

Online-Only Appendix
The Effect of Glycemic Exposure on the Risk of
Microvascular Complications in the Diabetes
Control and Complications Trial – Revisited

John M. Lachin Sc.D., Saul Genuth M.D., David M. Nathan M.D.,
Bernard Zinman M.D., and Brandy N Rutledge Ph.D.
for the DCCT/EDIC Research Group

January 3, 2008

A complete list of investigators and members of the Research Group appears in
N Engl J Med 2007; 356:1842-52.)

From: The Biostatistics Center, The George Washington University (J.M. Lachin,
B.N. Rutledge), Rockville, MD; Case Western Reserve University (S.M. Genuth),
Cleveland, OH; Massachusetts General Hospital and Harvard Medical School
(D.M. Nathan), Boston MA; Samuel Lunenfeld Research Institute, Mount Sinai
Hospital, University of Toronto (B Zinman).

Acknowledgment. *The DCCT and EDIC were supported by grants and contracts from the Division of Diabetes, Endocrinology and Metabolic Disease of the National Institute of Diabetes and Digestive and Kidney Diseases and The General Clinical Research Centers Program, National Center For Research Resources. The DCCT was also supported by the National Heart, Lung and Blood Institute and the National Eye Institute.*

Poisson Regression Model. The 1995 report from the DCCT (1) employed Poisson regression models (2) to provide estimates of the absolute risk of retinopathy progression as a function of the level of HbA1c over time, and of time itself. This Appendix provides a description of each model and its implications. In particular we describe the models used to describe the changing risk over time within the conventional and intensive groups presented in Figure 4 of reference (1), and that used to describe the change in risk over time at different levels of HbA1c in each group presented in Figure 6 of reference (1).

The Group by Time Model. To represent these relationships statistically, let g designate treatment group where the intensive (experimental) therapy is represented as $g = 0$ and the conventional (control) as $g = 1$. The groups are also represented as E or C , respectively. Let t denote a point in study time (years) and let A_t denote the updated mean HbA1c at time t . Denote the risk at time t as $\lambda(t)$.

The simplest model in (1) assessed the difference between groups in the effects of time on risk. This is the model displayed in Figure 4 of reference (1) that presents the model coefficients. The model includes effects for group (g), time (t) and their interaction ($g \times t$). Since g is either 0 or 1, this model can be expressed as separate log-linear models in the two groups with coefficients

$$\begin{array}{ll} \text{Experimental:} & \lambda_E(t) = \exp[\alpha_E + \beta_E t] \\ \text{Control:} & \lambda_C(t) = \exp[\alpha_C + \beta_C t] \end{array}$$

where α_E and α_C are the intercepts in each group and β_E and β_C are the slopes. Thus the model assumes that within each group, the risk changes as an exponential function of time. Equivalently, the model assumes that the log risk is a linear function of time. This is a highly simplistic assumption. A positive coefficient for time yields a concave (increasing) function.

The principal issue is whether the underlying Poisson model assumption is an accurate representation of the true relationships. The Poisson model risk estimates over time in the conventional group and intensive groups are shown in **Figure 1**, equivalent to Figure 4 of reference (1). However, at each successive visit a model-free or empirical estimate the underlying risk (hazard rate) at that point in time can be obtained as function of the proportion of subjects with an event at that time. These empirical estimates of the rate at each 6-monthly visit over time are also displayed on the figure. The model coefficients are presented in Figure 4 of (1). This figure shows that in general the model assumption regarding the effect of time is an adequate representation of the patterns of risk over time in the two groups through year 7. However, at year 8 and beyond there is a sharp 3-fold increase in risk in the conventional group that largely determines the marked model-estimated exponential rise in risk over time.

Further analysis comparing the 85 conventional group subjects followed to year 8, of whom 18 subsequently had an event, versus the 644 who did not reach the year 8 visit, indicates that there are marked and highly significant differences between these two subsets. Those followed to 8 years, by definition, were more likely to have been enrolled during the feasibility phase (II) than those followed

for less than 8 years (95 vs 8%), more likely to be adolescents (28 vs 12%) and secondary cohort (60 vs 47%) subjects, had longer duration of diabetes (mean 6.7 vs 5.3 y), longer duration of treatment (9 vs 6 y), and a lower mean HbA1c during the DCCT (mean 8.7 vs 9.1%), all at $p < 0.02$. Similar differences (other than HbA1c) were observed in the intensive group for those followed to 8 years versus not. Thus, some of the changing risk over time in each group is due to differences in patient characteristics among those at risk, especially at 8 or more years in the conventional group.

