Effect of Glycemic Exposure on the Risk of Microvascular Complications in the Diabetes Control and Complications Trial—Revisited

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OBJECTIVE—The Diabetes Control and Complications Trial (*Diabetes* 44:968–983, 1995) presented statistical models suggesting that subjects with similar A1C levels had a higher risk of retinopathy progression in the conventional treatment group than in the intensive treatment group. That analysis has been cited to support the hypothesis that specific patterns of glucose variation, in particular postprandial hyperglycemia, contribute uniquely to an increased risk of microvascular complications above and beyond that explained by the A1C level.

RESEARCH DESIGN AND METHODS—We performed statistical evaluations of these models and additional analyses to assess whether the original analyses were flawed.

RESULTS—Statistically, we show that the original results are an artifact of the assumptions of the statistical model used. Additional analyses show that virtually all (96%) of the beneficial effect of intensive versus conventional therapy on progression of retinopathy is explained by the reductions in the mean A1C levels, similarly for other outcomes. Furthermore, subjects within the intensive and conventional treatment groups with similar A1C levels over time have similar risks of retinopathy progression, especially after adjusting for factors in which they differ.

CONCLUSIONS—A1C explains virtually all of the difference in risk of complications between the intensive and conventional groups, and a given A1C level has similar effects within the two treatment groups. While other components of hyperglycemia, such as glucose variation, may contribute to the risk of complications, such factors can only explain a small part of the differences in risk between intensive and conventional therapy over time. ***Diabetes*** **57:995–1001, 2008**

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AER, albumin excretion rate; DCCT, Diabetes Control and Complications Trial; MBG, mean blood glucose; PH, proportional hazards.

The Diabetes Control and Complications Trial (DCCT) (1) previously presented epidemiologic analyses of the effect of glycemic exposure, as measured by the updated mean A1C and time in the trial, on the risk of retinopathy progression. Those analyses established a central role for glycemia in the development and progression of microvascular complications. However, one Poisson regression model analysis (Fig. 6 in ref. 1, Fig. 1 herein) suggested that subjects who maintained similar A1C levels had a higher risk of retinopathy progression over time in the conventional treatment group than in the intensive group. That figure was interpreted to suggest that "Other features of diabetic glucose control, which are not reflected by A1C, may add to or modify the risk of complications. For example, the risk of complications may be more highly dependent on the extent of postprandial glycemic excursions or be influenced by counterregulatory hormonal responses to hypoglycemia (1)."

Recently, this analysis was cited by Brownlee and Hirsch (2), based in part on a small study by Monnier et al. (3), to support the hypothesis that highly variable glucose levels contribute to the increased risk of complications with conventional versus intensive therapy, mediated by oxidative stress and free radical production, beyond that explained by A1C level. However, the prior DCCT analysis in ref. 1 did not directly assess whether subjects at the same A1C level have a higher risk of retinopathy progression with conventional versus intensive therapy. This prompted us to undertake a thorough reexamination of the prior analysis and to conduct additional analyses to provide a more direct answer to this question.

Here, we examine the contribution of the differences in mean A1C levels over time in the two treatment groups to the differences in outcomes and assess quantitatively the proportion of the treatment group effect that is explained by differences between groups in A1C alone. The remainder represents the possible contribution of treatment group differences in other factors, such as glycemic variation or postprandial levels, to treatment group differences in complication risks. Further analyses examine whether subjects within the intensive and conventional group with similar A1C levels have different risks of retinopathy progression when adjusted for other factors in which the groups differ. In an online-only appendix (available at http://dx.doi.org/10.2337/db07-1618), we also present a statistical reassessment of the prior analyses.

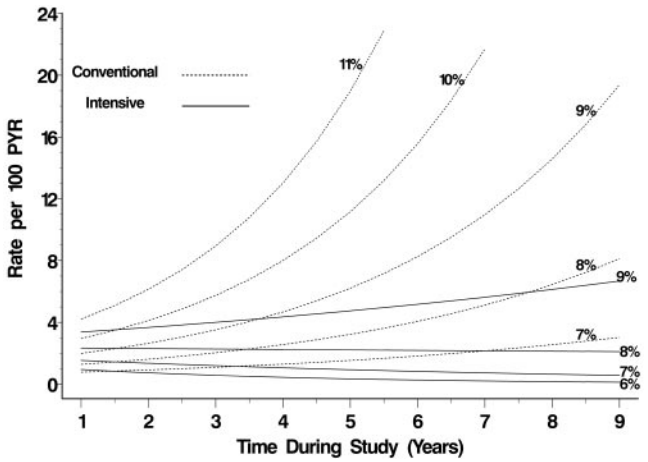

FIG. 1. Risk of sustained retinopathy progression at assumed fixed levels of A1C over time within the intensive and conventional treatment groups. Adapted from Fig. 6 of ref. 1.

