Diabetes and Thrombosis

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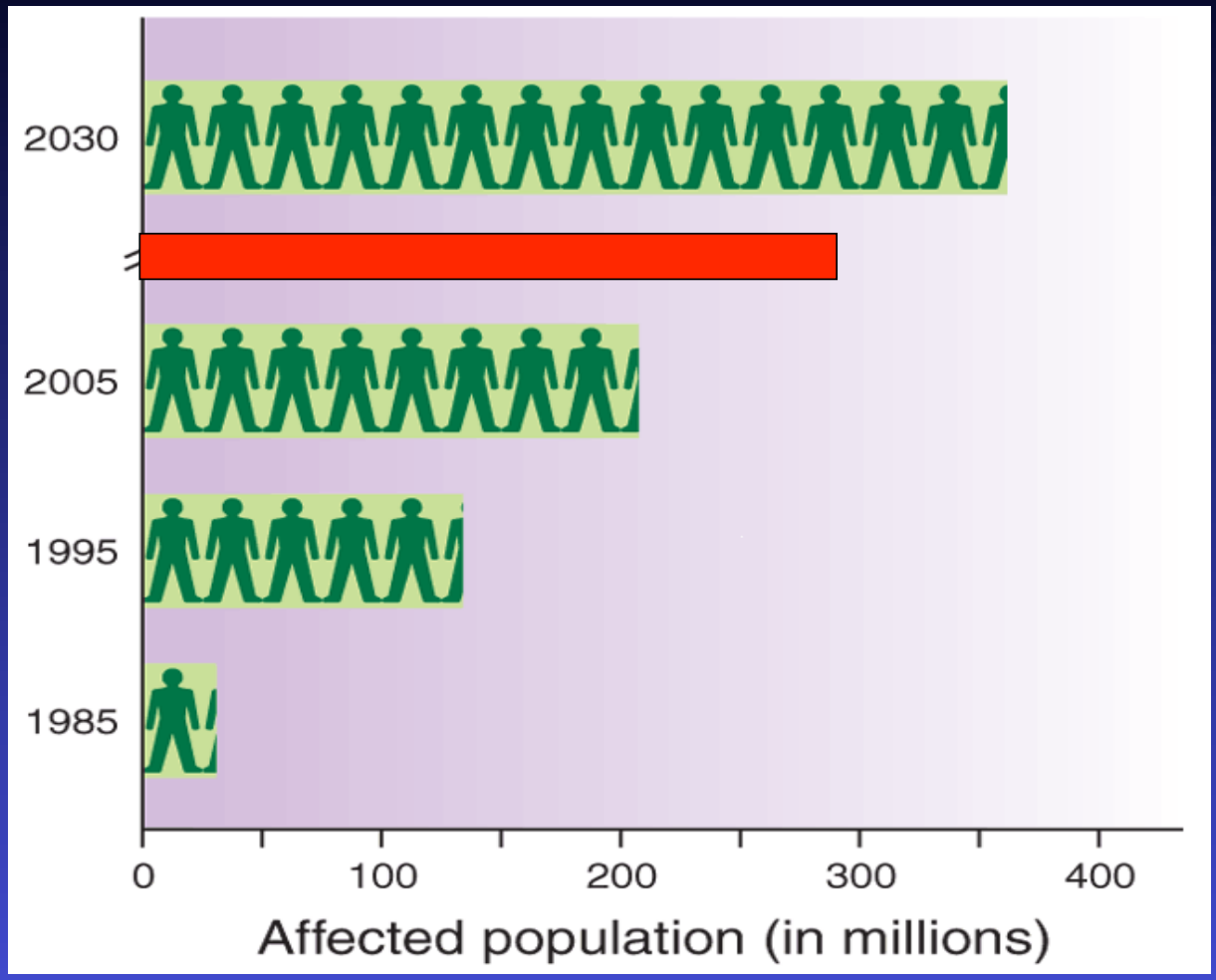
Overview

- Background and epidemiology
- Blood glucose and cardiovascular disease
- Diabetes as a prothrombotic condition
- Role of glycemic control in CVD prevention
- Can we prevent CVD in diabetic patients?

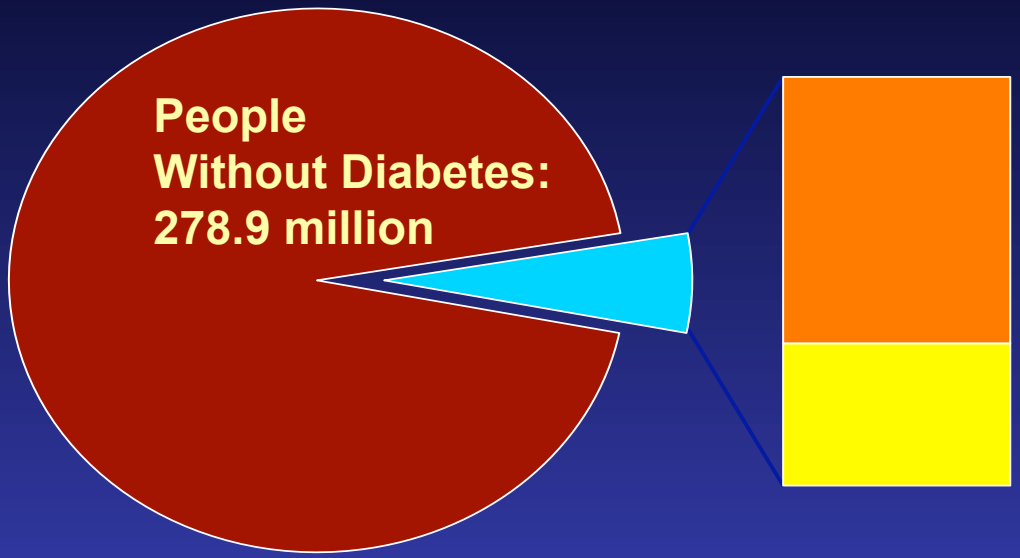
Background and epidemiology

Worldwide Diabetic Population



Smyth and Heron: Nature Medicine 12:75-80, 2005

Overview of Diabetes in the United States



People With Diabetes:
23.6 million
(7.8% of total population)

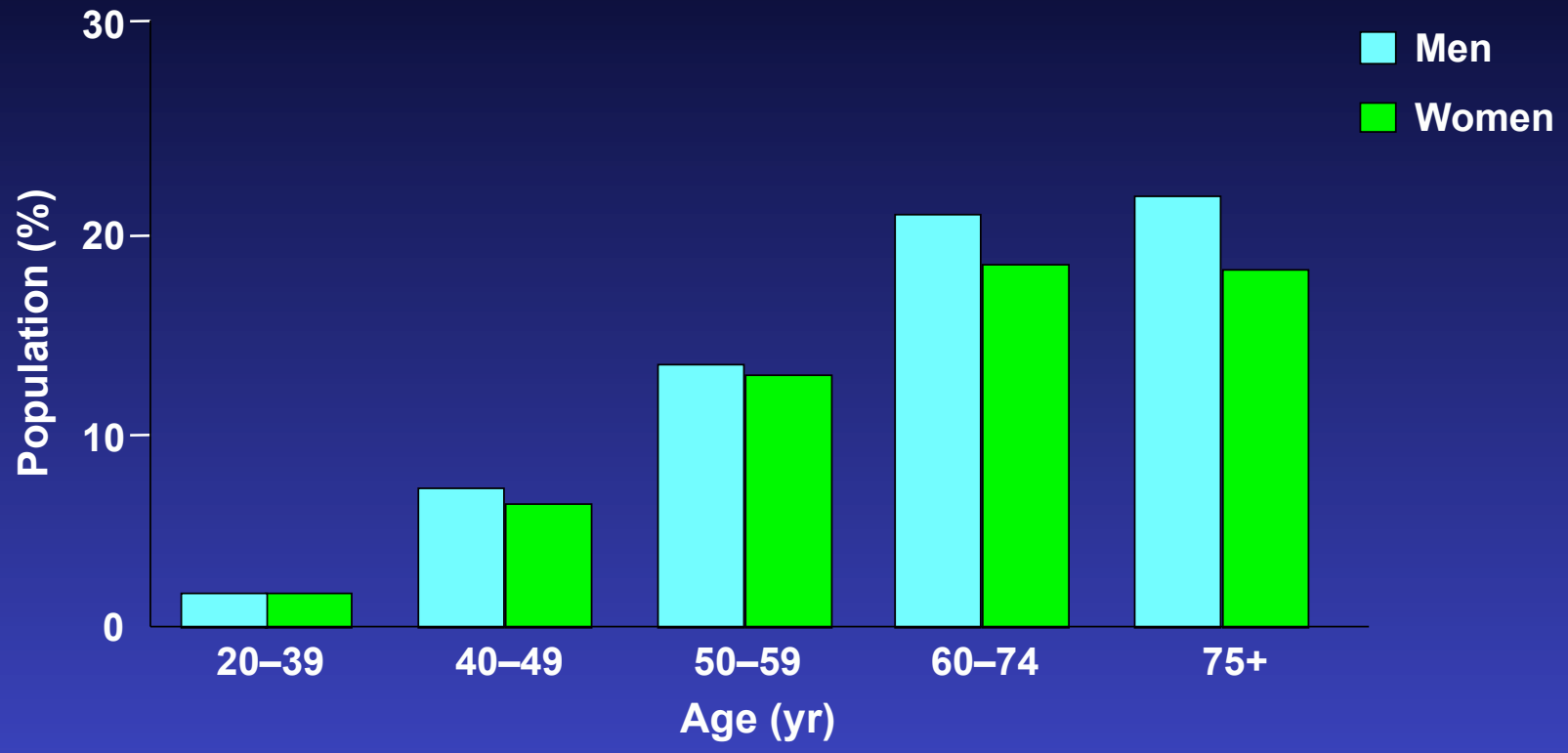
Diagnosed:
17.9 million

Undiagnosed:
5.7 million

- **Vast majority (90%-95%) of cases are type 2 diabetes**
- **One out of 3 children born in 2000 will develop diabetes during its life**
- **One out of 2 minority children born in 2000 will develop diabetes during its life**