HbA1c and Time Model. In (1) models were fit separately within each group as presented in Table 8 of reference (1) to assess the effects of HbA1c on risk over time within each group. These models can also be represented in a single model with a group effect, the updated mean HbA1c, time in study, and their two-way interactions and the three way interaction, with coefficients as shown in **Table 1.A**. These coefficients obtained from the combined group model are identical to those presented in Table 8 of (1) that were obtained from separate models within each group. The resulting risk estimates within each group at given levels of HbA1c over time are presented in **Figure 2.A**, adapted from Figure 6 of reference (1) with both groups displayed on the same panel. That analysis suggested that a subject with a given level of HbA1c treated conventionally had a higher risk than a subject at the same level treated intensively. Unfortunately, that model, and the resulting figure are flawed and the resulting disparity between the risks in the intensive and conventional groups is an artifact of the model.

The model in Table 1.A allows for different effects of HbA1c and the interaction of HbA1c and time in the two groups. However, the interaction between group and the updated mean HbA1c is not statistically significant ($p = 0.59$). This indicates that the two separate coefficients for the effect of HbA1c in Table 1.A (3.28 in conventional versus 2.29 in intensive) are not statistically different. Thus, the model could be refit with a single coefficient for HbA1c in the two groups. Likewise, the interaction between treatment group with time and updated HbA1c is not significant ($p = 0.36$), indicating that the model could be refit with a single coefficient for the time by HbA1c interaction in the two groups. **Table 1.B** presents the resulting combined groups reduced model. **Figure 2.B** then presents the resulting risk estimates in the two groups at the same level of HbA1c.

It is remarkable that Figure 2.B is visually indistinguishable from Figure 1.A. The only factors by which the groups differ in Model 1.B and Figure 2.B are the group-specific intercepts and the group-specific time effects. The effect of the mean HbA1c level, and its compounding (interaction) with time, are the same in the two groups. Thus, the differences in risk between groups at a given level of HbA1c in Figure 2.B (and also 2.A) are a reflection of the underlying model-estimated differences in risk over time, not the degree to which the compounding effect of time and HbA1c differs between groups (since it does not). This is further demonstrated by fitting an additional model with a common time effect within the two groups, as shown in **Table 1.C**. The resulting **Figure 2.C** shows no difference between groups at the same level of HbA1c. Thus, the factor that

makes it appear that there is a different risk in the two groups at the same level of HbA1c is not the difference between groups in the product of time and the log mean HbA1c, or a difference in the degree that time compounds the effects of HbA1c, it is the difference between groups in the effect of time itself.

These model artifacts can also be demonstrated statistically. The model presented in Table 1.A that was used to generate Figure 2.A herein, and Figure 6 of reference (1), can be expressed as

$$\begin{aligned} \text{Experimental: } \lambda_E(t) &= \exp[\alpha_E + \beta_{1E}t + \beta_{2E} \ln(A_t) + \beta_{12E} \ln(A_t)t] \\ \text{Control: } \lambda_C(t) &= \exp[\alpha_C + \beta_{1C}t + \beta_{2C} \ln(A_t) + \beta_{12C} \ln(A_t)t] \end{aligned}$$

However, the coefficients for the HbA1c were not statistically different, and neither were those for the interaction of time with the HbA1c. Thus, the model could be simplified with a common coefficient $\beta_{2E} = \beta_{2C} = \beta_2$ for the effect of the HbA1c, and a common coefficient $\beta_{12E} = \beta_{12C} = \beta_{12}$ for the interaction of time with HbA1c to yield

$$\begin{aligned} \text{Experimental: } \lambda_E(t) &= \exp[\alpha_E + \beta_{1E}t + \beta_2 \ln(A_t) + \beta_{12} \ln(A_t)t] \\ \text{Control: } \lambda_C(t) &= \exp[\alpha_C + \beta_{1C}t + \beta_2 \ln(A_t) + \beta_{12} \ln(A_t)t] \end{aligned}$$

The resulting model is presented in Table 1.B and was used to generate Figure 2.B herein.

