GLYCEMIA AND COMPLICATIONS IN THE DCCT AND PERSISTENCE OF EFFECTS DURING EDIC

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QUESTIONS

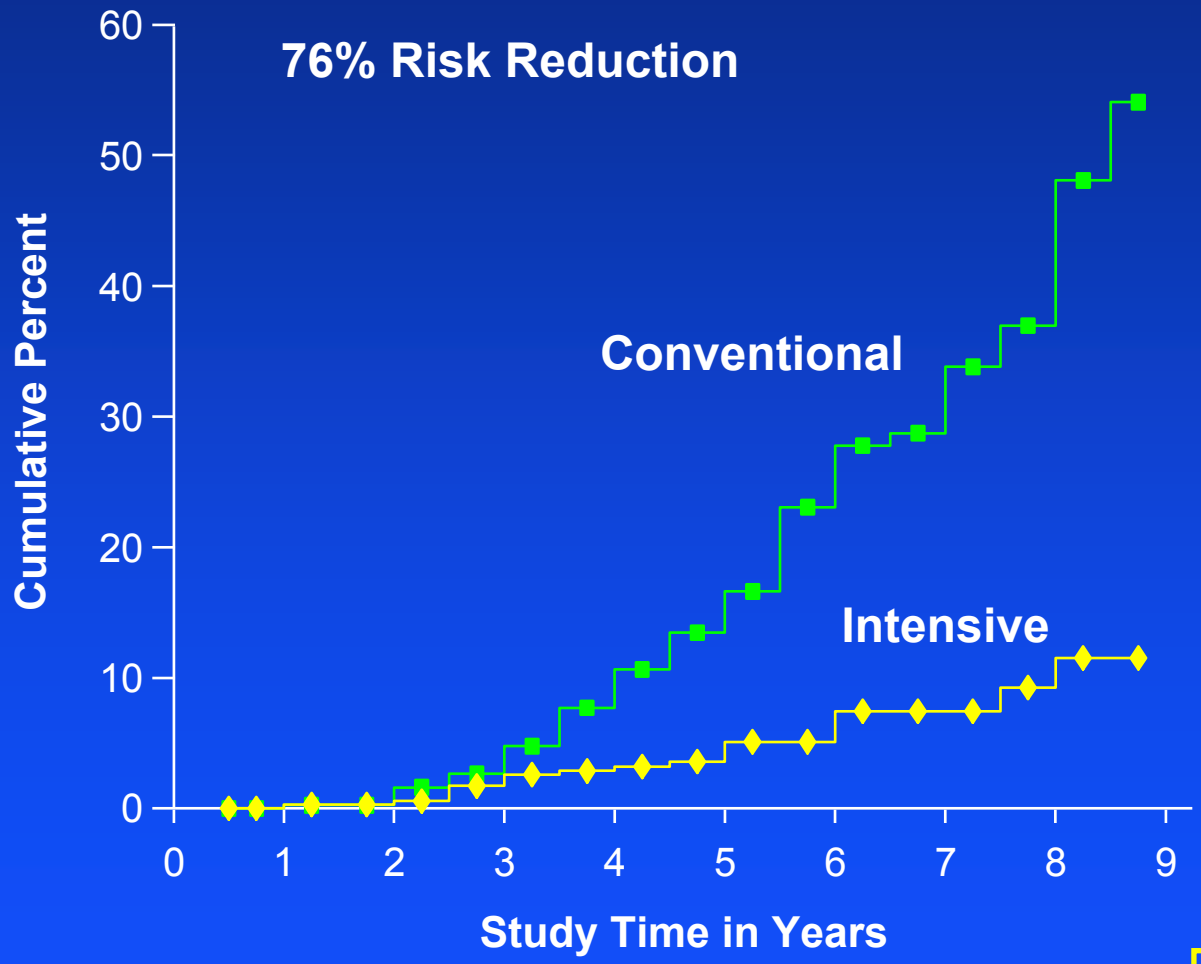
1. Nature of the *statistical* relationship between glycemia and *complications* during the DCCT?

   Threshold?

2. Basis for the prolonged effect of DCCT intensive therapy during EDIC?

   DCCT difference in glycemia alone?

Cumulative Incidence of Retinopathy Progression Primary Prevention Cohort



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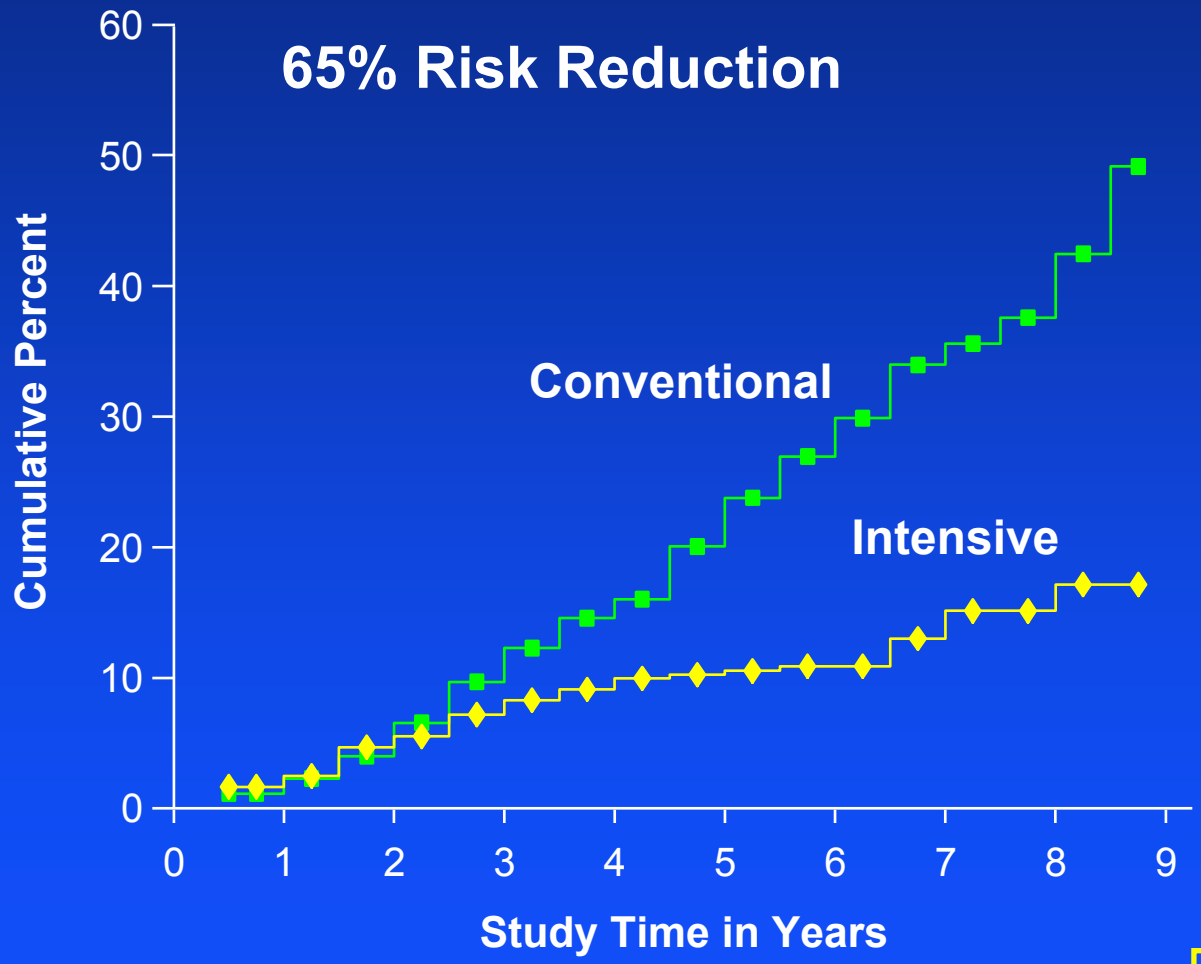
Cumulative Incidence of Retinopathy Progression Secondary Intervention Cohort