NIDDK: National Diabetes Statistics 2007

Estimated Prevalence of Diabetes in US: Adult Men and Women

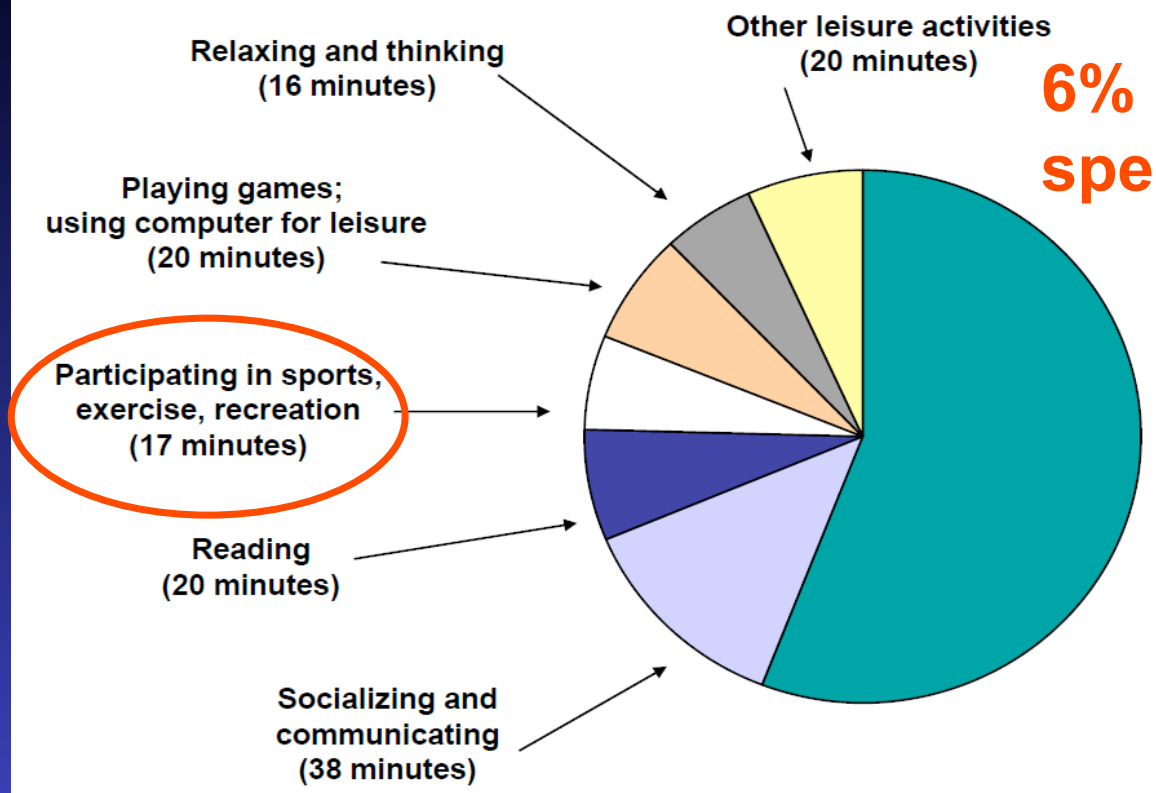


Harris MI et al. *Diabetes Care.* 1998;21:518

68% of US adults are overweight or obese

- 40% of US adults report no physical activity at all
- 31% of US adults reports at least 20’ of exercise 5 days/week
- 5% of adults, obtain 30’ of moderate activity 5 days/week

Leisure time on an average day

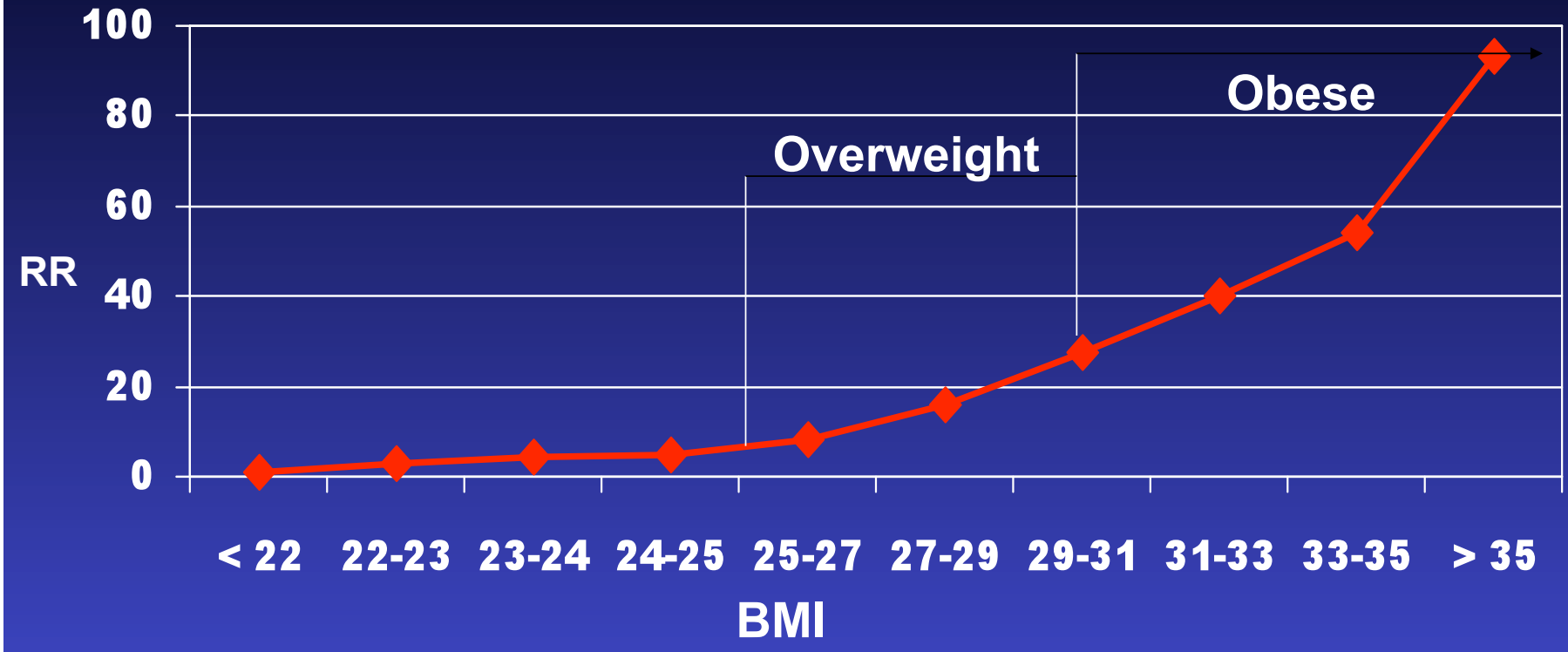


6% of leisure time spent exercising

NOTE: Data include all persons age 15 and over. Data include all days of the week and are annual averages for 2008.

SOURCE: Bureau of Labor Statistics

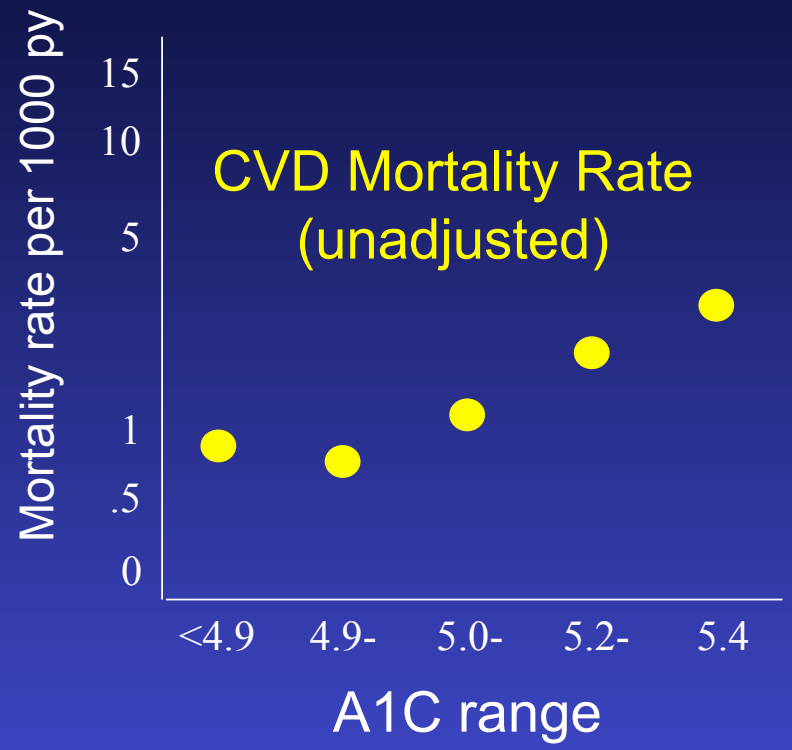
Risk of Development of Type 2 Diabetes Nurses Health Study

