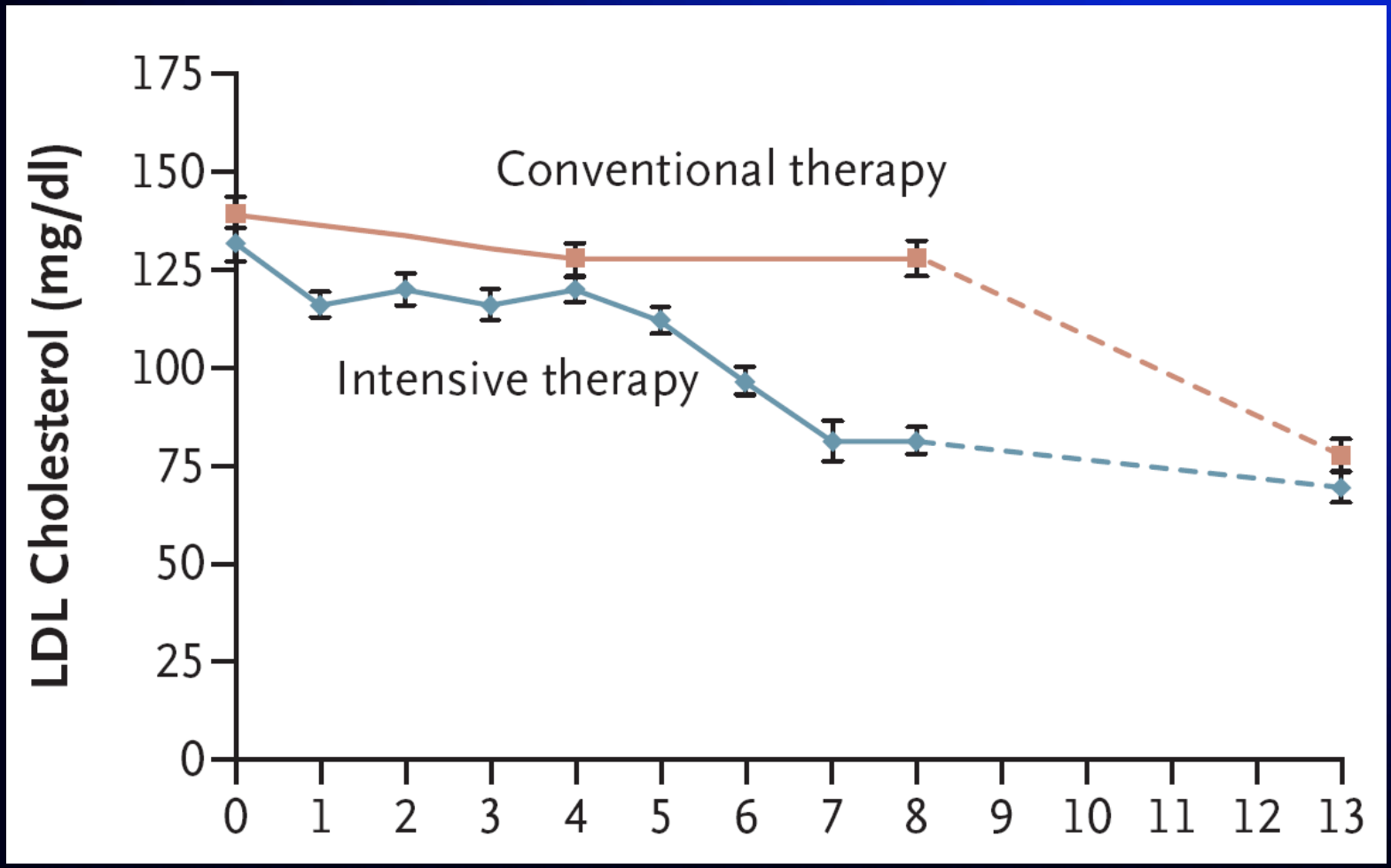
Ohkubo et al., Diabetes Res Clin Pract, 28, 1995