RESEARCH DESIGN AND METHODS

DCCT design and methods are described elsewhere (4). Of 1,441 subjects with type 1 diabetes, 711 were randomly assigned to intensive therapy aimed at maintaining glycemic levels as close as possible to the nondiabetic range, and 730 were assigned to conventional therapy with the goal of maintaining clinical well-being with no specific glucose targets.

Two cohorts of subjects were enrolled. The primary prevention cohort of 726 patients had 1–5 years' duration of diabetes with no retinopathy and albumin excretion rate (AER) <40 mg/24 h on study entry. The secondary intervention cohort of 715 patients had 1–15 years of diabetes with minimal to moderate retinopathy and AER <200 mg/24 h.

During the initial feasibility phase 2 period (1983–1984), 278 subjects were enrolled, with an emphasis on recruiting primary cohort subjects and adolescents. The additional 1,163 subjects were enrolled during the full phase 3 (1985–1989) with slightly different eligibility criteria (4).

A1C was measured in all patients quarterly. The updated mean of all quarterly A1C values was computed at each 6-monthly visit. A seven-point profile of capillary glucose values before and 90 min after each meal and at bedtime was also collected quarterly. The blood was collected in Profilsets (Boehringer-Mannheim Diagnostics, Indianapolis, IN), and the hemolysates were analyzed for glucose. The mean blood glucose (MBG) was computed from each quarterly profile, and the updated mean of all profiles was computed up to each 6-monthly visit. All measurements were performed in the DCCT Central Biochemistry Laboratory.

Severity of retinopathy was assessed by fundus photographs obtained every 6 months that were centrally graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) scale (5). Retinopathy progression was defined as a sustained progression of three or more steps from the level at baseline, confirmed on two successive 6-monthly visits. Nephropathy was assessed by annual timed urine collections for measurement of AER. Development of microalbuminuria was defined as an AER ≥40 mg/24 h among those with AER <40 mg/24 h at baseline. Albuminuria was defined as an AER ≥300 mg/24 h.

Statistical methods. Baseline characteristics of the treatment groups were compared using the Wilcoxon's rank-sum test for quantitative variables and the χ^2 or Fisher's exact test for categorical variables. Differences between groups with respect to characteristics over time in the study were compared using longitudinal normal errors repeated-measures linear models (6). A logistic regression model (7) assessed the effects of covariates on the odds of neuropathy at 5 years of follow-up. As in prior analyses (1), Poisson regression models (7) assessed the effects of covariates on the absolute risk of an event over time and the discrete Cox proportional hazards (PH) regression model (8), adjusted for tied event times, assessed the effects of covariates on relative risk. The PH model coefficient estimates were used in conjunction with the Breslow estimate of the background incidence function (8) to provide an estimate of the covariate-adjusted cumulative hazard function.

The strength of the effect of a covariate was described using the entropy R^2 in a logistic regression model (7) or Madalla's R^2 in a Poisson or PH regression model (7). The proportion of the DCCT treatment group effect explained by differences in other factors between groups was computed as the proportion reduction in the likelihood ratio χ^2 test value for treatment group after adjustment for the factor, relative to that without adjustment for the factor.

Analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC) and S-Plus version 7.0 (Insightful Corporation (1988–2005), Seattle, WA). Effects nominally significant at $P \leq 0.05$ are cited.

RESULTS

There were no significant differences between treatment groups in baseline characteristics except for a slightly greater level of retinopathy in the conventional group ($P < 0.01$) (Table 1). For each subject, the mean A1C over all quarterly visits was computed for that subject's period of follow-up, averaging 6.5 years. The average within-subject mean A1C was 9.1% in the conventional versus 7.2% in the intensive group ($P < 0.001$). (Table 1). Among those in the conventional group, 31% had a mean A1C between 8.5 and 9.49% versus 5% of the intensive group. Conversely, among those in the intensive group, 50% had a mean A1C between 6.5 and 7.49% versus 8% of the conventional group. Almost exactly 23% of intensive and conventional group subjects had a mean A1C between 7.5 and 8.49%.