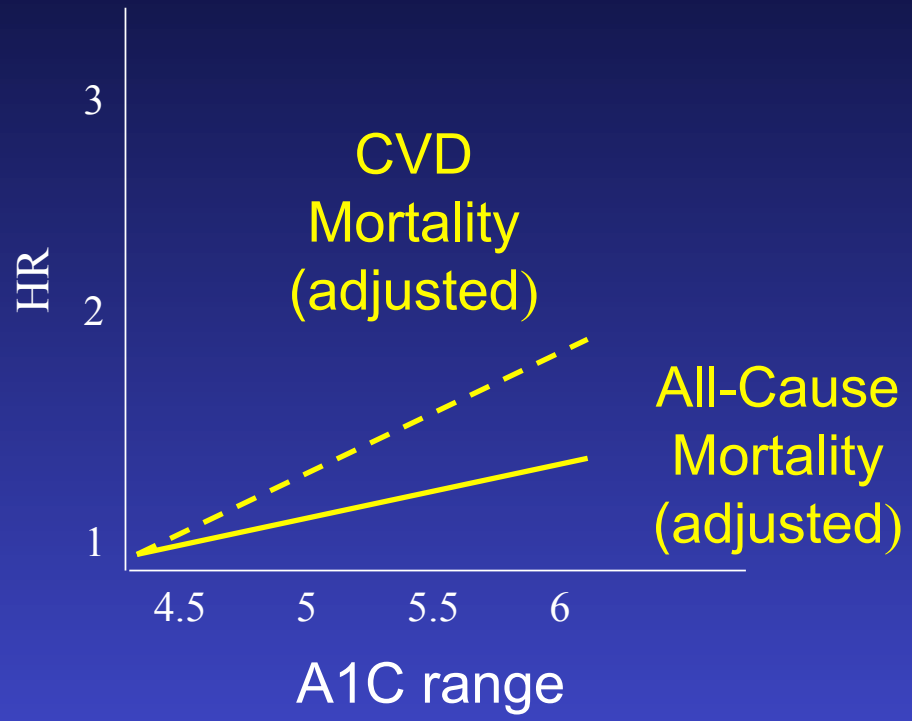


Ann Intern Med 1995;122:481-486

Blood Glucose and Cardiovascular Disease

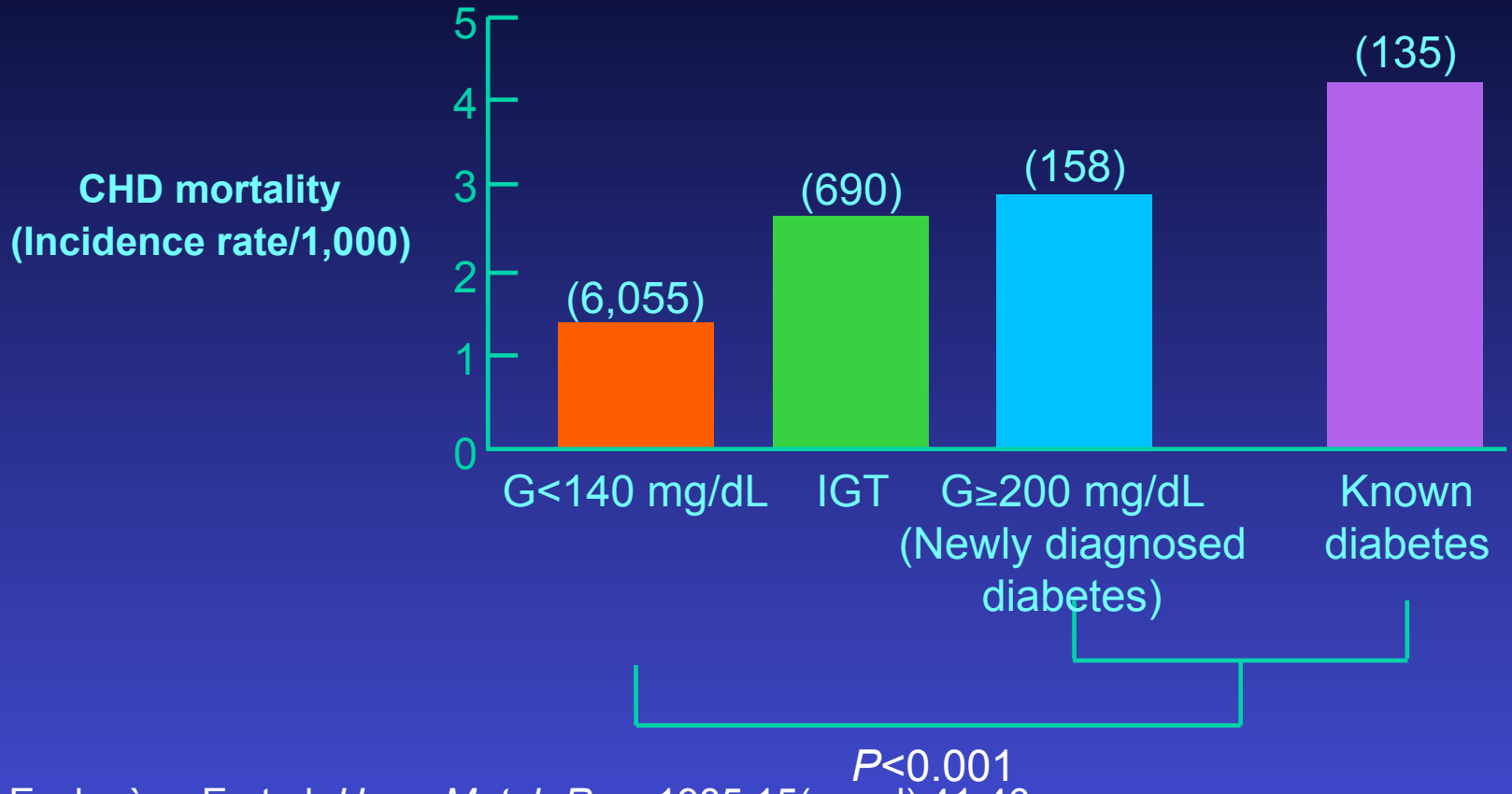
CVD Risk Increases As Glucose Levels (in Normal Range) Increase





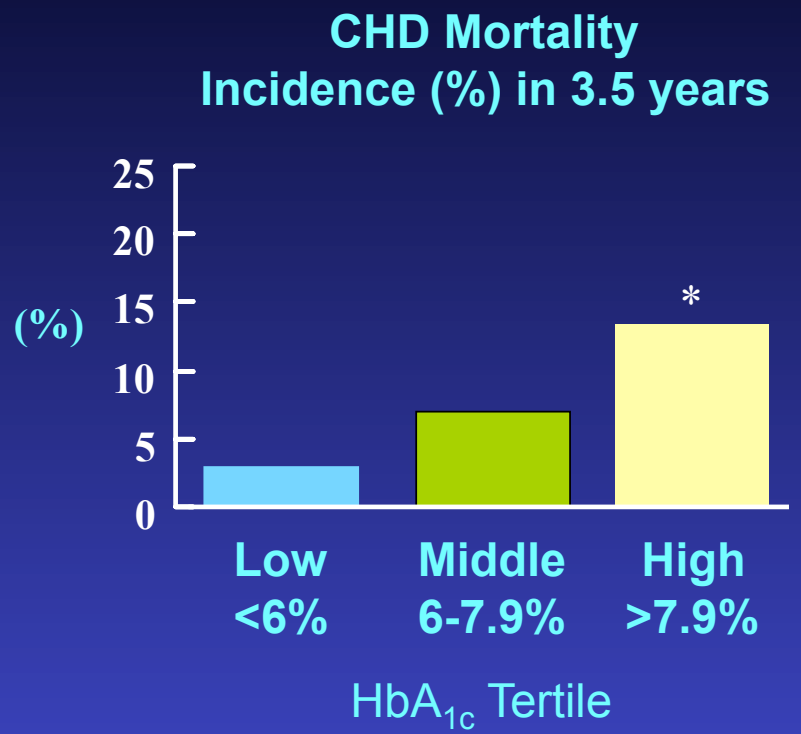
EL Barr et al. Diabetologia 2009; 52:415-424

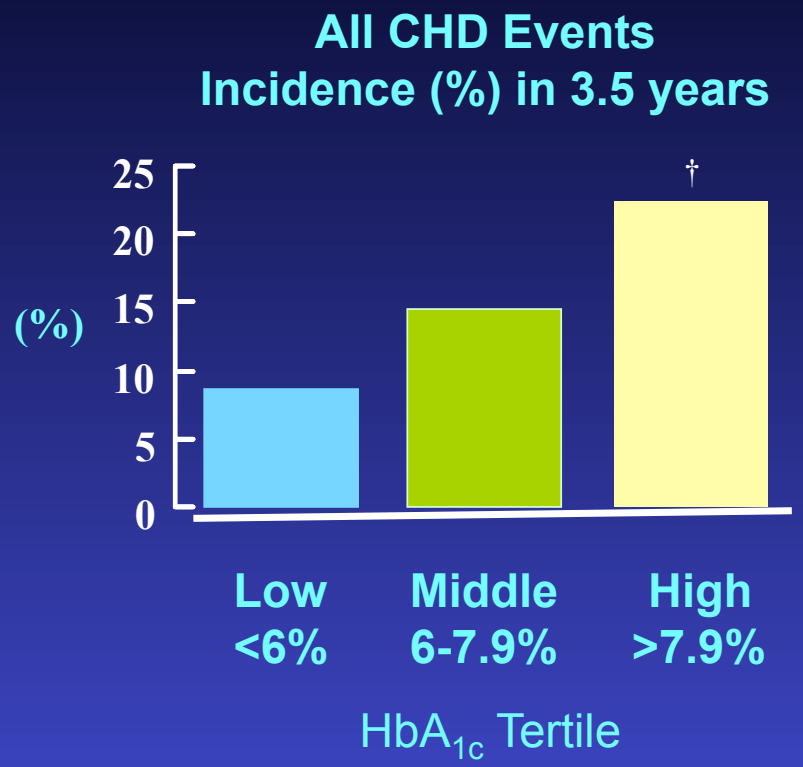
IGT Progressively Increases Risk of CHD Mortality: Paris Prospective Study



Eschwège E et al. *Horm Metab Res.* 1985;15(suppl):41-46.