Disease-Modifying Treatment of Diabetic Polyneuropathy



Steno Type 2 Study: Follow-Up after 13 Years

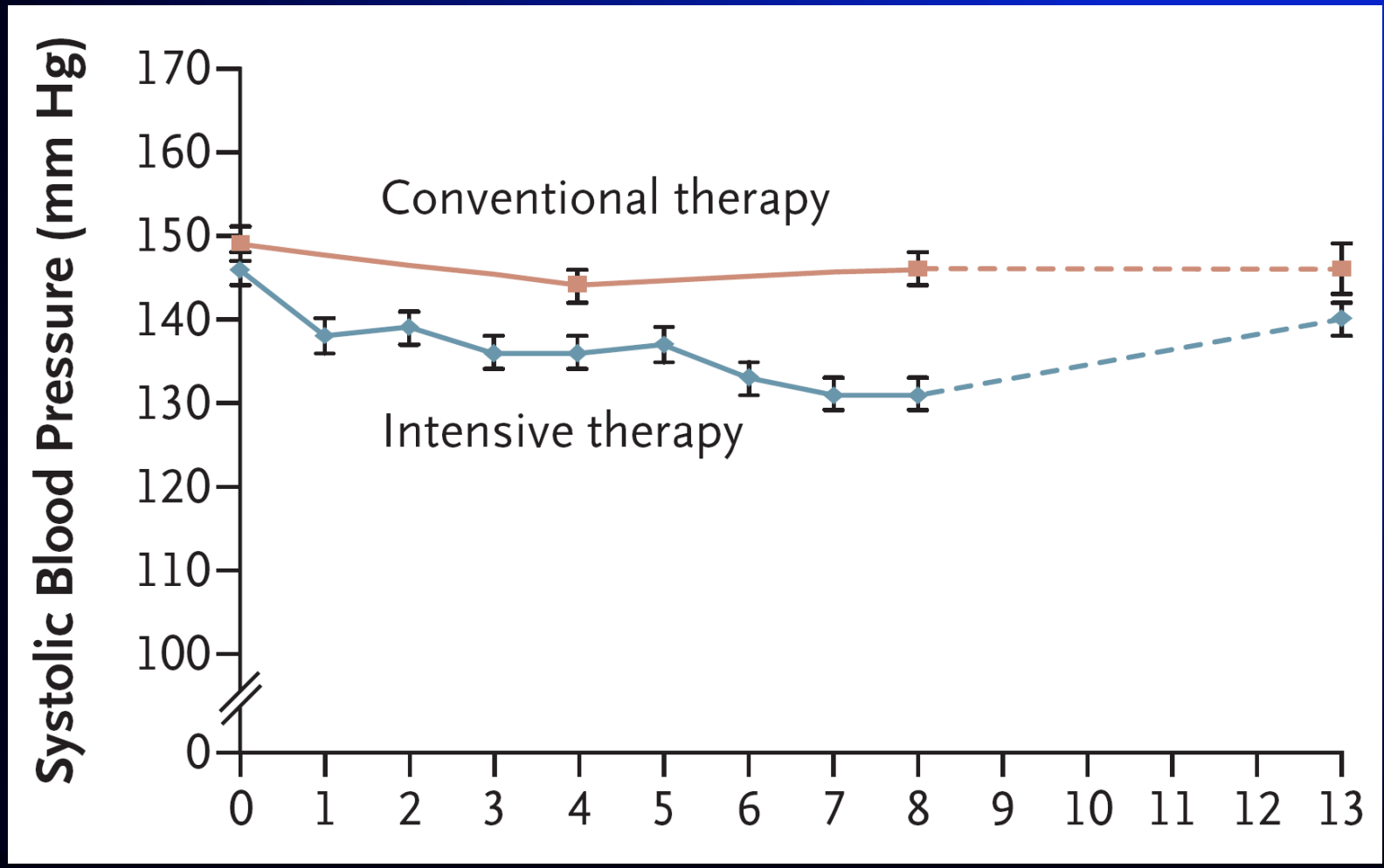
LDL cholesterol during the interventional part of the study for all patients (solid lines) and during the follow-up period (dashed lines)



