Multimodality Approach

Dmitri Vasin, M.D.
Renal Remission and HTN Consultants, PLLC
Bremerton, WA USA

Renal Remission Clinic
Hypertension Clinic
AtheroRegression Clinic
Minor Stroke and TIA Clinic

Methods

- We are using MULTIMODALITY approach to achieve the lowest possible CV risk status in an individual patient using individualized realistic lifestyle modification and pharmacologic therapy;
- We use multiple biochemical and serologic markers to monitor CV risk status
- We also use serial measurements of Carotid Intima-to Media Thickness to document stabilization and regression of atherosclerosis

Multimodality Approach

- Rapid sequence escalation of therapy with only few days between introduction and escalation of the medication doses
- Structured environment with use of flow sheets with medication start days, uptitration recorded
- Several months to a year plan of therapy, diagnostic studies, etc.

Multimodality Approach

- Natural history of Atherosclerosis and its manifestations is one of relentless progression resulting in disability and death in a majority of untreated and conventionally treated individuals
- Multimodality ("combination chemotherapy") protocols are being used with a high success rate in Oncology and in Nephrology (Multimodal Renal Remission Protocol), Diabetes (STENO Multifactorial Intervention), Stroke (Oxford Stroke Clinic Protocol)
- The same approach is being applied by us to Atherosclerosis and CV diseases resulting from it

Results of Multimodality Interventions

- 20% absolute reduction in all-cause mortality in Type II Diabetics (Gaede –STENO Diabetic Center Copenhagen, Denmark)
- 70% -83% reduction in renal disease progression and need for dialysis (Ruggenenti – Bergamo, Italy; Parving – STENO diabetic center Copenhagen, Denmark)
- 80% secondary stroke reduction (Rothwell – Oxford, UK)
- 95% recurrent heart attack prevention (Brown – Seattle, USA)

" The consequences of failing to induce a remission of cancer are considered so severe that reliance on a single agent is unthinkable.

Since a failure to induce remission in progressive nephropathy is often similarly lethal, appropriate remission strategies will almost certainly entail the use of similarly *multimodal therapies*."

Barry M. Brenner, MD

Samuel A. Levine Professor of Medicine
Harvard Medical School
Director, Renal Division
Brigham and Women's Hospital
Boston, MA

Proceedings from a symposium at the 8th Clinical Nephrology Meeting Sponsored by National Kidney Foundation 2/29/2000

Review

Progression, remission, regression of chronic renal diseases

Piero Ruggenenti, Arrigo Schieppati, Giuseppe Remuzzi

The prevalence of chronic renal disease is increasing worldwide. Most chronic nephropathies lack a specific treatment and progress relentlessly to end-stage renal disease. However, research in animals and people has helped our understanding of the mechanisms of this progression and has indicated possible preventive methods. The notion of renoprotection is developing into a combined approach to renal diseases, the main measures being pharmacological control of blood pressure and reduction of proteinuria. Lowering of blood lipids, smoking cessation, and tight glucose control for diabetes also form part of the multimodal protocol for management of renal patients. With available treatments, dialysis can be postponed for many patients with chronic nephropathies, but the real goal has to be less dialysis—in other words remission of disease and regression of structural damage to the kidney. Experimental and clinical data lend support to the notion that less dialysis (and maybe none for some patients) is at least possible.

With available treatments, dialysis can be postponed for many patients…,but the real goal has to be…remission of disease and regression of structural damage to the kidney.