Reassessment of the effect of retinopathy risk within groups. The DCCT previously presented separate Poisson absolute risk models of the overall increases in risk over time within the conventional and intensive treatment groups (Fig. 4 in ref. 1) and additional models of the changes in risk over time within each group at specific A1C levels (Fig. 6 in ref. 1). Additional Poisson models and statistical derivations are presented in the online-only appendix to show that these reported results in ref. 1 are misleading and incorrect.

In summary, the exponentially increasing risk in the conventional group over time, displayed in Fig. 4 of ref. 1 is an artifact of the Poisson model that specifies that the log of the risk increases as a linear function of time. This is the only type of relationship that the model can describe accurately, just like a simple linear regression can only describe a straight line relationship between two variables, regardless of the true relationship. Further analysis shows that the steep curvature in the conventional group is largely driven by a threefold increase in the incidence at 8 years of follow-up, compared with prior years. This jump in risk at 8 years and beyond is attributable in part to important covariate differences between those followed for 8 or more years versus those followed for less than 8 years. (See the online-only appendix for details.)

Figure 6 of ref. 1, reproduced as Fig. 1 herein, was generated from separate Poisson models for each treatment group that include effects for time, the log of the updated mean A1C, and the interaction (product) of time and logA1C, as shown in Table 8 of ref. 1. The latter interaction was interpreted in ref. 1 to represent the compounding effects of time and A1C within each group. These separate models can also be obtained from a single model for the two combined groups with added effects for treatment group and group-specific effects for time, A1C, and their product. However, in this model there is no statistical difference between groups in the effects of A1C or the interaction of time and A1C. Refitting the model with a common effect for A1C and the time by A1C interaction in the two groups, but separate effects for time, yields a figure that is indistinguishable from that in Fig. 1 (Fig. 2.A of the online-only appendix). Thus, the figure does not represent a differential effect of compounding of time and A1C; rather, it reflects the difference between groups in the model-assumed log-linear effects of time itself.

If there is a difference between groups in the effects of time, but no difference between groups in the effects of A1C or the product of time and the A1C, then statistical

TABLE 1
Distribution of characteristics at baseline and during follow-up to the time of retinopathy progression or the last visit during the study

	Conventional	Intensive	*P*
n	729	711	
Cohort			NS
Primary prevention	378 (51.9)	348 (48.9)	
Secondary intervention	351 (48.1)	363 (51.1)	
Retinopathy level (secondary cohort only) (%)			0.01
Level 20 (microaneurysms only)	203 (57.8)	249 (68.6)	
Level 30 (mild NPDR)	110 (31.3)	82 (22.6)	
Level 40 (moderate NPDR)	38 (10.8)	32 (8.8)	
Phase of entry (%)			NS
2: feasibility (1983–1984)	132 (18.1)	146 (20.5)	
3: full scale (1985–1989)	597 (81.9)	565 (79.5)	
Age (years)	26.5 ± 7.1	27.1 ± 7.1	NS
Caucasian race	703 (96.4)	686 (96.6)	NS
Male	394 (54.0)	366 (51.5)	NS
Duration of type 1 diabetes (years)			
Primary cohort	2.6 ± 1.4	2.6 ± 1.4	NS
Secondary cohort	8.6 ± 3.7	8.9 ± 3.8	NS
A1C (%)			
Eligibility screening	9.1 ± 1.6	9.1 ± 1.6	NS
During follow-up	9.1 ± 1.3	7.2 ± 0.9	<0.001
Categories (%)			
<6.5	7 (1.0)	136 (19.1)	<0.001
6.5–7.5	61 (8.4)	357 (50.2)	<0.001
7.5–8.5	171 (23.5)	163 (22.9)	NS
8.5–9.5	229 (31.4)	34 (4.8)	<0.001
≥9.5	261 (35.8)	21 (3.0)	<0.001
MBG (mmol/l)			
Baseline	12.8 ± 4.4	13.0 ± 4.6	0.60
During follow-up	12.9 ± 2.7	8.6 ± 1.6	<0.001
Duration of treatment (years)	6.4 ± 1.6	6.5 ± 1.6	NS

Data are *n* (%) or means ± SE. NPDR, nonproliferative diabetic retinopathy.

derivations show that the resulting plot of risk over time at a given A1C must show different risks within the two groups. This is an artifact of the model just as the exponential rise in risk within the conventional group is an artifact of the model. We now present two additional sets of analyses to assess the extent to which the treatment group differences in A1C explain the differences in risk of complications and whether there is a difference in risk between groups among subjects who achieved like levels of A1C during the study.