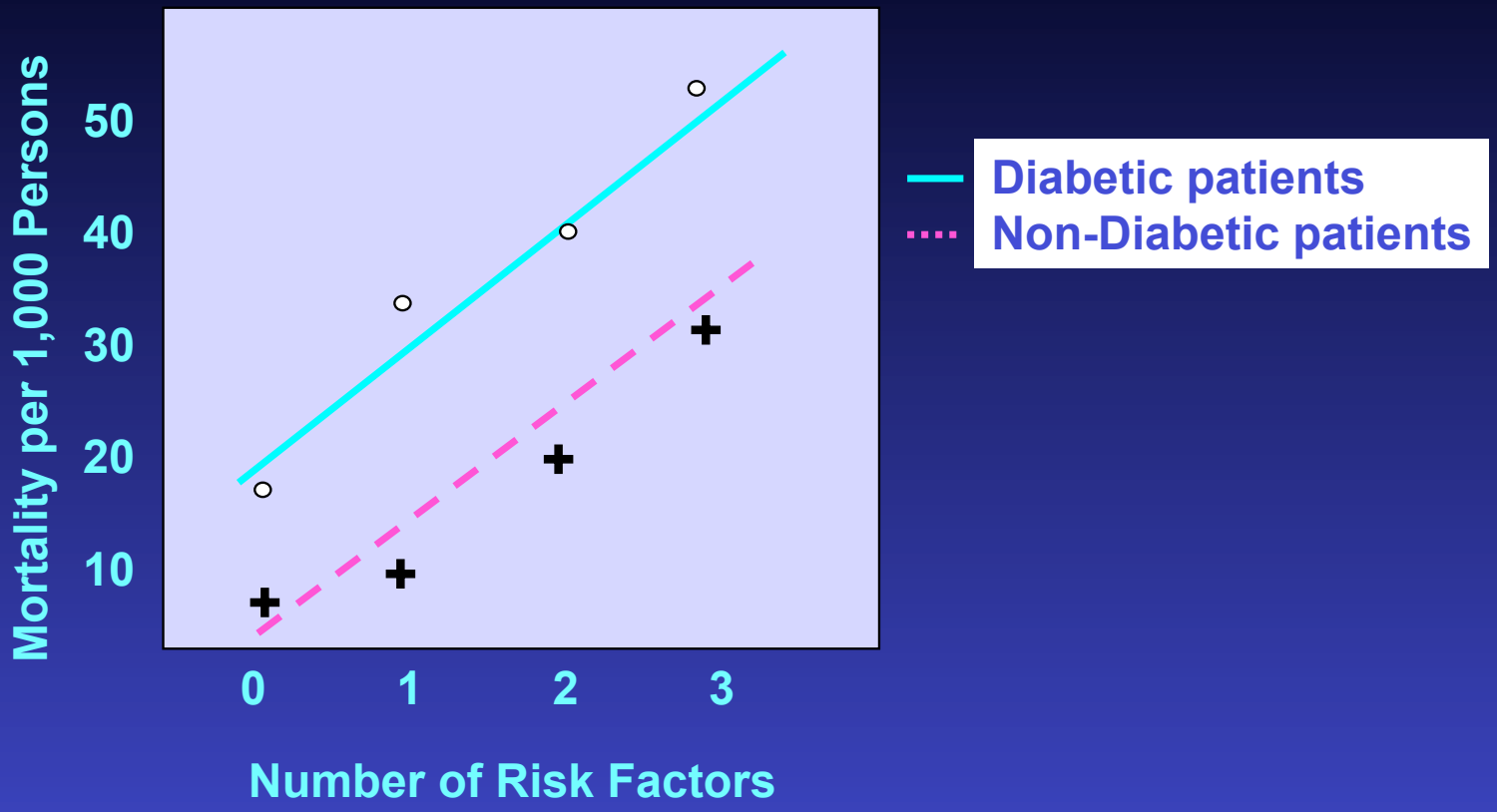
HbA_{1c} Predicts CHD in Type 2 Diabetes





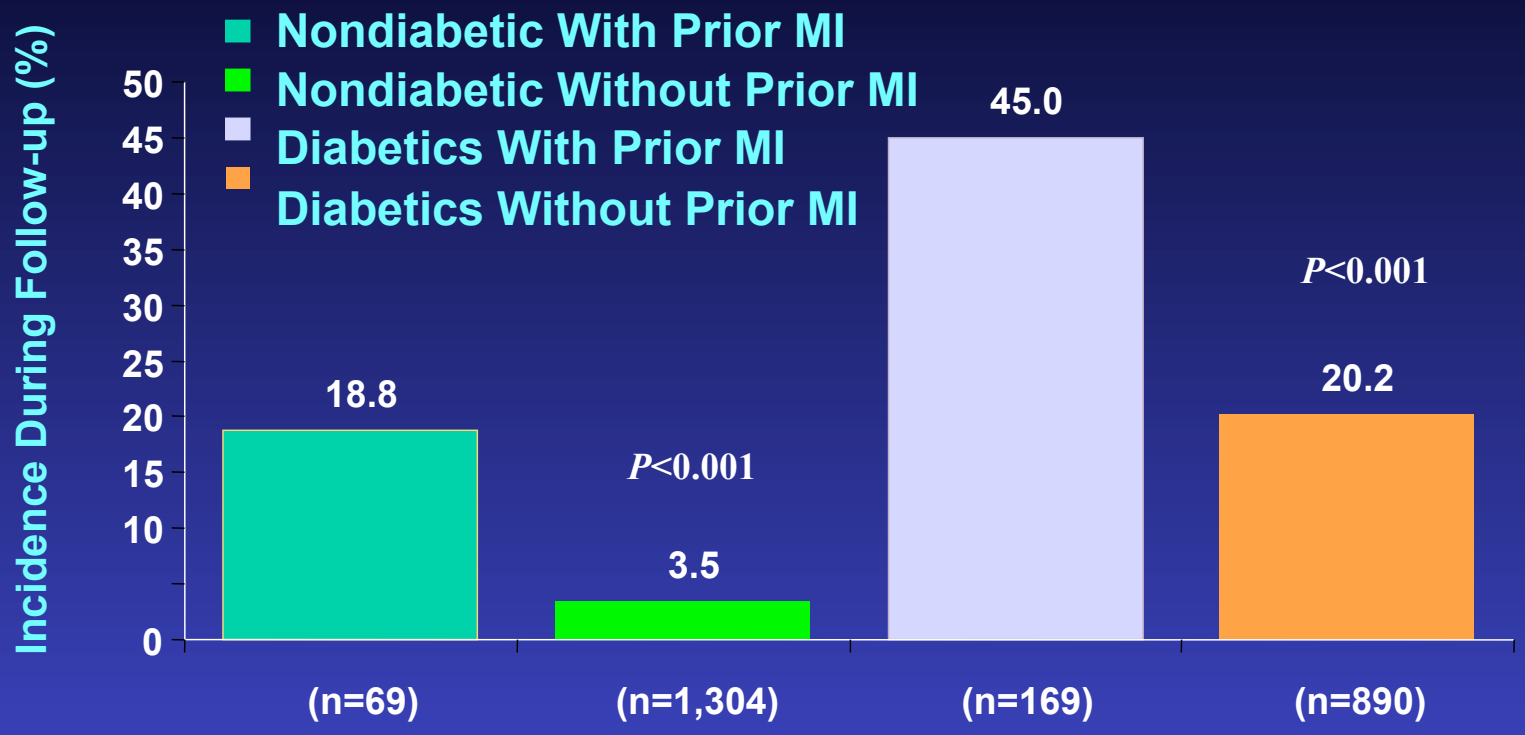
Kuusisto J, et al. *Diabetes* 1994;43:960–7