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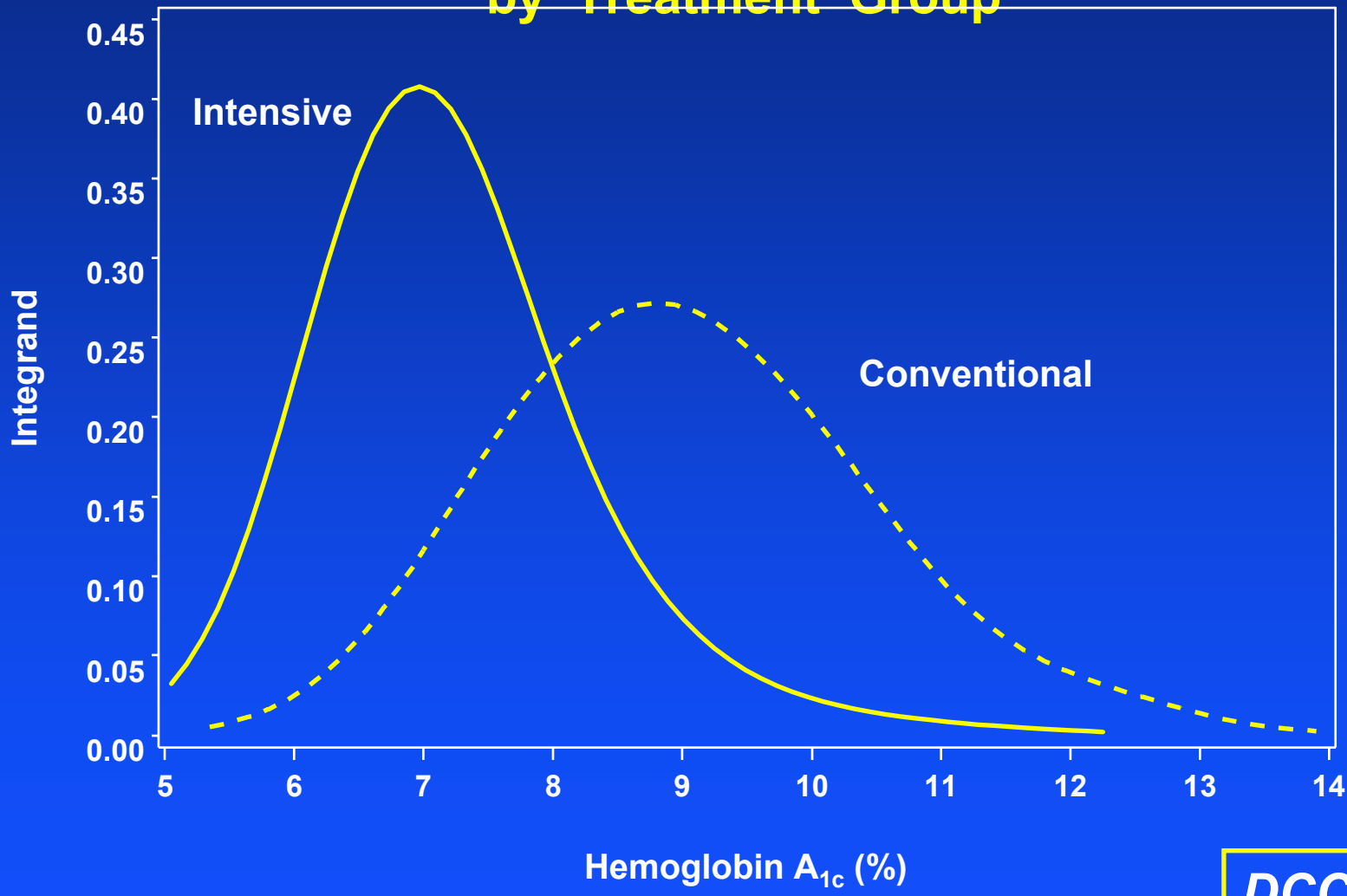
Mean HbA_{1c} at Semi-Annual Visits

by Treatment Group



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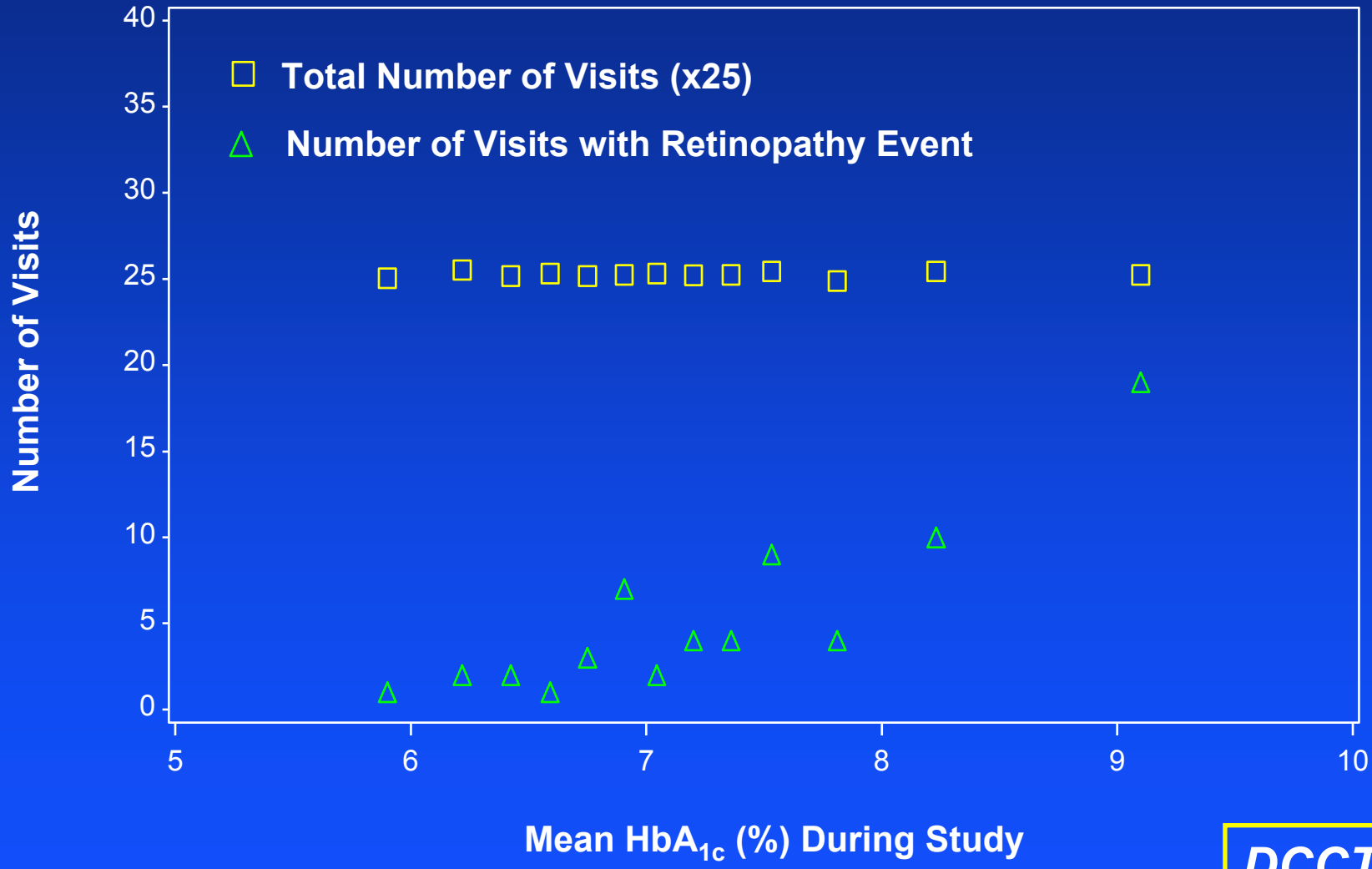
DISTRIBUTION OF HBA_{1C} AT PATIENT VISITS
1 Visit = 0.5 Years of Exposure