Ruggenenti, Lancet 2001; 357: 1601-08

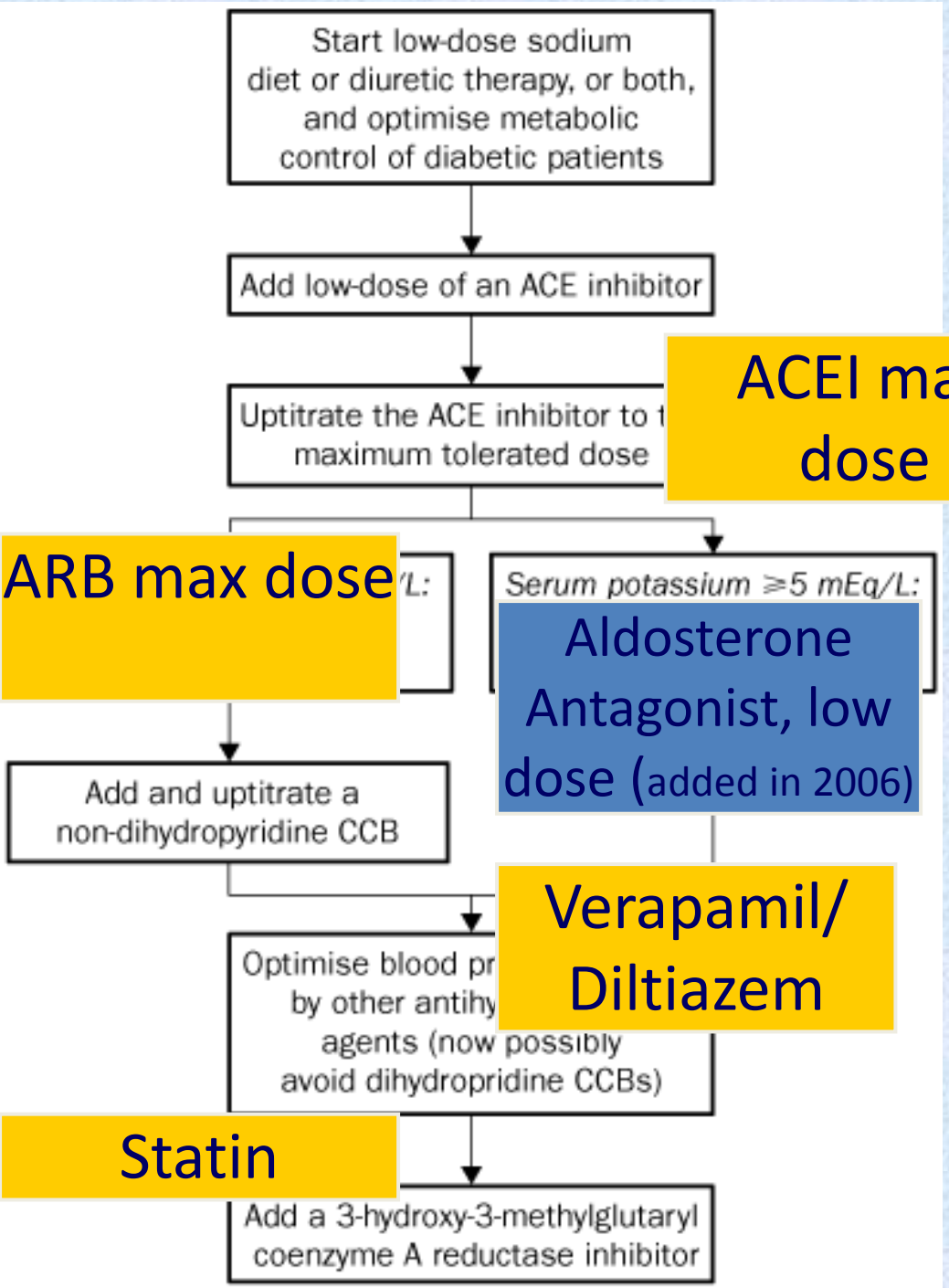
Definitions

Panel 1: **Definitions of progression, remission, and regression of proteinuric chronic nephropathies**

Variable	Progression	Remission	Regression
Proteinuria	≥1 g/24 h	<1 g/24 h	<0·3 g/24 h
Glomerular filtration rate	Declining*	Stable	Increasing
Renal structural changes	Worsening	Stable	Improving

*Faster than physiological decline associated with aging (1 mL/min/1·73 m² per month).

Ruggenenti, Lancet 2001; 357: 1601-08

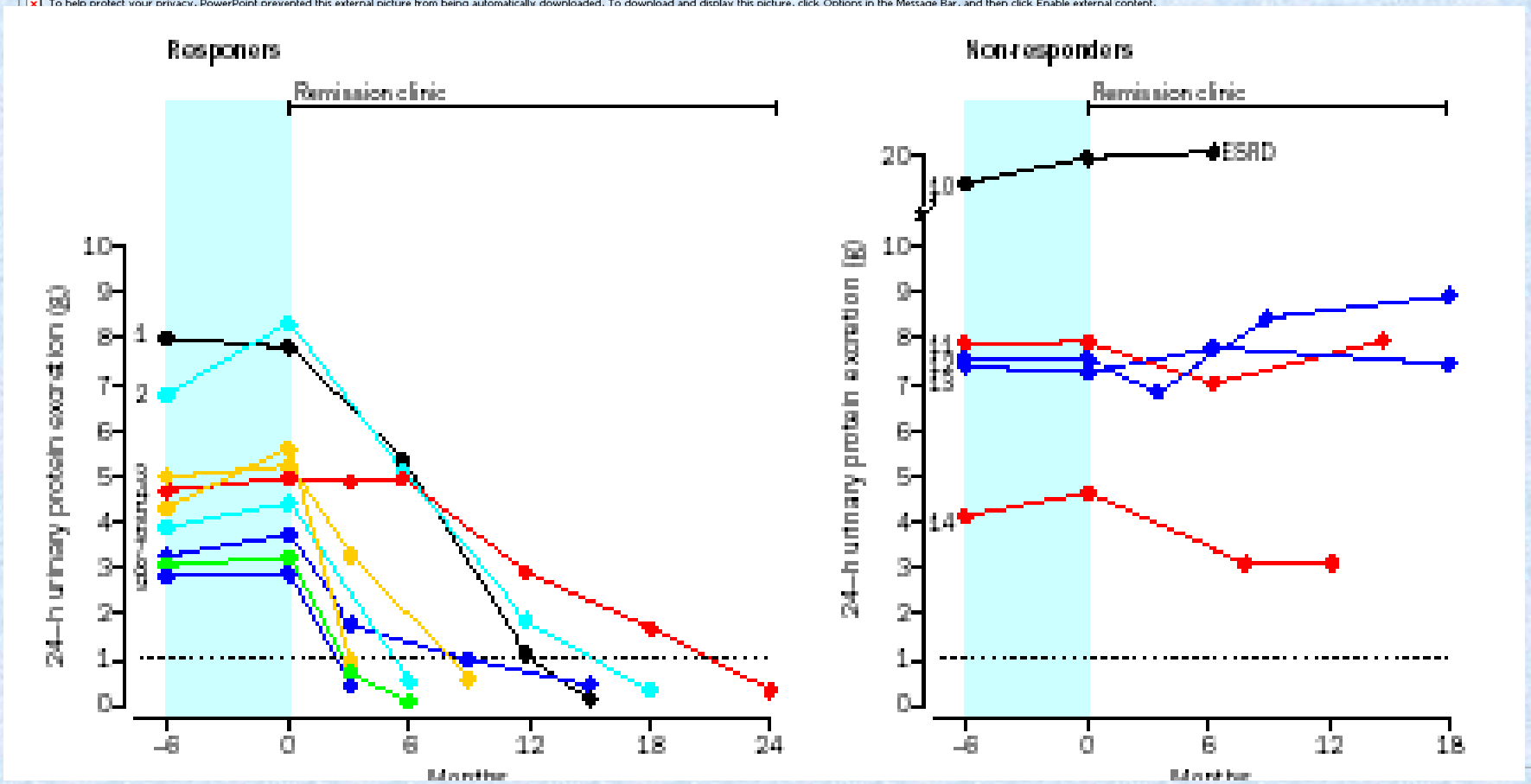


Algorithm of the ***multidrug approach*** to patients with chronic nephropathy and persistent nephrotic-range proteinuria (remission clinic)

In all patients hyperkalemia was limited by dietary prescription, diuretic therapy, and optimal treatment of metabolic acidosis and hyperglycaemia (in diabetics).