Impact of Diabetes on Cardiovascular Mortality



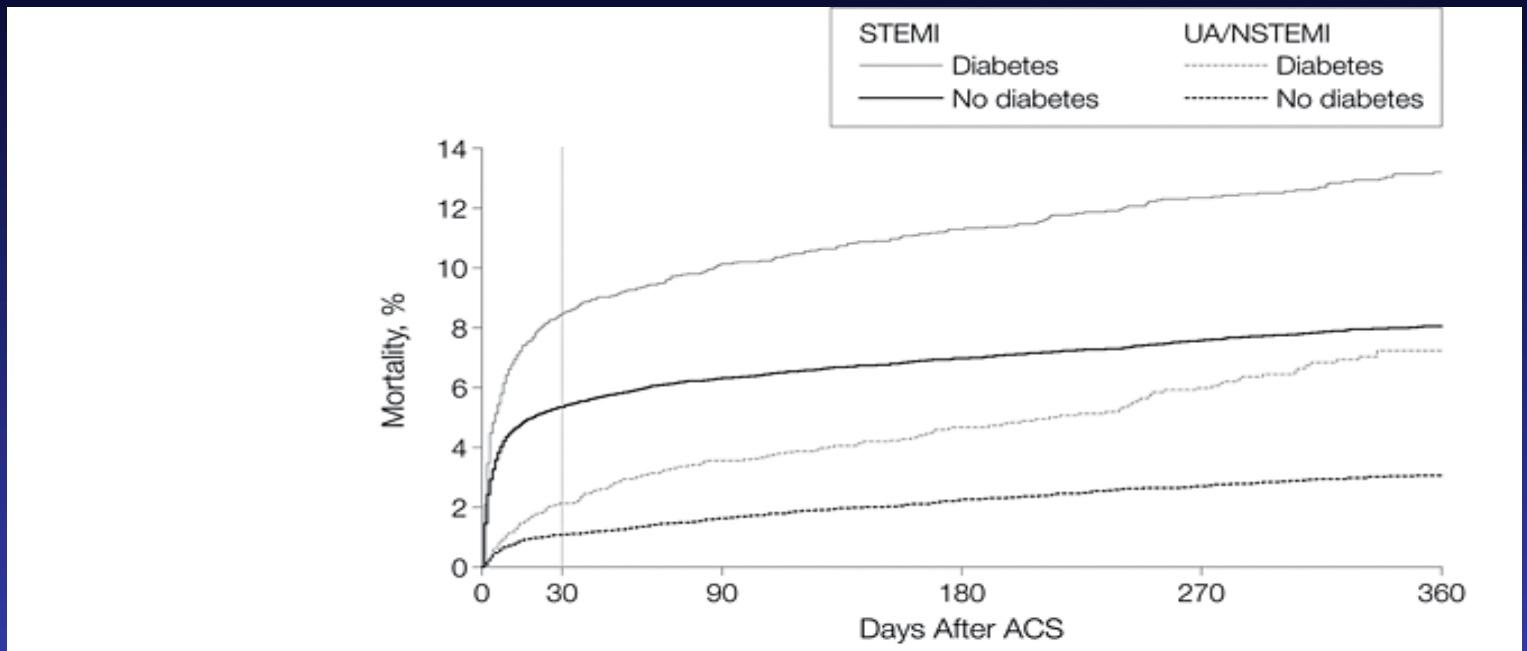
Stamler J, et al. *Diab Care* 1979;2:142
Stamler J, et al. *Diab Care* 1993;16:434-444.

Incidence of Fatal or Nonfatal MI in Relation to History of MI in Nondiabetic vs Diabetic Subjects: 7-Year Follow-up



Haffner S, et al. *N Engl J Med*. 1998;339:229-234.

Diabetes and Mortality Following Acute Coronary Syndromes

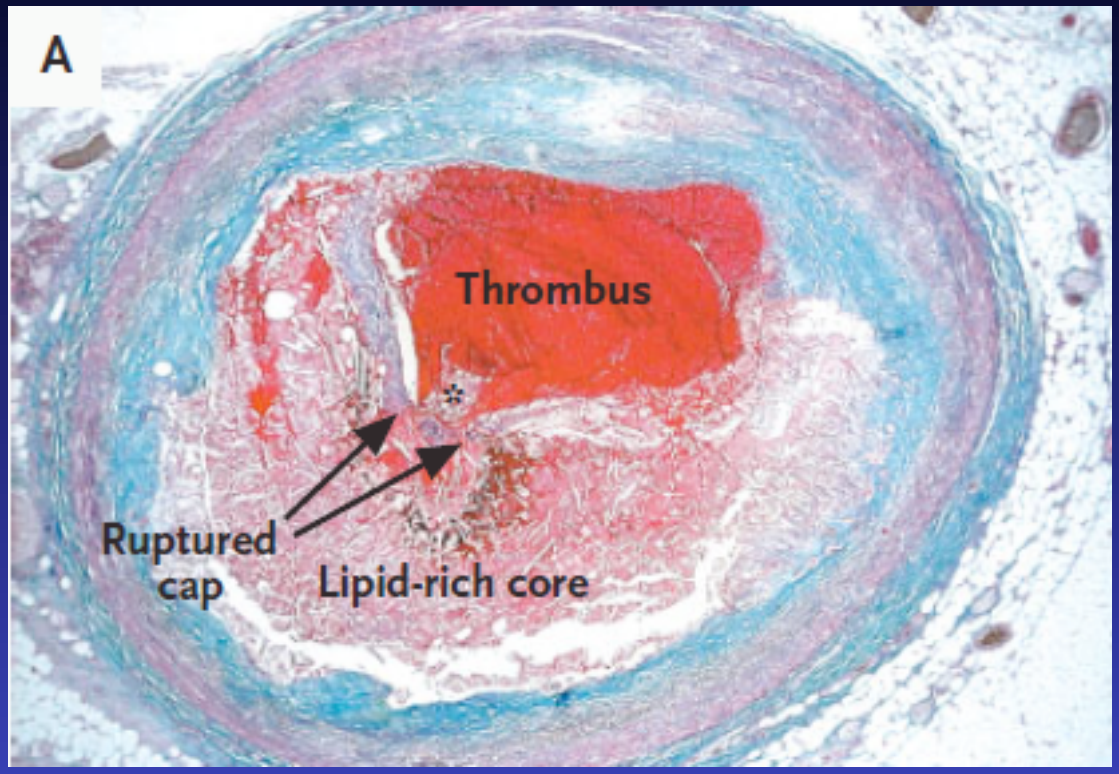


No. at Risk						
STEMI						
Diabetes	7156	6508	2947	2653	2118	1610
No diabetes	39421	37136	16685	15274	12276	9351
UA/NSTEMI						
Diabetes	3457	3313	2923	2339	1317	924
No diabetes	12002	11658	10505	8191	5141	4008

Donahoe SM et al, *JAMA* 2007;298:765-775

Diabetes as a prothrombotic condition

Thrombosed Coronary Artery



N Engl J Med 2005; 352:1685-95

Large Thrombi in the Retina of a Diabetic Patient

Diabetes 2001; 50:1432-39

DIABETES

Decreased Fibrinolysis

(elevated levels of PAI-1, decreased levels of tPA)

Hypercoagulability

(increased levels of fibrinogen, factor VII)

Endothelial Dysfunction

(increased levels of von Willebrand factor, ICAM-1, leucocyte adhesion molecules

Platelet Abnormalities

(increased aggregation and decreased sensitivity to anti-aggregants)

Role of glycemic control in CVD prevention

Will treatment of hyperglycemia reduce diabetes complications?

- Microvascular
  - Overwhelming consensus is, "yes"
- Macrovascular
  - Emerging data suggest
    - "Yes" in patients with short duration of disease and low CVD risk
    - "No" in patients with longstanding diabetes and significant atherosclerotic disease

Intensive Glycemic Control in Patients with Lower CVD Risk

Randomized controlled trials	DCCT (T1DM)	UKPDS (T2DM)
A1C (%)	9 vs. 7	8 vs. 7
Average follow-up (yrs)	6.5	10
Microvascular complications	Decreased	
CVD events	**No benefit**	

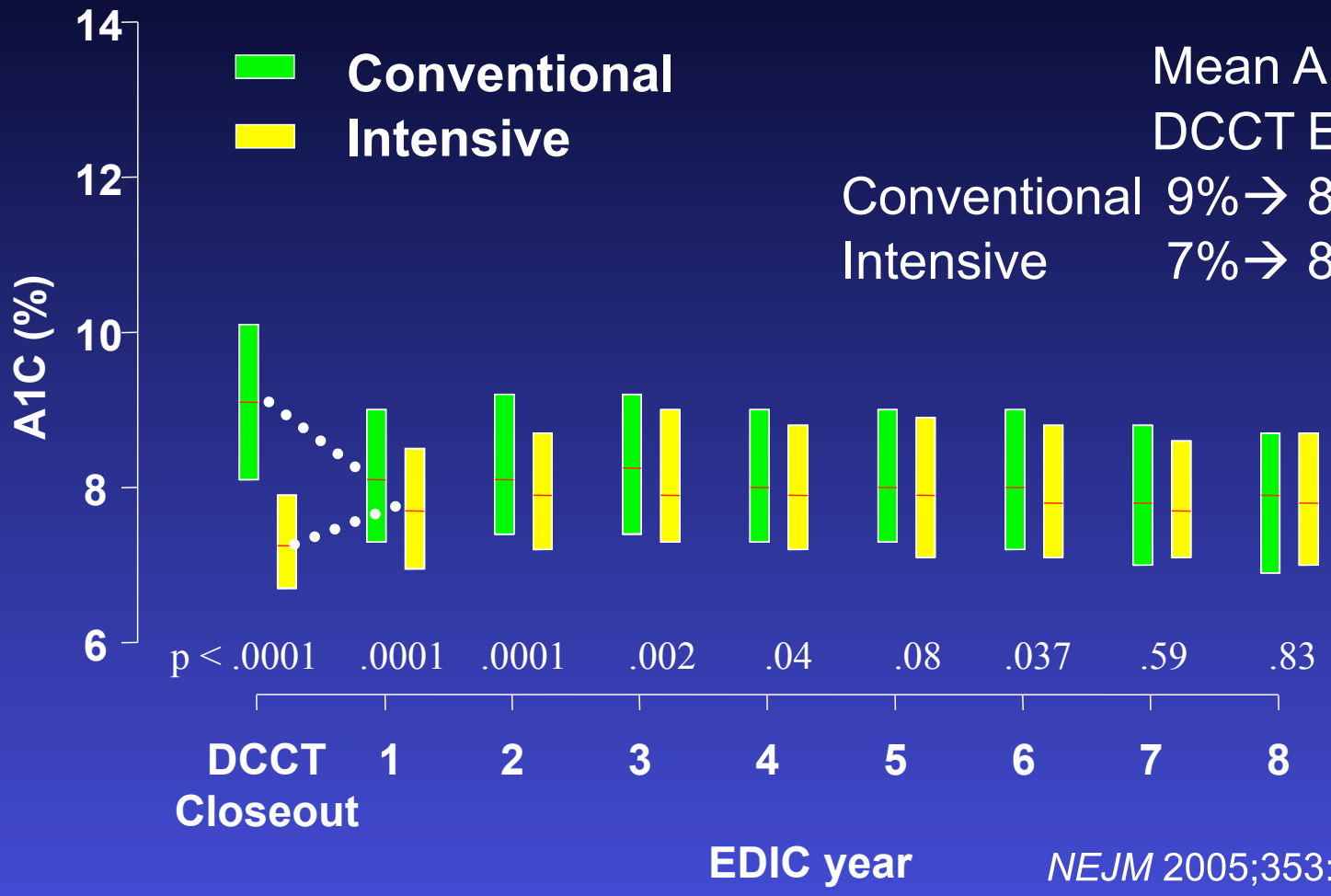
DCCT. NEJM, 329(14), 1993; UKPDS Group. Lancet, 352:837-853, 1998