Intensive Treatment Group



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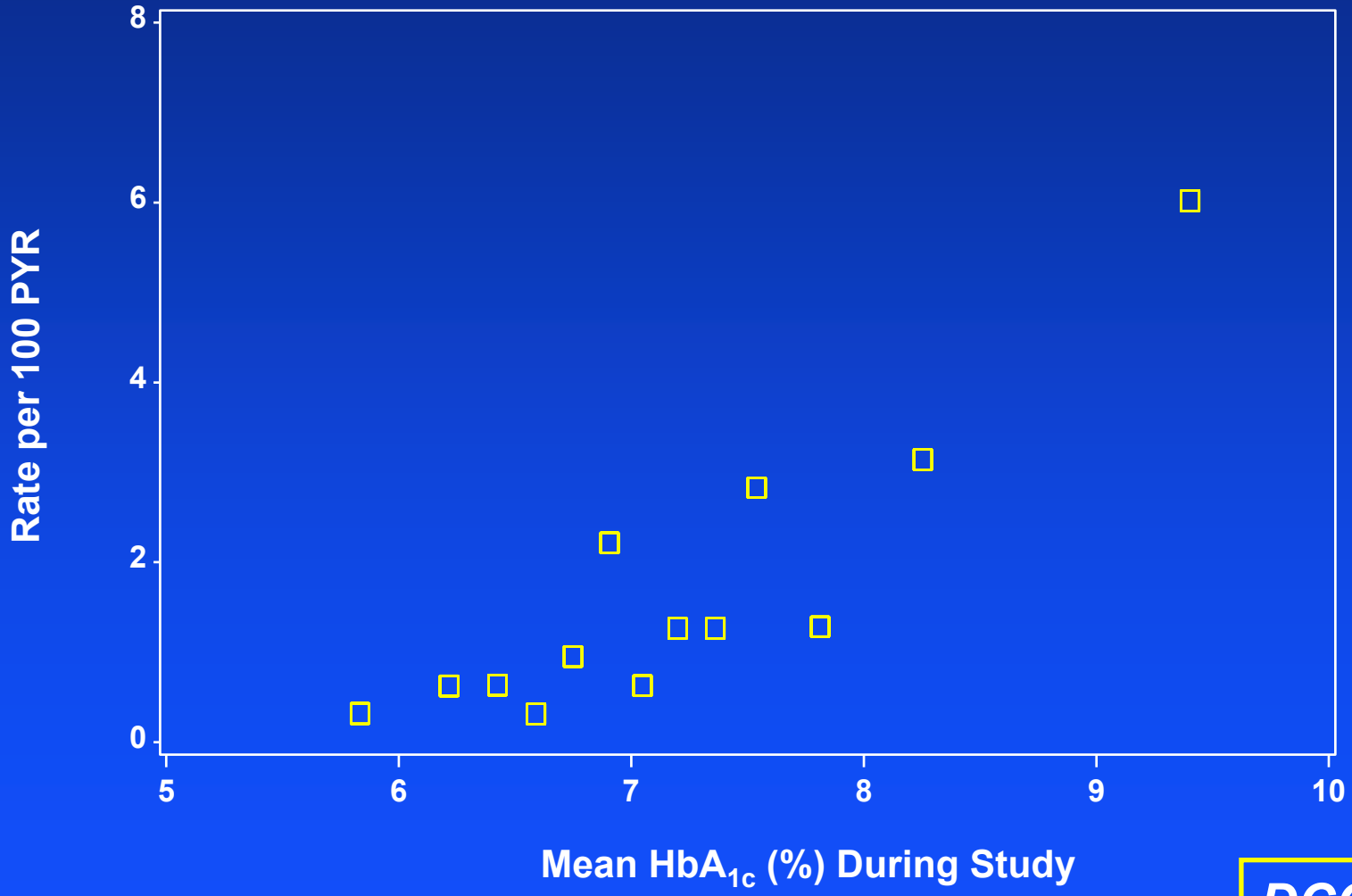
Crude Rates of Retinopathy Progression