Gæde et al., *N Engl J Med* 2008; 358: 580-591

Steno Type 2 Study: Follow-Up after 13 Years

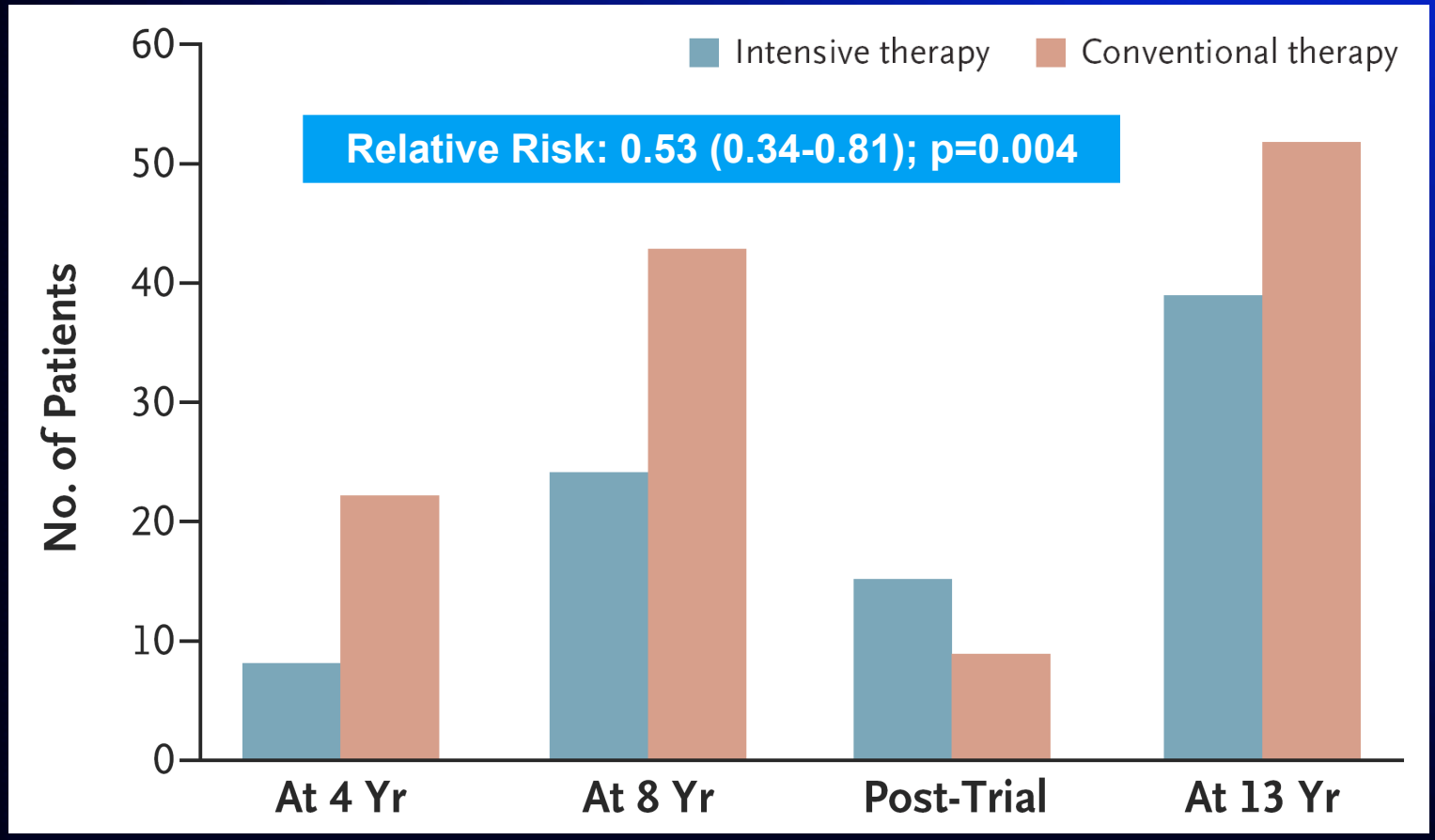
Systolic blood pressure during the interventional part of the study for all patients (solid lines) and during the follow-up period (dashed lines)



