Type 1 Diabetes

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The DCCT/EDIC Study Population

- 1,441 participants ages 13-39 years
- Serum creatinine < 1.2 mg/dL
- Creatinine clearance > 100 mL/min/1.73m^2
- Primary prevention cohort (N=711):
  - Diabetes duration 1-5 years
  - Albumin excretion rate < 40 mg/d
  - No retinopathy
- Secondary prevention cohort (N=730):
  - Diabetes duration 1-15 years
  - Albumin excretion rate ≤ 200 mg/d
  - At least one retinal microaneurysm

DCCT Diabetes Control and Complications Trial

EDIC EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS

DCCT/EDIC Study Interventions

The DCCT (1983-1993)

- Intensive diabetes therapy:
  - ≥ 3 insulin injections per day or insulin pump
  - Goal normal glucose
- Conventional therapy:
  - 1-2 injections per day
  - Goal prevent symptoms of hyperglycemia
- Mean duration of therapy 6.5 years

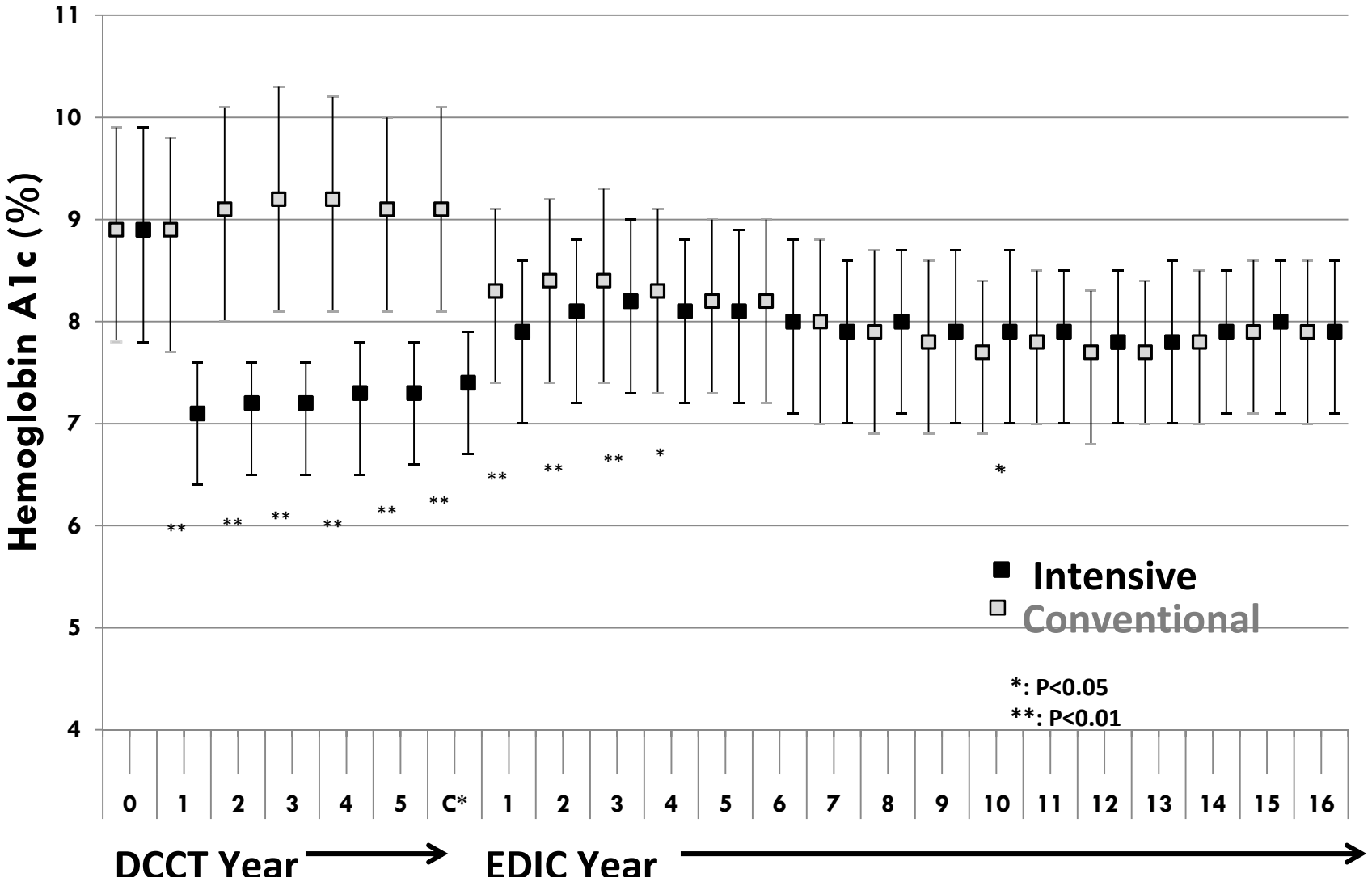
The EDIC Study (1994-)

- Observational follow-up
- Intensive therapy participants encouraged to continue intensive therapy
- Conventional therapy participants instructed in intensive therapy
- Participants returned to original care providers
- Ongoing annual study visits

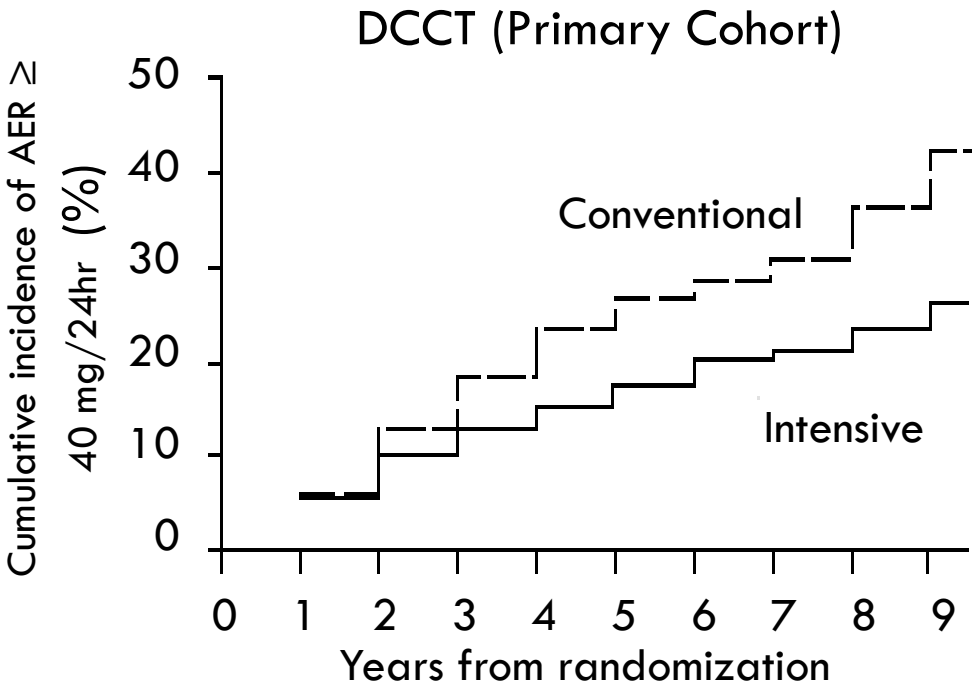
DCCT Diabetes Control and Complications Trial

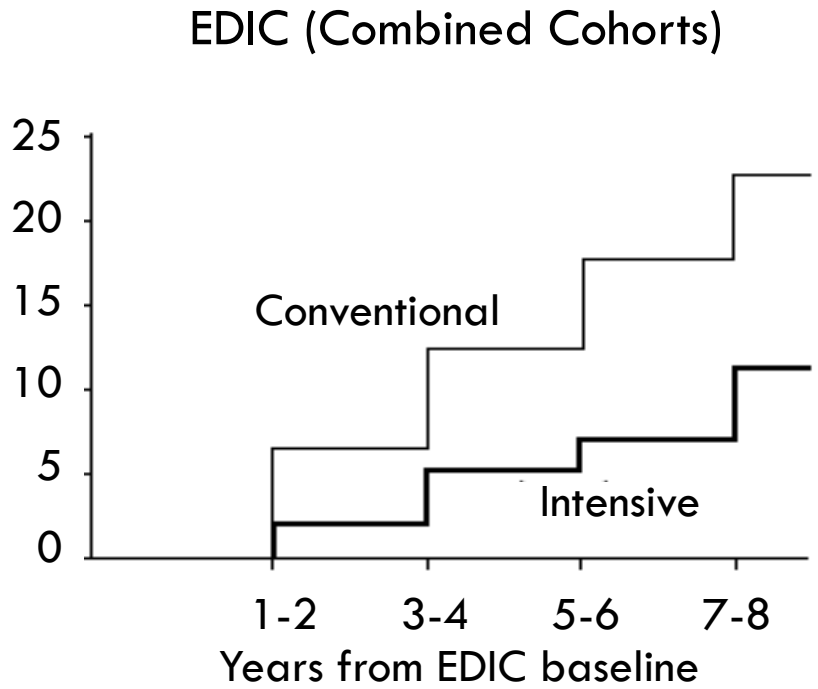
EDIC EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS

DCCT/EDIC Hemoglobin A1c



Intensive Diabetes Therapy Reduced the Risk of Microalbuminuria





Risk reductions:

- 1° cohort 34% (2%,56%)
- 2° cohort 43% (21%, 58%)

Risk reductions:

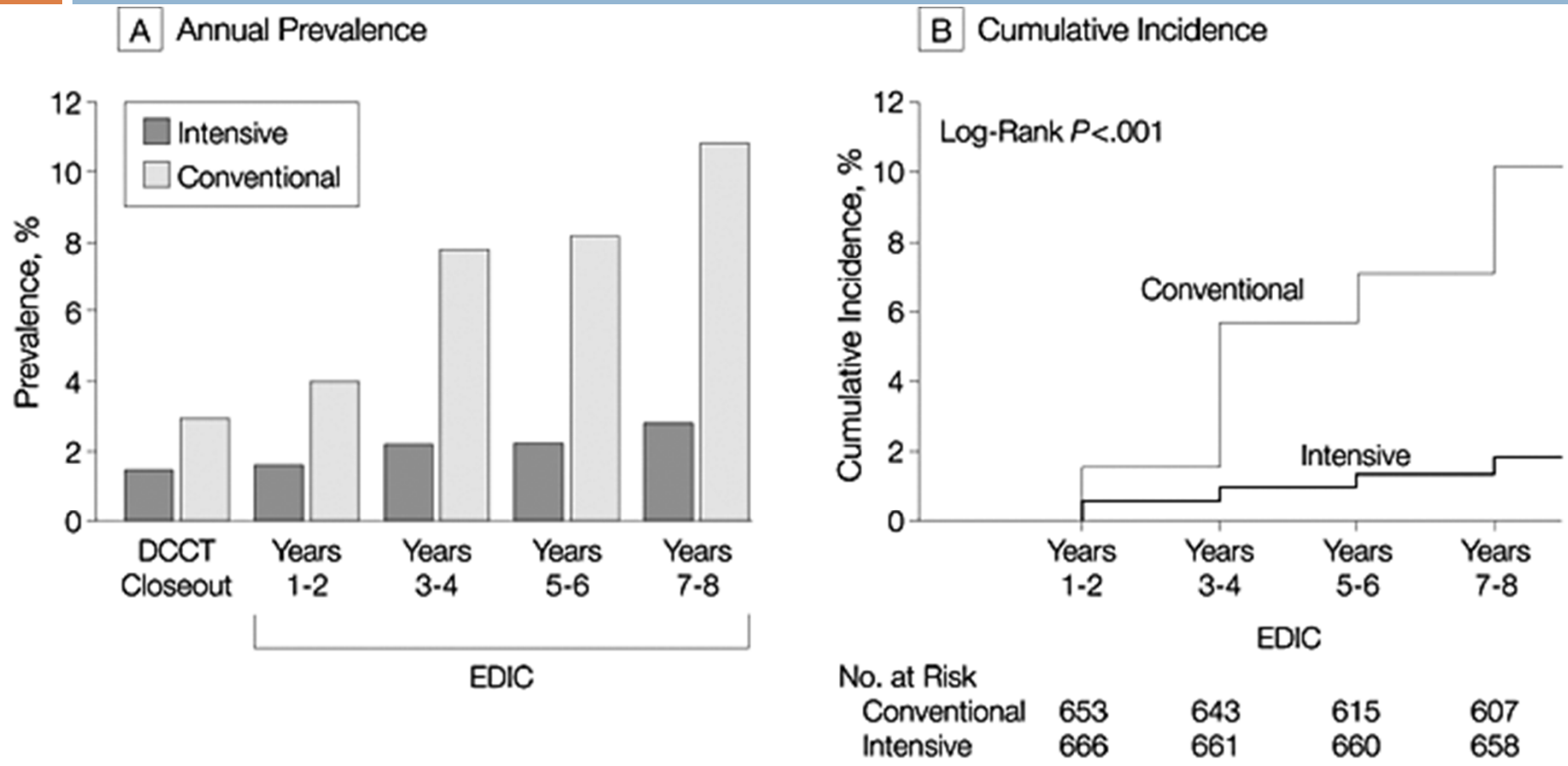
- Microalbuminuria 59% (39%, 73%)
- Macroalbuminuria 84% (67%, 92%)

Kidney Int 1995, *JAMA* 2003

DCCT Diabetes Control and Complications Trial

EDIC EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS

Annual Prevalence and Cumulative Incidence of Albuminuria in EDIC Subjects According to Original Treatment Cohorts



At DCCT Closeout, Cumulative Incidences of Albuminuria were 3.8% in Intensive and 6.3% in Conventional cohorts

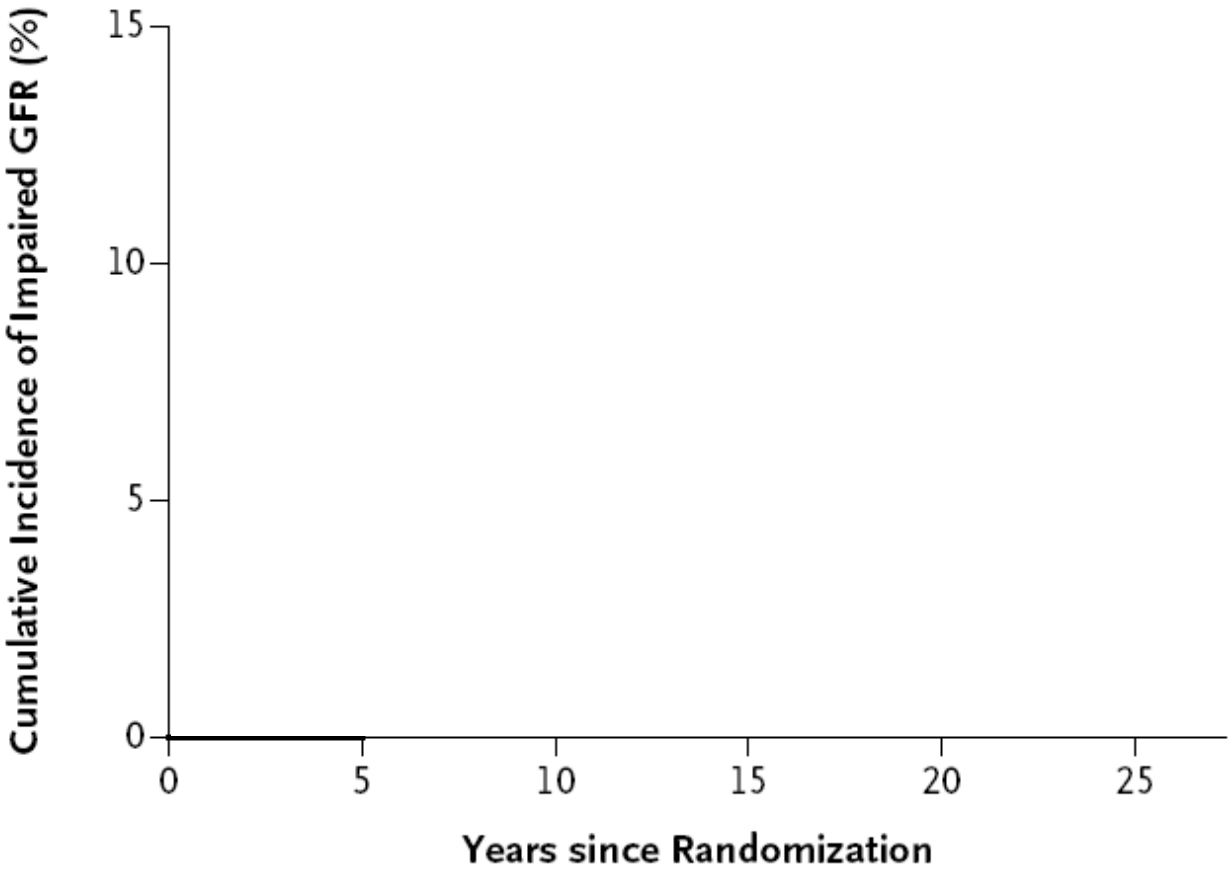
JAMA 2003:290:2159

GFR Study: Participant Characteristics

	At DCCT Baseline (1983-1989)		At EDIC Year 16 (2008-2010)	
	Intensive N = 711	Conv N = 730	Intensive N = 618	Conv N = 604
Age (years)	27 (7)	27 (7)	50 (7)	49 (7)
Diabetes duration (years)	6 (4)	6 (4)	29 (5)	28 (5)
ACEI/ARB use*	0	0	53%	57%
BMI (kg/m^2)	23 (3)	24 (3)	29 (13)	28 (13)
BP (mmHg)	115/73	115/73	122/73	121/72
AER ≥ 30 mg/24h	12%	10%	19%	23%
S creat (mg/dL)	0.68 (0.14)	0.68 (0.14)	0.85 (0.33)	0.89 (0.59)

DeBoer et al., NEJM 2011

Cumulative Incidence of Impaired eGFR (sustained <60mL/min/1.73m$^{2)}$



No. at Risk						
Intensive therapy	711	704	684	672	619	108
Conventional therapy	730	719	697	657	594	90

DeBoer et al., NEJM 2011

Primary & Secondary GFR Outcomes

	Number of Events		Relative Risk Reduction	
	Intensive Therapy	**Conventional** Therapy	Risk Reduction (%, 95% CI)	P-value
Impaired GFR*	24	46	50 (18, 69)	0.006
eGFR < 45 mL/min/1.73m^2	24	39	40 (1, 64)	0.045
eGFR < 30 mL/min/1.73m^2	13	23	44 (-9, 72)	0.088
End stage renal disease	8	16	51 (-14, 79)	0.098
Impaired GFR* or death	53	80	37 (10, 55)	0.011

* Sustained eGFR < 60 mL/min/1.73m^2 (primary outcome of this study)

Risk reduction is relative difference in risk of impaired GFR (in percent) comparing intensive to conventional diabetes therapy

DeBoer et al., NEJM 2011

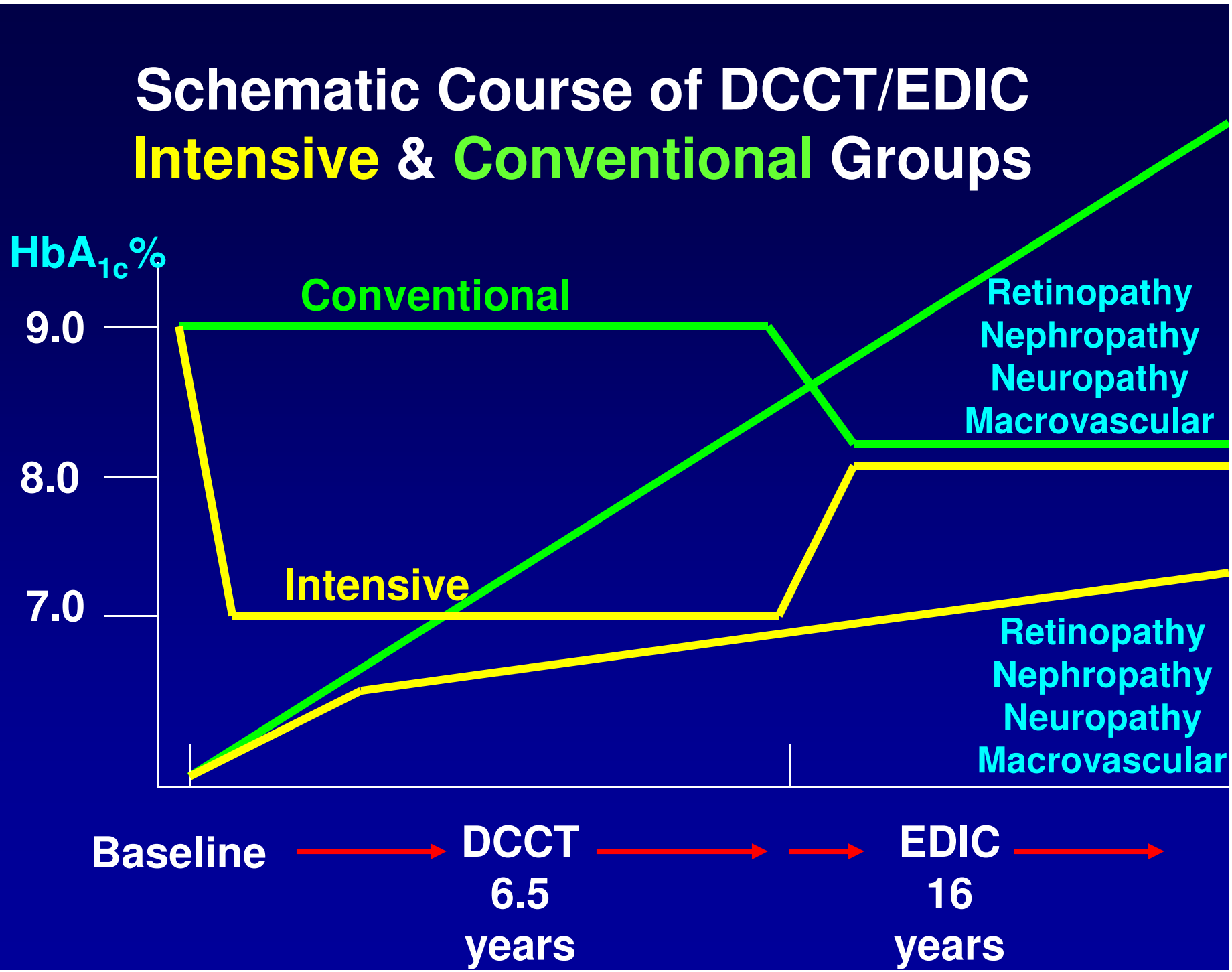
Summary of DCCT/EDIC

- **An average of 6.5 years intensive diabetes therapy reduced the risks of:**
  - **Microalbuminuria by 59%**
  - **Macroalbuminuria by 84%**
  - **Impaired GFR (<60) by 50%**
- **Effect only evident after many years follow-up**
- **Similar relative risk reductions were observed for advanced levels of GFR loss**
- **Benefits for GFR loss were attenuated by statistical adjustment for hemoglobin A1c or** AER