Consider the change in risk from one year to the next within the conventional (control) group, i.e. from time t to time $t + 1$. The ratio of the risks at these two points in time then is

$$\frac{\lambda_C(t+1)}{\lambda_C(t)} = \frac{\exp[\alpha_C + \beta_{1C}(t+1) + \beta_2 \ln(A_{t+1}) + \beta_{12} \ln(A_{t+1})(t+1)]}{\exp[\alpha_C + \beta_{1C}t + \beta_2 \ln(A_t) + \beta_{12} \ln(A_t)t]}$$

If we assume that the HbA1c is constant over time, i.e. that $A_t = a$ for all values of t , then this reduces to

$$\frac{\lambda_C(t+1)}{\lambda_C(t)} = \exp[\beta_{1C} + \beta_{12} \ln(a)]$$

so that

$$\lambda_C(t+1) = \lambda_C(t) \exp[\beta_{1C} + \beta_{12} \ln(a)] \quad (1)$$

Likewise, in the intensive (experimental) group

$$\lambda_E(t+1) = \lambda_E(t) \exp[\beta_{1E} + \beta_{12} \ln(a)]$$

Thus, within each group, per unit (year) increase in time, for a given (fixed) HbA1c value over time, the model assumes that there is a constant *proportionate* increase in risk as time increases. Again note that the effect of the product of time and HbA1c is not significantly different between groups and the model assumes a common coefficient (β_{12}). Thus, the model assumes that the difference between the groups in the levels of risk over time at a given HbA1c is

wholly attributable to the differences between groups in the effect of time itself, represented by the coefficients β_{1C} and β_{1E} .

Figure 1 shows the overall risk for each group over time that can be considered as the risk for subjects at the average level of HbA1c within each group over time, about 9% in the conventional group and 7% in the intensive group. The derivation shows that for a given HbA1c, the time by HbA1c interaction results in the same proportionate splaying of the risk lines in the two groups as a function of the level of HbA1c. Since the conventional group risk is increasing at a faster exponential rate than the intensive group risk over time, but each curve is splayed to the same relative degree, it follows that the resulting plot *must* show a difference between groups at a given point in time with the same assumed value of the HbA1c. This is simply an artifact of the underlying model assumptions.

In conclusion, the simple Poisson model provides a reasonable description of the changes in risk over time in the two groups (Figure 1.A) but the steepness of the exponential rise in risk over time is in part driven by changes in the characteristics of those followed to 8 years versus those who were followed for less. The Poisson model that includes the interaction between time and log HbA1c can not distinguish between the effects of HbA1c or the product of time and the HbA1c between the two groups (Figures 2.A versus B). The only remaining difference between groups is the effect of time itself. Due to the way that the model is formulated, it follows that the model must show a different risk between groups at a given assumed level of HbA1c. This is an artifact of the model. It was incorrect in (1) to interpret this model as demonstrating that there were additional factors associated with conventional treatment that exacerbated the risk of retinopathy progression above and beyond that contributed by the HbA1c alone.

References.

1. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44: 968-983, 1995.
2. Lachin JM. *Biostatistical Methods: The Assessment of Relative risks*. New York: John Wiley & Sons, 2000.

Table 1. Unadjusted absolute risk (Poisson) regression model coefficient estimates and 95% confidence intervals from models with an interaction between the updated mean HbA1c and time in study. **A.** Separately within each treatment group (Table 8 of reference 1). **B.** From a combined groups reduced model with non-significant group effects and interactions removed. **C.** From a reduced model with a common time effect within the two groups.