Gæde et al., *N Engl J Med* 2008; 358: 580-591

Steno Type 2 Study: 13-Year Follow-Up

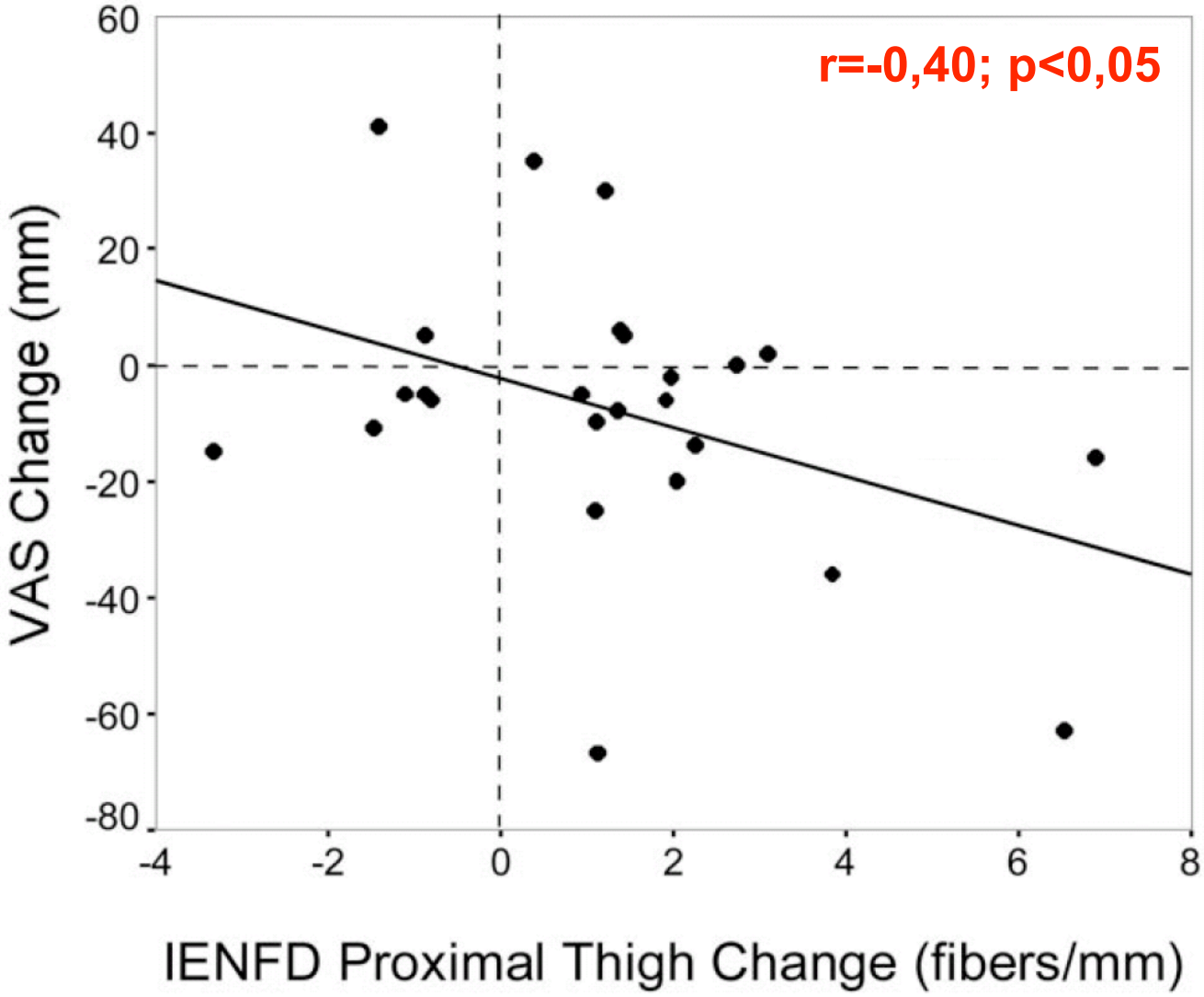
Multifactorial risk intervention slows the progression of reduced heart rate variability