Explanation of the effect of DCCT treatment group. The DCCT (Fig. 3 in ref. 1) also presented a relative risk PH model in the combined groups, adjusted for the baseline level of retinopathy and glycemia, in which there is a 42% decrease in risk of retinopathy progression per 10% reduction in the updated mean A1C that explains R^2 = 10.6% of the variation in risk. That result was verified using PH models in ref. 1. There was no difference in the A1C effect between groups even though the groups differed by ~2% in the mean A1C (%) during the study. Table 2 shows the percentage of the treatment group effect on various outcomes in PH models that is explained by the differences in the updated mean A1C between groups.

In the combined cohorts, intensive therapy reduced the risk of sustained progression of retinopathy by 73% compared with conventional therapy after adjusting for the retinopathy level on entry and the pre-DCCT level of hyperglycemia (screening A1C). The test of the treatment group effect has a χ^2 test value of 96.7 that explains R^2 = 6.6% of the variation in risk. After adjustment for the current updated mean A1C for each subject as a time-dependent covariate, the treatment group effect is reduced to $\chi^2 = 3.72$, which is not statistically significant at $P < 0.05$. This represents a 96.2% reduction in the treatment group χ^2 test value. Thus, DCCT treatment group alone explains 6.6% of the variation in the risk of retinopathy progression in the cohort, and the difference between groups in the current mean A1C explains 96.2% of this treatment group effect, i.e., virtually all of the treatment effect.

Likewise, Table 2 presents the risk reduction with intensive versus conventional treatment for other outcomes in the combined DCCT cohort, the test of significance of the treatment group effect, the proportion of variation in risk explained (R^2), and the percentage of the treatment group effect that in turn is explained by the differences in mean A1C during the DCCT. For each complication other than clinically significant macular edema, there is a significant treatment effect. The risk reductions presented herein differ from those in prior publications owing to the adjustment for the pre-DCCT A1C and duration of diabetes. While treatment group alone does not explain a large fraction of the variation in risk (R^2 values ranging from 1 to 7%), virtually all of the treatment effect is explained by the difference in current DCCT mean A1C values during the study.

Direct comparison of treatment groups with similar A1C levels. Separate analyses were also conducted comparing the treatment groups among subjects who maintained a mean A1C during the DCCT in the intervals of 6.5–7.49, 7.5–8.49, and 8.5–9.49%. Within each of these subgroups, the intensive versus conventional group sub-

TABLE 2
Adjusted risk reduction (95% CI) with intensive versus conventional treatment in the combined primary and secondary cohorts of the DCCT; the likelihood ratio χ^2 test statistic values, P values, and R^2 values for the group effect; and the percentage of the group χ^2 value explained by the log of the current mean A1C

	Risk reduction (%) (95% CI)	χ^2 test	P	R^2	% Explained by A1C
Retinopathy*					
Single three-step progression	57 (48–65)	78.3	<0.0001	5.3	95.8
Sustained three-step progression	73 (65–80)	96.7	<0.0001	6.6	96.2
SNPDR	64 (42–77)	21.0	<0.0001	1.4	99.9
Any laser	61 (34–77)	13.6	0.0003	0.9	99.5
CSME	29 (−5 to 52)	3.0	0.084	0.2	99.9
Nephropathy†					
Microalbuminuria‡	40 (23–53)	16.2	<0.0001	1.1	99.2
Albuminuria	59 (28–77)	10.0	0.0016	0.7	96.7
Neuropathy at 5 years§	68 (50–80)	27.8	<0.0001	3.9	91.8

*From a relative risk (hazards) estimate in a PH model stratified by the ETDRS level of retinopathy at baseline and adjusted for the pre-DCCT glycemic exposure represented by the preexisting duration of diabetes separately for the primary and secondary cohorts and the level of log(A1C) on eligibility screening. †From a PH model adjusted for primary vs. secondary cohort on entry, the log(AER) on entry, and the pre-DCCT glycemic exposure. Microalbuminuria is AER >40 mg/24 h, albuminuria AER >300 mg/24 h. ‡Subjects with microalbuminuria on entry deleted from analysis. §From an OR in a logistic regression of odds, adjusted for primary vs. secondary cohort and the pre-DCCT glycemic exposure represented by the preexisting duration of diabetes separately for the primary and secondary cohorts, and the level of log(A1C) on eligibility screening. CSME, clinically significant macular edema; SNPDR, severe nonproliferative diabetic retinopathy.

jects differed in many respects at baseline and in the levels of A1C or MBG, or the duration of treatment, during the study (Table 3).