Ruggenenti, Lancet 2001; 357: 1601-08
http://www.technomedicum.fi/ERRI/Diabetes-Ruggenenti.pdf

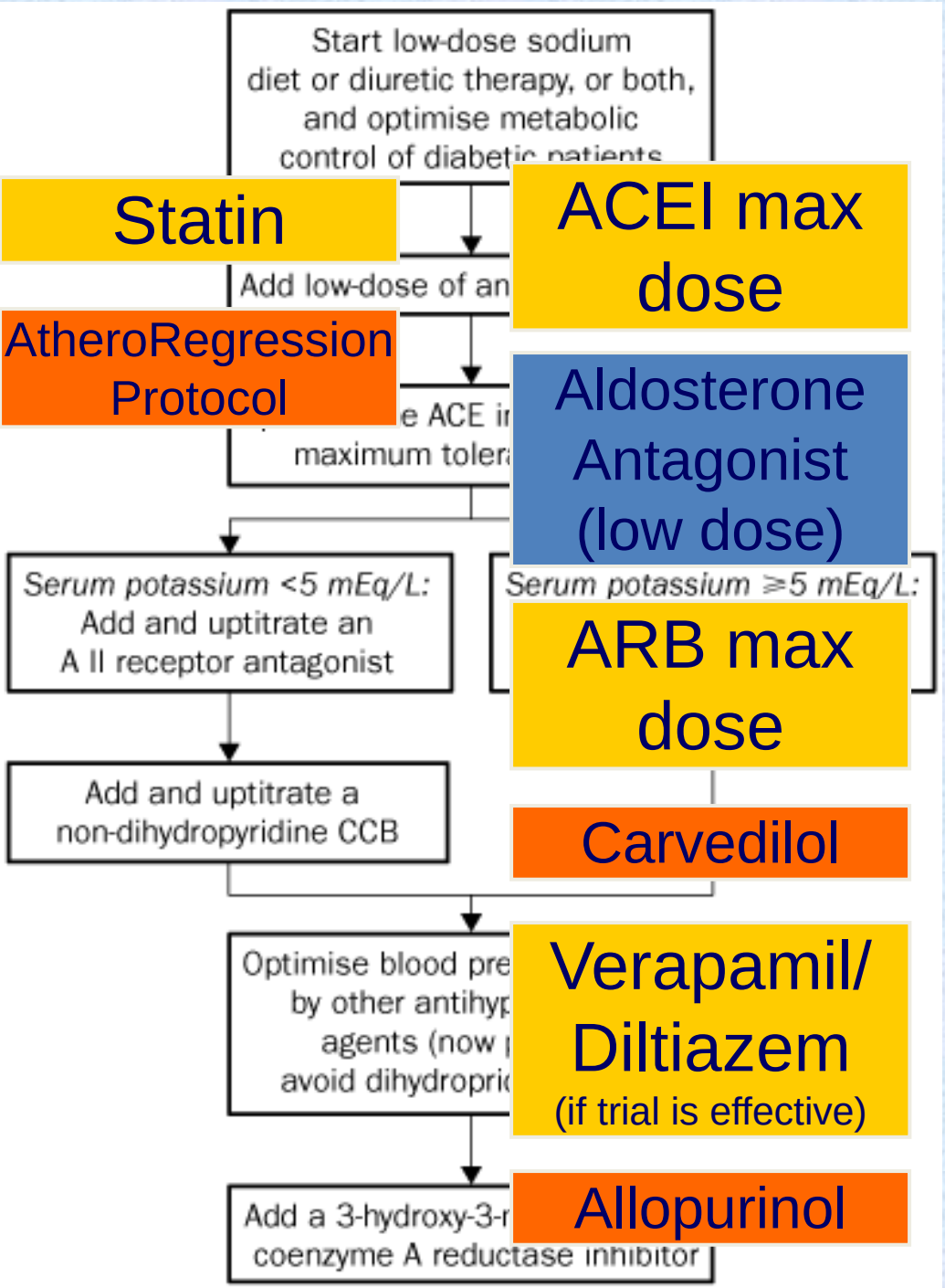
Course of urinary protein excretion rate in 13 patients with chronic nephropathies and persistent, nephrotic-range proteinuria admitted to remission clinic



Diagnosis and corresponding patient numbers were: Type 1 diabetic nephropathy (1), systemic lupus erythematosus (2, 6), chronic glomerulonephritis (3, 5), idiopathic membranous nephropathy (4, 11, 14), IgA nephropathy (7, 9), minimal change disease (10), and focal and segmental glomerulosclerosis (12, 13). Diagnosis was unknown in one patient (8).

Renal Remission Protocol Bremerton

See Renal Remission Presentations for Details



Algorithm of the multidrug approach to patients with chronic nephropathy and persistent nephrotic-range proteinuria (remission clinic)

In all patients hyperkalemia was limited by dietary prescription, diuretic therapy, and optimal treatment of metabolic acidosis and hyperglycaemia (in diabetics).