Gæde et al., *N Engl J Med* 2008; 358: 580-591

Lifestyle intervention over 12 months in impaired glucose tolerance (IGT)

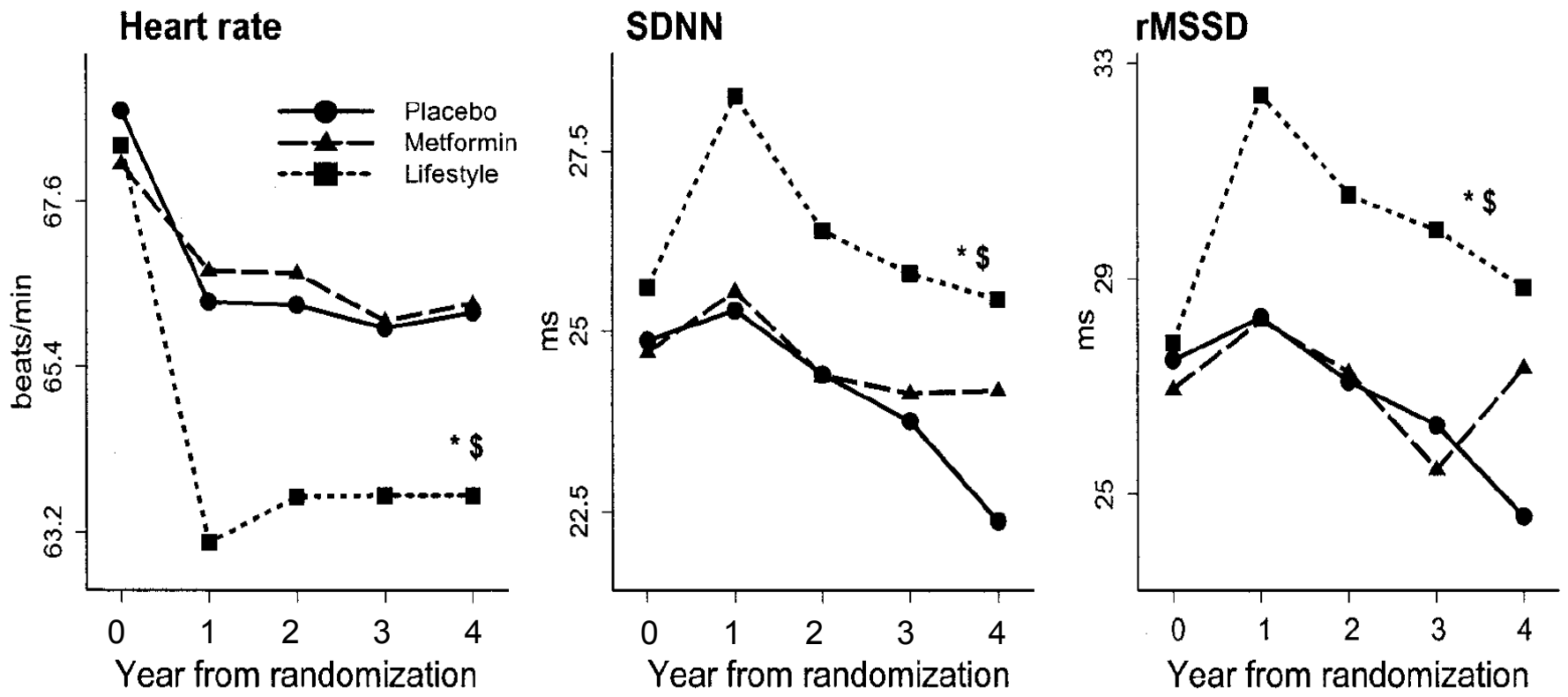
Correlation between epidermal reinnervation and pain relief (VAS)