Delayed Benefits ("Legacy Effect") of Intensive Glucose Control

Observational Monitoring Following RCT	DCCT (T1DM)	UKPDS (T2DM)
A1C (%)	~ 8	
Average follow-up (yrs)	RCT 6.5 Monitor 9	RCT 10 Monitor 8.5
Microvascular complications	Decreased	
CVD events	**Decreased**	

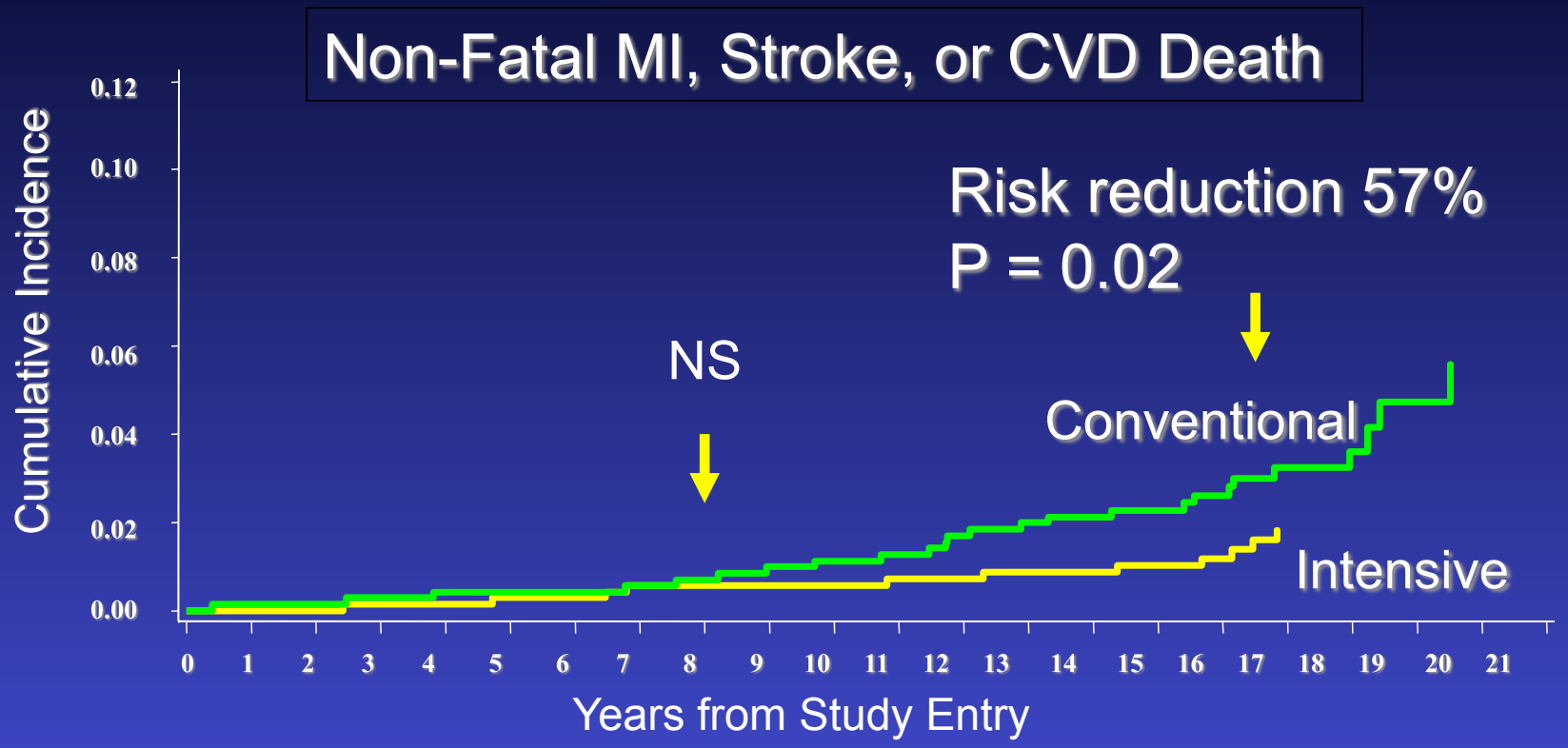
DCCT/EDIC NEJM 2005: 353:2643-2653; UKPDS 80. NEJM 2008; 359.

DCCT/EDIC: No Differences in Post Trial A1C Levels



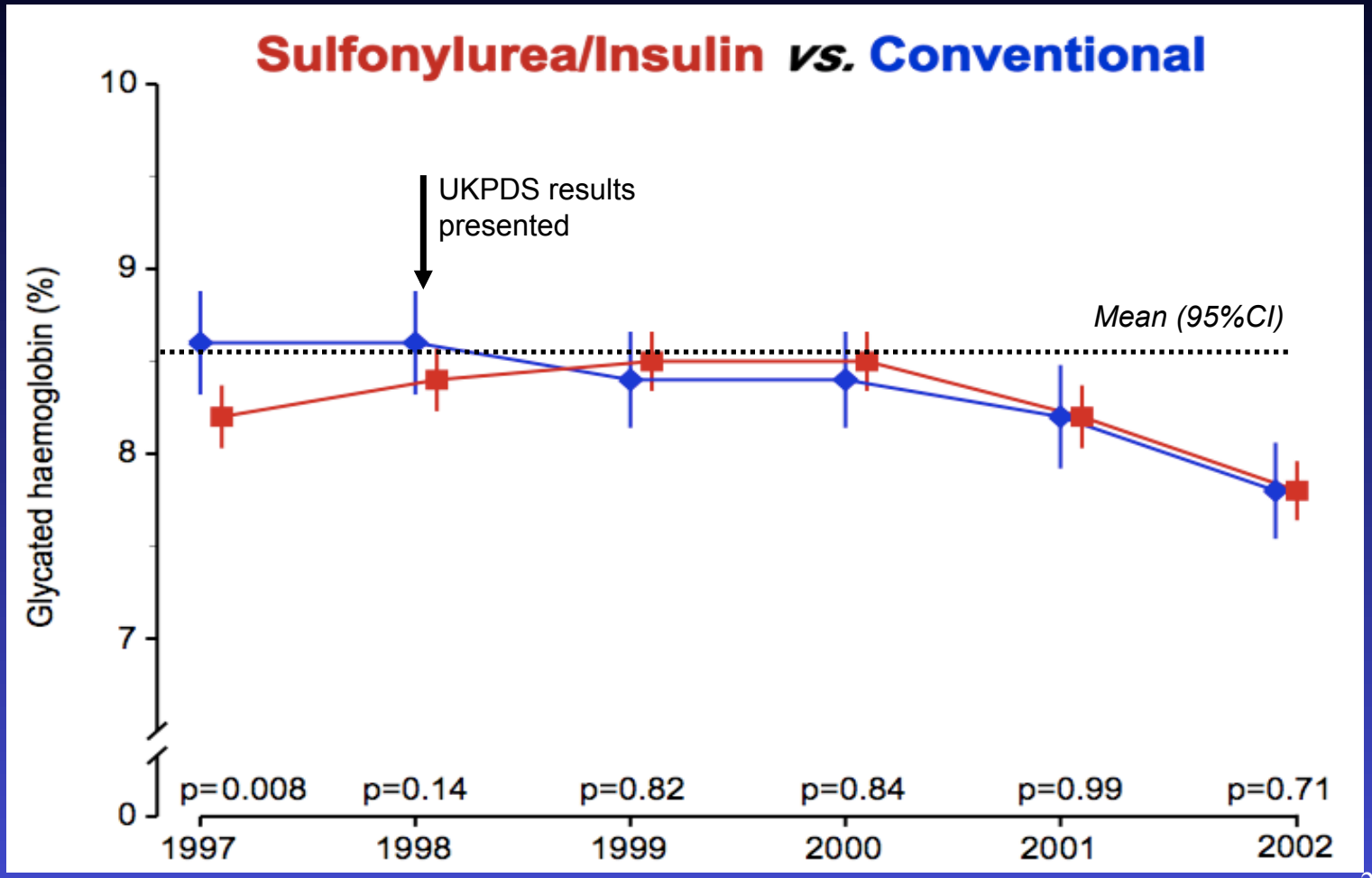
NEJM 2005;353:2643-2653

EDIC: Decreased CVD Events Eight Years After DCCT Closeout



DCCT/EDIC *N Engl J Med* 2005: 353:2643-2653.