- **Updated Ruggenenti protocol, modified.**
  - **K+ >5.0 patients undergo aggressive nutritional counseling**
  - **K+ repeated x 2, if < 5.0 both times ACEI/ARB added**
  - **Proteinuria and BP measured before and after NDHPCCB; CCB discontinued if Δ Pr/Cr <20% or Δ SBP < 7 mm/Hg**

Ruggenenti original (2001)

Ruggenenti updated (2006)
Vasin (2004)

Vasin (2006)

Ruggenenti, Lancet 2001; 357: 1601-08

http://www.technomedicum.fi/ERRI/Diabetes-Ruggenenti.pdf

Results of Renal Remission Clinic Bremerton as of 2006

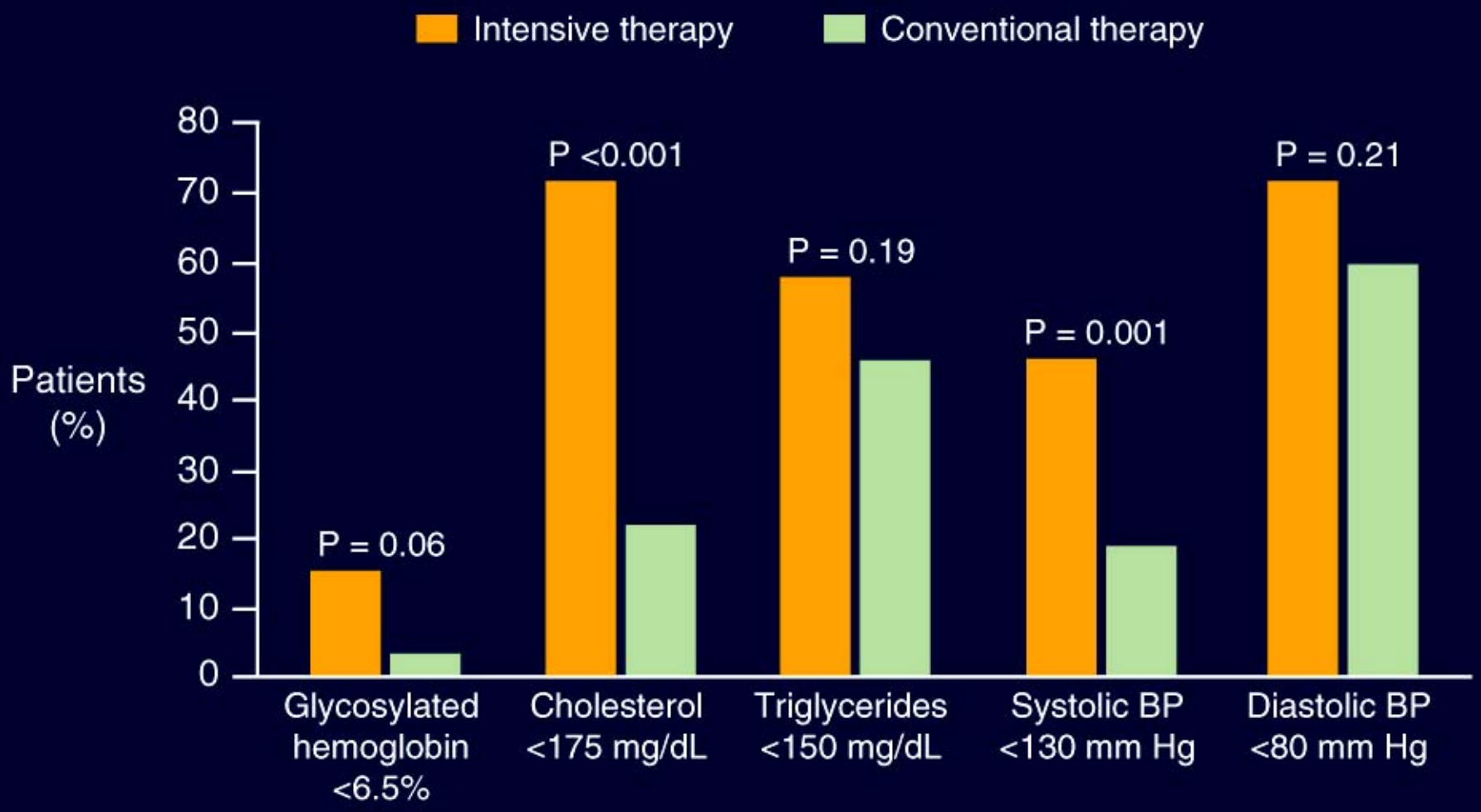
- 22 patients with sufficient data/follow up
- 6 (27%) “classic” responders
- 9 (41%) “non-classic” responders
- 7 (32%) “non-responders”
- One RRC patient had sudden death
- None of RRC patients required dialysis so far

Steno-2: Goals of intensive pharmacologic strategy

Therapy	Goal
ACE inhibitors	All patients (ARBs, if contraindicated)
Aspirin	All patients (150 mg/d)
BP control	<130/80 mm Hg
Glucose control	A_{1C} <6.5%
Lipid control	Total-C <175 mg/dL (<4.53 mmol/L) Triglycerides <150 mg/dL (<1.7 mmol/L)