Intensive Treatment Group



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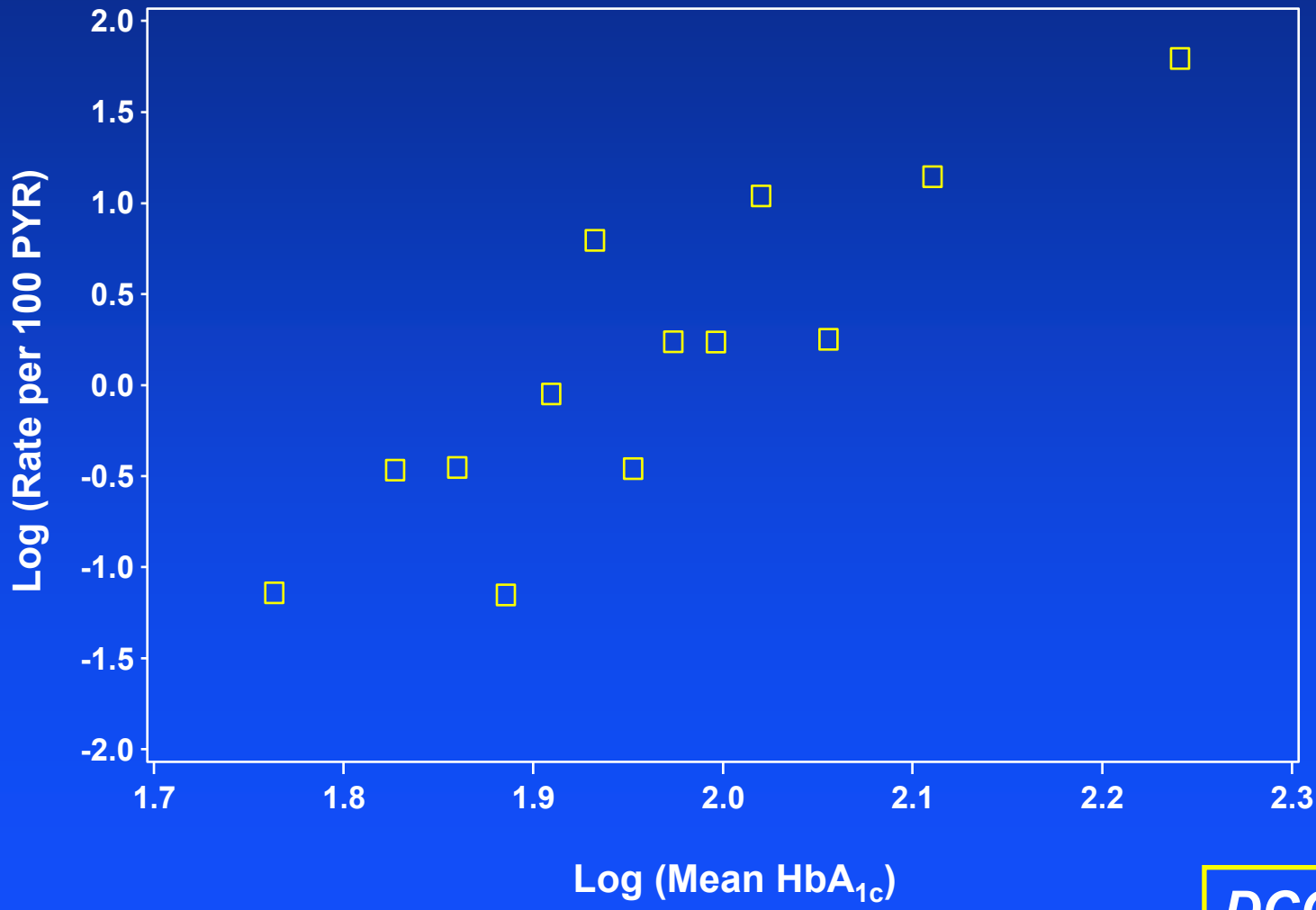
Crude Rates of Retinopathy Progression

Intensive Treatment Group



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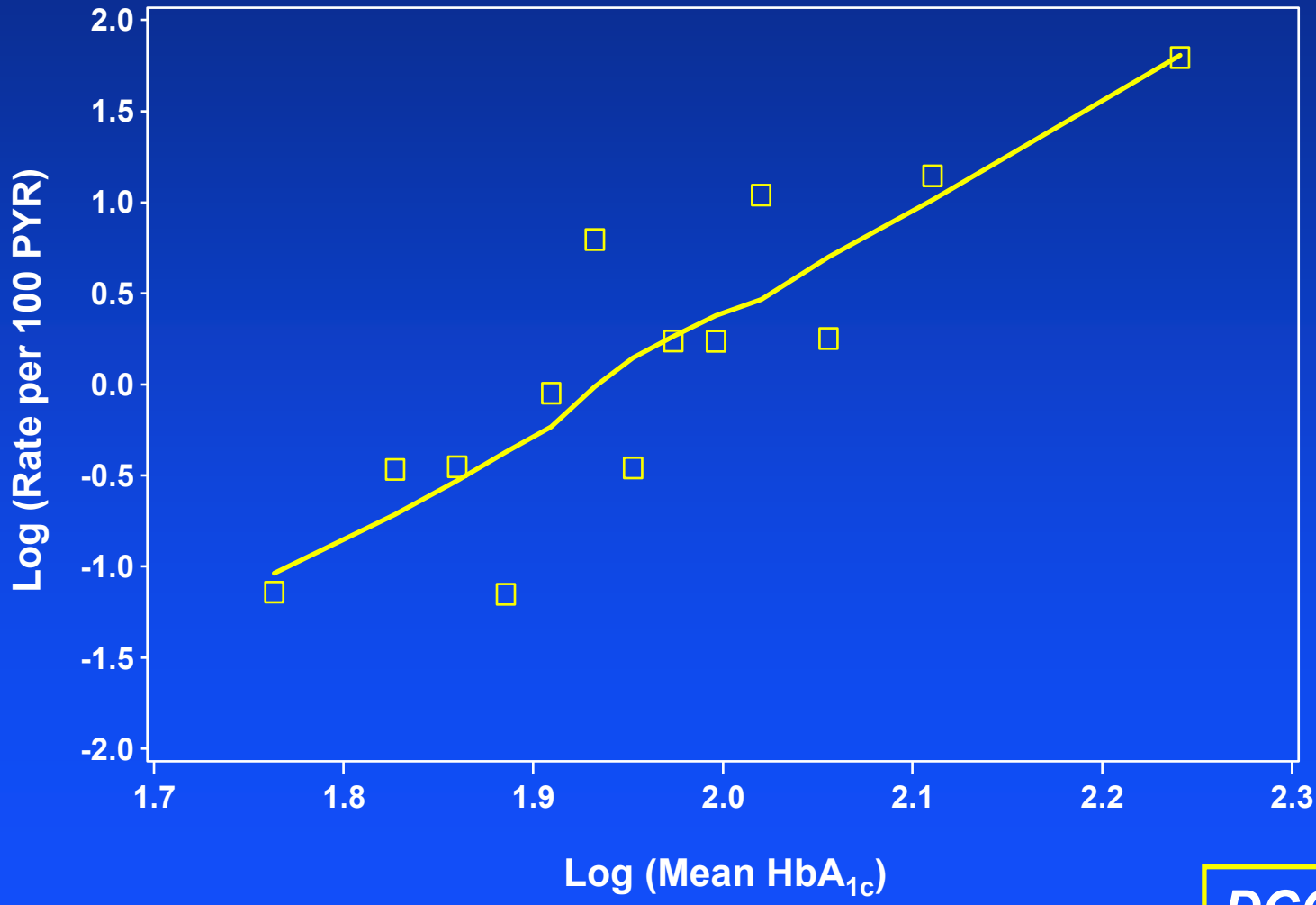
Smoothed Estimate of Retinopathy Progression With Crude Event Rates