UKPDS: Post-Trial Changes in A1C



UKPDS 80. *N Eng J Med* 2008; 359

Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

		1997	2007
Any diabetes related endpoint	*RRR:*	12%	**9%**
	P:	0.029	**0.040**
Microvascular disease	*RRR:*	25%	**24%**
	P:	0.0099	**0.001**
Myocardial infarction	*RRR:*	16%	**15%**
	P:	**0.052**	**0.014**
All-cause mortality	*RRR:*	6%	**13%**
	P:	**0.44**	**0.007**

UKPDS 80. *N Eng J Med* 2008; 359.

Intensive vs. Standard Glucose Control in T2DM With High CVD Risk

	ACCORD[1]	ADVANCE[2]	VADT[3]
N	10,251	11,140	1,791
Age (yrs)	62	66	60
Duration diabetes (yrs)	10	8	11.5
Baseline A1C (%)	8.1	7.2	9.4
Intense A1C goal (%)	<6	≤ 6.5	action >6.5
CVD risk	High		
Follow-up (yrs)	3.5 (stopped early)	5	5.6

1. NEJM 2008;358:2545-59, 2. NEJM 2008;358:2560-72, 3.NEJM 2009;360:129-139

Intensive vs. Standard Glucose Control in T2DM With High CVD Risk

	ACCORD[1]	ADVANCE[2]	VADT[3]
A1C standard (%)	7.5	7.0	8.5
A1C intensive (%)	6.4	6.3	6.9
Hypoglycemia	Greater with intensive treatment		
Weight gain			
CVD benefit*	**None**		
Death*	**Increased**	No difference	

1. NEJM 2008;358:2545-59, 2. NEJM 2008;358:2560-72, 3.NEJM 2009;360:129-139

*intensive vs. standard

Intensive Glucose Control Summary 1

- Benefits on microvascular and neuropathic complications is well established
- Evidence for CVD benefit is strongest in T1DM
  - There may be a “legacy effect” in which benefits of glucose control do not appear until years following intensive glucose control

Intensive Glucose Control Summary 2

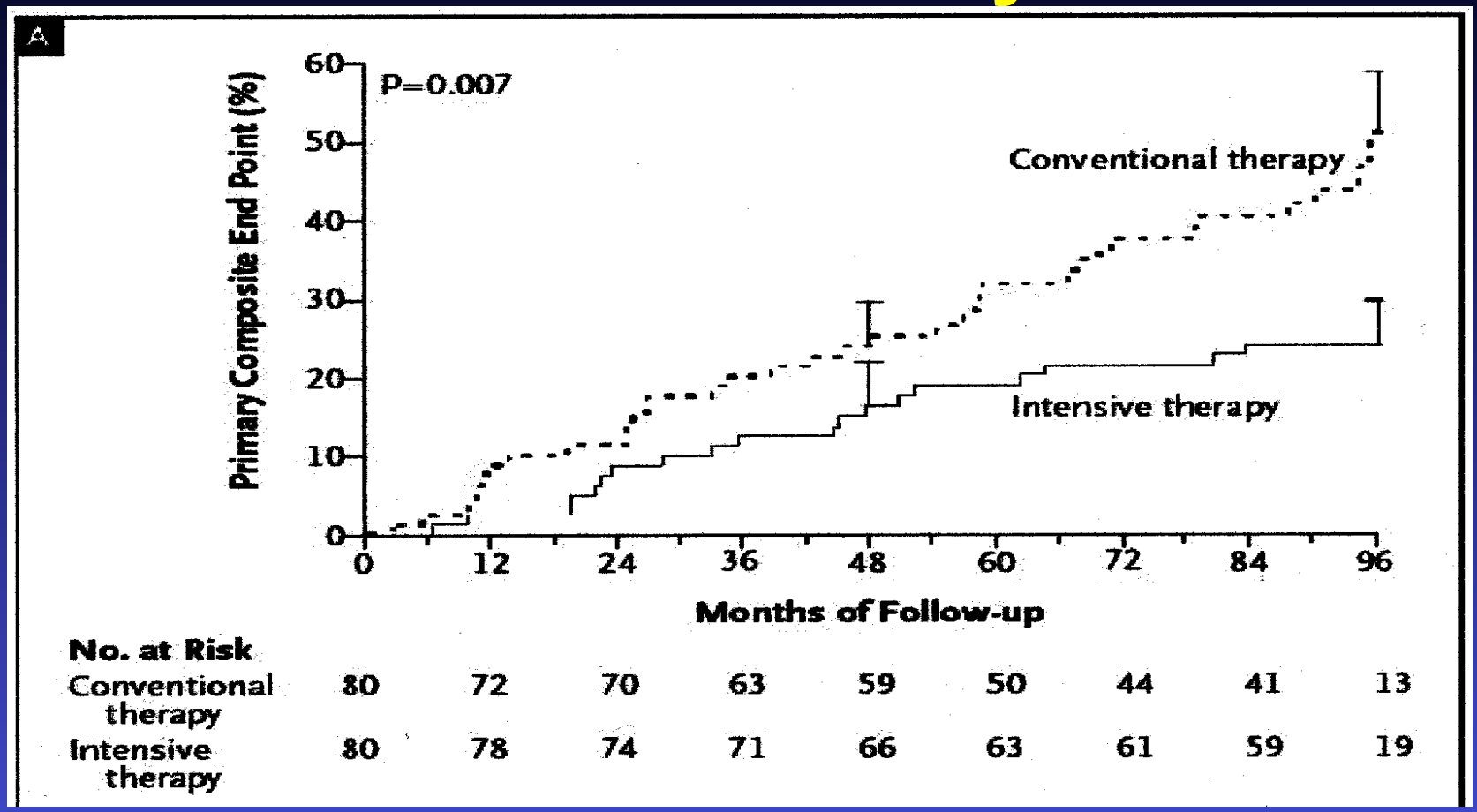
- Possible CVD benefits in patients with shorter duration of diabetes and without established atherosclerotic disease
- Potential risks may outweigh benefits when
  - Long duration of diabetes
  - Known history of severe hypoglycemia
  - Advanced atherosclerosis,
  - Advanced age/frailty

Can we prevent CVD in diabetic patients?

Steno-2 Study

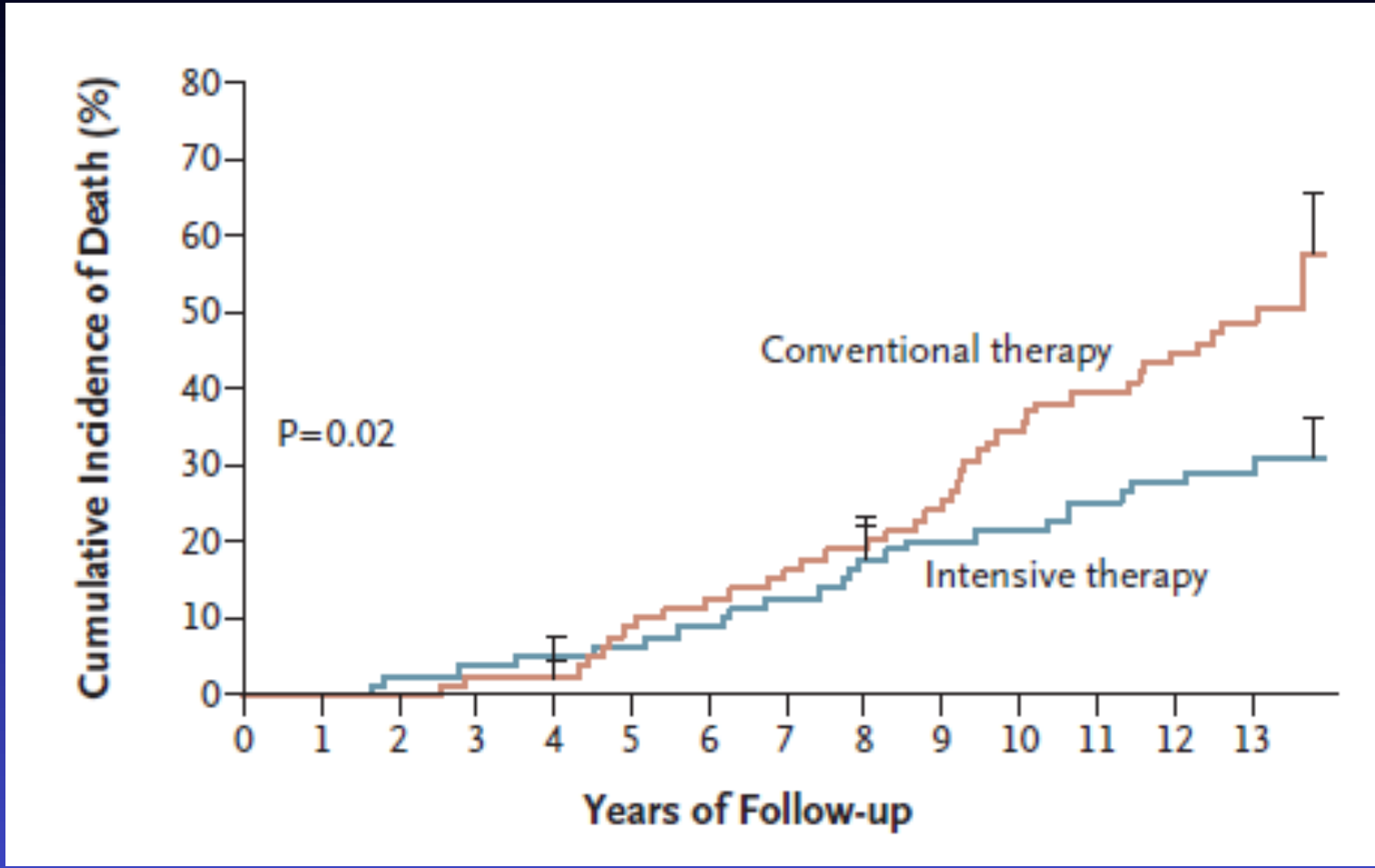
- 160 type 2 diabetic patients randomized to conventional or intensive treatment
- Mean follow-up of 7.8 years
- Treatment goals (changed over time) included A1c, BP and lipids
- Interventions in intensive therapy group:
  - Diet (total fat < 30%, saturated fats < 10%)
  - Exercise (30 minutes 3-5 days/week)
  - Aspirin 150 mg
  - Captopril 50 mg bid
  - Vitamin C, Folic Acid, D-a-tocopherol, Chromium[35]