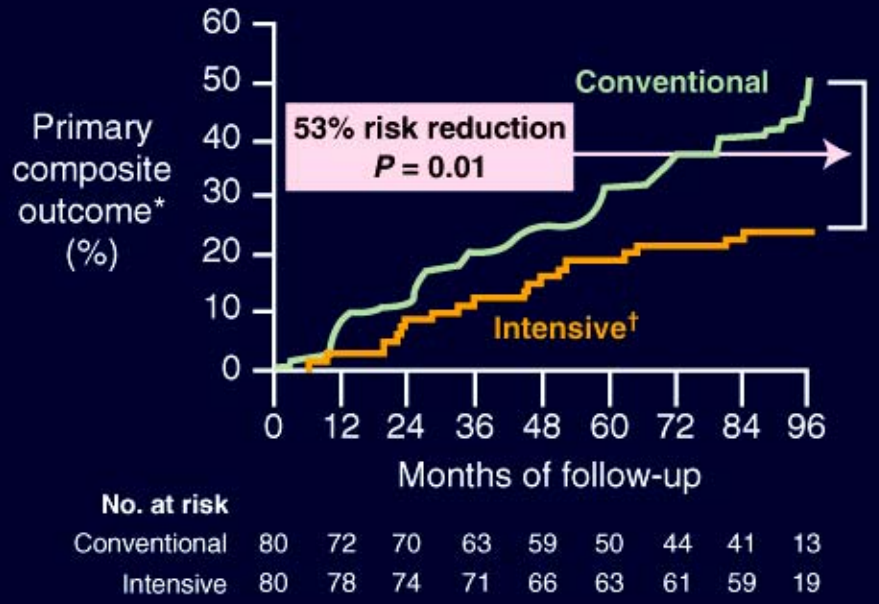
Gæde P et al. *N Engl J Med.* 2003;348:383-93.

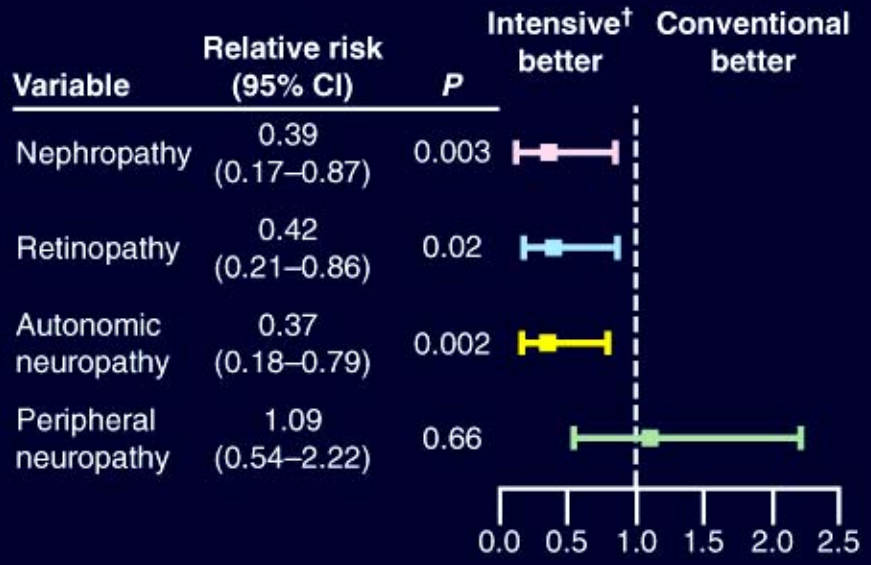
Steno-2: Risk factor control



Gæde P et al. *N Engl J Med.* 2003;348:383-93.

Steno-2: Effects of multifactorial intervention on macrovascular and microvascular outcomes





*CV death, MI, stroke, revascularization, amputation

†Total fat intake <30%, >30 min exercise 3–5x weekly, ACE inhibitor, aspirin, BP <130/80 mm Hg, total-C <175 mg/dL, TG <150mg/dL, A_{1C} <6.5%

Gæde P et al. *N Engl J Med.* 2003:348:383-93.

Steno-2: Goals of intensive pharmacologic strategy

Therapy	Goal
ACE inhibitors	All patients (ARBs, if contraindicated)
Aspirin	All patients (150 mg/d)
BP control	<130/80 mm Hg
Glucose control	A_{1C} <6.5%
Lipid control	Total-C <175 mg/dL (<4.53 mmol/L) Triglycerides <150 mg/dL (<1.7 mmol/L)

Gæde P et al. *N Engl J Med.* 2003;348:383-93.

Steno -2
13 years follow up

Gaede NEJM 2008;358:580-91

Steno-2 Thirteen Years Follow-up

- Intensive versus conventional therapy
  - Absolute risk of death down 20%
  - Absolute risk of CV death down 13%
  - Absolute risk of death in control group 50 %, in intensive group 30%
  - Absolute risk reduction of ESRD 6.3% (84% RR reduction)

"The rate of death among patients in conventional therapy group was 50%, a finding that underscores poor prognosis for such patients in the absence of intensive treatment."

Gaede NEJM 2008;358:580-91

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

Peter Gæde, M.D., D.M.Sc., Henrik Lund-Andersen, M.D., D.M.Sc., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

From the Steno Diabetes Center, Copenhagen (P.G., H.L.-A., O.P.); Department of Ophthalmology, Glostrup University Hospital, Glostrup (H.L.-A.); Department of Medical Endocrinology, Rigshospitalet Copenhagen University Hospital, Copenhagen (H.-H.P.); and Faculty of Health Sciences, University of Aarhus, Aarhus (H.-H.P., O.P.) — all in Denmark. Address reprint requests to Dr. Pedersen at the Steno Diabetes Center, 2820 Gentofte, Copenhagen, Denmark, or at oluf@steno.dk.

N Engl J Med 2008;358:580-91.