Diabetes Control and Complications Trial

EDIC EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS

Schematic Course of DCCT/EDIC
Intensive & Conventional Groups



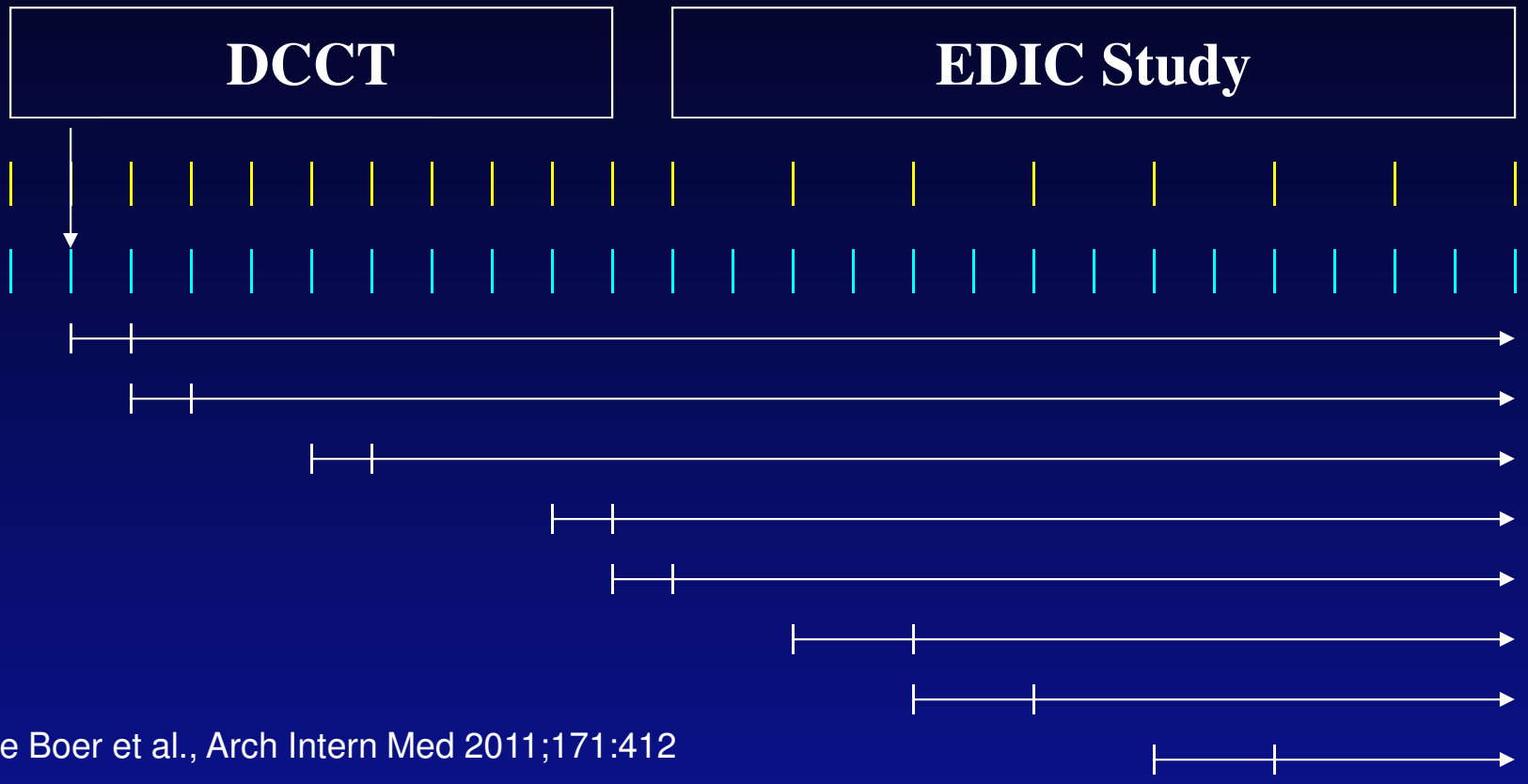
DCCT/EDIC Conclusions

- The benefit of intensive treatment in reducing complications can be virtually all accounted for by the reduction in hyperglycemia
- Tissue damage from any particular level of glycemic exposure outlasts the period of glycemic exposure and blunts the subsequent response to intensive treatment
- The long lasting effects of glycemic exposure may be explained, at least in part, by the generation of advanced glycation end products with long half lives

DCCT / EDIC Study

Incident Persistent Microalbuminuria Cohort
N = 325
AER ≥ 30 mg/24hr on 2 consecutive study visits

Follow-up: median 13 years, maximum 23 years



de Boer et al., Arch Intern Med 2011;171:412

Characteristics at Diagnosis of Sustained Microalbuminuria

N	325
Age (years)	33 ± 10
Male gender	193 (59%)
Duration of diabetes (years)	14 ± 6
DCCT treatment assignment	
Intensive therapy	115 (35%)
Conventional therapy	210 (65%)
Time of diagnosis	
During DCCT	170 (52%)
During EDIC Study	155 (48%)

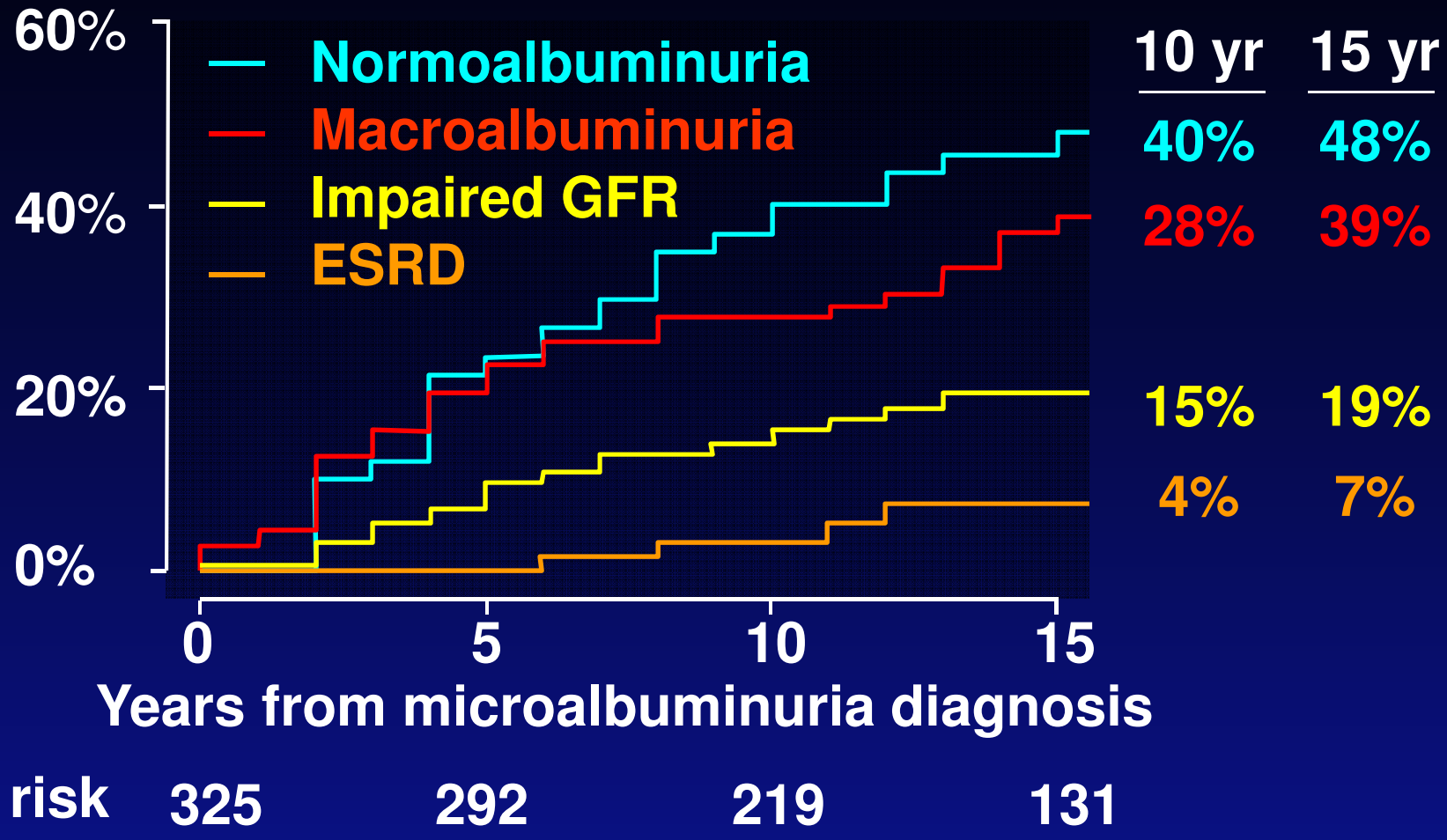
de Boer et al., Arch Intern Med 2011;171:412

Characteristics at Diagnosis of Sustained Microalbuminuria (2)

Retinopathy	231 (87%)
Active smoking	99 (32%)
RAAS inhibitor use	24 (7%)
Lipid-lowering medication	16 (5%)
BMI (kg/m2)	26.0 ± 4.1
SBP (mmHg)	122 ± 14
DBP (mmHg)	78 ± 9
Hemoglobin A1c (%)	9.4 ± 1.8
Estimated GFR (mL/min/1.73m^2)	114 ± 32

de Boer et al., Arch Intern Med 2011;171:412

Sustained Microalbuminuria
Progression and Regression



de Boer IH *et al, Arch Int Med* 2011

Risk Factors for Renal Outcomes

	Renal Outcome					
	Macro-Albuminuria		Impaired GFR		Normo-Albuminuria	
Risk factor	HR	P	HR	P	HR	P

Adjusted for age, gender, and duration of diabetes at microalbuminuria diagnosis

de Boer et al., Arch Intern Med 2011;171:412

Risk Factors for Renal Outcomes

	Renal Outcome					
	Macro-Albuminuria		Impaired GFR		Normo-Albuminuria	
Risk factor	HR	P	HR	P	HR	P
Female gender	0.52	0.005	1.10	0.7	2.53	<0.001

Adjusted for age, gender, and duration of diabetes at microalbuminuria diagnosis

de Boer et al., Arch Intern Med 2011;171:412

Risk Factors for Renal Outcomes

	Renal Outcome					
	Macro-Albuminuria		Impaired GFR		Normo-Albuminuria	
Risk factor	HR	P	HR	P	HR	P
Female gender	0.52	0.005	1.10	0.7	2.53	<0.001
SBP (10 mmHg)	1.30	0.003	1.06	0.6	0.85	0.04
DBP (10 mmHg)	1.38	0.01	1.21	0.23	0.71	0.004

Adjusted for age, gender, and duration of diabetes at microalbuminuria diagnosis

de Boer et al., Arch Intern Med 2011;171:412

Risk Factors for Renal Outcomes

	Renal Outcome					
	Macro-Albuminuria		Impaired GFR		Normo-Albuminuria	
Risk factor	HR	P	HR	P	HR	P
Female gender	0.52	0.005	1.10	0.7	2.53	<0.001
SBP (10 mmHg)	1.30	0.003	1.06	0.6	0.85	0.04
DBP (10 mmHg)	1.38	0.01	1.21	0.23	0.71	0.004
Time-updated SBP	1.71	<0.001	1.91	<0.001	0.82	0.08
Time-updated DBP	2.03	<0.001	2.17	<0.001	0.68	<0.001

Adjusted for age, gender, and duration of diabetes at microalbuminuria diagnosis

de Boer et al., Arch Intern Med 2011;171:412

Risk Factors for Renal Outcomes

	Renal Outcome					
	Macro-Albuminuria		Impaired GFR		Normo-Albuminuria	
Risk factor	HR	P	HR	P	HR	P
HbA1c (%)	1.25	<0.001	1.33	<0.001	0.76	<0.001

Adjusted for age, gender, and duration of diabetes at microalbuminuria diagnosis

de Boer et al., Arch Intern Med 2011;171:412

Risk Factors for Renal Outcomes

	Renal Outcome					
	Macro-Albuminuria		Impaired GFR		Normo-Albuminuria	
Risk factor	HR	P	HR	P	HR	P
HbA1c (%)	1.25	<0.001	1.33	<0.001	0.76	<0.001
Time-updated HbA1c (%)	1.25	<0.001	1.13	0.16	0.79	<0.001

Adjusted for age, gender, and duration of diabetes at microalbuminuria diagnosis

de Boer et al., Arch Intern Med 2011;171:412

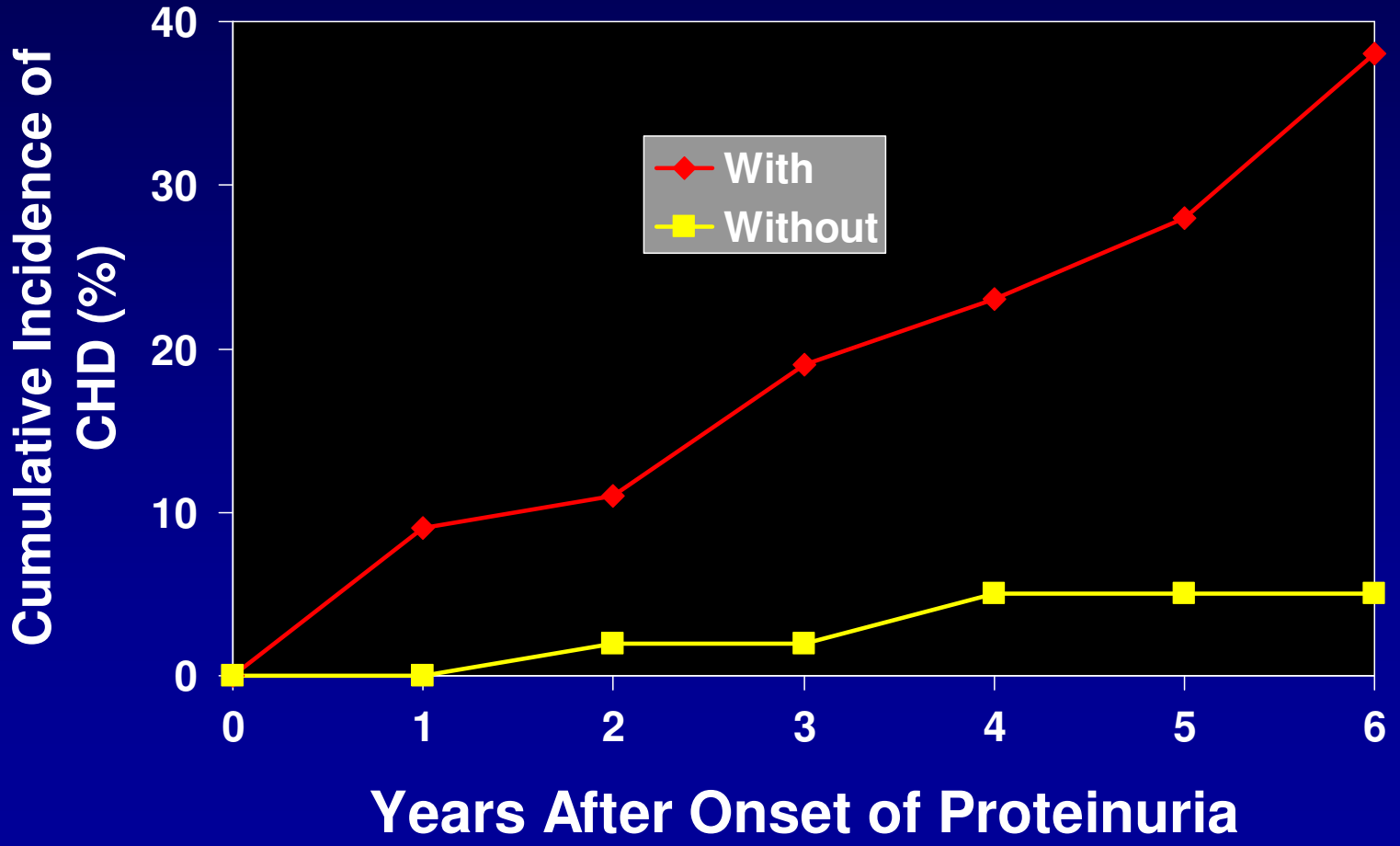
Risk Factors for Renal Outcomes

	Renal Outcome					
	Macro-Albuminuria		Impaired GFR		Normo-Albuminuria	
Risk factor	HR	P	HR	P	HR	P
HbA1c (%)	1.25	<0.001	1.33	<0.001	0.76	<0.001
Time-updated HbA1c (%)	1.25	<0.001	1.13	0.16	0.79	<0.001
Intensive therapy	0.64	0.06	0.65	0.14	1.92	0.002

Adjusted for age, gender, and duration of diabetes at microalbuminuria diagnosis

de Boer et al., Arch Intern Med 2011;171:412

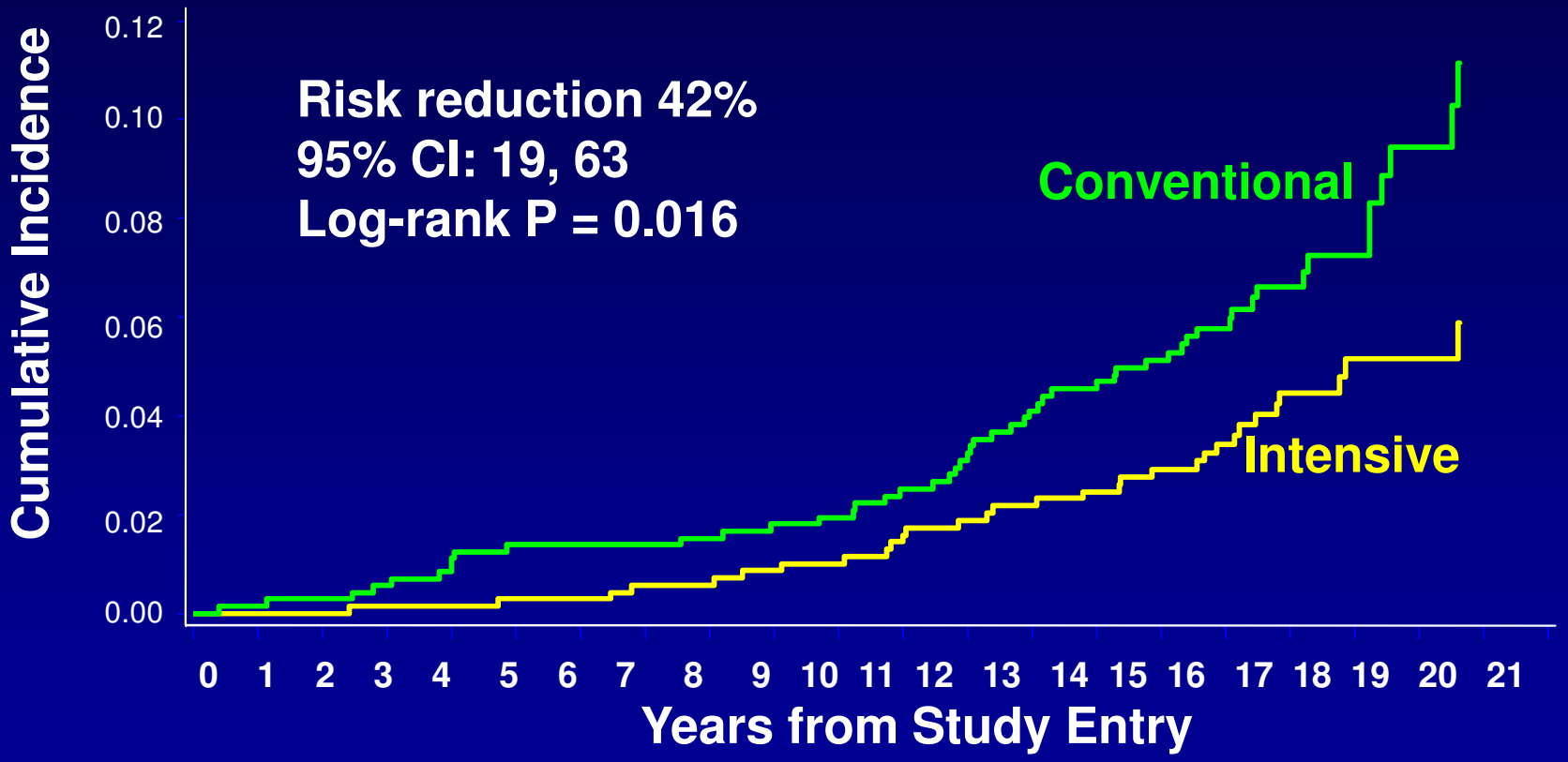
Cumulative Incidence of Coronary Heart Disease in Type 1 Patients with and without Proteinuria



Jensen et al., Diabetologia 1987;30:144

Cardiovascular Events

Cumulative Incidence of First of Any Event



Number at Risk

Intensive:	705	683	629	113
Conventional:	714	688	618	92

N Engl J Med 2005;353:2643-2653

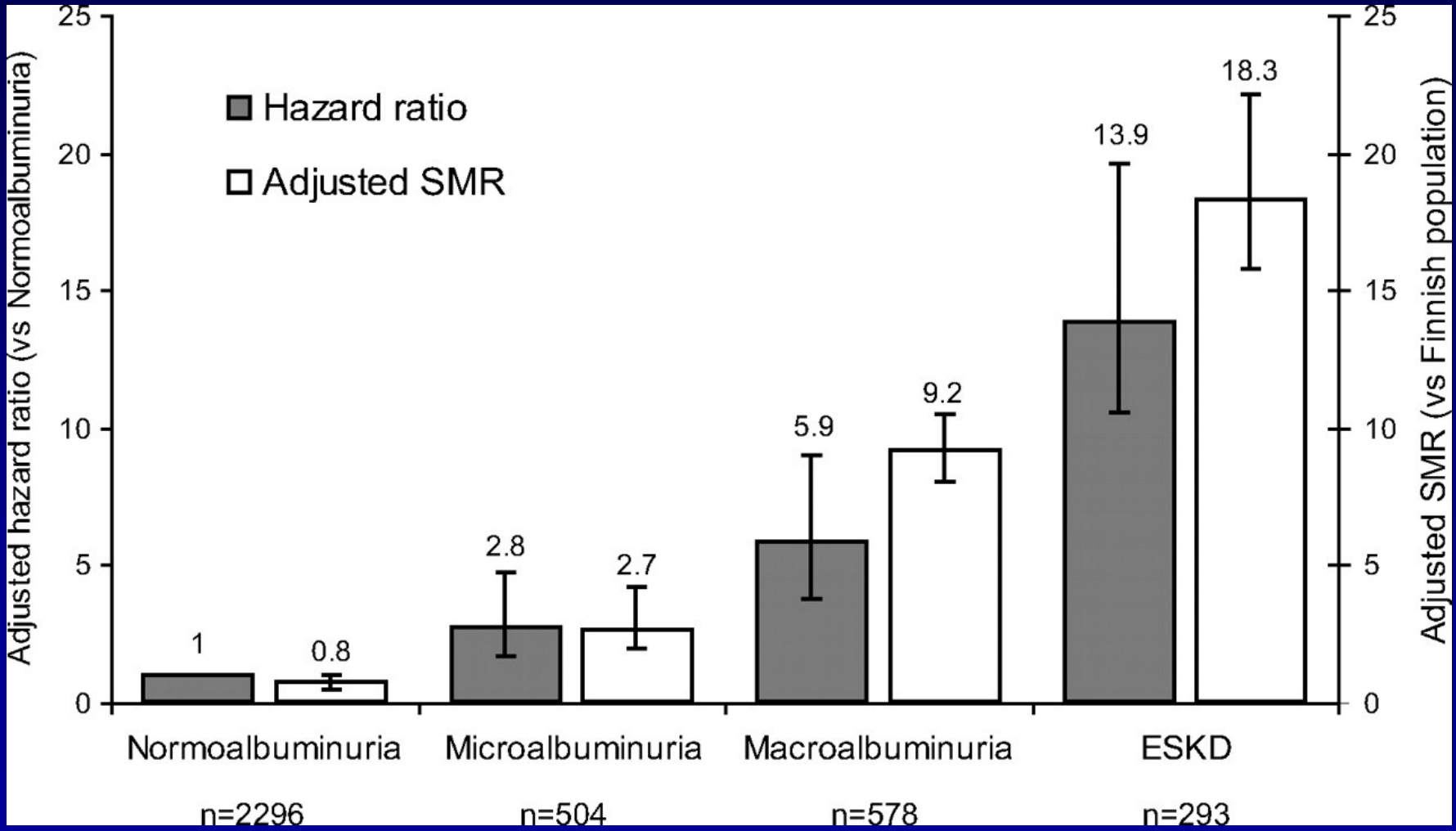
20 Year Mortality Risk in Type 1 Diabetes:
Pittsburgh Epidemiology of Diabetes Complications Study

Kidney Status	% of Group	Standardized Mortality Ratio
Normal AER	52.7%	2.0 (1.2-2.8)
AER Remained Normal over 20 years	43.0%	1.2 (0.5-1.9)
Microalbuminuria	21.3%	6.4 (4.4-8.4)
Macroalbuminuria	22.2%	12.5 (9.5-15.4)
ESRD	3.8%	29.8 (16.8-42.9)

- At Baseline: age 28 yrs, duration of DM 19 yrs
- Median Follow-up of 20 yrs (age 48 yrs, DM duration 39 yrs)
- **Conclusion:** In the absence of renal disease, 20 year mortality risk in type 1 diabetes is comparable to that of the general population

Orchard et al., Diabetologia 2010;53:2312

Risk of Mortality in Individuals with Type 1 Diabetes from the Finndiane Study Associated Each Level of Albuminuria and End-stage Kidney Disease (ESKD).