Intensive Treatment Group



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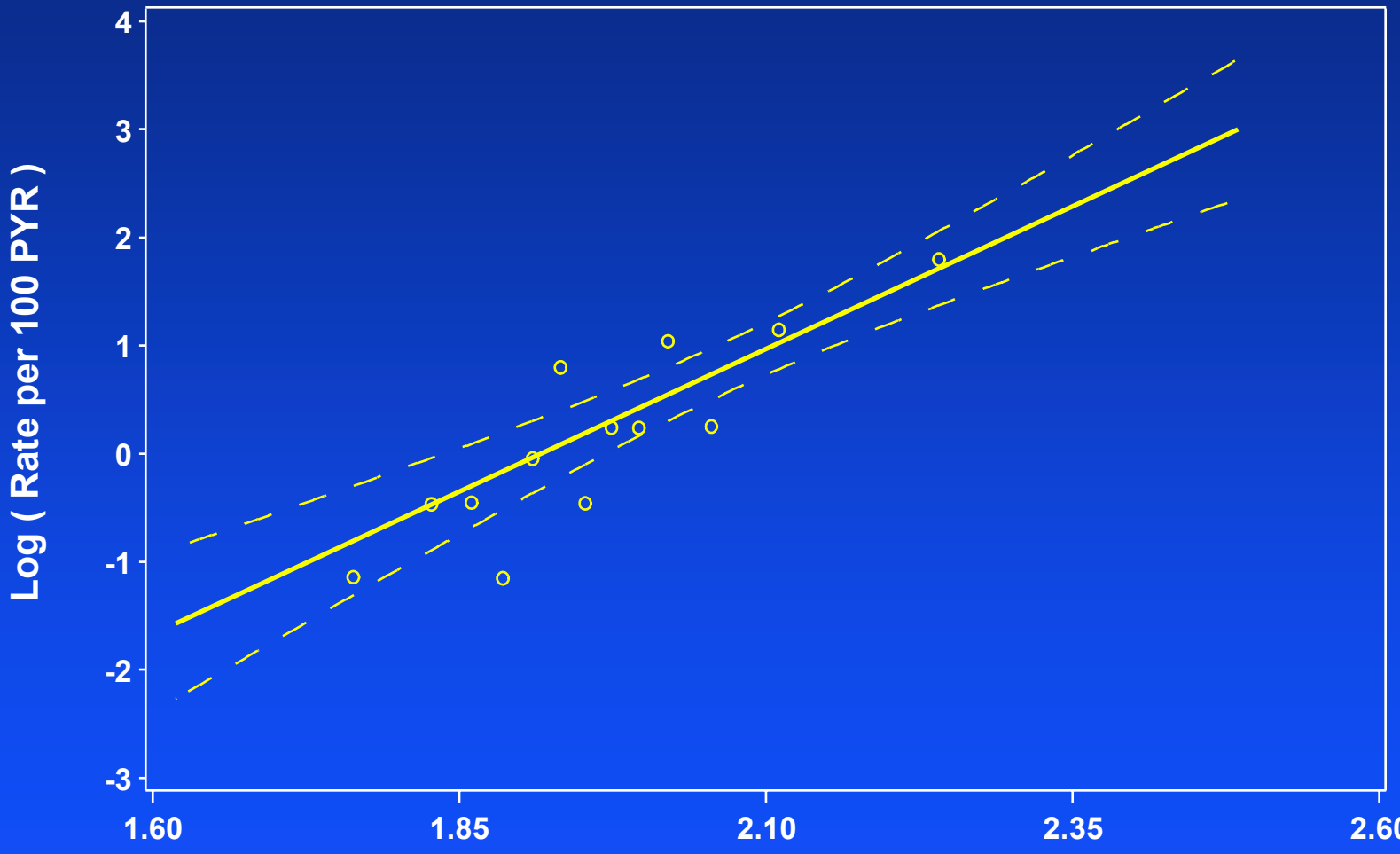
Risk of Retinopathy Progression

Intensive Treatment Group



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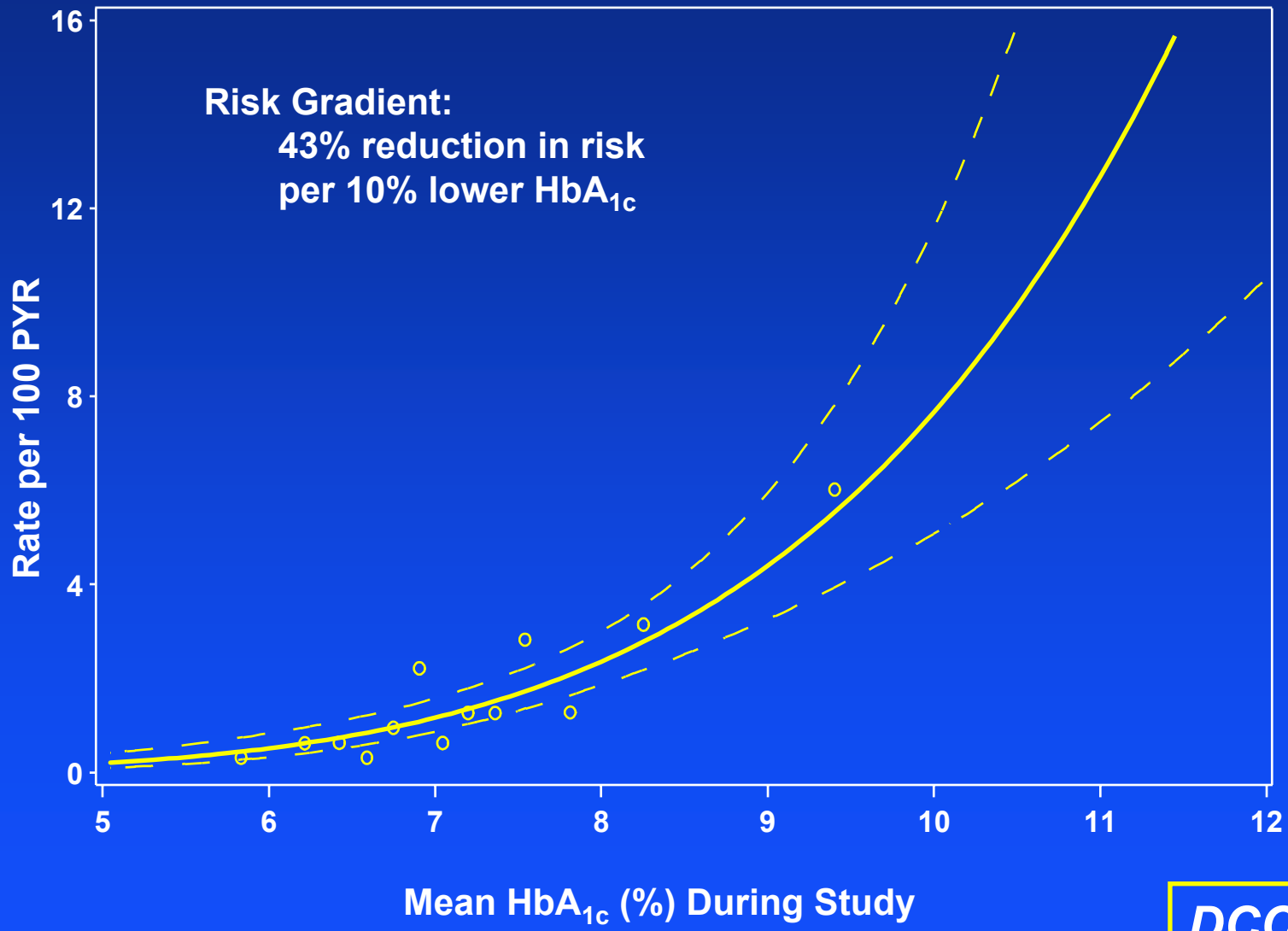
Risk of Retinopathy Progression