Steno-2 Study



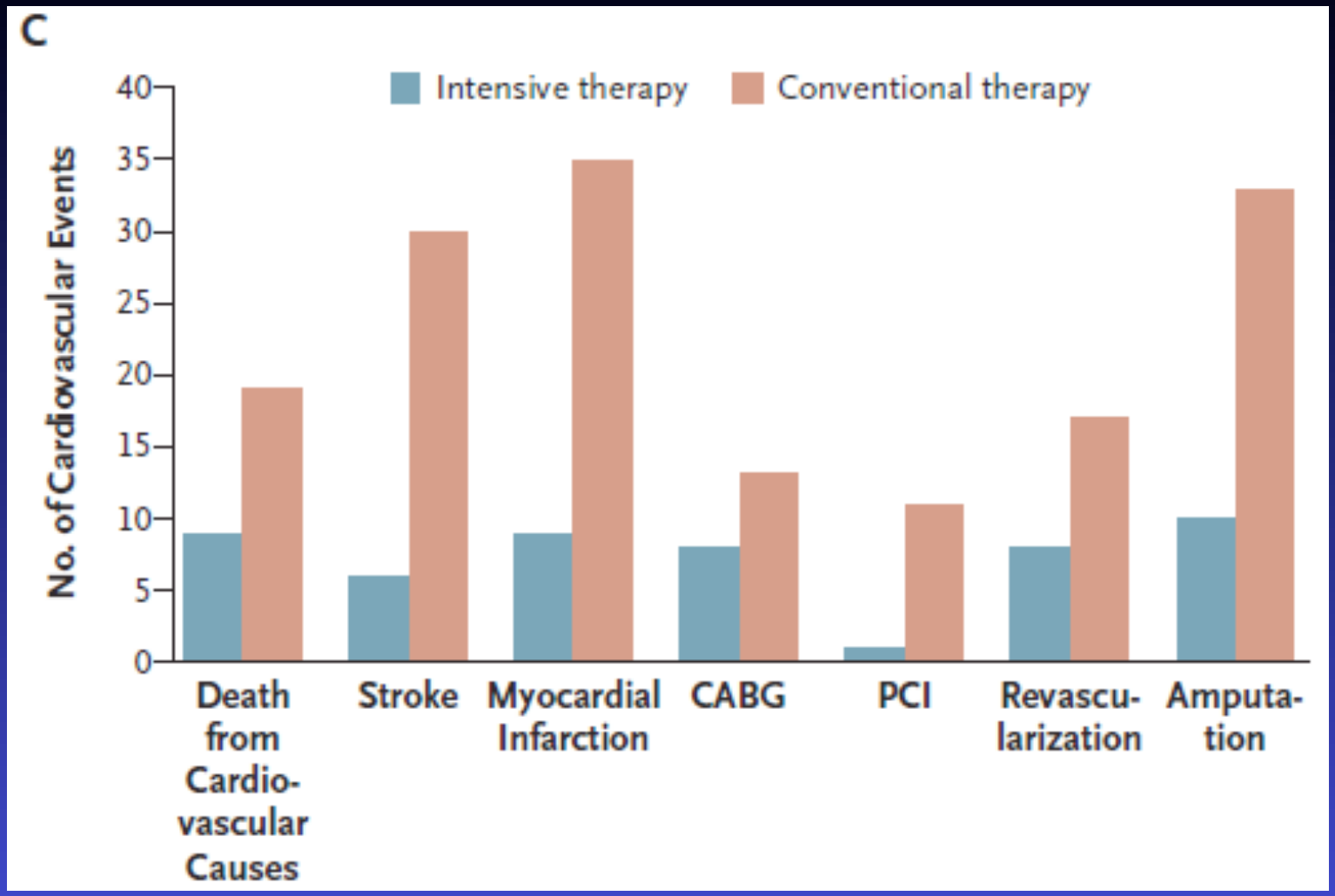
N Engl J Med 348:383-393,2003

Steno-2 Study



N Engl J Med 2008; 358:580-91

Steno-2 Study

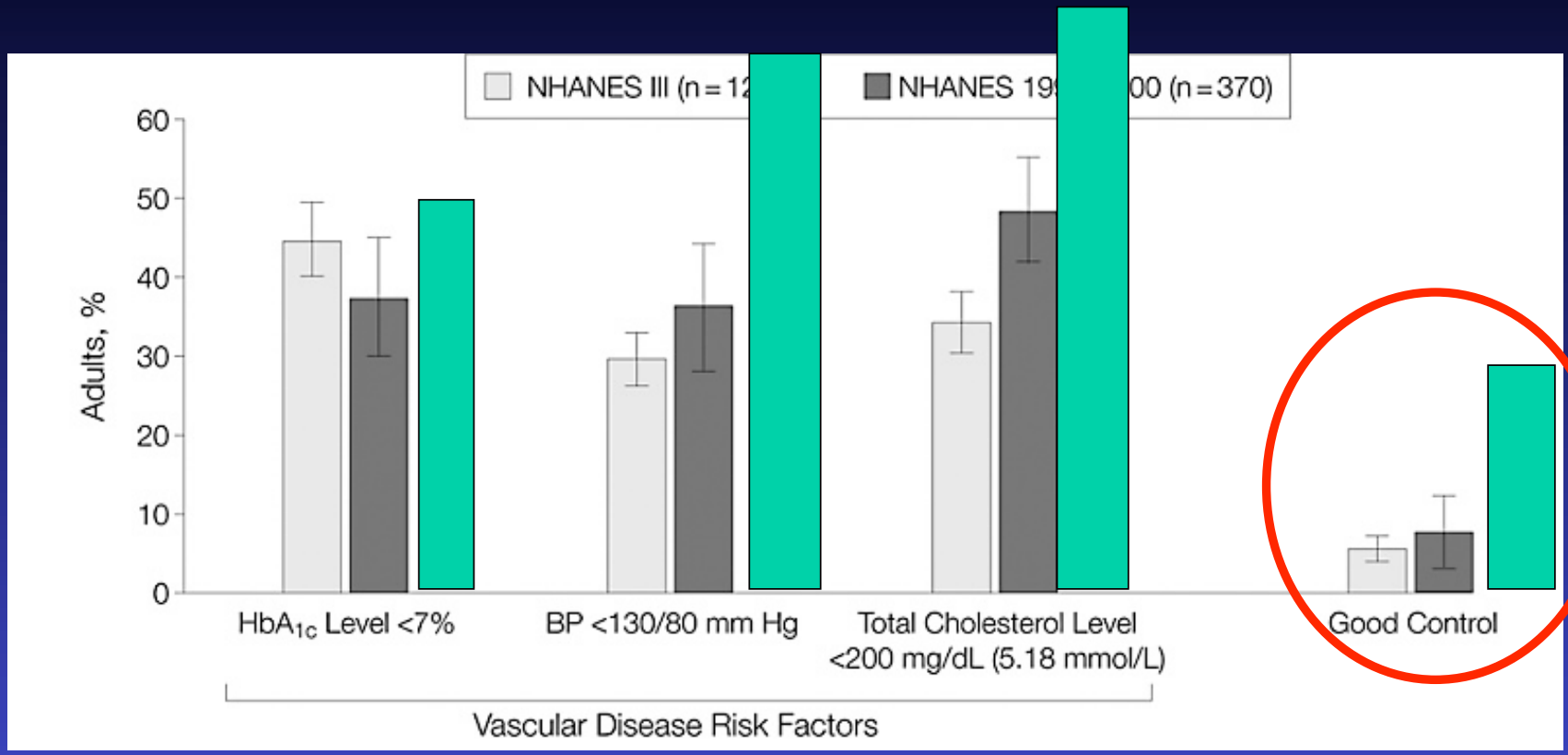


N Engl J Med 2008; 358:580-91

Are we achieving these goals?

Not really!

Percentage of Adults with Recommended Levels of Risk Factors



Saydah et al. JAMA 291:335, 2004; Bari 2D Study, N Engl J Med 360:2503, 2009

Comments or Questions?