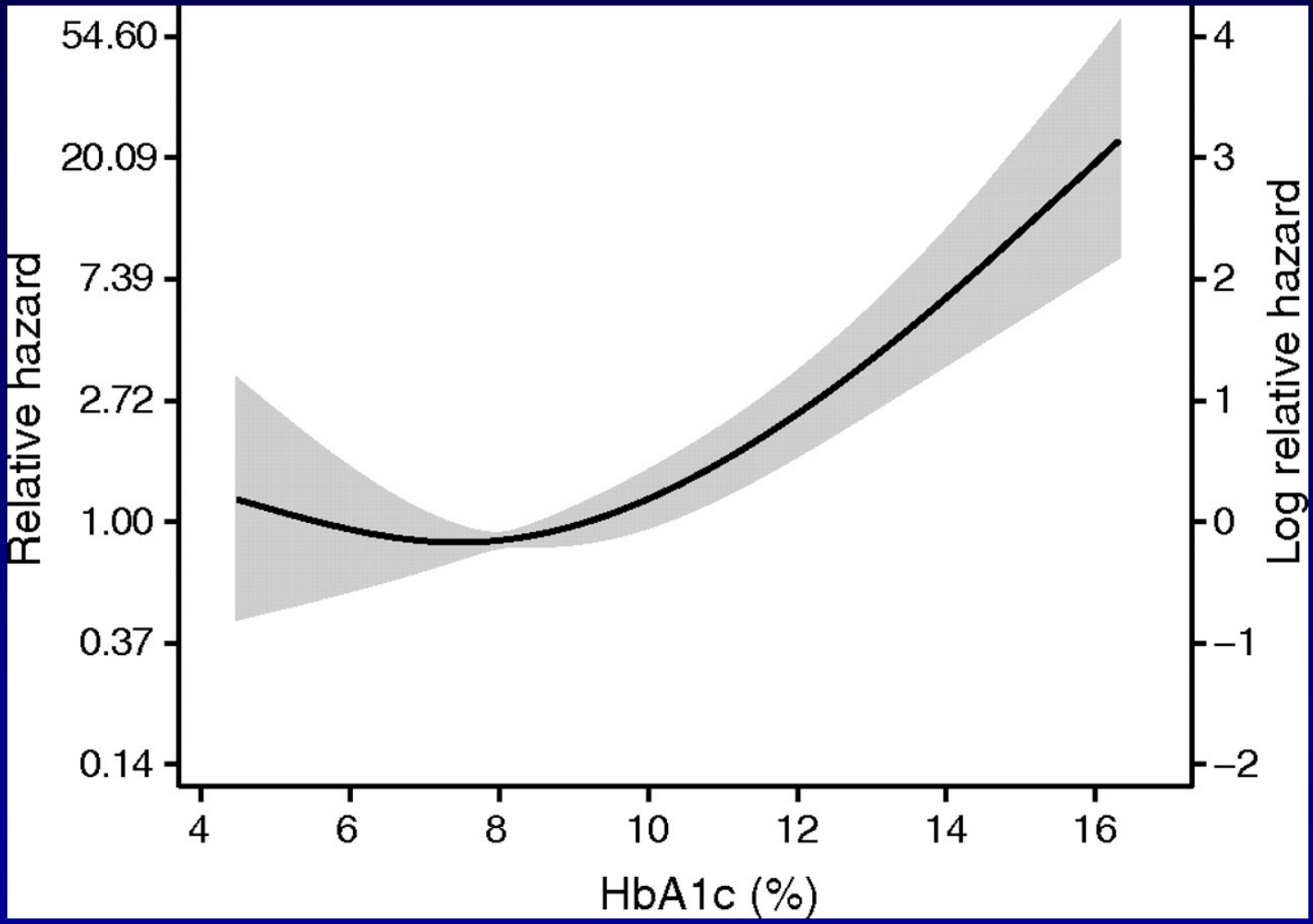
Groop P et al. Diabetes 2009;58:1651

Summary and Conclusions

- Glycemic control is able greatly delay (and possibly prevent?) the development of microalbuminuria, macroalbuminuria and decreased GFR
  - Early institution of intensive therapy has lasting effects
  - Benefits of intensive therapy must be balanced against risks of hypoglycemia
- Because of the link between CKD and CVD, could this delay/prevention of CKD be the link to delay/prevention of CVD?

Thank You

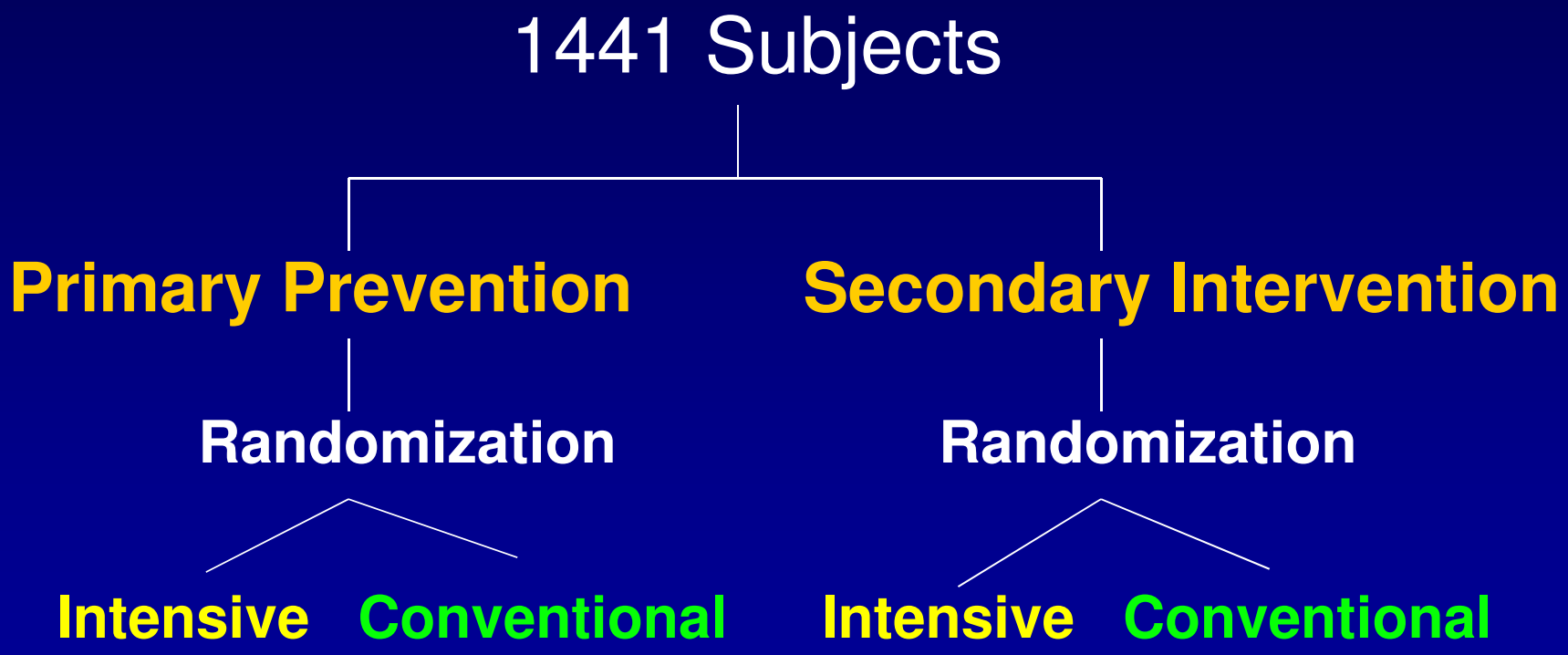
Relationship of A1C to the Hazard Ratio for Mortality in Individuals with Type 1 Diabetes without ESRD



Relationship between A1c and mortality risk similar across different albuminuria subgroups

Groop P et al. Diabetes 2009;58:1651

Randomization



DCCT

CONVENTIONAL THERAPY

INTENDED TO MIMIC CONVENTIONAL CARE*

- Clinical Goals: No Symptoms of Hyperglycemia or Hypoglycemia
- 1 or 2 Injections Per Day
- Daily Self Monitoring
- Quarterly Hba1c
- Pregnant Women Treated Intensively
- Diet and Exercise Education
- Quarterly Visits

DCCT

Intensive Therapy

- Same clinical goals as conventional therapy (no symptoms of hyper- or hypoglycemia)

PLUS

- Maintain blood glucose levels as close to non-diabetic range as possible

Pre-prandial	Post-prandial	Weekly 3 AM
70-120 mg/dL	< 180	> 65

- HbA1c < 6.05% (mean + 2 SD)
- Use of Multiple Daily Injections or pump
- SMBG 4 or more times per day

RISK REDUCTION WITH INTENSIVE THERAPY

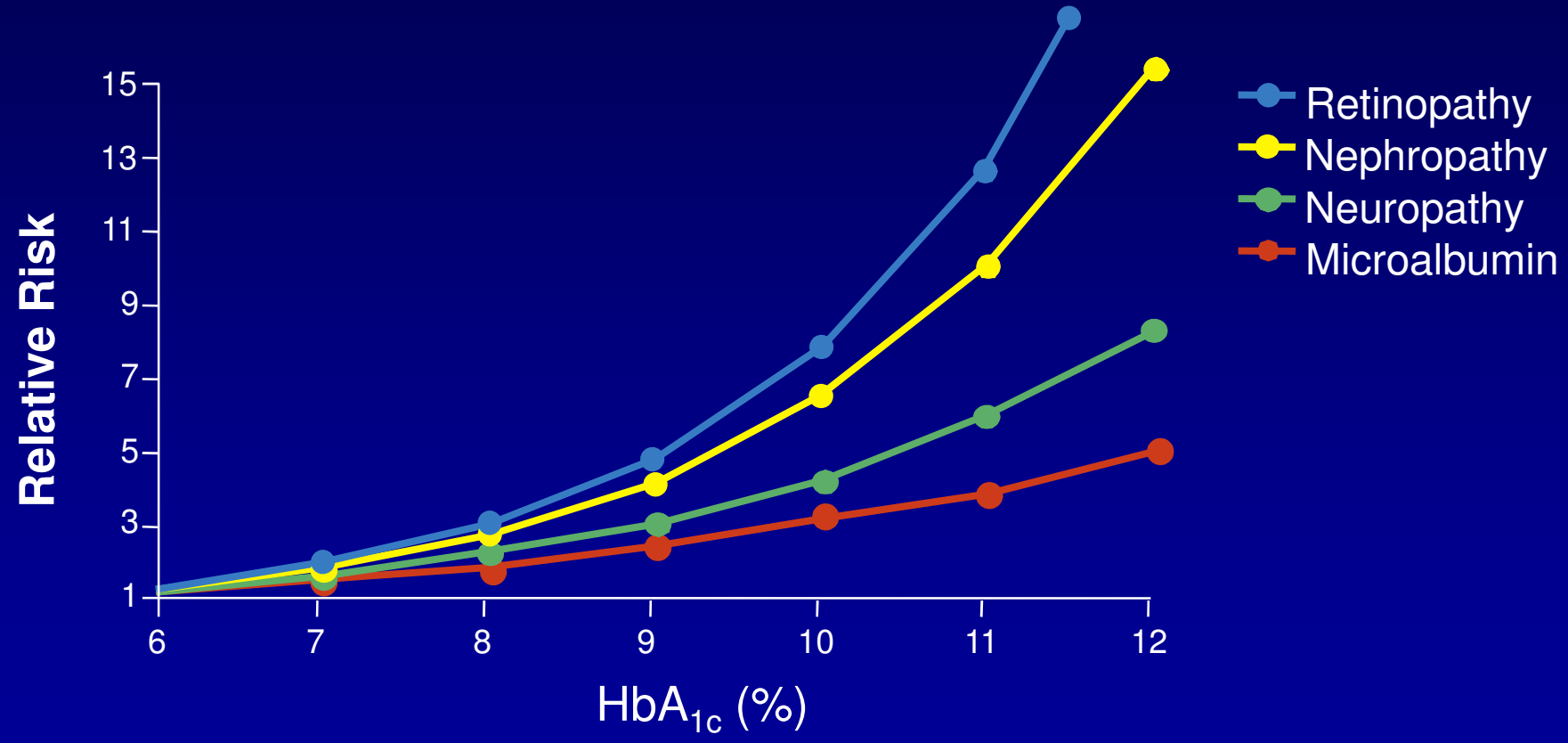
COMBINED COHORTS

OUTCOME REDUCTION (C.I.)	RISK	
AER ≥ 40 MG/ 24 H	35%	(16 - 49)
AER ≥ 300 MG/ 24 H	56%	(21 - 75)

DCCT

DCCT

Relationship of HbA_{1c} to Risk of Microvascular Complications



Skyler. *Endocrinol Metab Clin.* 1996;25:243-254, with permission.

SEVERE HYPOGLYCEMIA

COMBINED COHORT

	EPISODES / 100 PATIENT- YR		RISK
	INTENSIVE	CONVENTIONAL	RATIO
SEVERE	62	19	3.3
COMA / SEIZURE	16	5	3.0
ER / HOSPITAL	9	4	2.3
DEATHS	0	0	----

DCCT

Epidemiology of Diabetes Interventions and Complications

A Long-term Observational Study of the Diabetes Control and Complications Trial Cohort

DCCT/EDIC

Rationale for EDIC

- The DCCT cohort was too young (34 y at study end) and had too brief a duration of diabetes (12 y at end) to be at risk for macrovascular disease or the more severe manifestations of microvascular complications
- During the 10 years of EDIC, the cohort will reach an age and duration of diabetes that will allow the study of macrovascular and more severe microvascular complications

DCCT/EDIC

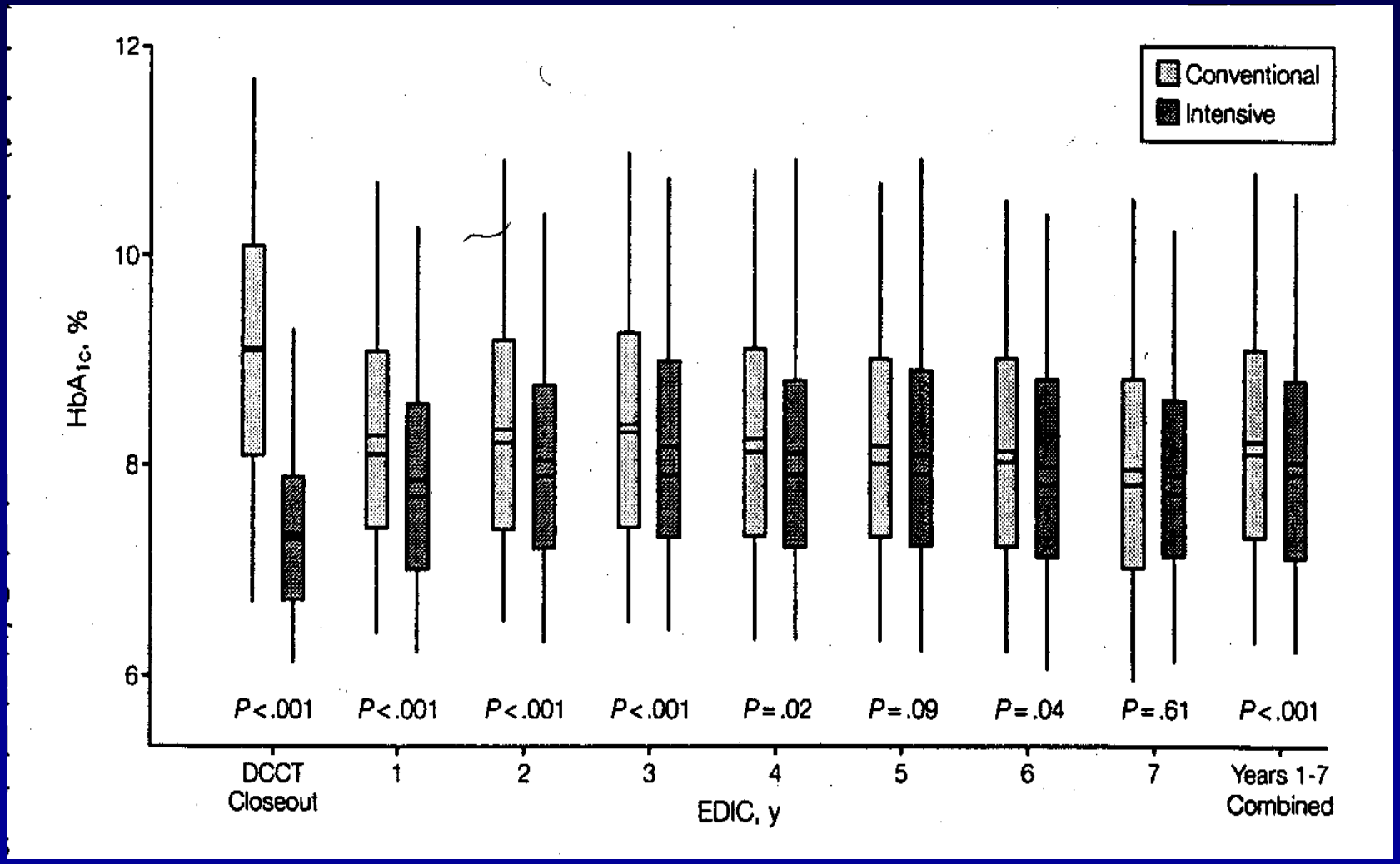
Epidemiology of Diabetes and Its Complications (EDIC)

- At the conclusion of the DCCT, all subjects in the conventional treatment group were instructed in intensive diabetes management
- All routine diabetes and other medical care were subsequently carried out by primary care providers, only some of whom were DCCT physicians/nurses. All subjects were encouraged to continue intensive diabetes management and to maintain HbA1c levels as close to normal as possible
- 1394 of 1430 surviving subjects (97%) agreed to participate in EDIC and were asked to have annual assessments of retinopathy, nephropathy, neuropathy, and macrovascular disease

DCCT/EDIC

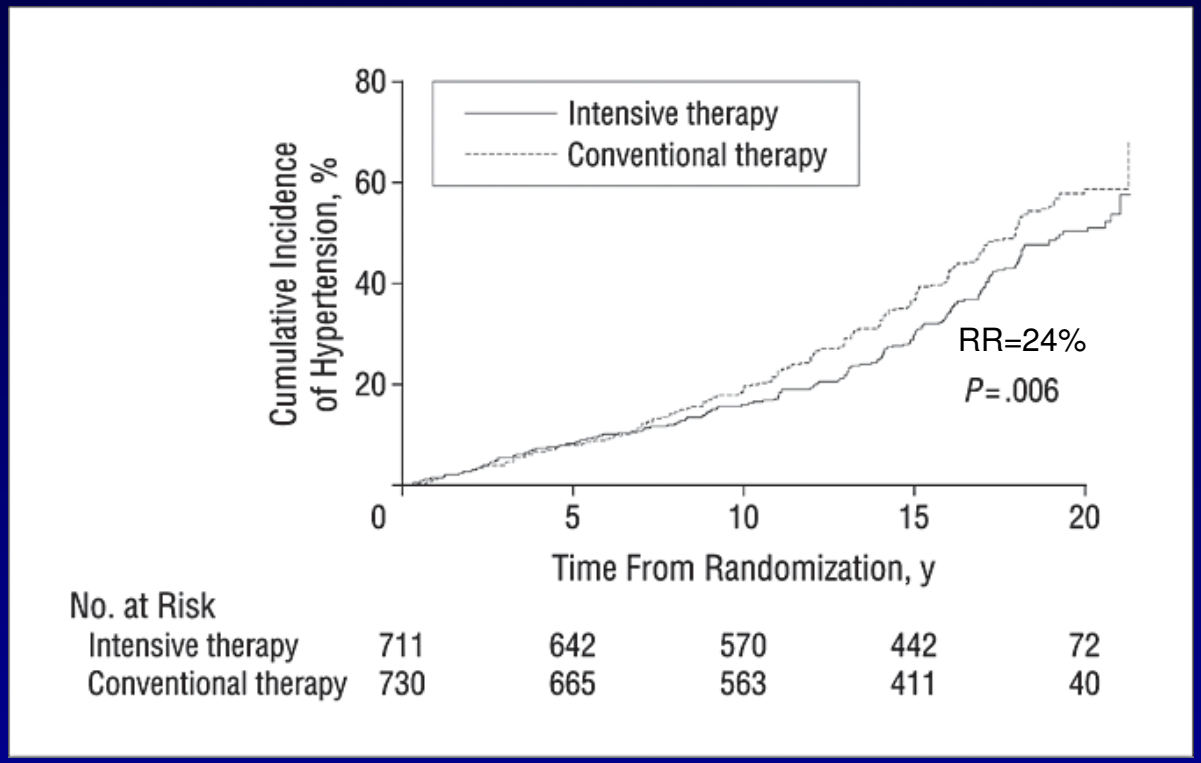
Seven Year EDIC Followup Results

HbA1c



DCCT/EDIC

Cumulative Incidence of Hypertension by DCCT Treatment Assignment



- In multivariate model, increased risks of hypertension:

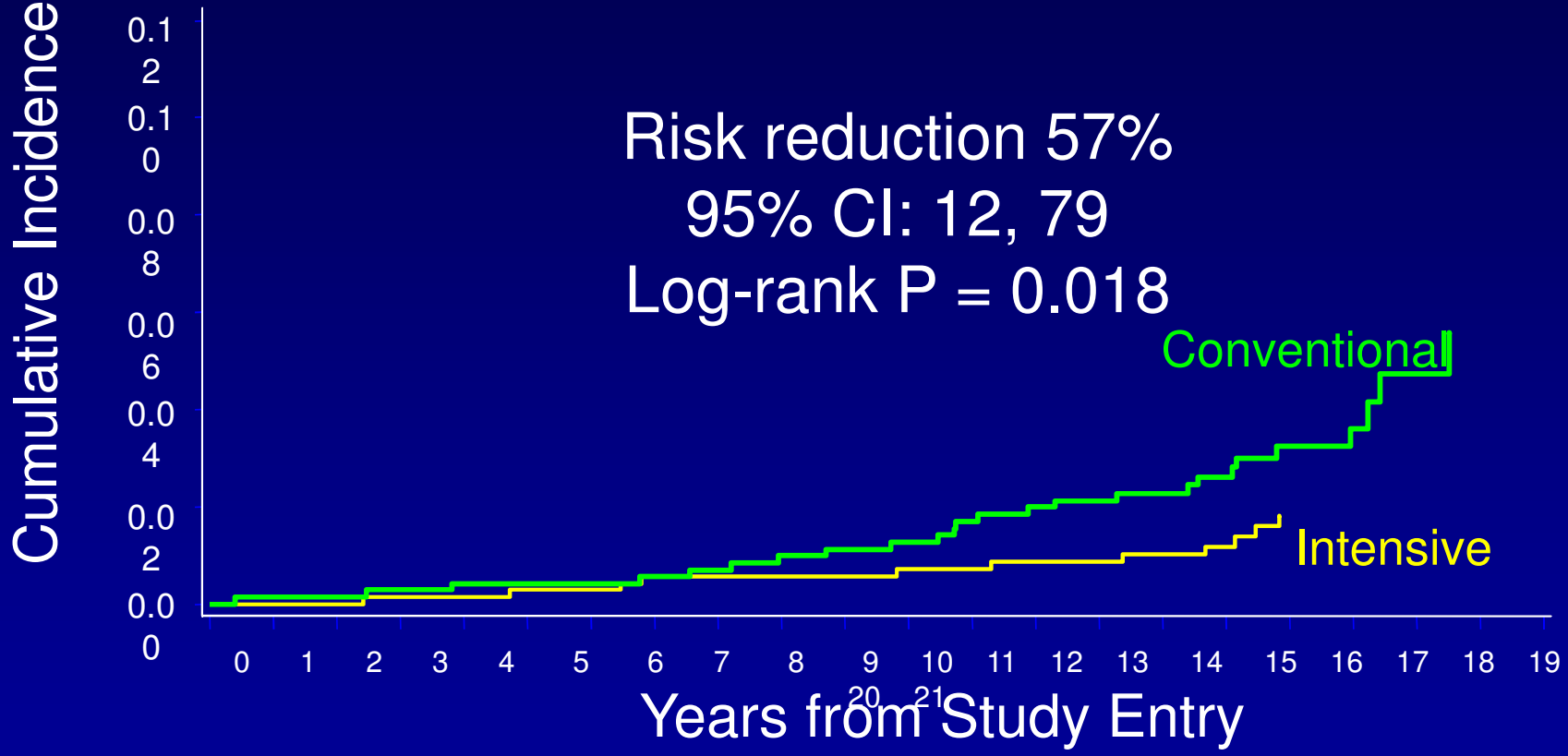
HbA1c – for each 1% increase	1.25 (1.14-1.37)
Change in BMI – for each 1 kg/m^2	1.11 (1.08 – 1.13)
Albumin excretion rate – for each doubling	1.40 (1.31-1.49)*

- AER <30 mg/24 h before development of hypertension in > 2/3 of incident hypertension cases.

Retnakaran R, et al. Arch Intern Med 2008;168:1867-1873.