Smith et al., Diabetes Care 2006; 29: 1294-9

Effect of Lifestyle Intervention on Heart Rate Variability over 4 Years in Prediabetes

Diabetes Prevention Program (DPP)

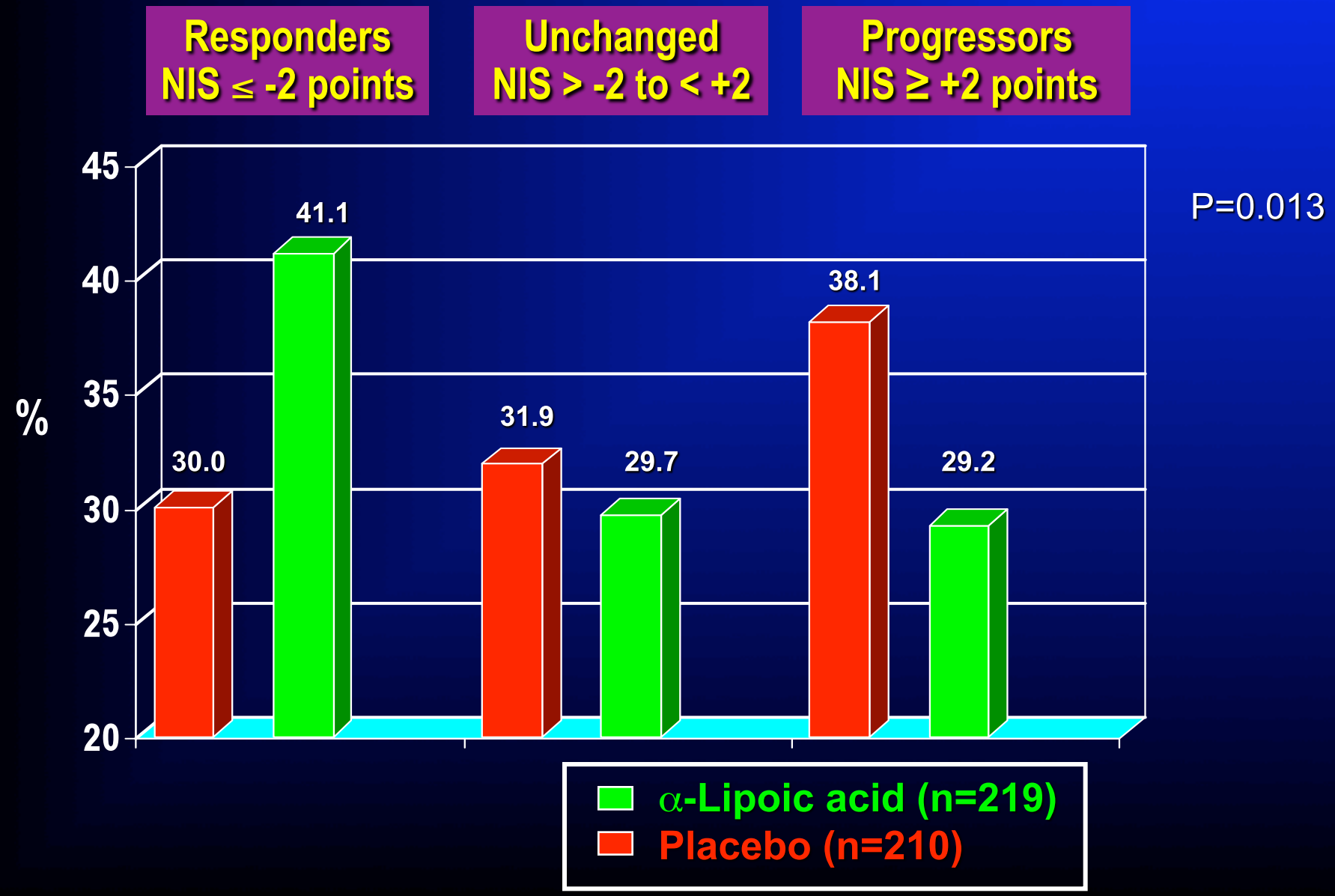


Carnethon et al., Diabetes Care 2006; 29: 914-9

Neurological Assessment of Thioctic Acid in Diabetic Neuropathy (NATHAN) 1 Study

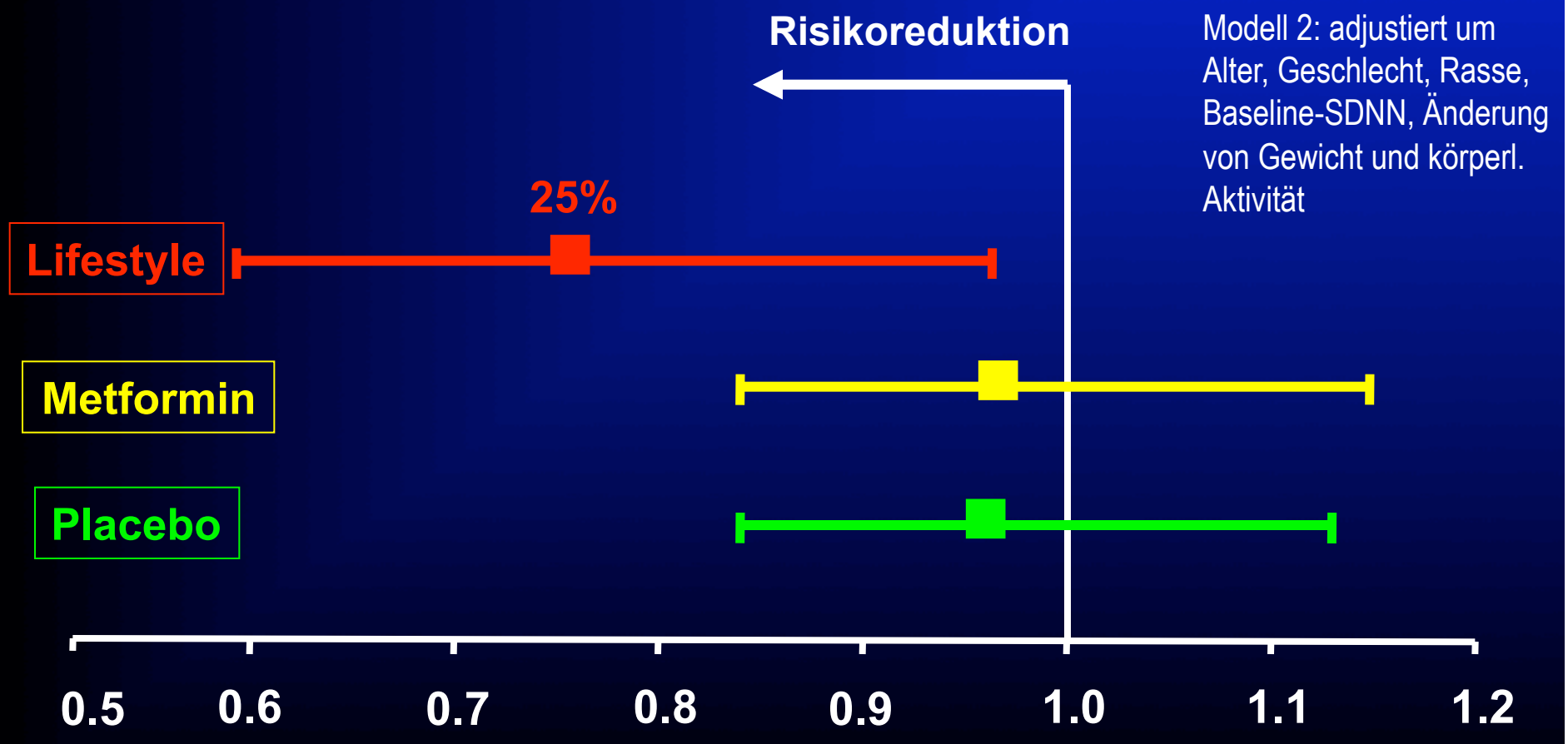
Design:	Randomized, double-blind, placebo-controlled, multicenter trial (36 centers)
Subjects:	Two parallel groups of Type 1/Type 2 patients vs placebo
Medication:	α-Lipoic acid (thioctic acid) 600 mg or placebo qd orally
Duration:	Screening: 2 wk, placebo run-in: 6 wk, treatment: 192 wk, follow-up: 4 wk
Endpoints:	NIS-LL+7 tests, NIS, QST, HRV
DPN severity:	Stage 1 or 2a (mild to moderate) polyneuropathy