ABSTRACT

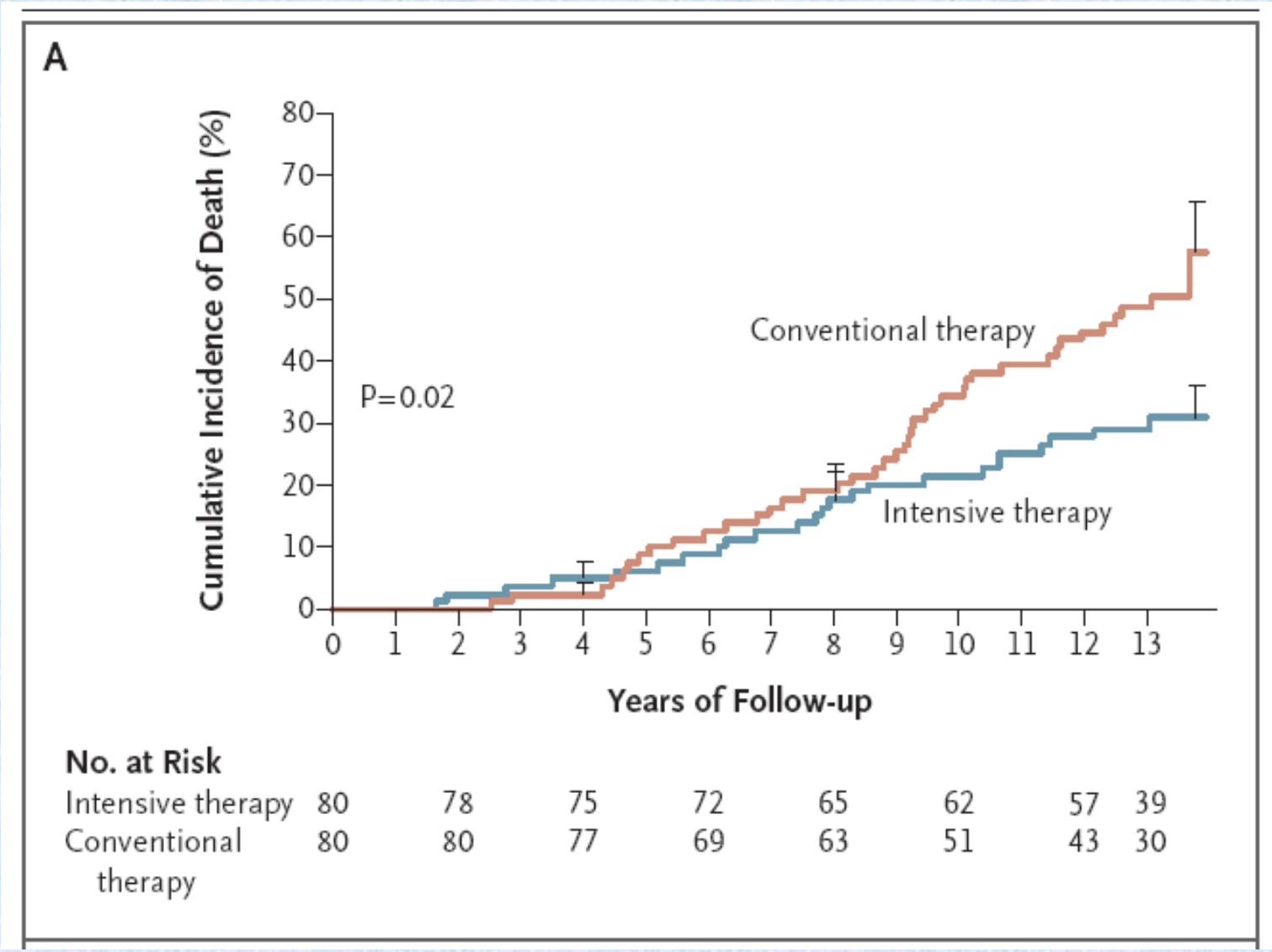
BACKGROUND

Intensified multifactorial intervention — with tight glucose regulation and the use of renin–angiotensin system blockers, aspirin, and lipid-lowering agents — has been shown to reduce the risk of nonfatal cardiovascular disease among patients with type 2 diabetes mellitus and microalbuminuria. We evaluated whether this approach would have an effect on the rates of death from any cause and from cardiovascular causes.