Cardiovascular Events

Non-Fatal MI, Stroke or CVD Death



Number at Risk

Intensive:	**705**	**686**	**640**	**118**
Conventional:	**721**	**694**	**637**	**96**

N Engl J Med 2005;353:2643-2653

METABOLIC MEMORY:
The Imprinting Hypothesis

Hyperglycemia leads to physiologic changes that ultimately determine risk of complications

Evidence:

- 3 - 4 y lag in emergence of DCCT treatment effect
- Greater benefit of Intensive Rx when implemented early after onset of diabetes
- Persistence of DCCT treatment group effects on microvascular complications during EDIC
- Emergence of DCCT group effect on atherosclerosis

DCCT/EDIC

Characteristics of DCCT/EDIC Participants According to GFR and AER Status

	GFR ≥ 60			GFR < 60		
	AER <30	AER 30-299	AER ≥ 300	AER < 30	AER 30-299	AER ≥ 300
Number	629	517	92	79	55	69
Intensive Rx (%)	54	50	29*	53	40	26*
DCCT Baseline						
Age (yrs)	28	25	25*	31	29	26*
Duration (mos)	63	77	69*	55	77	85*
BP > 130/80 (%)	22	19	24	16	24	32*
AER (mg/24h)	10	21	26*	9	19	23*
DCCT Mean HbA1c	7.8	8.2	9.3*	8.0	9.0	9.9*
EDIC Mean HbA1c	7.8	8.1	8.8*	7.9	8.6	9.1*

GFR Course of Subjects Following the Development of a Sustained eGFR < 60 ml/min/1.73m^2

- eGFRs calculated for each year following the observation of a sustained eGFR < 60 ml/min/1.73m^2 during DCCT/EDIC
- Subjects analyzed by whether or not they had elevated AER levels prior to initial sustained eGFR < 60 ml/min/1.73m^2
- The intercept and rate of change of GFR values following the initial sustained eGFR < 60 ml/min/1.73m^2 were estimated from the General Linear Mixed Model after adjustment for ACE inhibitor use and mean blood pressure as time-dependent covariates, with a random intercept and slope among subjects
- Later years with < 4 observations/year were dropped due to less reliability
- eGFR values in patients with Renal Replacement Therapy imputed to be 15 ml/min/173m^2

Stage 5 Chronic Kidney Disease in DCCT/EDIC

- 22 Patients developed Stage 5 Chronic Kidney Disease
  - 20 Patients had albuminuria prior to the development of Stage 5 CKD
  - 2 patients without prior albuminuria had been lost to follow-up and presented 5-10 years later in Stage 5 CKD

Summary

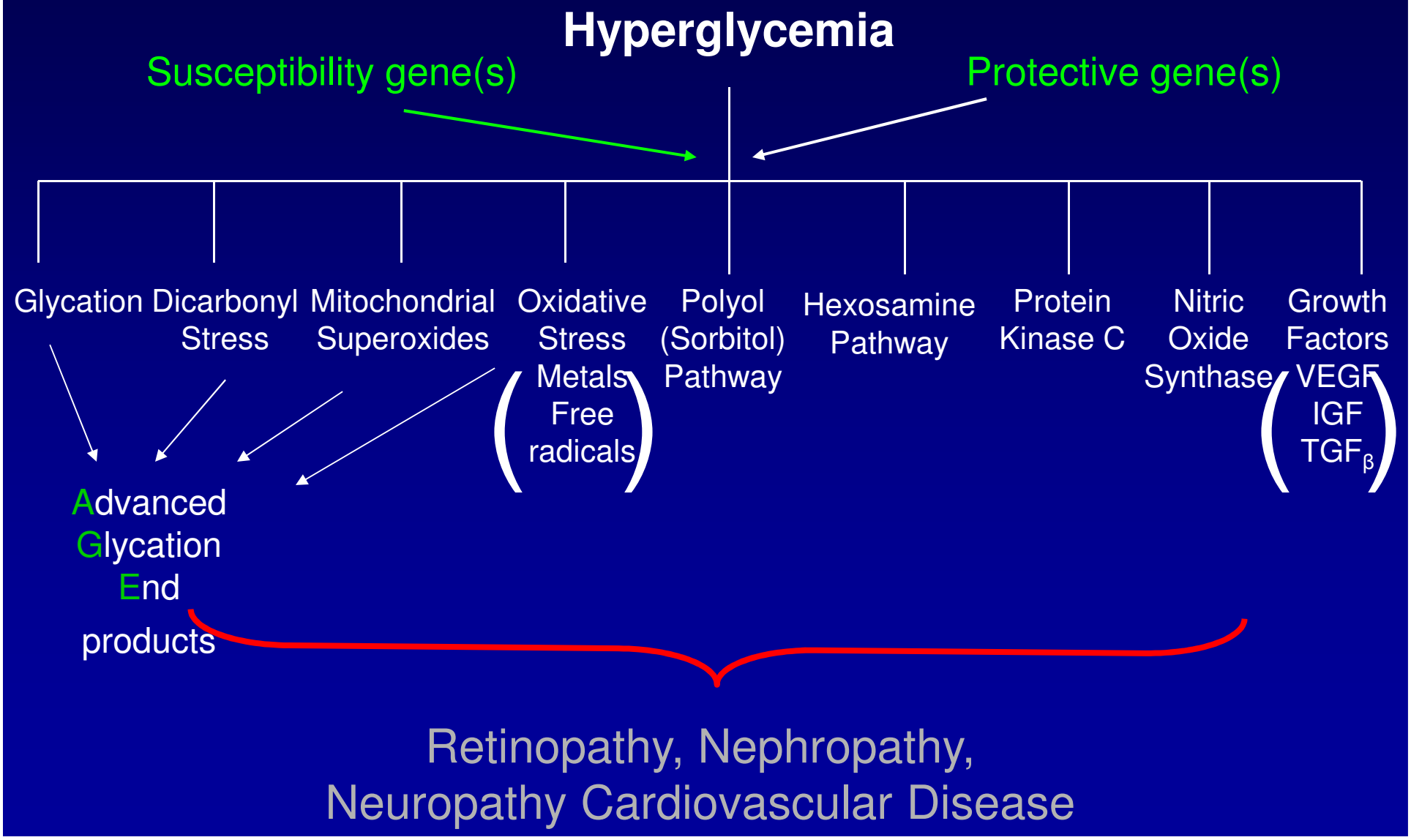
- Of the original 1441 Subjects in the DCCT, 203 (14%) developed a single eGFR < 60 ml/min/1.73m^2
  - 89 (50%) of those with a subsequent visit had a sustained eGFR < 60 on 2 more visits
- Of 89 with sustained eGFR <60 ml/min/1.73m^2:
  - 54 (61%) had prior albuminuria
  - 14 (16%) had prior microalbuminuria
  - 21 (23%) never had had an elevated AER
- Longitudinal analysis of those with sustained eGFR <60 ml/min/1.73m^2 shows a much greater risk of continued progressive fall in eGFR if albuminuria (but not microalbuminuria) had been present prior to the initial low level of eGFR
- Because glycemic control reduced the development of albuminuria, it may ultimately also have affected the decline in GFR, but this evidence is indirect

Metabolic Imprinting

Do DCCT/EDIC measurements provide any clues regarding the mechanisms of tissue damage from hyperglycemia and that might explain metabolic imprinting?

DCCT/EDIC

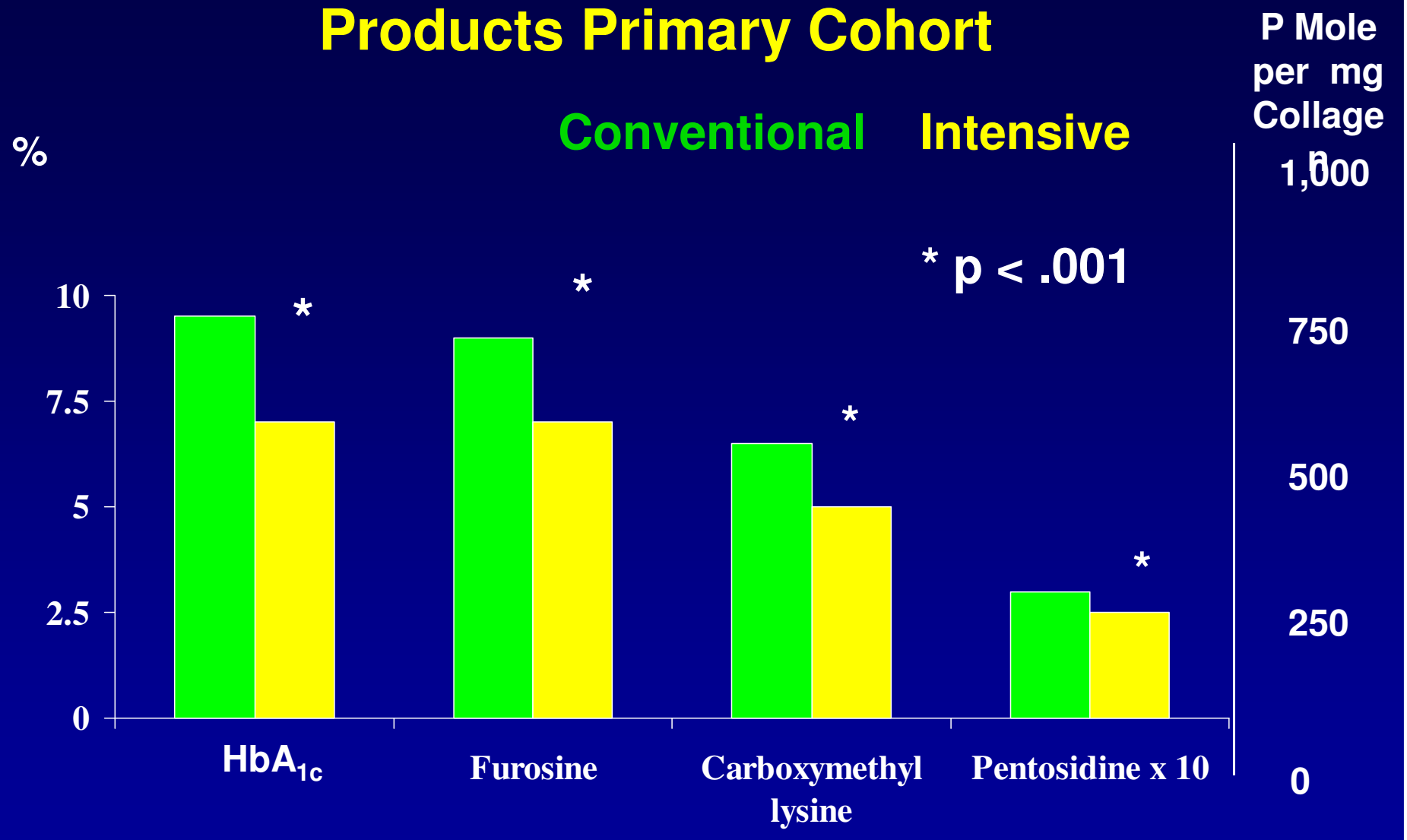
PATHOGENESIS OF DIABETIC COMPLICATIONS



Methods

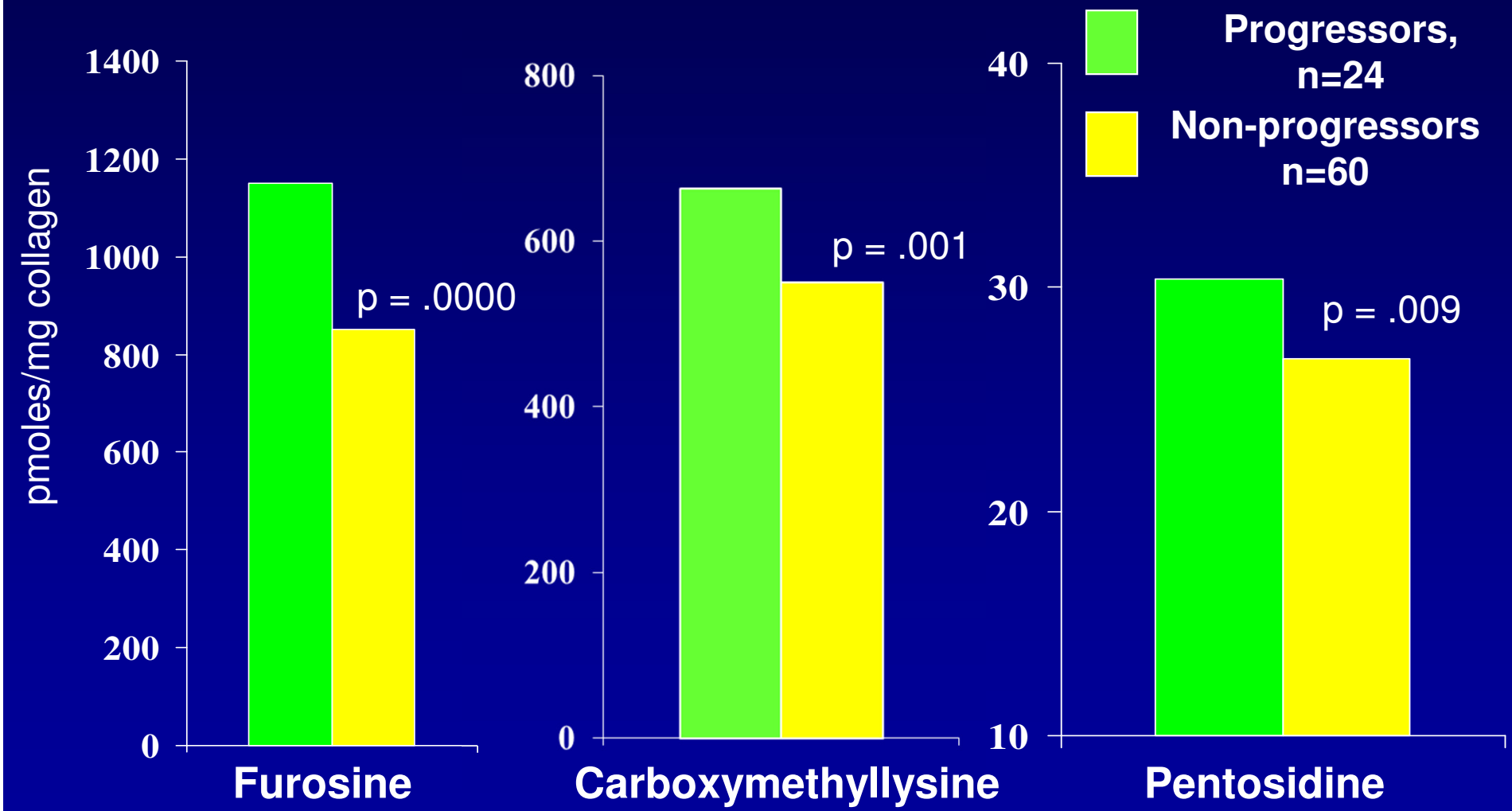
- A skin biopsy sample was obtained before the DCCT closeout in 215 participants.
- Glycated collagen (furosine), the advanced glycation endproducts (AGE's) pentosidine and carboxymethyllysine were measured
- Physicochemical changes in collagen (reduced solubility after pepsin or acid treatment) were measured

Effect of Intensive Rx on Collagen Glycation Products Primary Cohort



DCCT/EDIC

Preceding Skin Collagen AGE Levels in 4 Year EDIC Retinopathy Progressors Versus 4 Year EDIC Retinopathy Non-Progressors in Former DCCT Conventional Group Participants



EDIC Retinopathy & Nephropathy Progression at 4 years

- Skin Collagens (Furosine and CML) have a strong association with risk of further retinopathy and nephropathy progression in EDIC independently of the DCCT or EDIC HbA_{1c}
- Collagens explain 94.5% of the association of DCCT HbA1c with EDIC retinopathy risk
- Collagens explain 97.7% of the reduction in risk with DCCT intensive therapy

DCCT/EDIC

Metabolic Imprinting

Glycation and/or glycoxidation may be a mechanism by which hyperglycemia leads to long-term cellular injury and may explain the metabolic memory phenomenon.

DCCT/EDIC

Frequency of Albuminuria and Retinopathy in Subjects with GFR above and below 60 ml/min/m^2 in Subjects with Type 2 Diabetes ≥ 40 Years of Age (NHANES III)

	GFR ≥ 60	GFR < 60
Microalbuminuria	32%	45%
Macroalbuminuria	5%	19%
Retinopathy	15%	28%
No retinopathy or albuminuria		30%

Kramer et al., JAMA 2003;289:3273

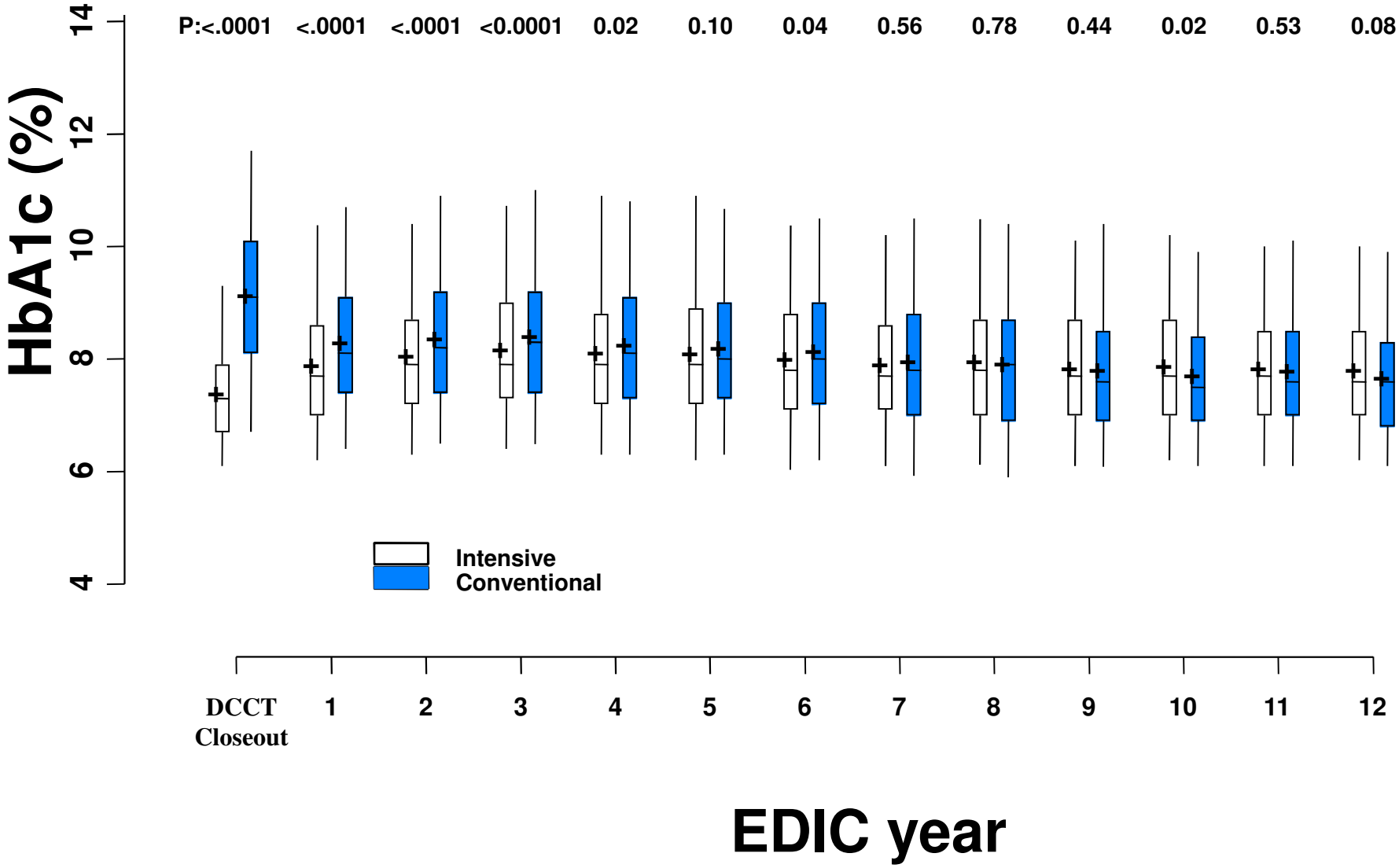
Participant Characteristics at EDIC Year 11/12

	Conventional (n=667)	Intensive (n=668)	P value
Age (yrs)	45.5	46.2	0.08
Duration Diabetes (yrs)	24.2	24.6	0.09
AER > 40 mg/24h, N (%)*	67 (12.7%)	47 (8.4%)	0.02
AER > 300 mg/24h, N (%)*	44 (7.3%)	17 (2.8%)	0.0002
BP > 130/80 mmHg, confirmed, N (%)	261 (39.5%)	251 (37.6%)	0.49
MAP (mmHg), mean (SD)	89.6 (9.8)	89.9 (.5)	0.56
eGFR† (mL/min/1.73m^2), mean (SD)	81.8 (19.6)	83.7 (17.6)	0.32

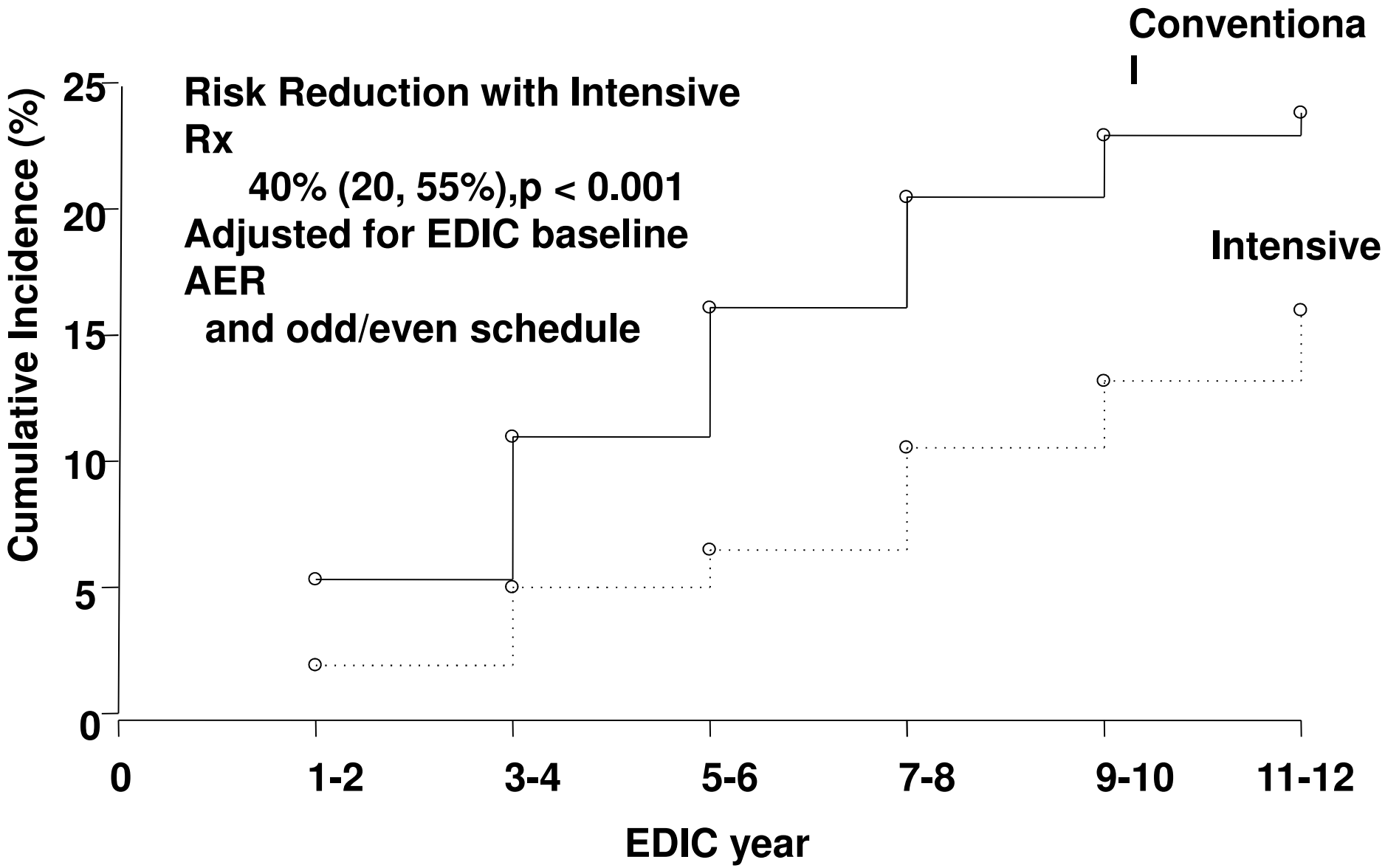
*subjects with AER < 40 mg/24h at DCCT baseline and DCCT close-out