Parameter	A. Separate Group Models (DCCT, 1995, Table 8)		B. Combined Groups Reduced Model*		C. Reduced Model with Common Time Effect	
	Conventional	Intensive	Conventional	Intensive	Conventional	Intensive
Intercept	-11.41 (-16.21, -6.62)	-8.52 (-14.38, -2.66)	-10.69 (-14.58, -6.80)	-9.91 (-13.42, -6.39)	-7.72 (-11.01, -4.42)	-7.83 (-11.03, -4.62)-)
Log Mean HbA1c	3.28 (1.18, 5.39)	2.29 (-0.57, 5.16)	2.96 (1.26, 4.67)		1.73 (0.25, 3.22)	
Time	-0.72 (1.76, 0.33)	-1.75 (-3.13, -0.36)	-0.97 (-1.85, -0.10)	-1.19 (-1.99, -0.39)	-1.66 (-2.38, -0.93)	
Log mean HbA1c (%) x time (years)	0.46 (-0.01, 0.92)	0.83 (0.17, 1.50)	0.57 (0.19, 0.95)		0.85 (0.53, 1.18)	

Model includes effects for the intercept and group, resulting in a separate intercept within each group, log Mean HbA1c, time and group*time (resulting in separate time effects within each group), and an interaction between log Mean HbA1c and time. Other interactions were not significant at $p < 0.05$.

Figure 1. Risk of sustained retinopathy progression over time within the intensive and conventional treatment groups obtained from the Poisson models as presented in Figure 4 of (1), along with the empirical estimate of the underlying risk (hazard rate) within each 6-monthly interval.