Intensive Treatment Group



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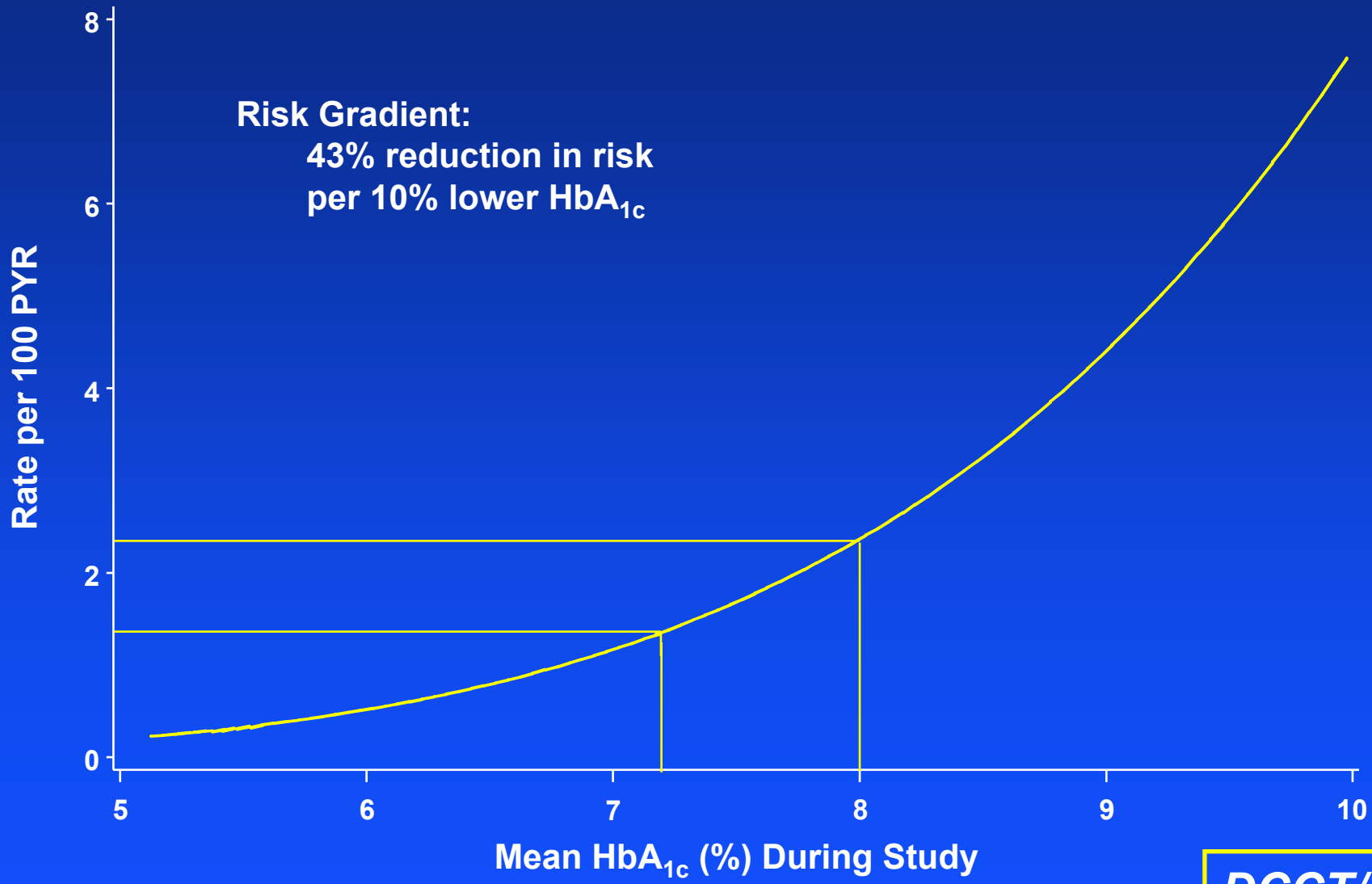
Risk of Retinopathy Progression vs Mean HbA_{1c}

Intensive Treatment Group



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RISK FACTORS FOR RETINOPATHY PROGRESSION

- ***Conventional Rx:***

  Exposure time compounds HbA_{1c} effects on risk

- ***Total lifetime glycemic exposure:***

  HbA_{1c} before and during DCCT
  Pre-existing IDDM Duration
  Exposure time in the DCCT

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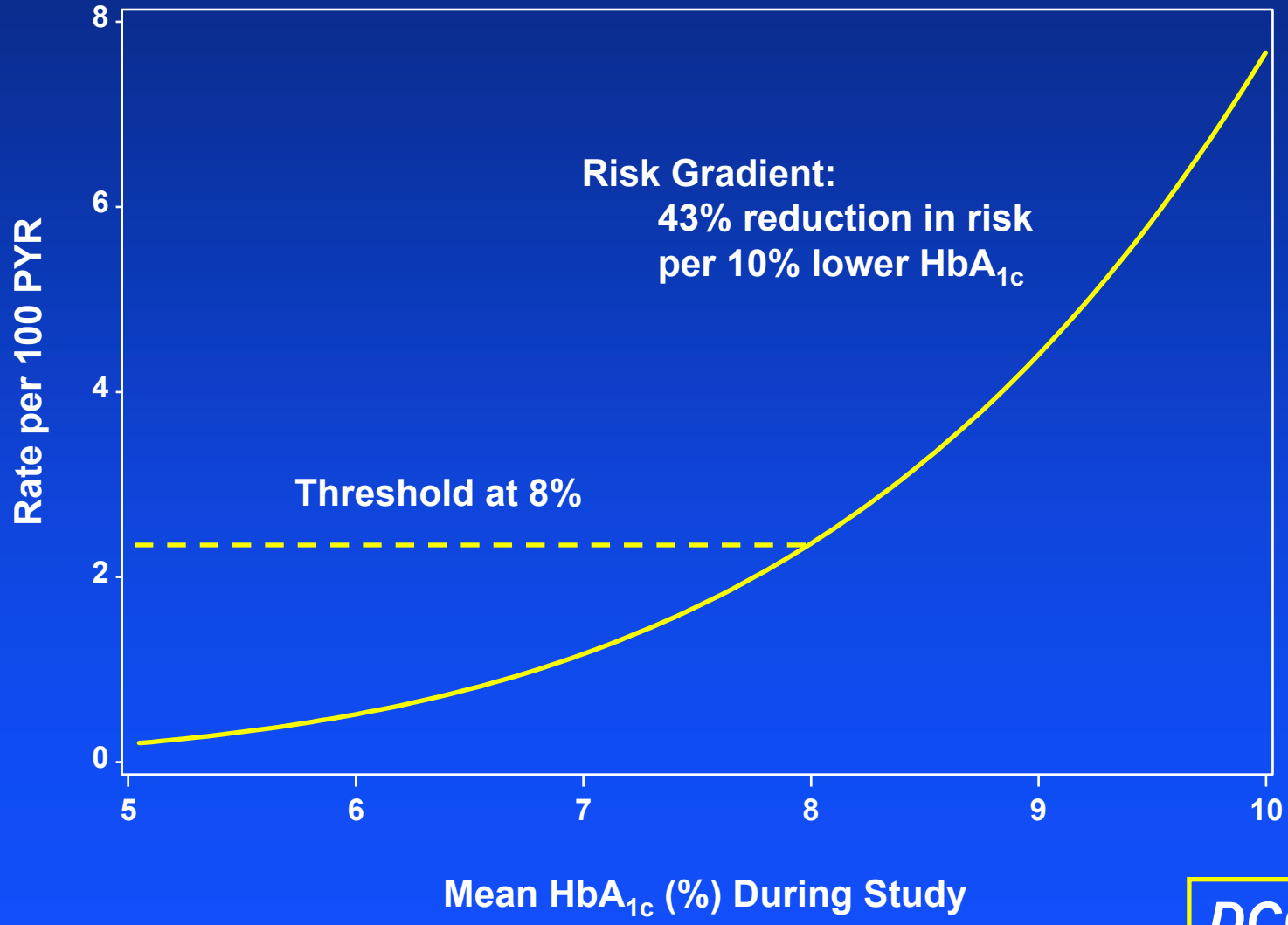
Threshold Model for Risk of Retinopathy Progression