†modified MDRD equation

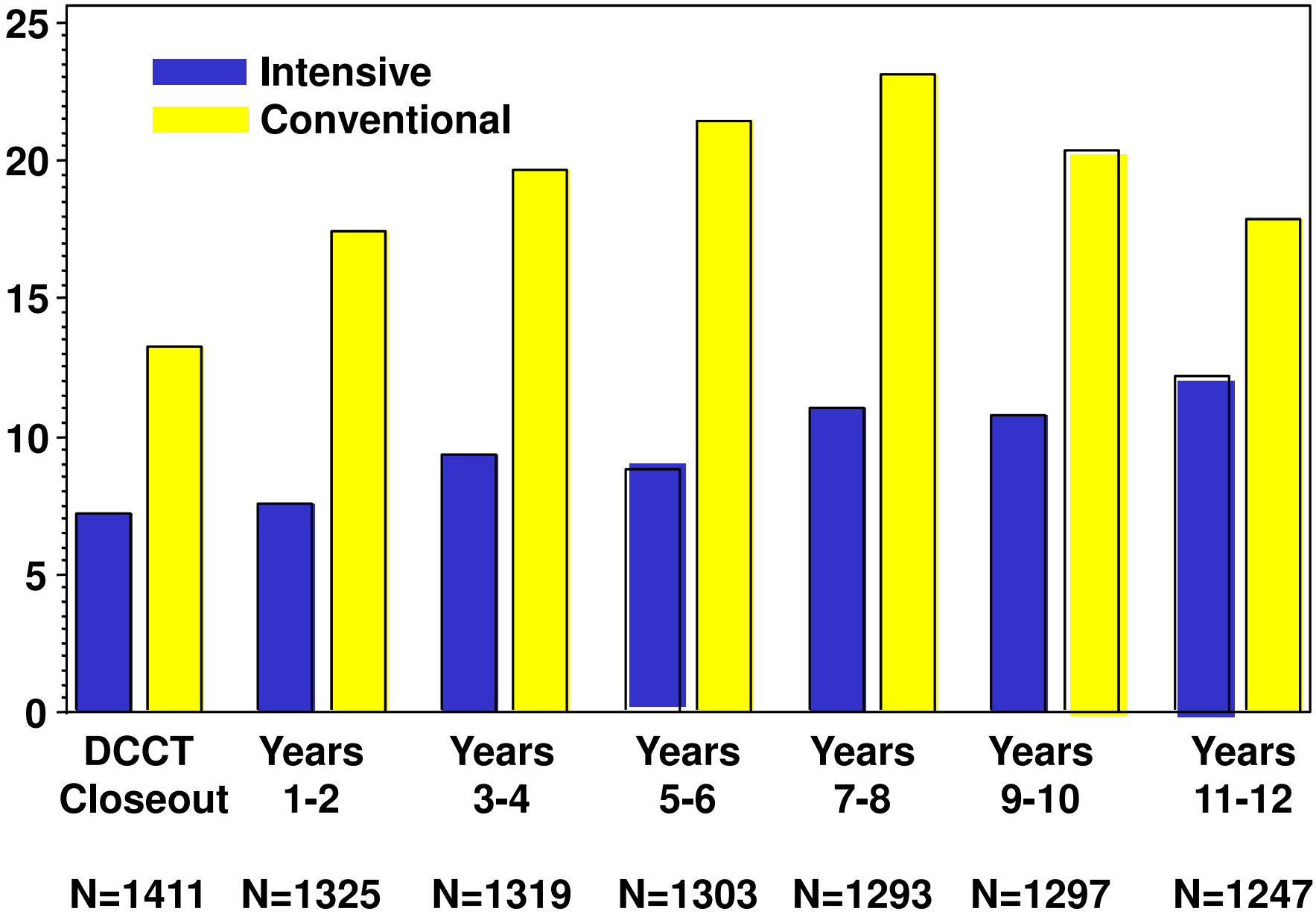
Distribution of HbA1c Concentrations by Randomized Treatment Group at the End of the DCCT and in Each Year of the EDIC Study



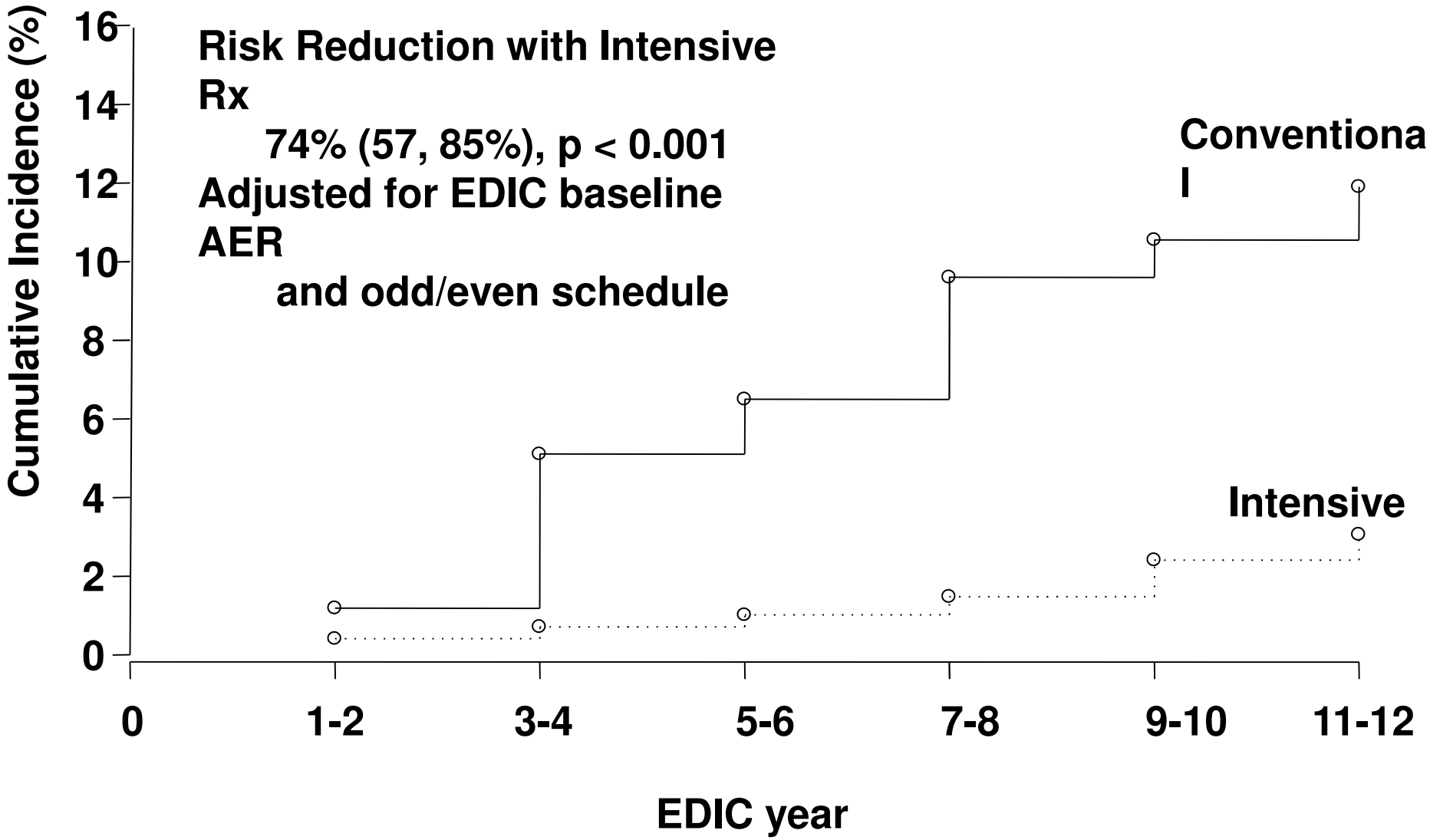
Cumulative Incidence of New Microalbuminuria During EDIC (AER > 40 mg/24h)



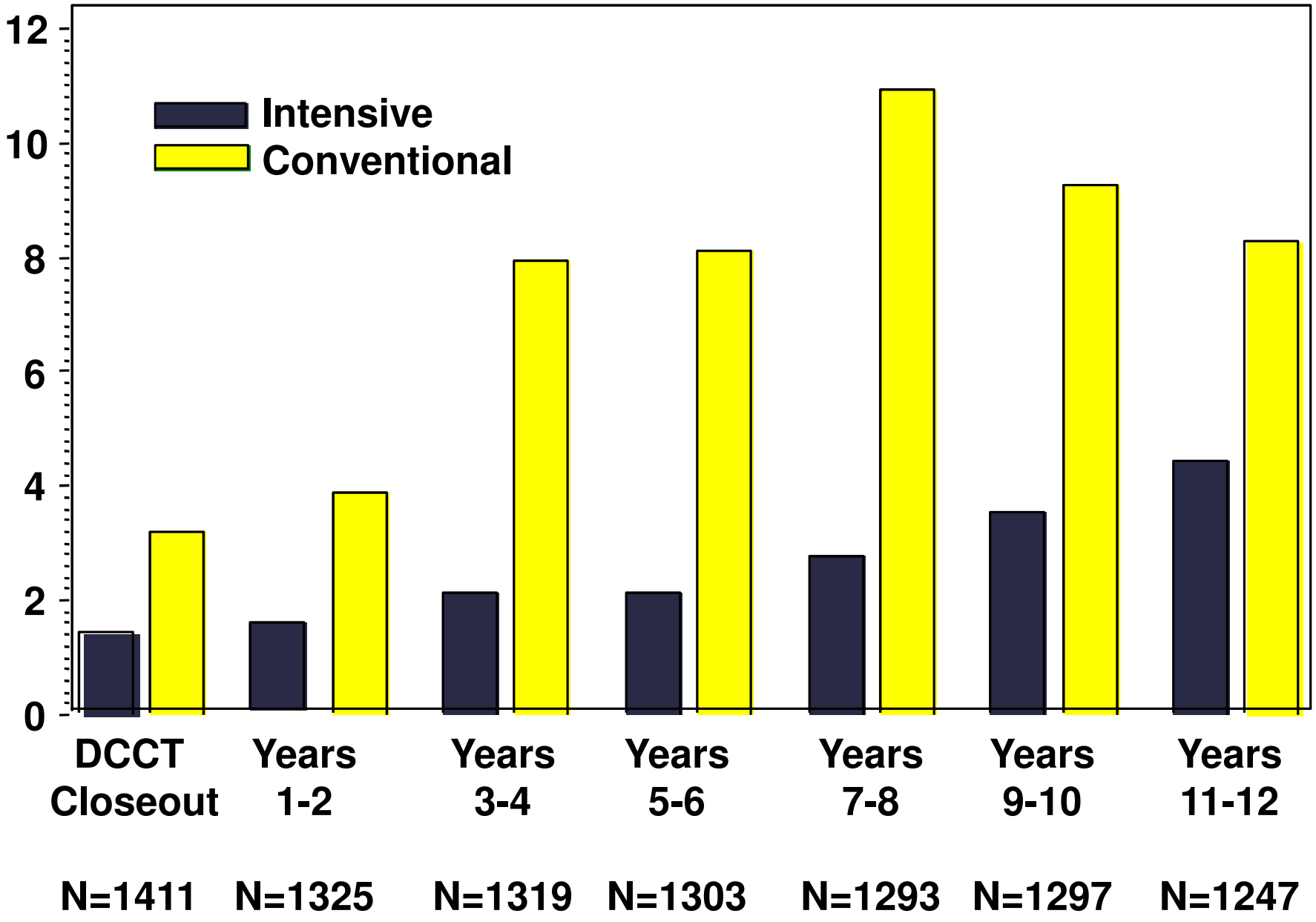
Prevalence of Microalbuminuria (AER=>40)



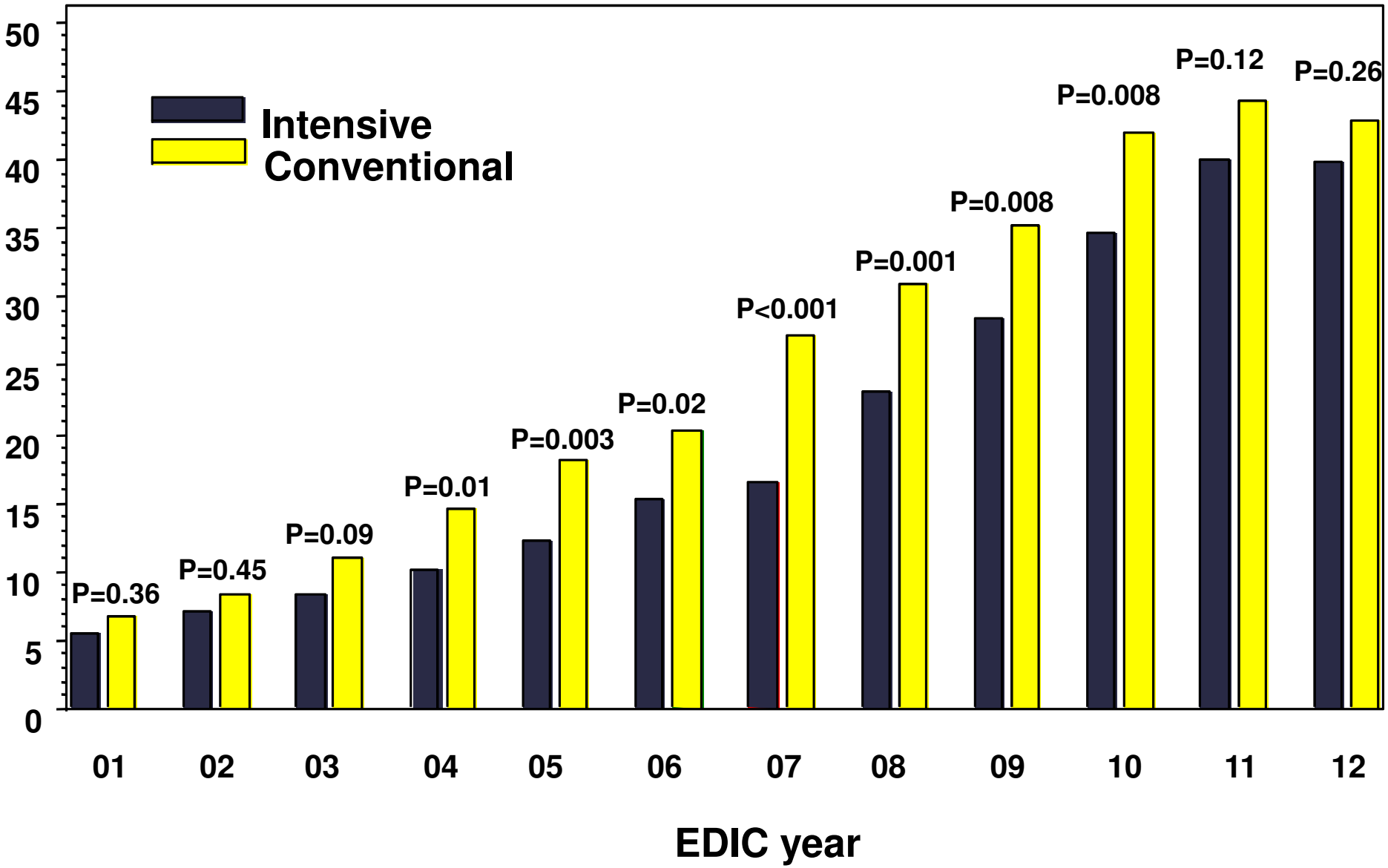
Cumulative Incidence of New Albuminuria During EDIC
(AER > 300 mg/24h)



Prevalence of Albuminuria (AER≥300)



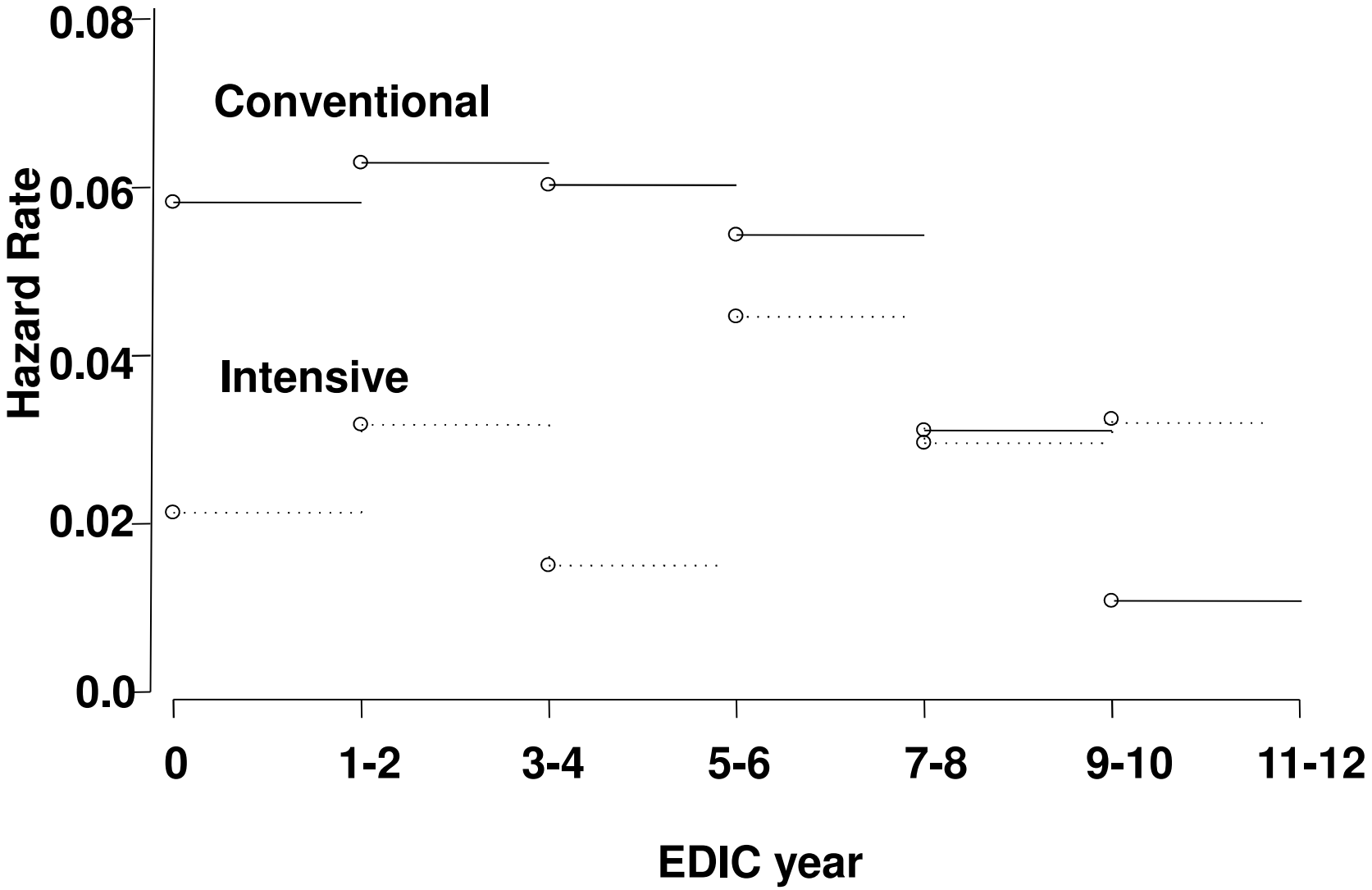
Prevalence of ACEI/ARB Use Over Time



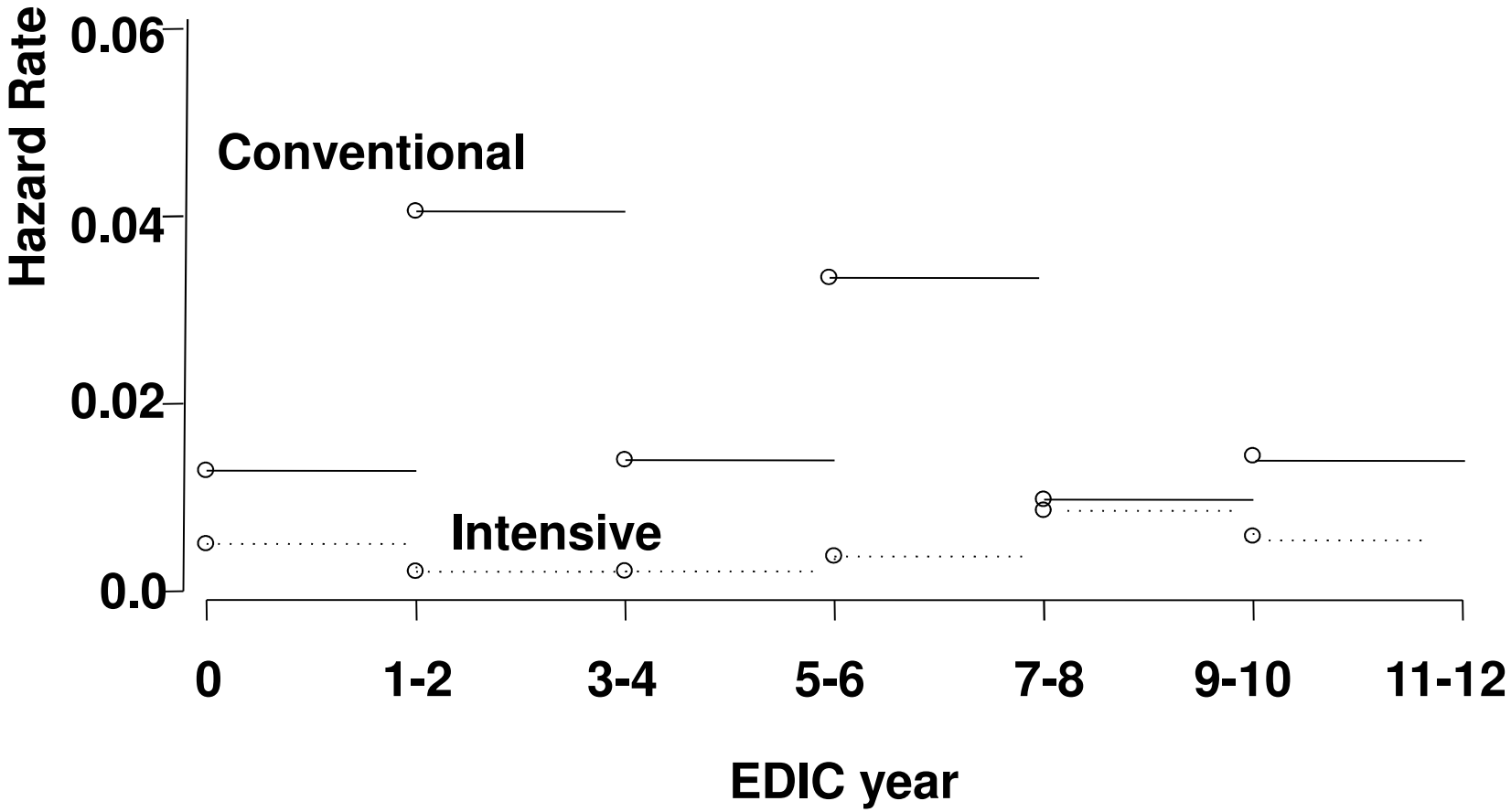
Hazard Rate Analysis

- **Hazard Rates were analyzed over time by prior treatment group for the new development of microalbuminuria and albuminuria for only those individuals in EDIC who had normal urine albumin excretion at the beginning of EDIC**

Microalbuminuria (AER ≥ 40 mg/24h) Hazard Rate Over Time



Albuminuria (AER ≥ 300 mg/24h) Hazard Rate Over Time



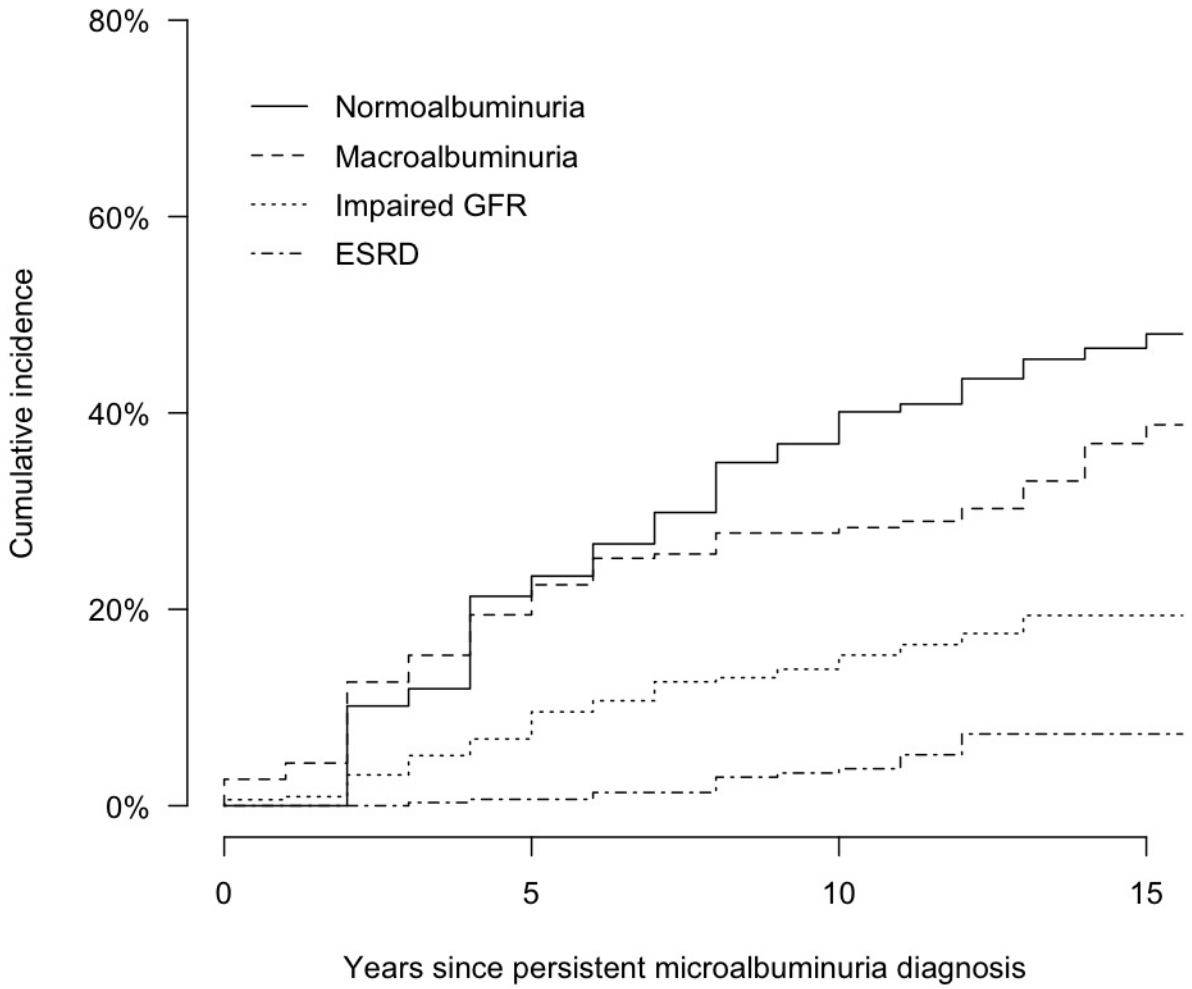
Kidney Function Outcomes through Year 12 of EDIC