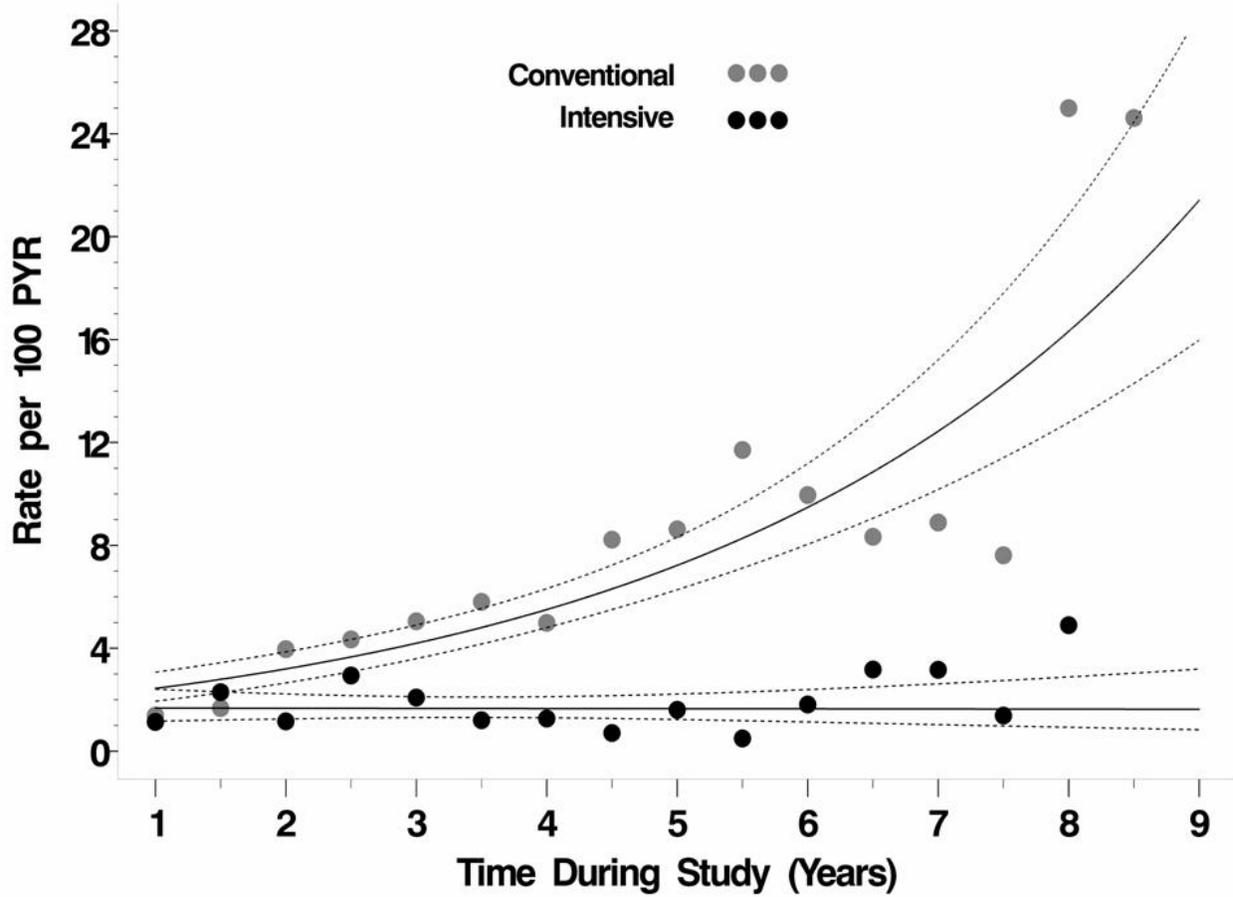
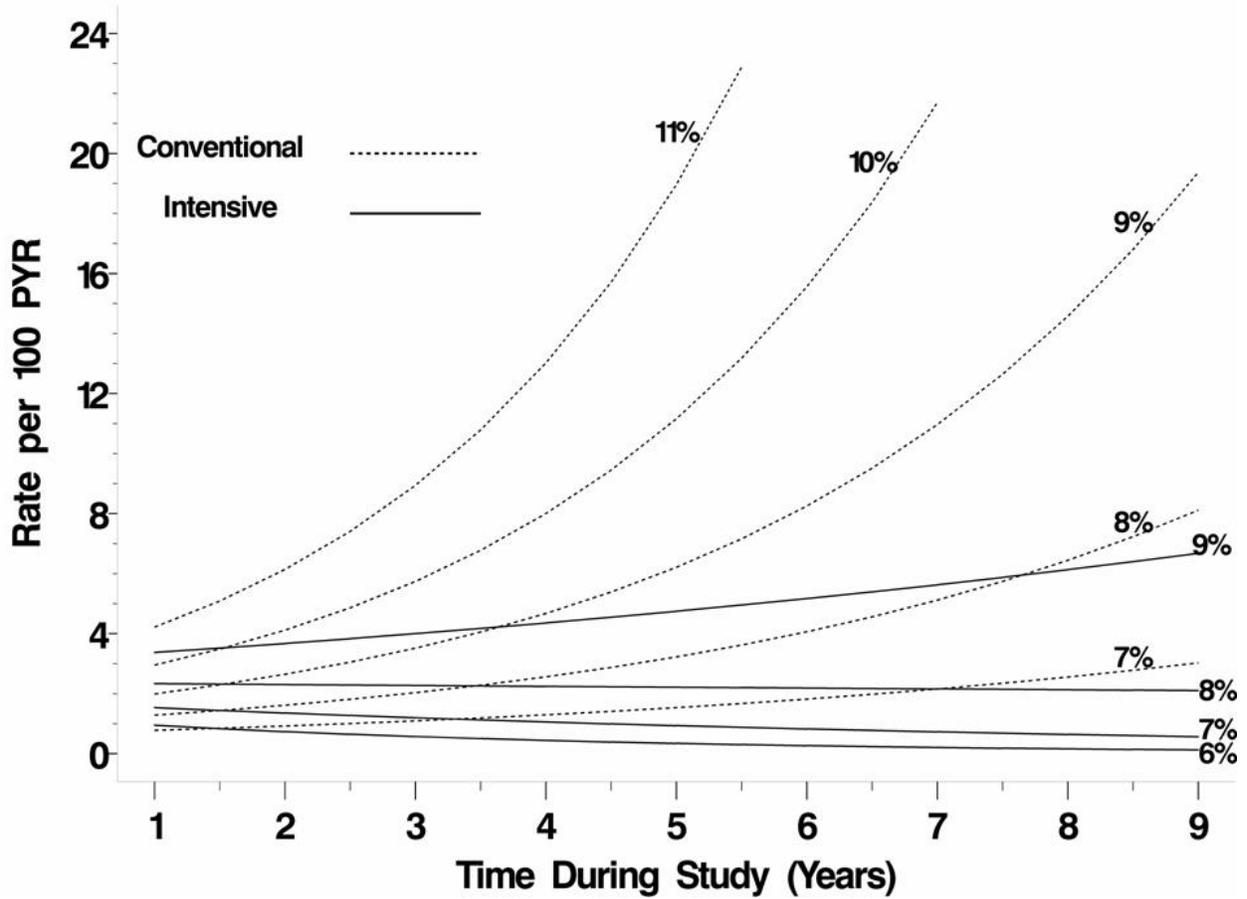
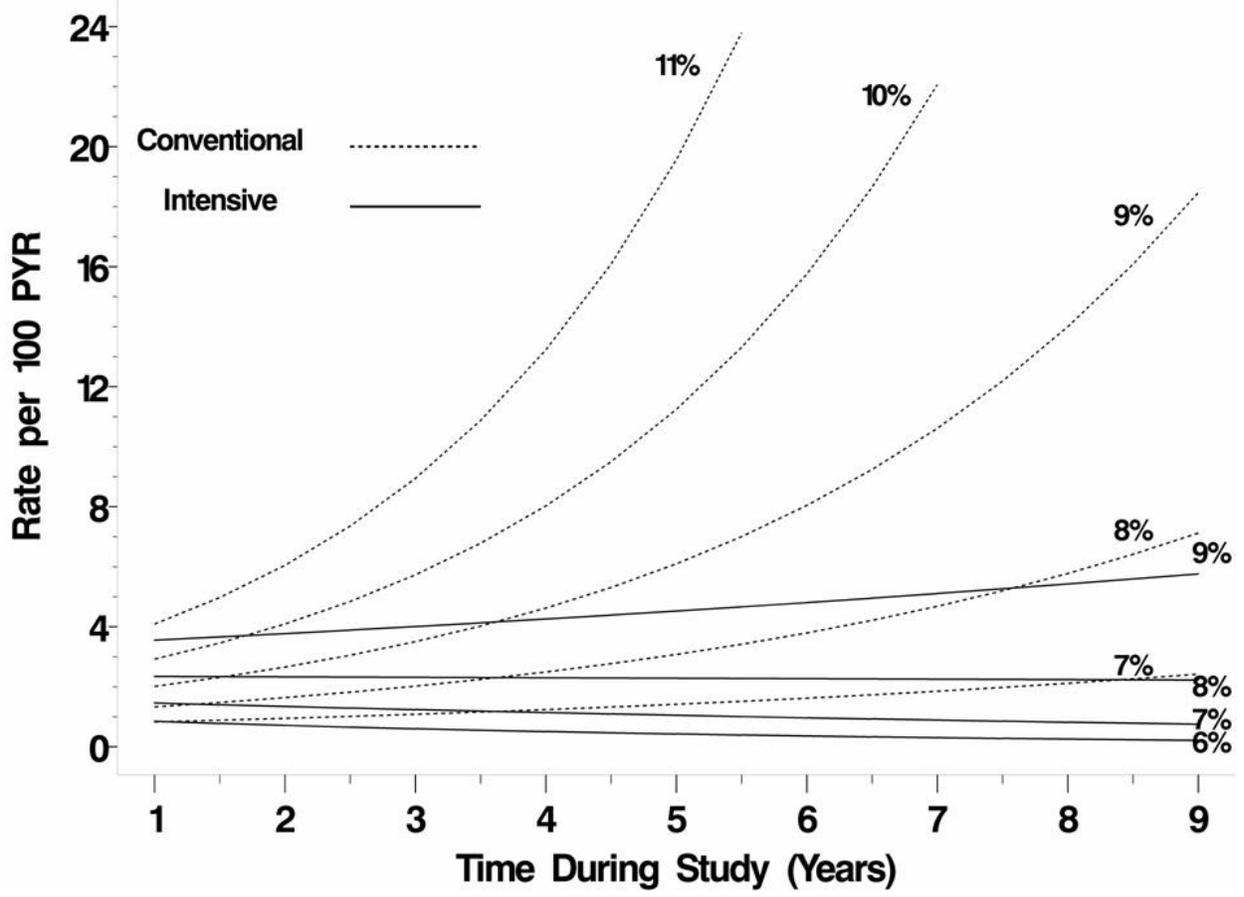


Figure 2. Risk of sustained retinopathy progression at assumed fixed levels of HbA1c over time within the intensive and conventional treatment groups obtained from the Poisson models presented in Table 1: **A.** Separately within each treatment group (DCCT, 1995, Table 8). **B.** From a combined groups reduced model with non-significant group effects and interactions removed. **C.** From a reduced model with a common time effect within the two groups.

A



B



C.