Intensive Treatment Group



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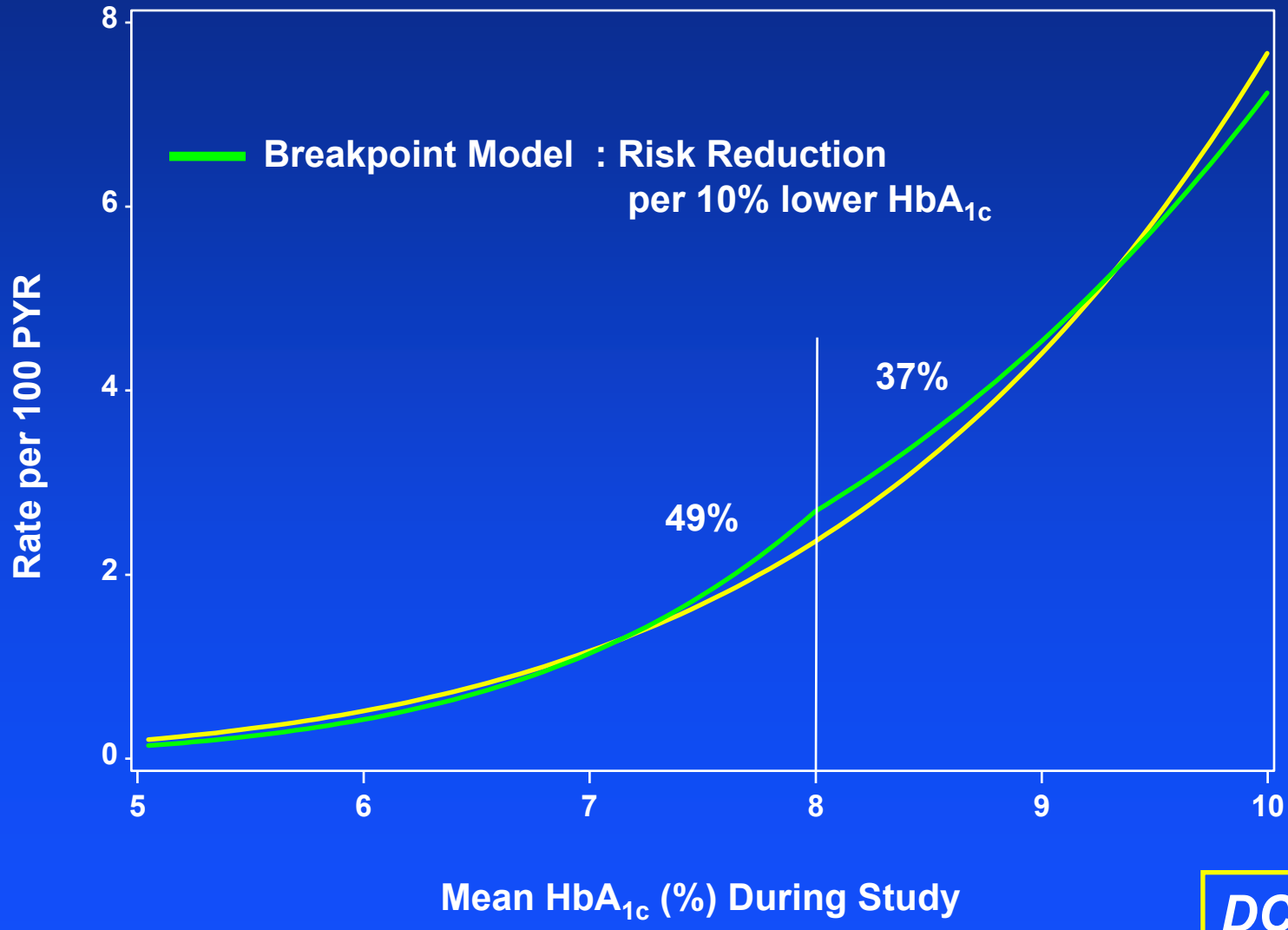
Breakpoint Exponential Model for Risk of Retinopathy Progression

Intensive Treatment Group



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RISK GRADIENTS FOR OTHER COMPLICATIONS

per 10% lower HbA1c

	All	≤ 8%	> 8%
Progression of retinopathy	43*	49*	37*
Microalbuminuria (or albuminuria)	28*	23*	33*
Confirmed Clinical Neuropathy	32*	30	35

*$p < 0.05$

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OTHER POSSIBLE RISK FACTORS FOR RETINOPATHY PROGRESSION

Current Mean HbA1c Remains Dominant After Adjusting for Baseline and Current Values of

- Insulin Dose and C-peptide
- Lipids
- Blood Pressure
- Smoking
- Body Mass, Obesity
- Dietary Factors