Outcome	Total (n-1335)	Intensive (n=668	Conventional (n=667	P-Value
Doubling of Serum Creatinine	52 (3.9%)	19 (2.8%)	33 (5.0%)	0.05
Serum Creatinine > 2 mg/dL	25 (1.9%)	8 (1.2%)	17 (2.6%)	0.51
Dialysis or Transplantation	18 (1.4%)	4 (0.6%)	14 (2.1%)	0.02
eGFR* < 60 ml/min/1.73m^2	164 (12.3%)	59 (8.8%)	105 (15.7%)	<0.001

*modified MDRD equation

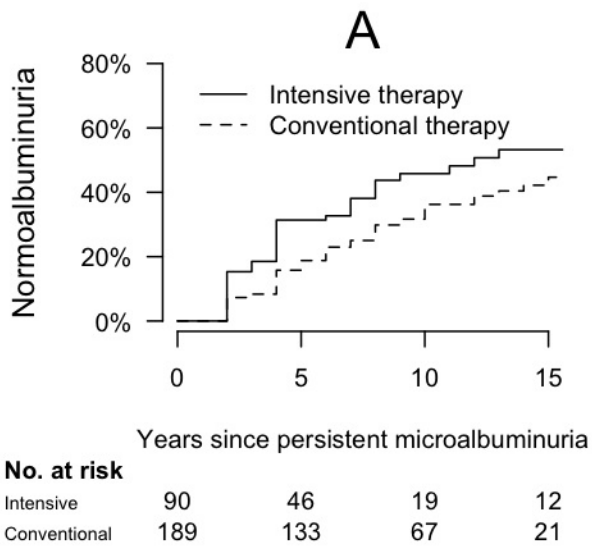
Diabetic Nephropathy

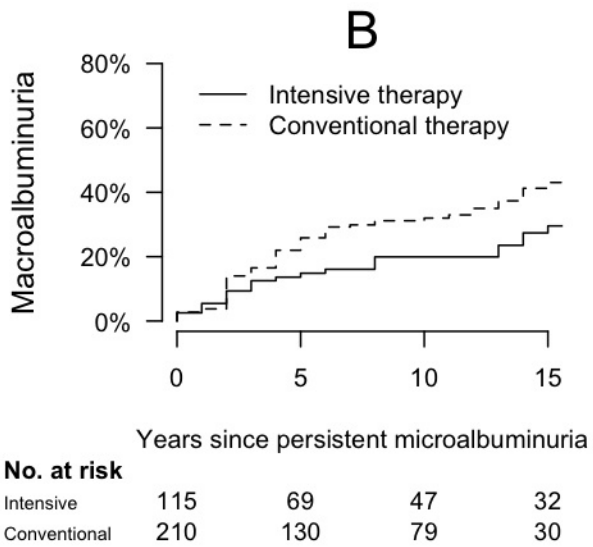
- **DCCT participants previously assigned to intensive therapy continue to enjoy a reduced overall incidence of diabetic kidney disease 11-12 years after the DCCT. Benefits are also seen in measures of GFR.**
- **Regression of diabetic kidney disease as well as a decrease in the hazard rate appears to be occurring 9 – 12 years after the DCCT among participants previously assigned to conventional therapy, possibly due to improved glycemic control over time within this group.**
- **Further follow-up of these participants will allow confirmation of these preliminary findings.**

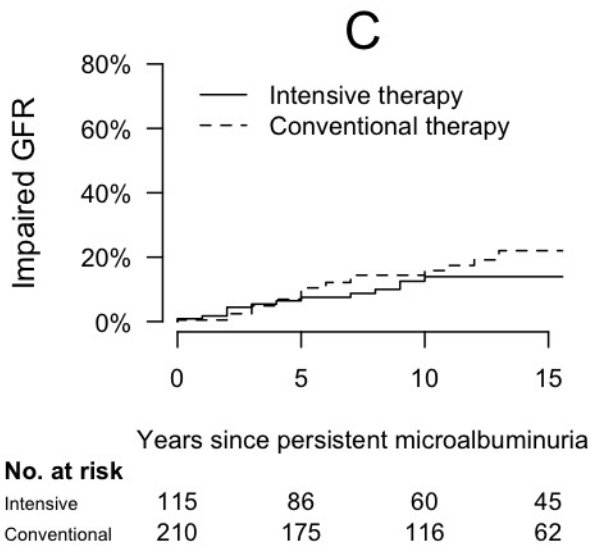


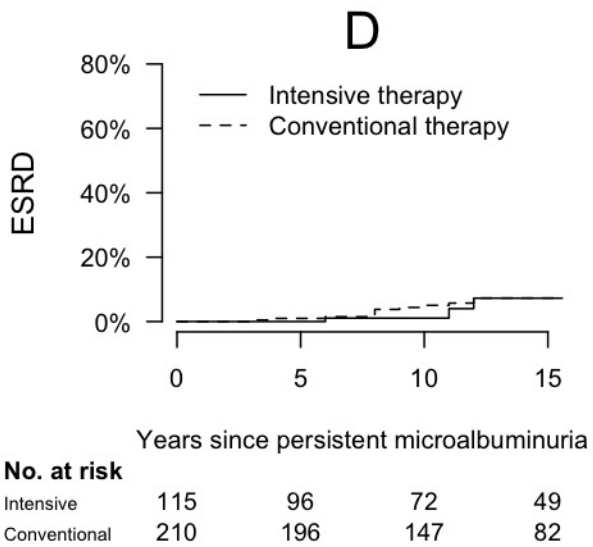
No. at risk

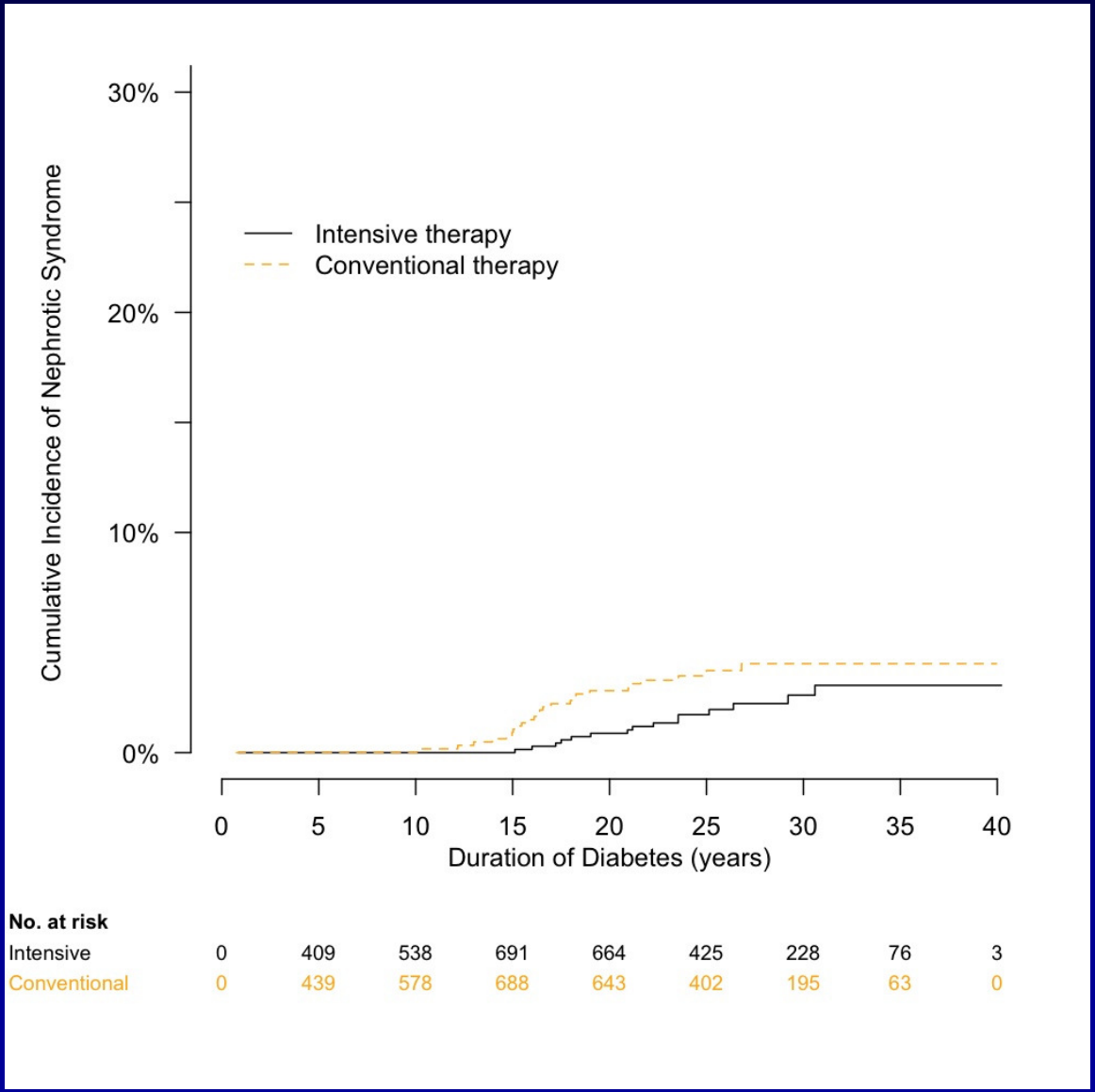
Normoalbuminuria	279	179	86	33
Macroalbuminuria	325	199	126	62
Impaired GFR	325	261	176	107
ESRD	325	292	219	131


A
Normoalbuminuria
80%
60%
40%
20%
0%
Intensive therapy
Conventional therapy
0
5
10
15
Years since persistent microalbuminuria
No. at risk
Intensive 90 46 19 12
Conventional 189 133 67 21

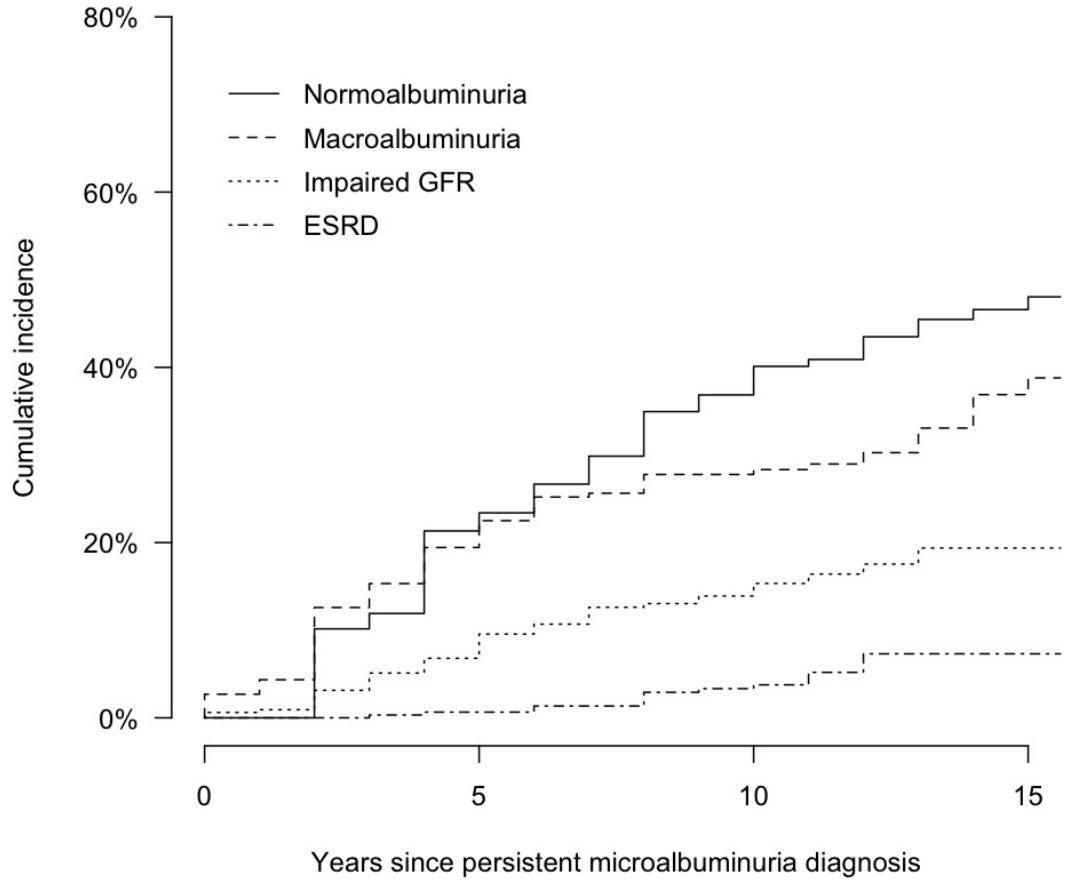

B
Macroalbuminuria
80%
60%
40%
20%
0%
Intensive therapy
Conventional therapy
0
5
10
15
Years since persistent microalbuminuria
No. at risk
Intensive 115 69 47 32
Conventional 210 130 79 30


C
Impaired GFR
80%
60%
40%
20%
0%
Intensive therapy
Conventional therapy
0
5
10
15
Years since persistent microalbuminuria
No. at risk
Intensive 115 86 60 45
Conventional 210 175 116 62


D
ESRD
80%
60%
40%
20%
0%
Intensive therapy
Conventional therapy
0
5
10
15
Years since persistent microalbuminuria
No. at risk
Intensive 115 96 72 49
Conventional 210 196 147 82


30%
20%
10%
0%
Cumulative Incidence of Nephrotic Syndrome
Intensive therapy
Conventional therapy
0
5
10
15
20
25
30
35
40
Duration of Diabetes (years)
No. at risk
Intensive 0 409 538 691 664 425 228 76 3
Conventional 0 439 578 688 643 402 195 63 0

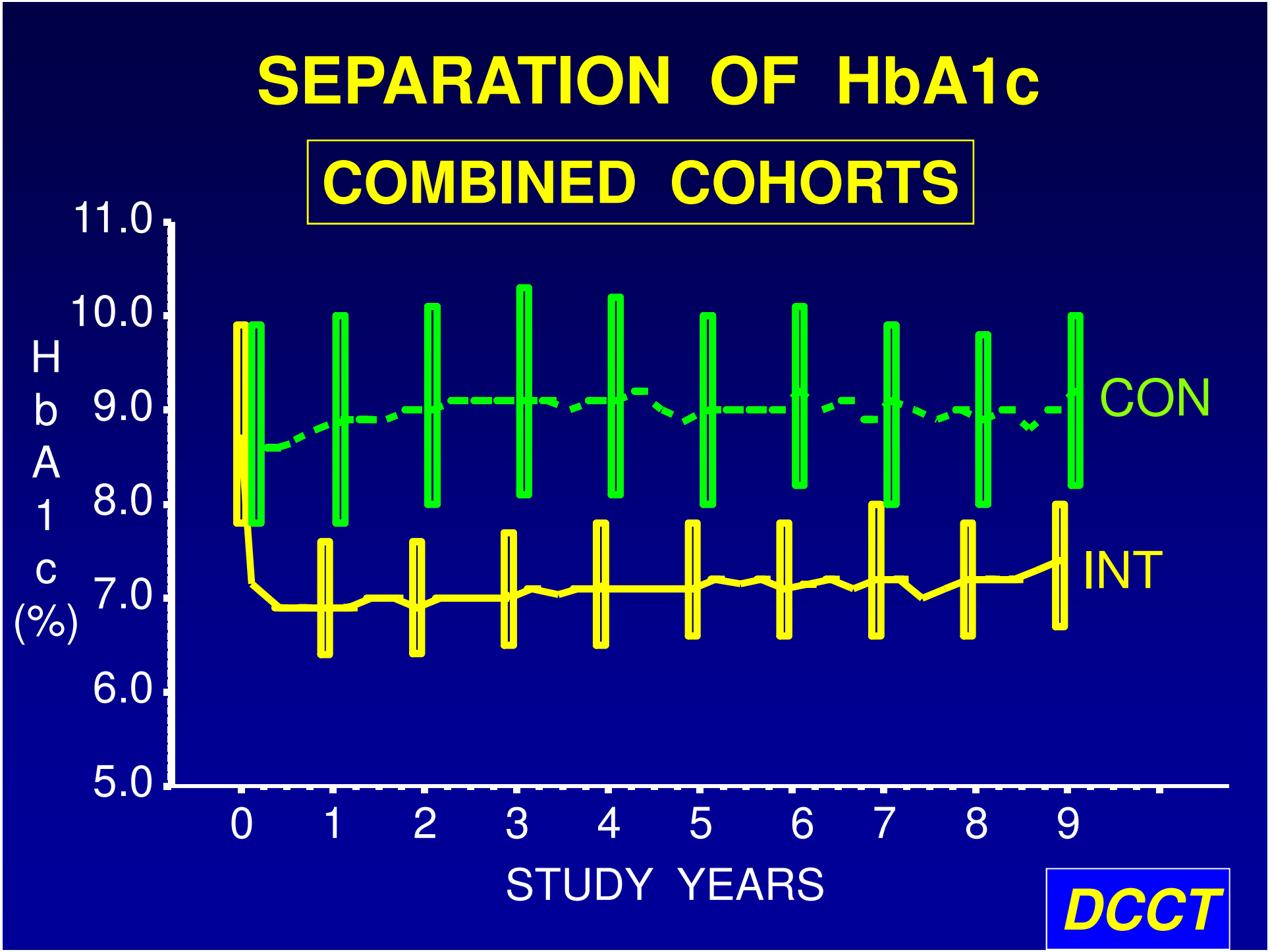
Microalbuminuria can regress



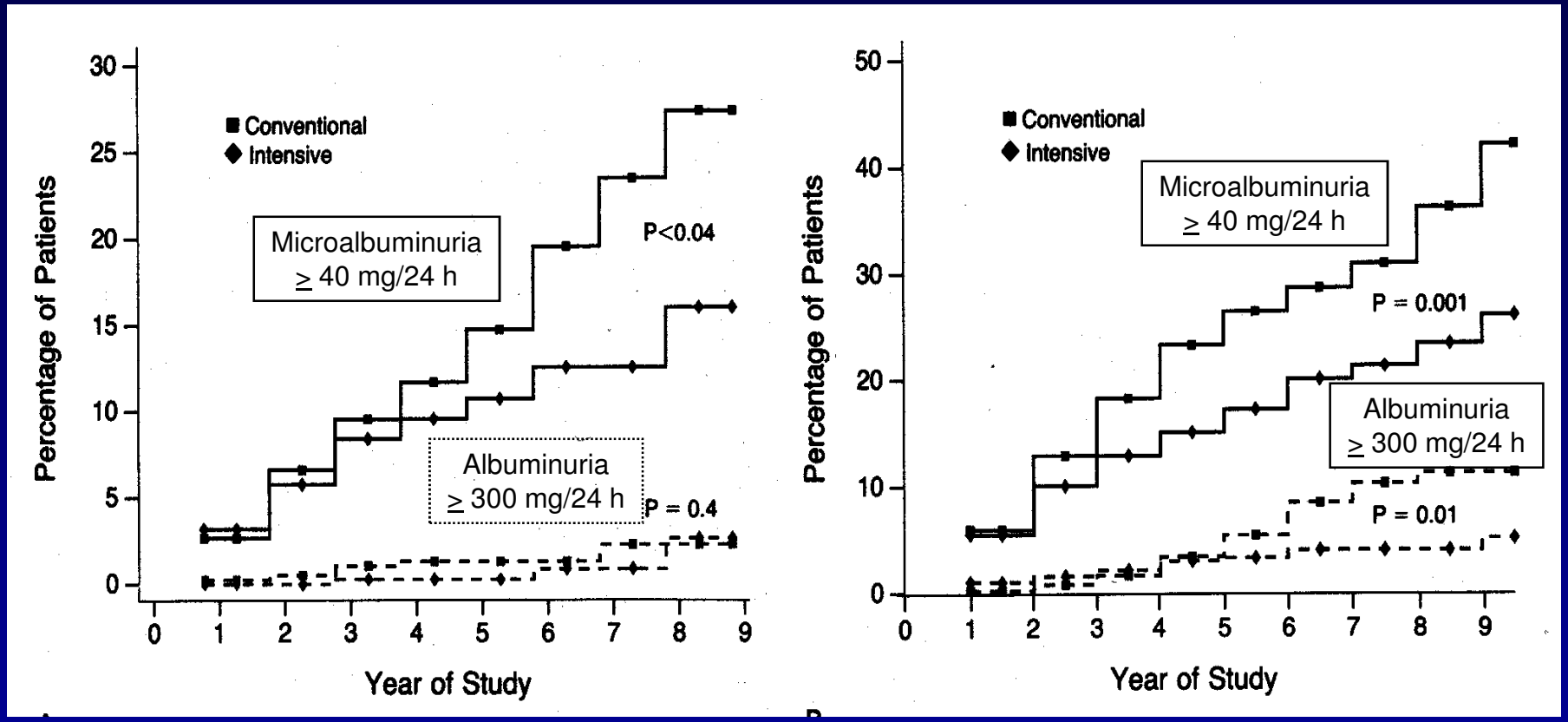
No. at risk				
Normoalbuminuria	279	179	86	33
Macroalbuminuria	325	199	126	62
Impaired GFR	325	261	176	107
ESRD	325	292	219	131

- 325 participants with incident persistent AER ≥ 30 mg/24hr
- Four subsequent renal outcomes evaluated in parallel

de Boer IH *et al, Arch Int Med* 2011


SEPARATION OF HbA1c
COMBINED COHORTS
11.0
10.0
9.0
8.0
7.0
6.0
5.0
HbA1c (%)
CON
INT
0
1
2
3
4
5
6
7
8
9
STUDY YEARS
DCCT

Nephropathy



Primary Prevention **Secondary Intervention**

DCCT

Good Glycemic Control (Lower HbA_{1c}) Reduces Complications

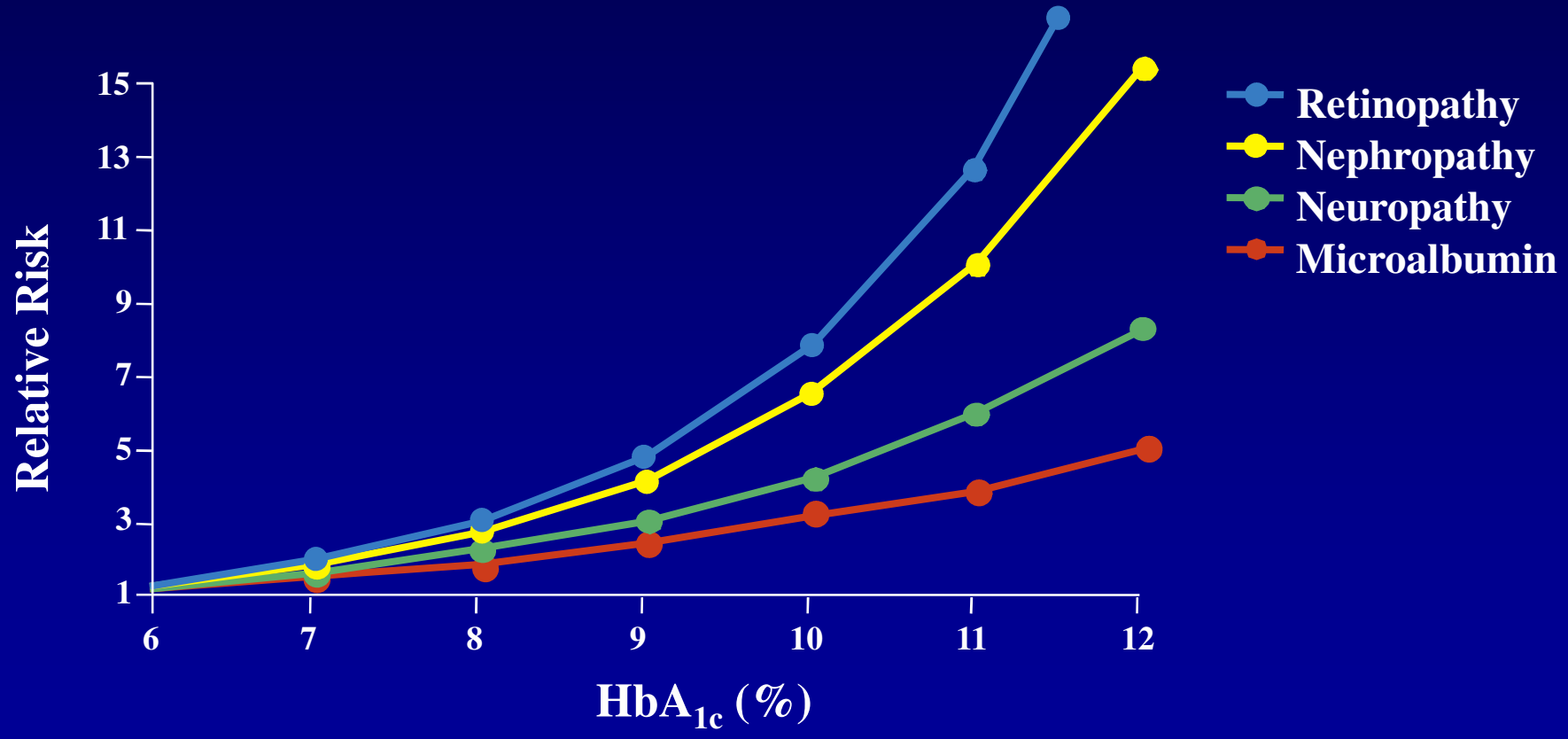
HbA_{1c}	DCCT 9 → 7%	Kumamoto 9 → 7%	UKPDS 8 → 7%
Retinopathy	76%	69%	17-21%
Nephropathy	54%	70%	24-33%
Neuropathy	60%	-	-
Macrovascular disease	41%*	-	16%*