METHODS

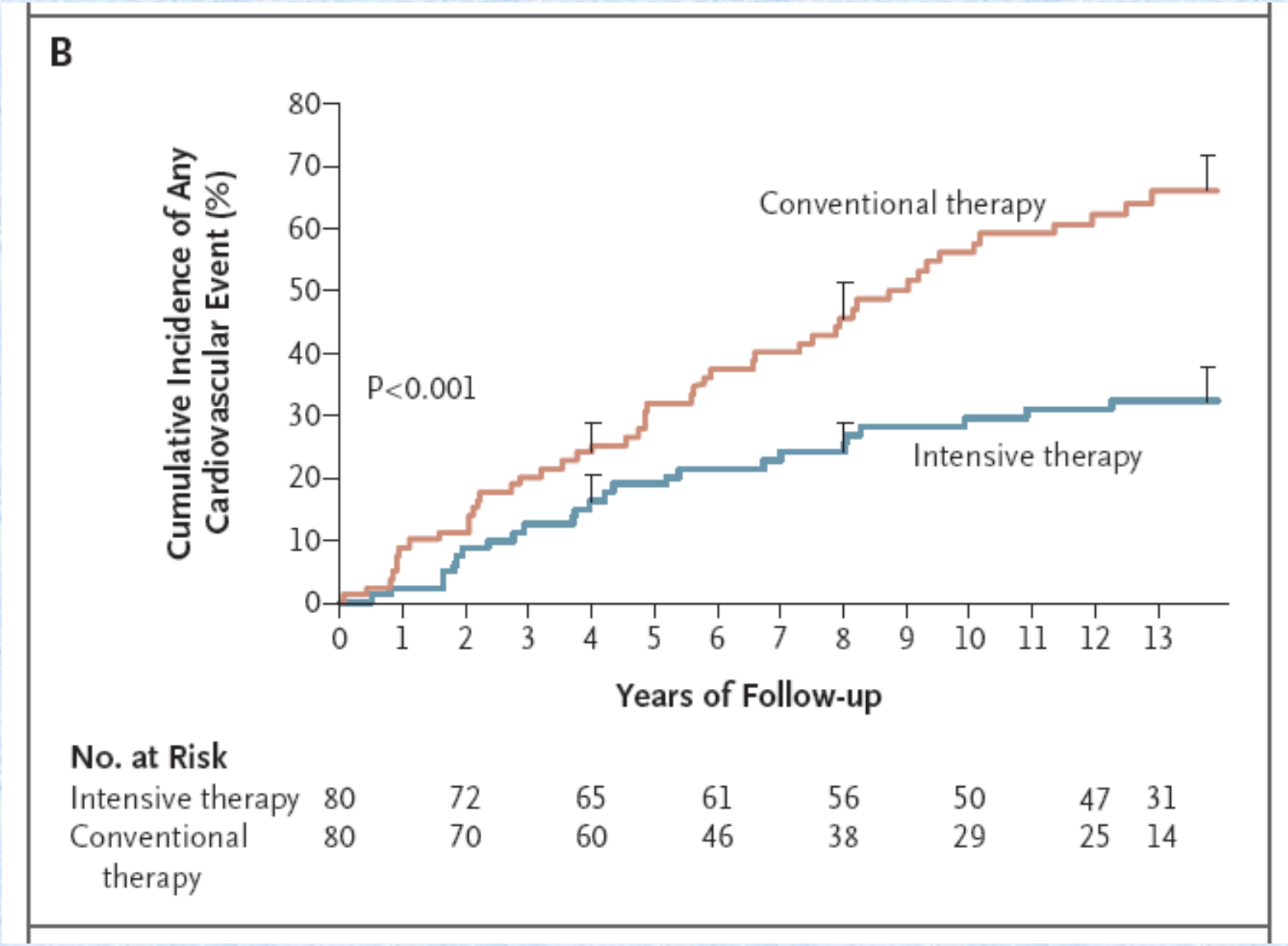
In the Steno-2 Study, we randomly assigned 160 patients with type 2 diabetes and persistent microalbuminuria to receive either intensive therapy or conventional therapy; the mean treatment period was 7.8 years. Patients were subsequently followed observationally for a mean of 5.5 years, until December 31, 2006. The primary end point at 13.3 years of follow-up was the time to death from any cause.