NATHAN 1 Study: NIS Responders vs NIS Progressors



Lifestyle-Intervention reduziert das Risiko für Diabetes in Assoziation mit Verbesserung der HRV (SDNN pro 17 ms Anstieg)

Diabetes Prevention Program (DPP)



Modell 2: adjustiert um Alter, Geschlecht, Rasse, Baseline-SDNN, Änderung von Gewicht und körperl. Aktivität

Carnethon et al., Diabetes Care 2006; 29: 914-9

Will power lasts about two weeks and is soluble in alcohol.

Mark Twain

ADA Criteria for the Diagnosis of Pre-Diabetes

NGT = Normal glucose tolerance
IFG = Impaired fasting glucose
IGT = Impaired glucose tolerance

State	FPG level (mg/dl)	2-h plasma glucose in OGTT (mg/dl)*
PREDIABETES		
IFG	100–125	<200
Isolated IFG	100–125	<140
IGT	<126	140–199
Isolated IGT	<100	140–199
Combined IFG/IGT	100–125	140–199
NGT	<100	<140

*Standard 75-g OGTT.

Genuth S et al., *Diabetes Care* 2003; 26: 3160–3167

IMPAIRED GLUCOSE TOLERANCE—DOES IT CAUSE NEUROPATHY?

JAMES W. RUSSELL, MD, MS, MRCP,[1,2] and EVA L. FELDMAN, MD, PhD[1]

Muscle Nerve 24: 1109-1112, 2001

Peripheral Neuropathy With Impaired Glucose Tolerance

John T. Kissel, MD

A Sweet Smell of Success?

ARCH NEUROL/VOL 63, AUG 2006

DOES IMPAIRED GLUCOSE METABOLISM CAUSE POLYNEUROPATHY? REVIEW OF PREVIOUS STUDIES AND DESIGN OF A PROSPECTIVE CONTROLLED POPULATION-BASED STUDY

PETER J. DYCK, MD,[1] P. JAMES B. DYCK, MD,[1] CHRISTOPHER J. KLEIN, MD,[1] and STEPHEN D. WEIGAND, MSc[2]

Muscle Nerve **36:** 536–541, 2007

Reasons for difficulties to define the causative role of prediabetes for painful neuropathy

- Selection bias
- Few population-based studies including NGT controls
- Variable definitions of neuropathy & metabolic abnormality
- Inadequate assessment of micro-/macroangiopathy
- Inadequate statistical power
- Lack of prospective cohort studies