* not statistically significant

DCCT Study Group: N Engl J Med 329:977-86, 1993
Ohkubo Y: Diabetes Res Clin Prac 28:103-17, 1995
UKPDS Study Group: Lancet 352:837-53, 1998

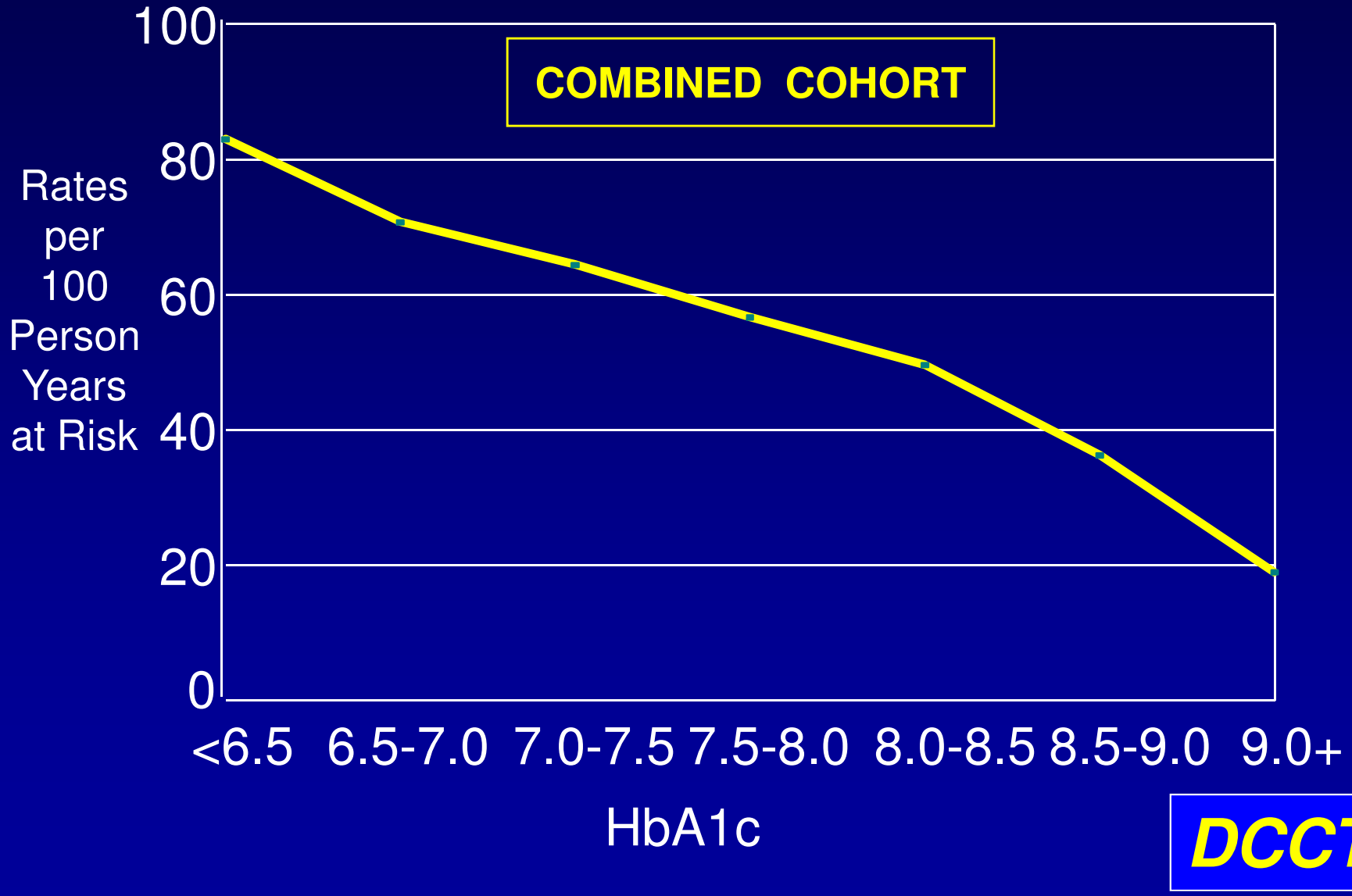
DCCT

Relationship of HbA_{1c} to Risk of Microvascular Complications

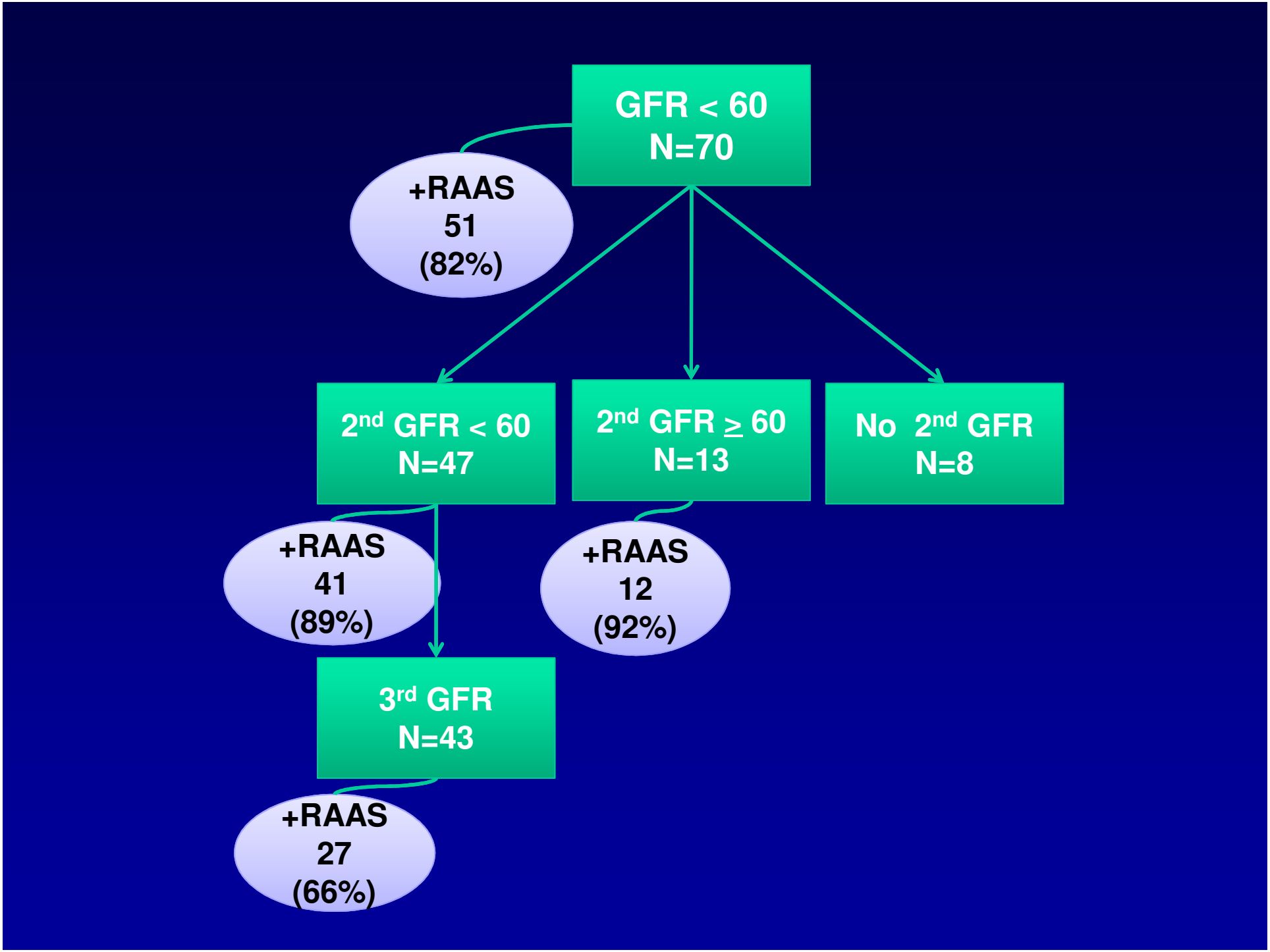


Skyler. *Endocrinol Metab Clin.* 1996;25:243-254, with permission.

ASSOCIATION BETWEEN SEVERE HYPOGLYCEMIA AND MOST RECENT HbA1c: INTENSIVE THERAPY



DCCT


GFR < 60
N=70
+RAAS
51
(82%)
2nd GFR < 60
N=47
2nd GFR ≥ 60
N=13
No 2nd GFR
N=8
+RAAS
41
(89%)
+RAAS
12
(92%)
3rd GFR
N=43
+RAAS
27
(66%)

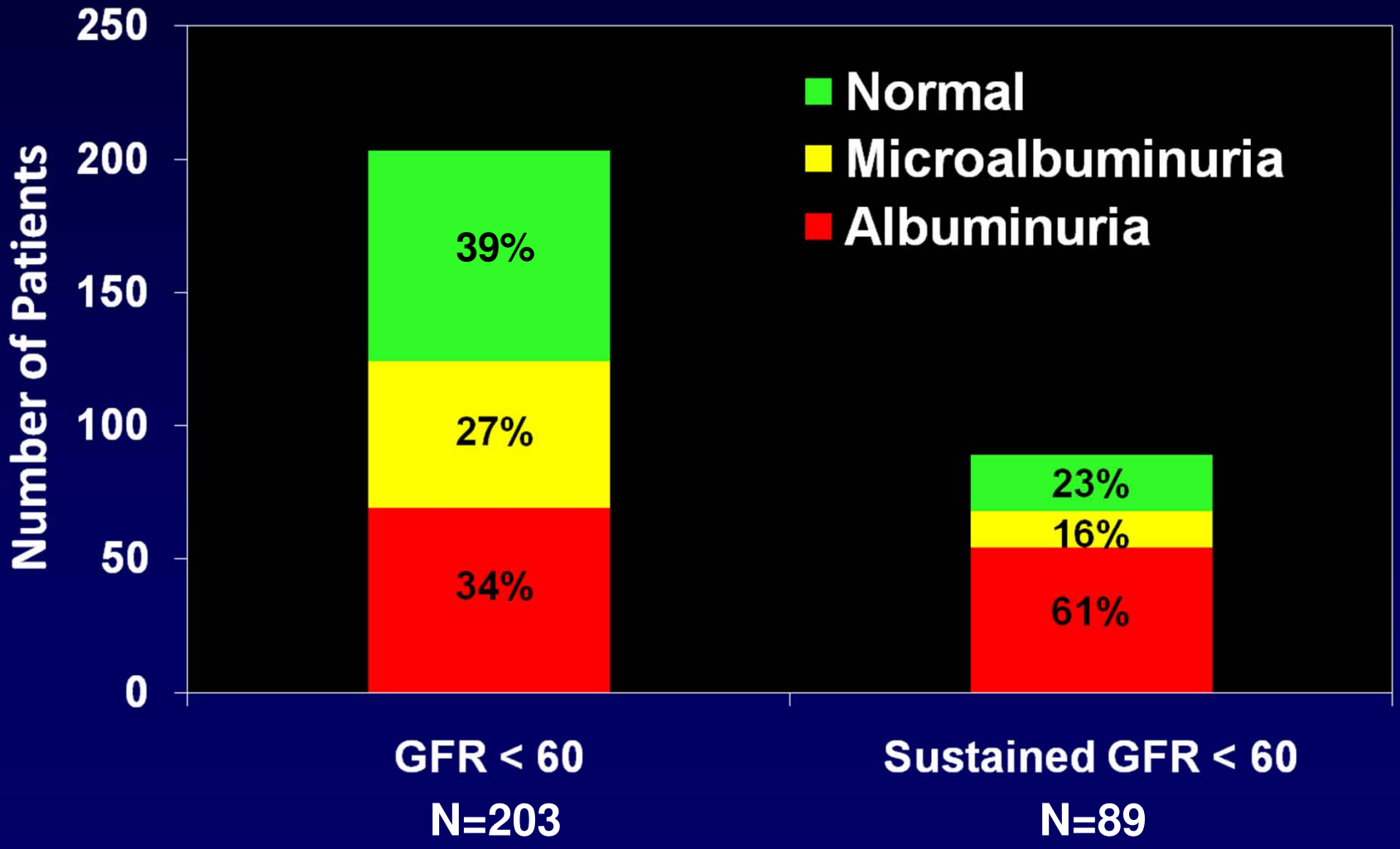
Results: Incidence Rates

Outcome	Events (n)	Person-years (n)	Incidence rate (%/yr)	RAAS inhibitor (%)
Macroalbuminuria	98	2578	3.8	37
Impaired GFR	60	3416	1.8	71
ESRD	21	4026	0.5	-
Normoalbuminuria	117	1302	9.1	25

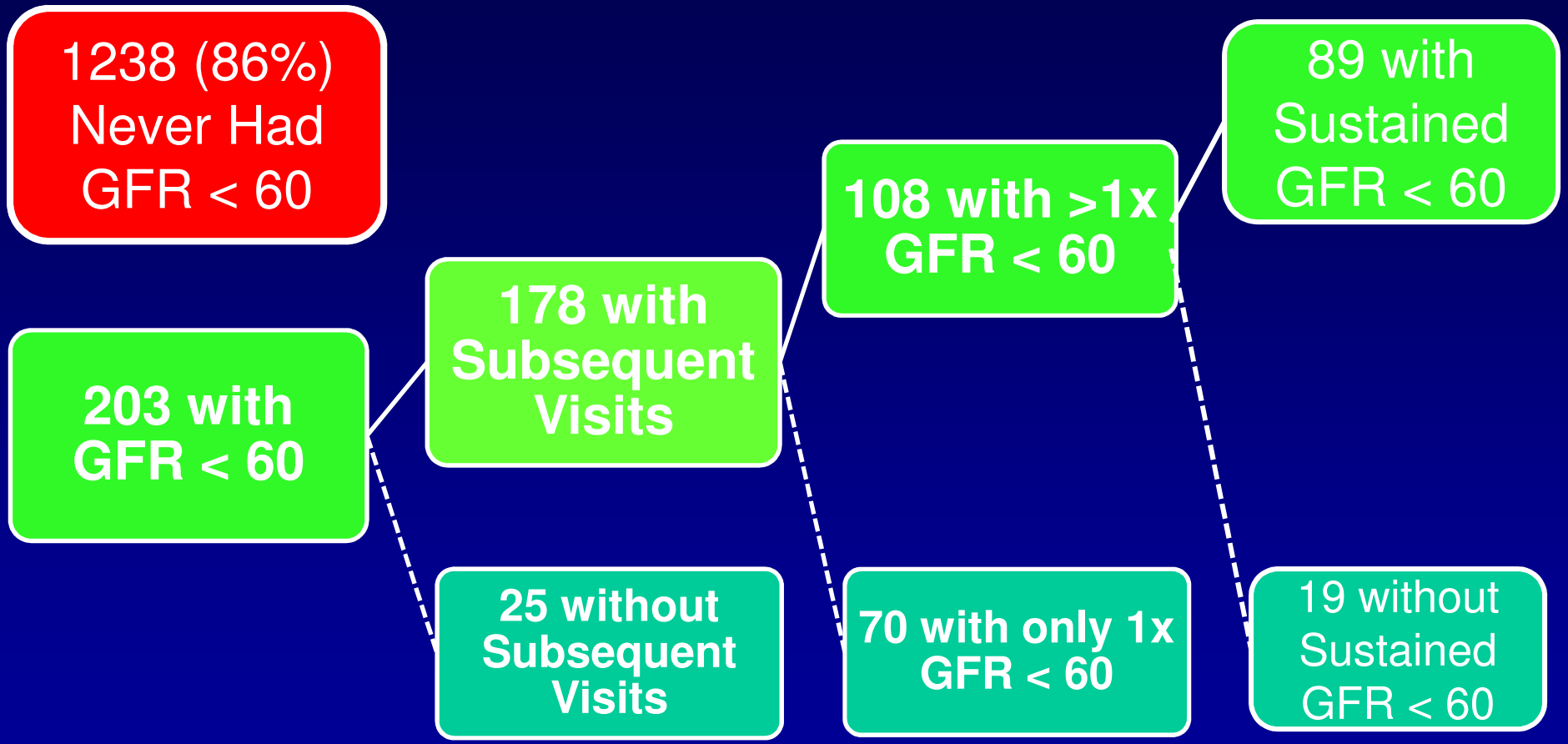
Follow-up: median 13 years, maximum 23 years

de Boer et al., Arch Intern Med 2011;171:412

Albumin Excretion Rates Preceding Diagnosis of Impaired Kidney function ([Sustained] GFR < 60 ml/min/1.73m^2) in DCCT/EDIC Subjects

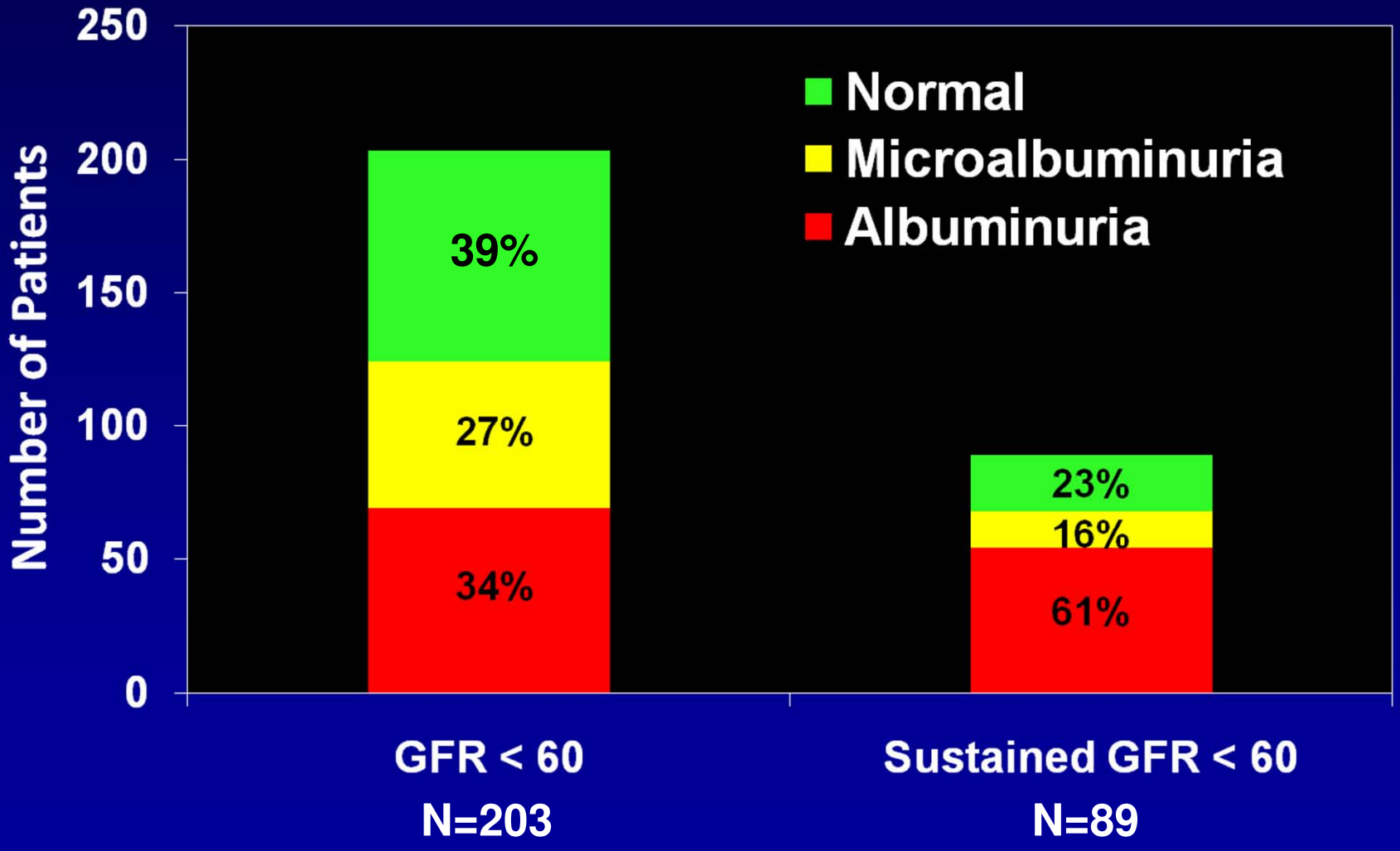


eGFR Status for DCCT/EDIC Subjects from DCCT Through EDIC Year 14

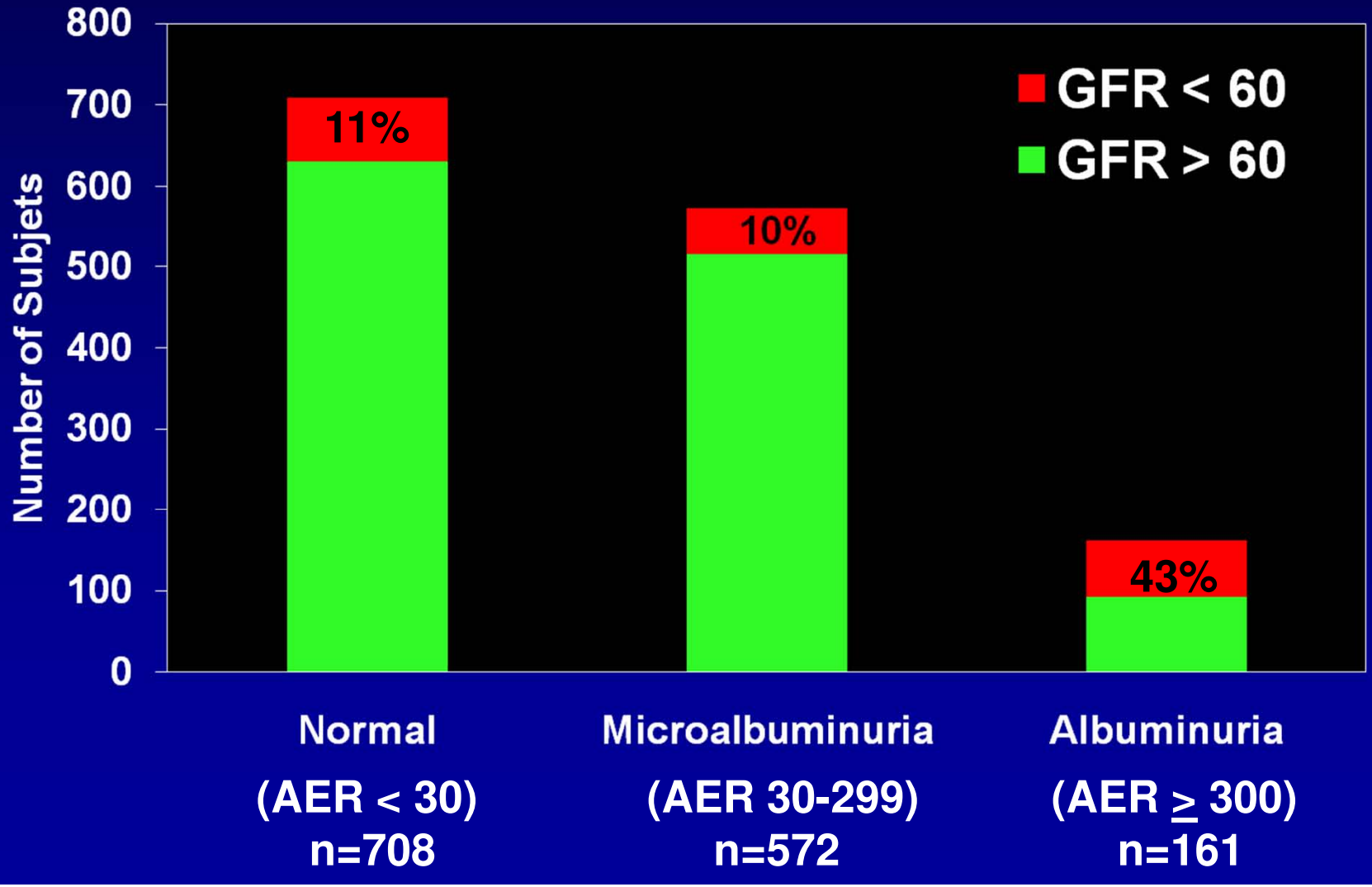


First GFR < 60 occurred in DCCT in 29 (14%) of patients
First GFR < 60 occurred in EDIC in 174 (86%) of patients