Steno-2 Followup at 13 years



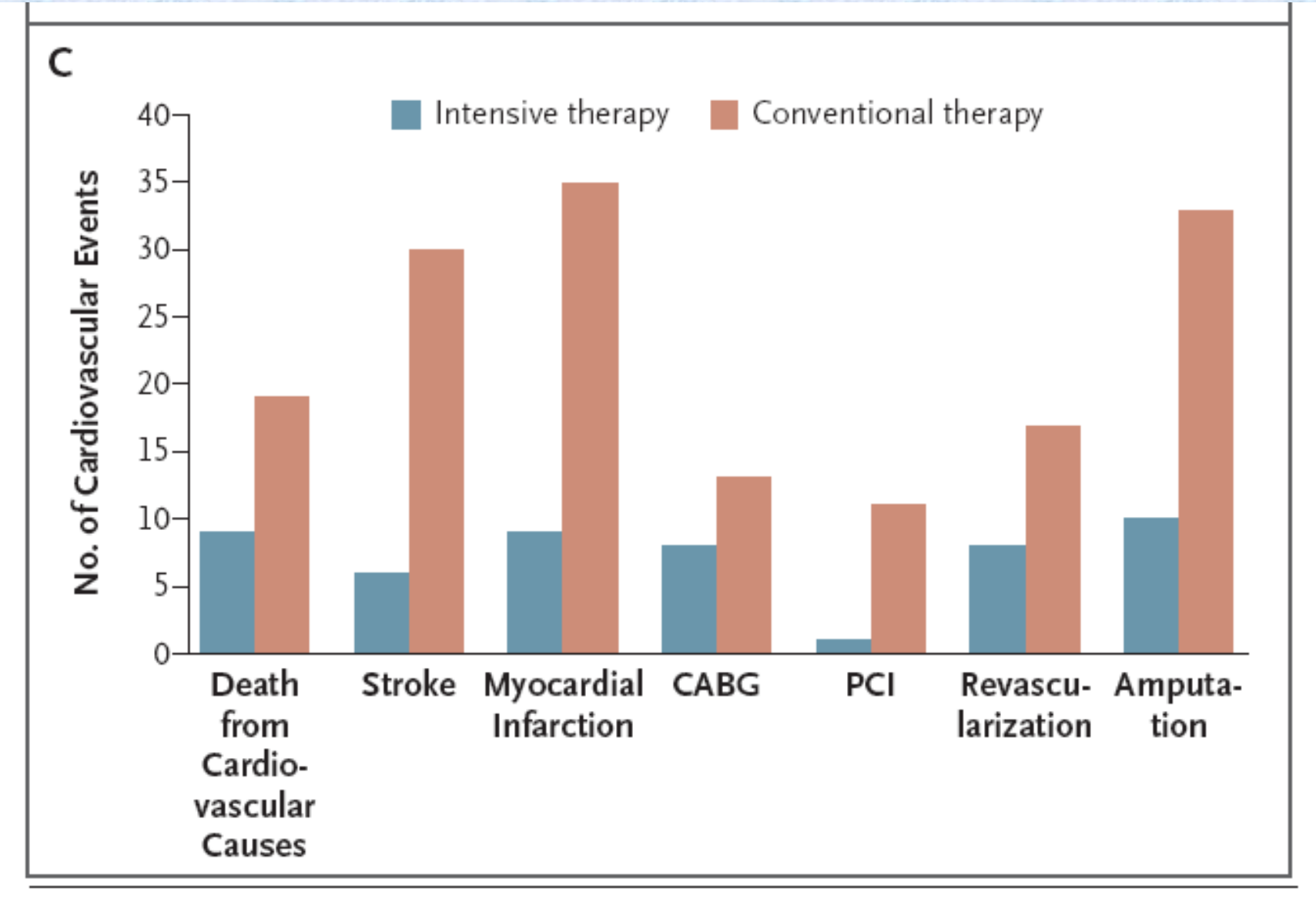
Gaede NEJM 2008;358:580-91

Steno-2 Followup at 13 years



Gaede NEJM 2008;358:580-91

Steno-2 Followup at 13 years



Gaede NEJM 2008;358:580-91

Steno-2 Followup at 13 Years

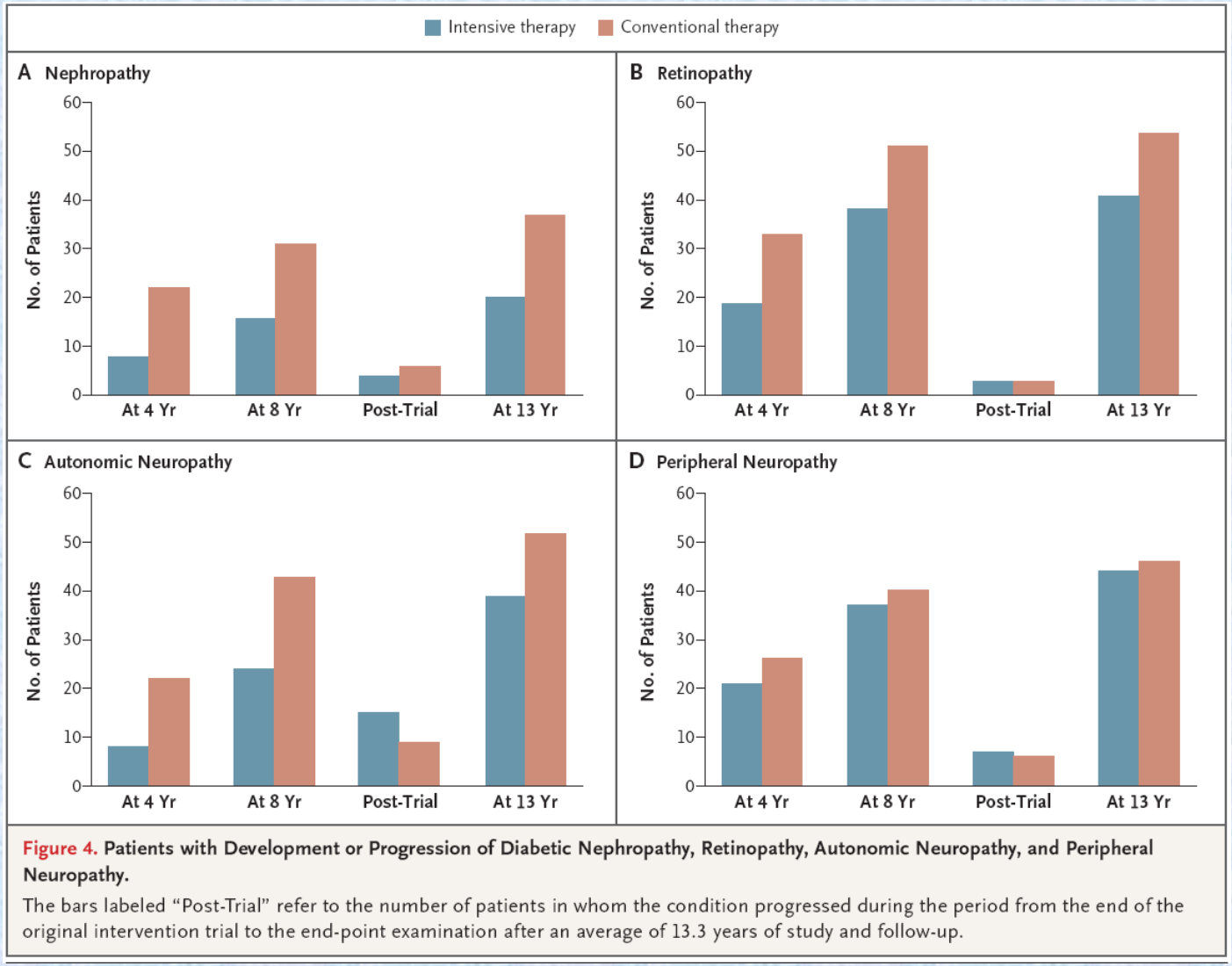


Figure 4. Patients with Development or Progression of Diabetic Nephropathy, Retinopathy, Autonomic Neuropathy, and Peripheral Neuropathy.

The bars labeled "Post-Trial" refer to the number of patients in whom the condition progressed during the period from the end of the original intervention trial to the end-point examination after an average of 13.3 years of study and follow-up.

Gaede NEJM 2008;358:580-91

Standard Approach

- Conservative goals (slowing the disease)
- Conservative and outdated targets that in reality frequently are not reached
- Escalation of therapy frequently occurs AFTER the subsequent non-lethal event (stroke or heart attack)
- We consider this to be an inferior and ethically questionable strategy

“Try not. Do or Do Not. There is No Try”

Master Yoda