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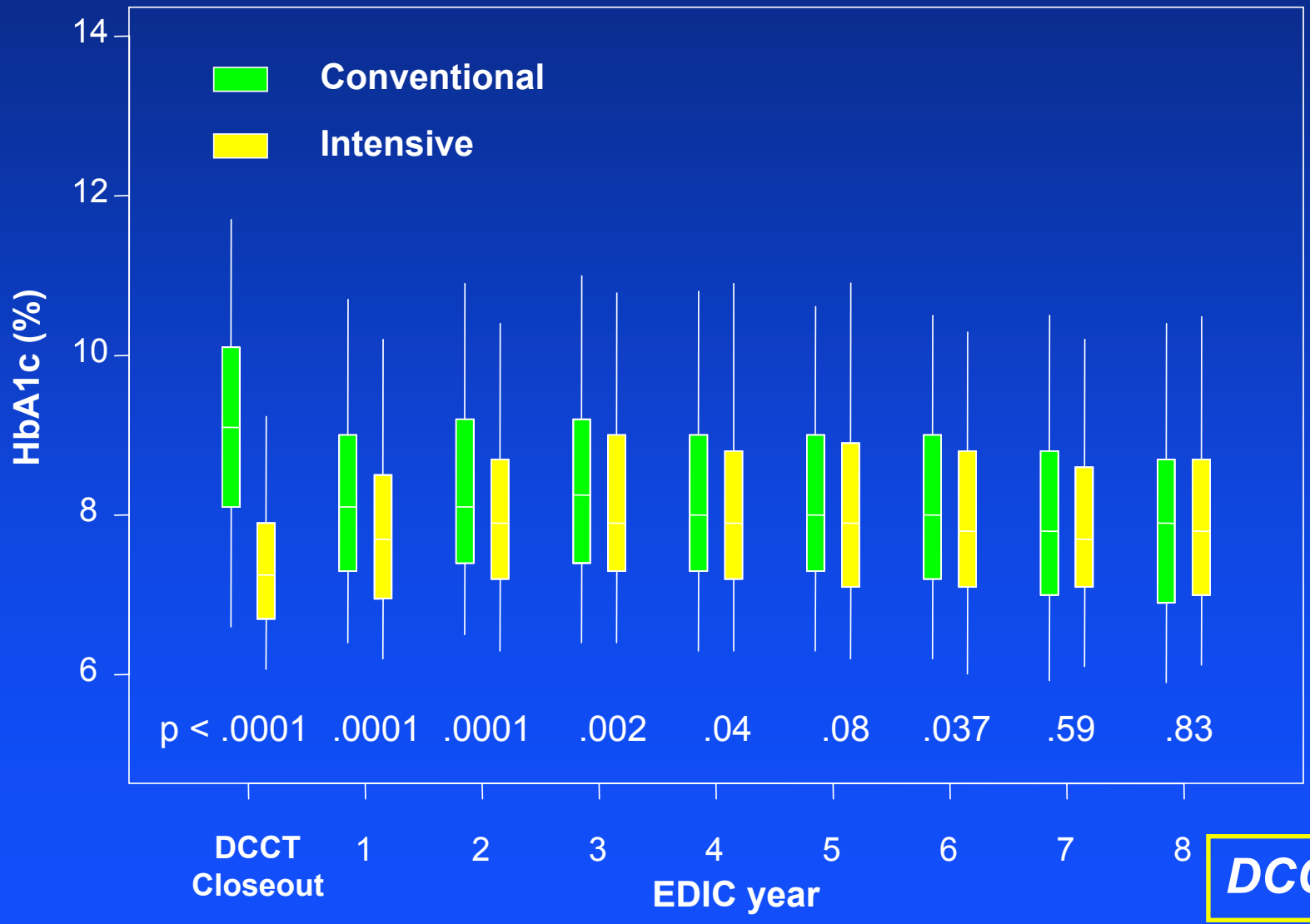
Distribution of HbA1c in the Former DCCT Intensive and Conventional Groups During EDIC



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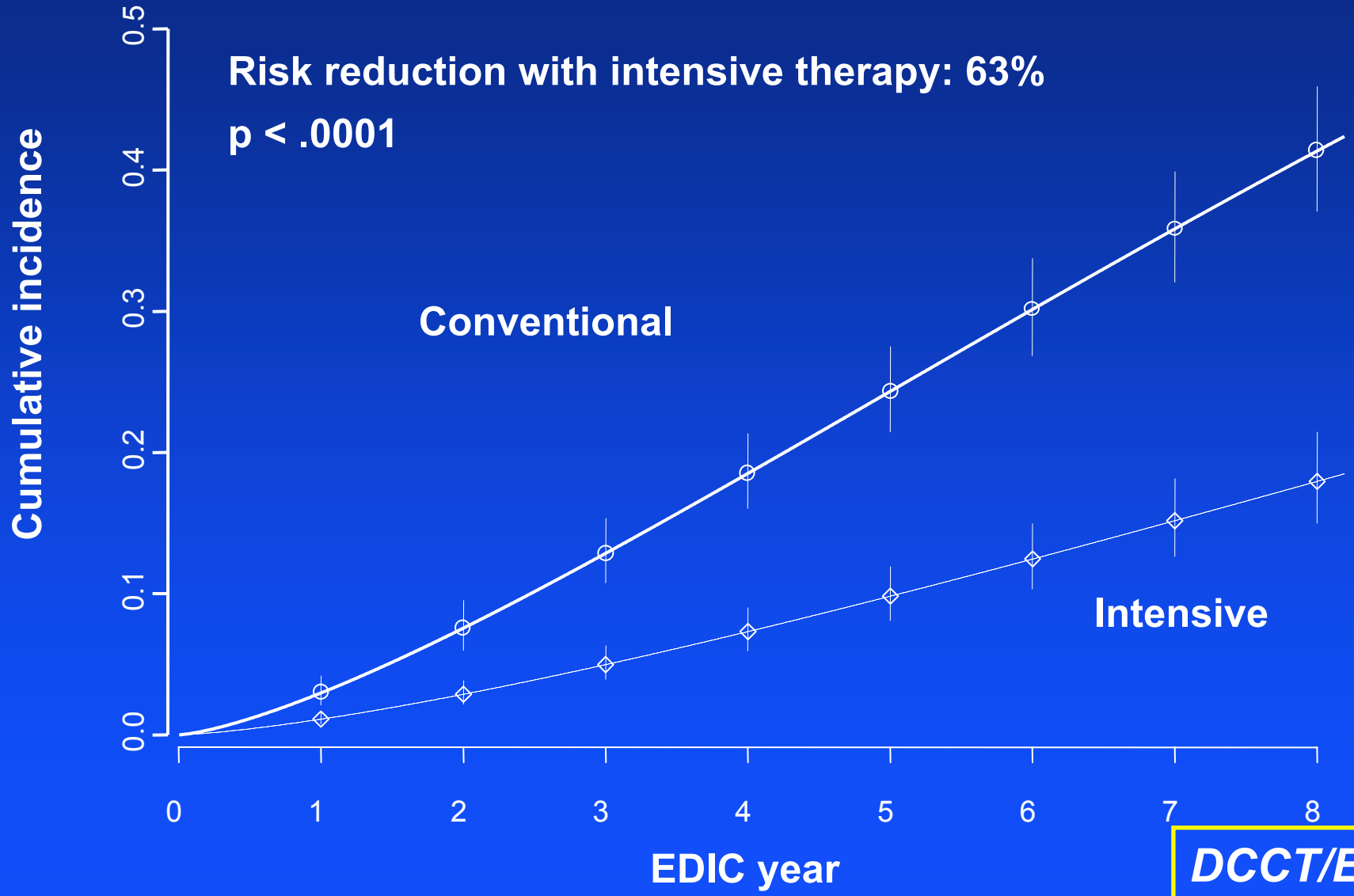
Further Three-step Progression of Retinopathy From DCCT Close-out through EDIC Year 8



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CONCLUSIONS

1. Dominant determinant of risk of complications is lifetime exposure to hyperglycemia

   No threshold or breakpoint short of normoglycemia

   Intrinsically related to level and duration of glycemia

   Effects of hyperglycemia are long lasting

2. Risk of complications increases with time, exponentially with higher levels of blood glucose

   Effects of prior hyperglycemia are not wholly reversible

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CONCLUSIONS (cont.)

3. The relationships between level of HbA1c and time observed during the DCCT predict persistence of effects during EDIC.

4. Hyperglycemia leads to metabolic or other changes that in turn determine microvascular risk

   3-4 y lag in manifestation of treatment effect.

   Persistence of DCCT treatment group effects

DCCT RECOMMENDATION

Intensive therapy with the goal of achieving normal glycemia should be implemented as early as possible in as many type 1 patients as is safely possible.

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