Albumin Excretion Rates Preceding Diagnosis of Impaired Kidney function ([Sustained] GFR < 60 ml/min/1.73m^2)

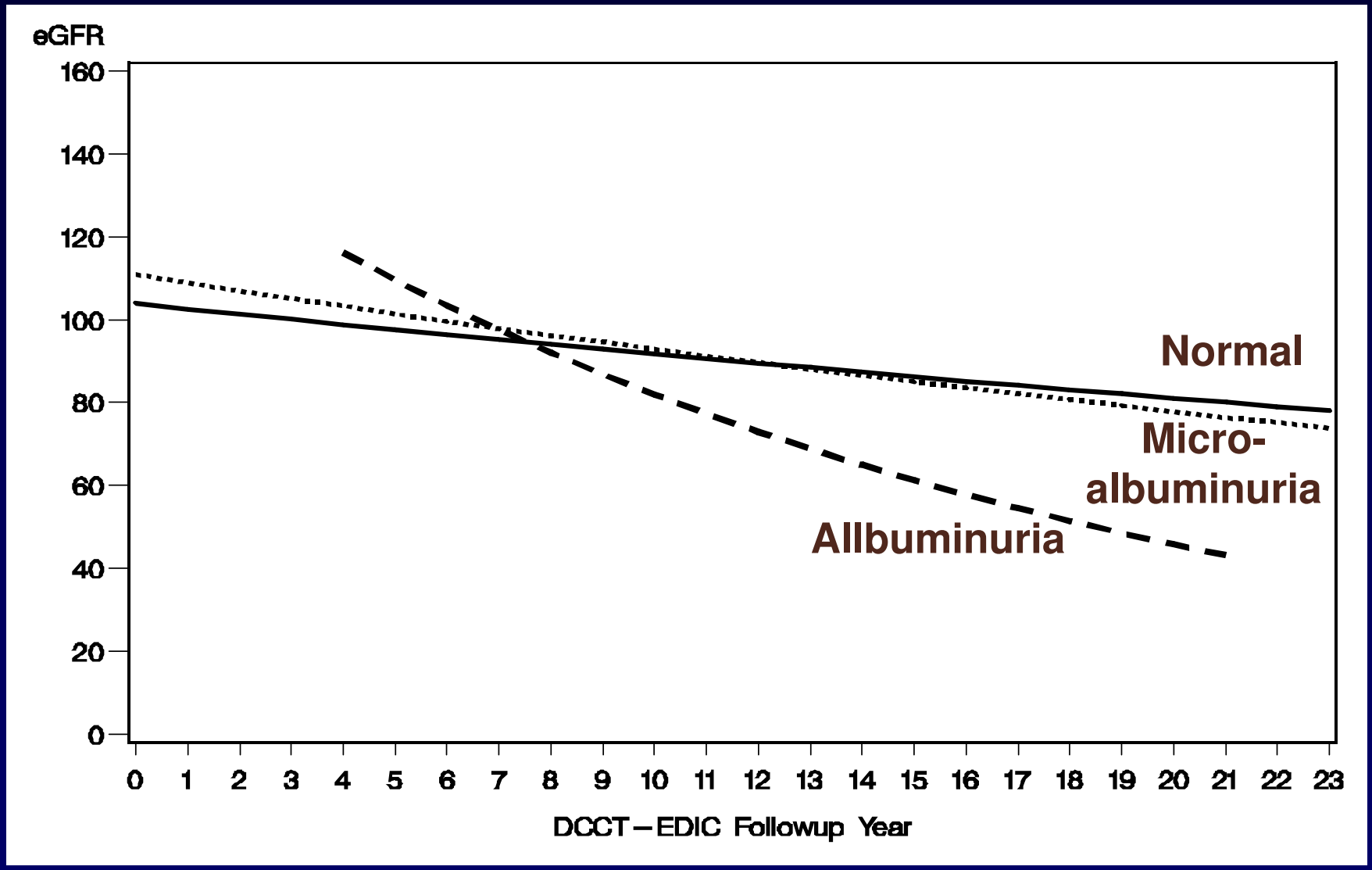


Cumulative Incidence of Impaired Kidney Function (GFR < 60) by Albumin Excretion Rate for DCCT/EDIC subjects through EDIC Year 14

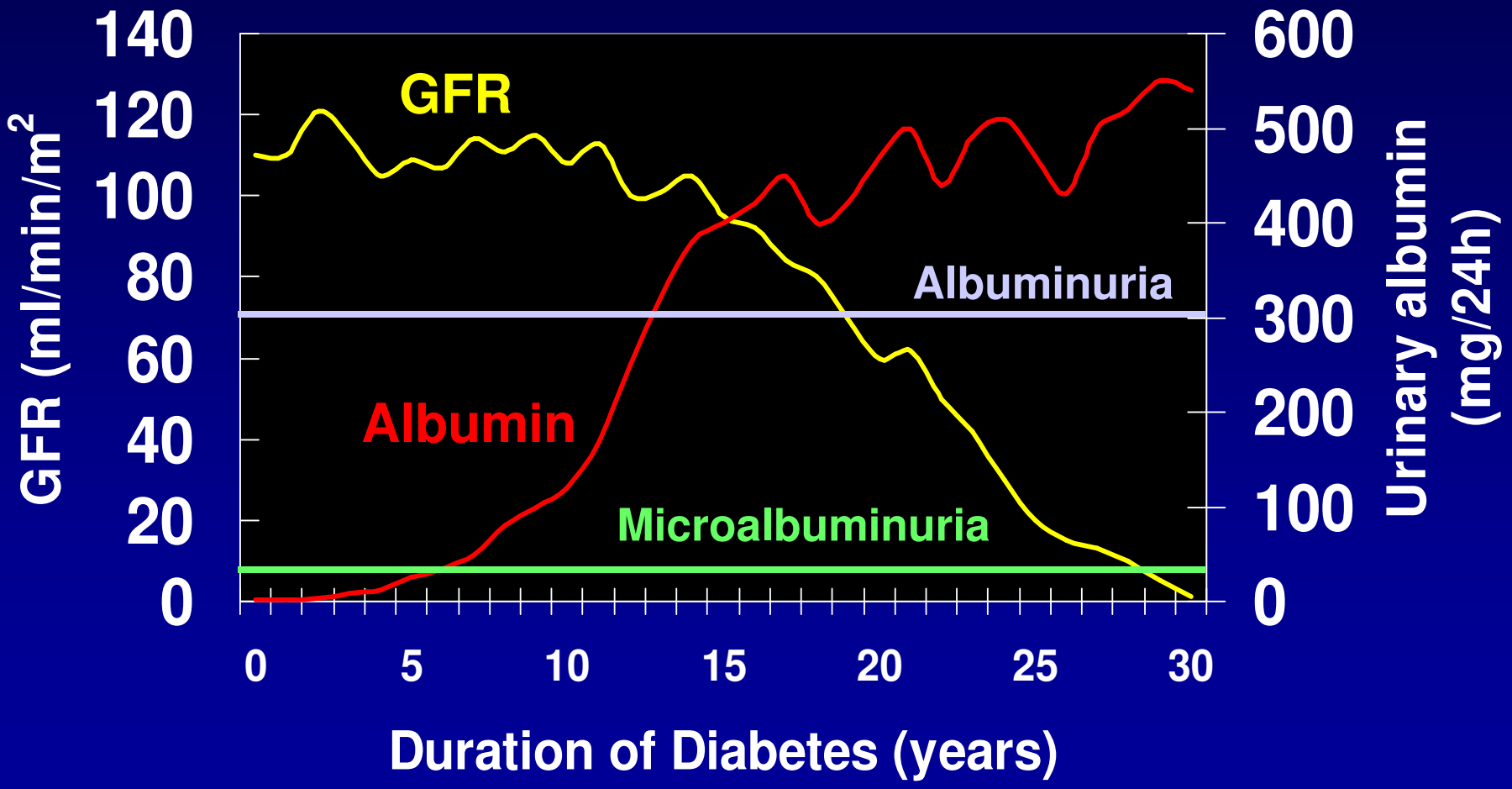


Are there differences in the rates of progression of kidney disease in those with GFR levels < 60 ml/min/1.73m^2 who do or do not have increased levels of AER?

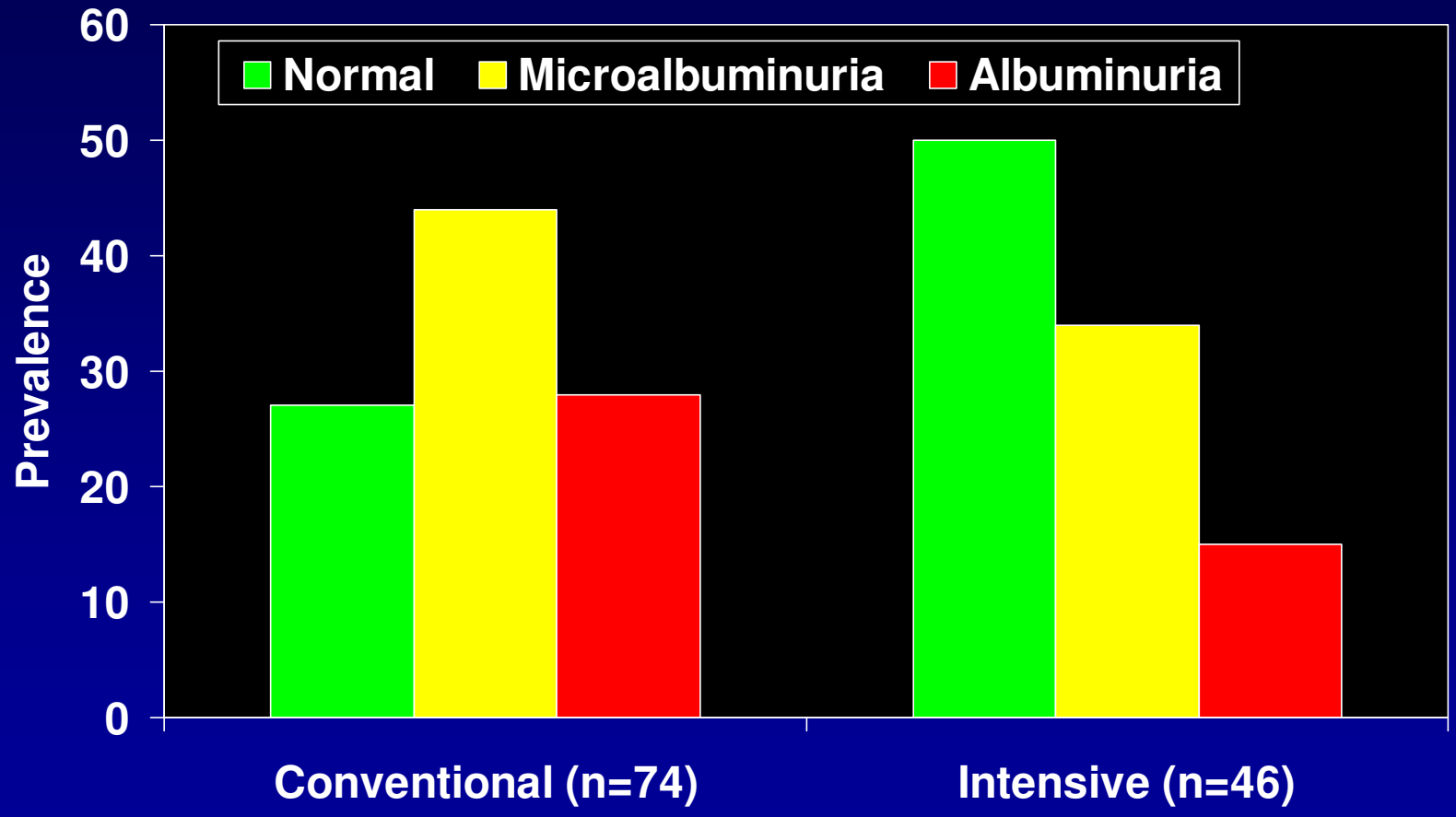
Estimates of the mean levels of eGFR at each DCCT-EDIC follow-up year among subjects currently with normal AER, or microalbuminuria or albuminuria at that time



Natural History of Diabetic Nephropathy

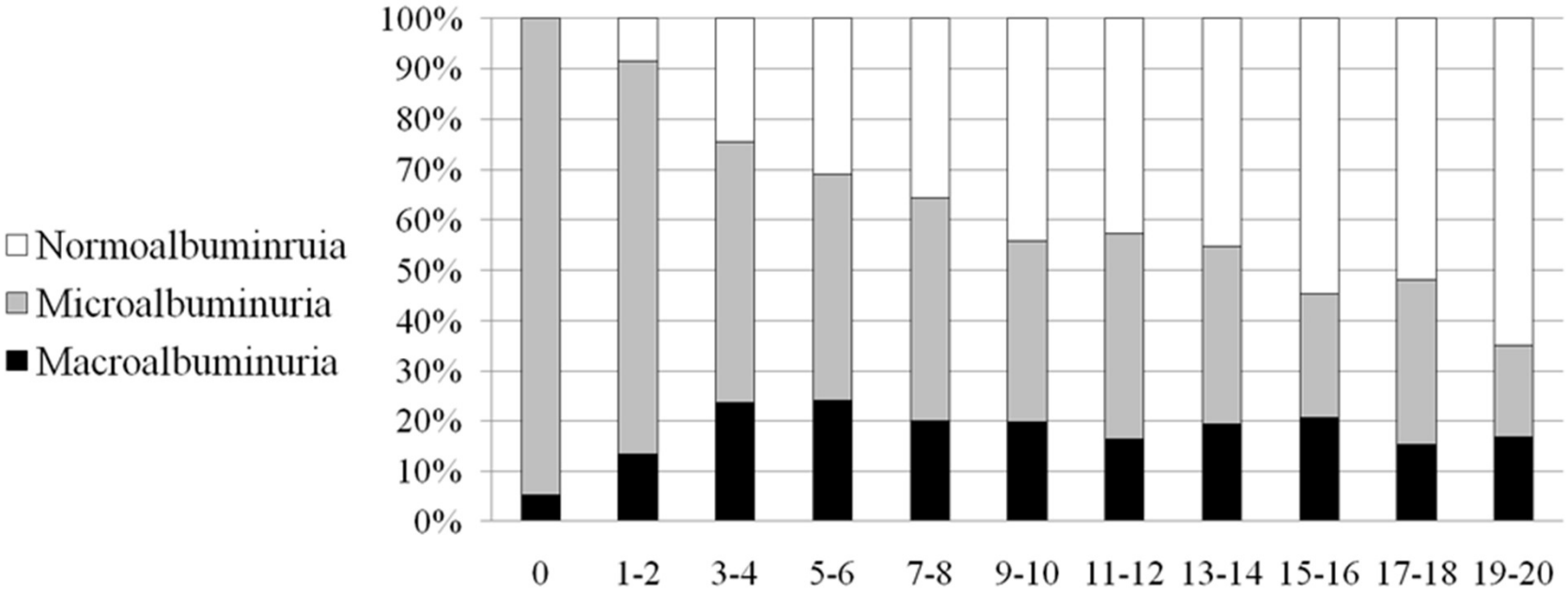


Renal Status of Subjects with Sustained Microalbuminuria During the DCCT at Year 6 of EDIC



p= 0.03 for differences in proportions

JAMA 2003;290:2159



No. of participants	325	315	281	255	230	208	166	135	117	85	54
Prevalence of RAAS inhibitor use (%)											
Normoalbuminuria	-	0	22	27	34	34	39	39	50	55	51
Microalbuminuria	7	24	30	44	51	69	59	71	86	71	80
Macroalbuminuria	6	31	55	72	67	78	93	92	92	85	89

de Boer et al., Arch Intern Med 2011;171:412

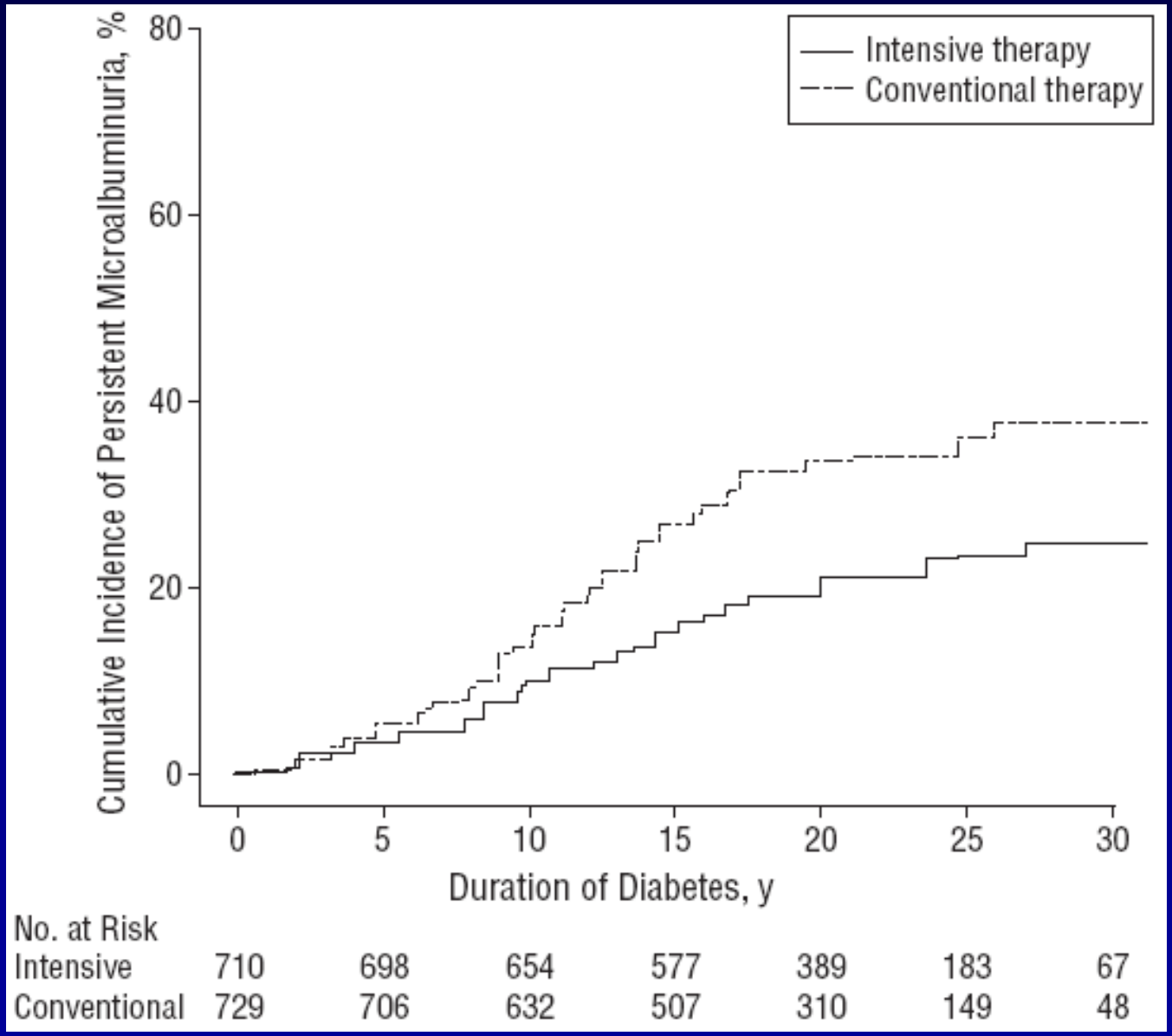
Risk Factors for Renal Outcomes

	Renal Outcome					
	Macro-Albuminuria		Impaired GFR		Normo-Albuminuria	
Risk factor	HR	P	HR	P	HR	P
Female gender	0.52	0.005	1.10	0.7	2.53	<0.001
SBP (10 mmHg)	1.30	0.003	1.06	0.6	0.85	0.04
DBP (10 mmHg)	1.38	0.01	1.21	0.23	0.71	0.004
Time-updated SBP	1.71	<0.001	1.91	<0.001	0.82	0.08
Time-updated DBP	2.03	<0.001	2.17	<0.001	0.68	<0.001
LDL-C (10 mg/dL)	1.12	0.01	1.04	0.5	0.88	0.001
Triglyceride (10 mg/dL)	1.06	0.01	1.04	0.2	0.93	0.007

Adjusted for age, gender, and duration of diabetes at microalbuminuria diagnosis

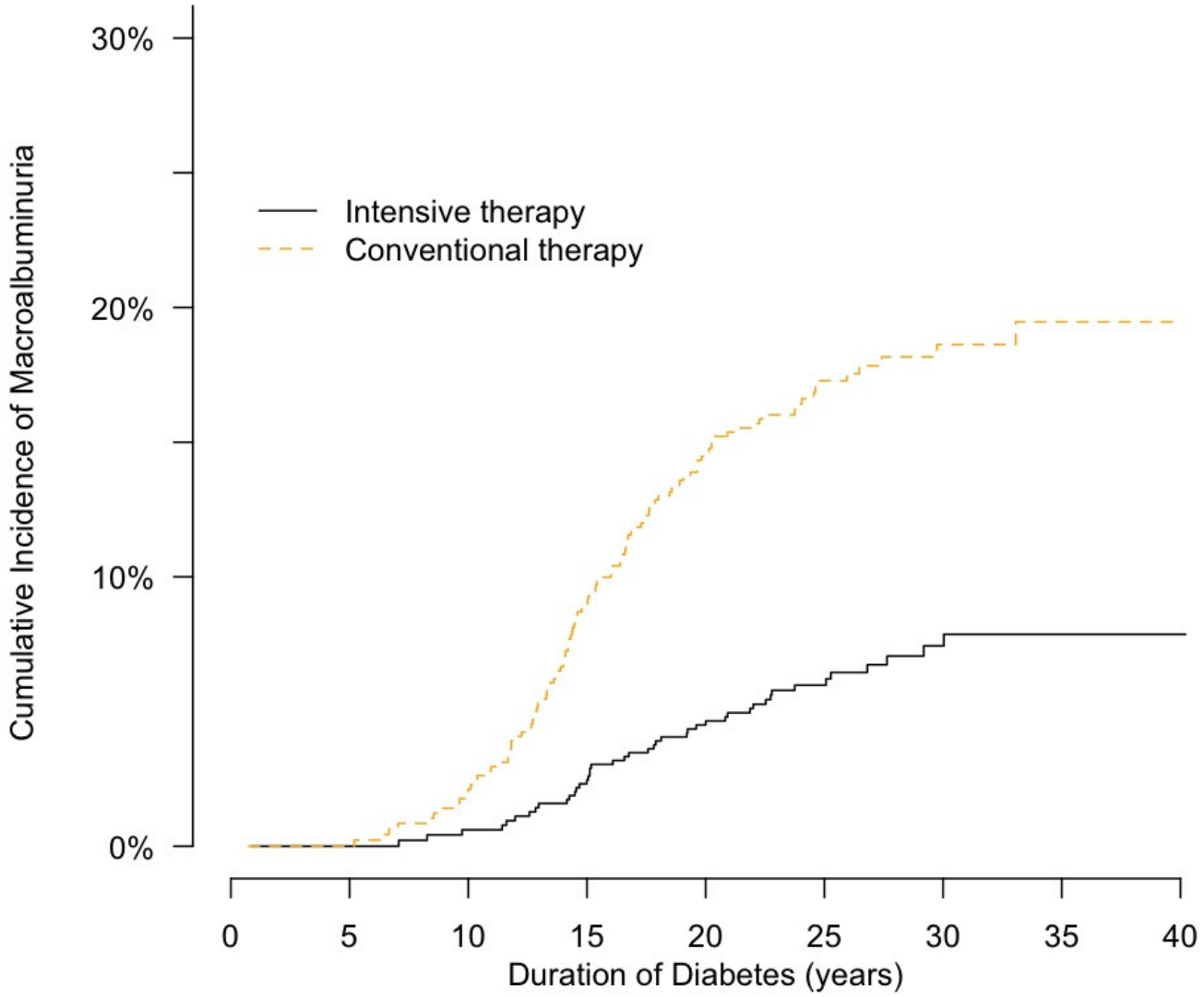
de Boer et al., Arch Intern Med 2011;171:412

Glycemic Control Prevents Microalbuminuria



de Boer et al., Arch Intern Med 2011;171:412

Development of Sustained Albuminuria by Treatment Group



No. at risk

Intensive	0	409	535	676	643	403	216	71	3
Conventional	0	439	567	640	575	353	168	58	0