Among those with a mean A1C in the interval of 6.5–7.49%, containing 61 conventional and 357 intensive group subjects, with respective mean A1C levels of 7.1 and 7.0% during the DCCT, the relative risk (conventional-to-intensive) of sustained retinopathy progression without adjustment for other characteristics is 0.93 (95% CI 0.32–2.66; $P = 0.8851$), there being no difference in risk between groups. After adjustment for the updated mean A1C and MBG and other factors by which the groups differed at $P \leq 0.05$ (Table 3), there remains no difference between groups. Figure 2*A* presents the covariate-adjusted cumulative incidence with a relative risk estimate of 1.02 (95% CI 0.30–3.45; $P = 0.9811$).

Among those with a mean A1C in the interval of 7.5–8.49%, containing 171 conventional and 163 intensive group subjects, with respective mean A1C levels of 8.0 and 7.9%, the unadjusted relative risk is 1.06 (95% CI 0.58–1.93; $P = 0.8582$). Adjusting for the updated mean A1C and MBG and other factors by which the groups differed at $P \leq 0.05$ (Table 3), the relative risk is 1.02 (0.44–2.37; $P = 0.9712$) (Fig. 2*B*).

Among those with a mean A1C in the range of 8.5–9.49%, without adjustment for other factors, the 229 conventional group subjects with a mean A1C of 9.0% had a 1.74-fold higher risk (95% CI 0.83–3.65, $P = 0.1448$) than that of the 34 intensive group subjects with mean A1C of 8.9%. Compared with the conventional group (Table 3), the intensive group subjects included a lower fraction recruited during the phase 3 recruitment phase, with a higher fraction being adolescents with a lower mean age, with a higher eligibility mean A1C and baseline MBG, but with a lower overall mean MBG during the study (all $P \leq 0.05$). After adjusting for these factors (Fig. 2*C*), the cumulative incidence of sustained retinopathy progression was not significantly different between the treatment groups (relative risk 1.08 [95% CI 0.44–2.64]; $P = 0.8669$). There were too few conventional group subjects with a mean A1C <6.5% and too few intensive subjects with a mean A1C >9.5% to permit reliable analysis (Table 1).

DISCUSSION

Previously published analyses from the DCCT presented in Fig. 6 of ref. 1 (Fig. 1 herein) suggested that, at the same level of A1C, subjects treated conventionally had a higher risk of complications than those treated intensively. The online-only appendix of this article presents a statistical assessment to show that the results of that analysis are a statistical artifact of the Poisson model used to perform the analyses and are incorrect.

In this article, we present new analyses to describe *1*) the extent to which the reduced risk of complications with intensive versus conventional therapy is explained by the differences in the mean A1C between treatment groups during the DCCT and *2*) whether subjects with the same level of A1C in the conventional treatment group have a higher risk of retinopathy progression over time as compared with those in the intensive treatment group.

Explained group effect. In a time-to-event PH model, the R^2 is proportional to the magnitude of the χ^2 test value, which represents the strength of the effect of a covariate on risk. Compared with other models, such as the logistic regression model, the R^2 in a PH model is lower because the PH model is attempting to predict when a subject will have an event, not just whether a subject will have an event.

Intensive therapy reduced the risk of sustained retinopathy progression, the primary DCCT outcome, by 73%, the effect being highly statistically significant and clinically compelling. This treatment group effect explained 6.6% (R^2) of the variation in risk among subjects. Virtually all (96%) of this treatment group effect on the risk of the primary outcome is explained by the differences between treatment groups in the level of the mean A1C over time (Table 2). Similar results are seen with the intensive versus conventional treatment group effect on the risk of other outcomes during the DCCT. Thus, glycemic variation and other measures of glycemia, on their own or through an intercorrelation with A1C, and other biological mechanisms independent of glycemia, such as hypertension, may be predictive of risk of complications and may explain some of the treatment group effect on complications.

TABLE 3
Characteristics of intensive and conventional treatment group subjects with a mean A1C in the intervals 6.5–7.49, 7.5–8.49, and 8.5–9.49% during the DCCT

	DCCT updated mean A1C								
	6.5–7.49%			7.5 - 8.49%			8.5–9.49%		
	Conventional	Intensive	*P*	Conventional	Intensive	*P*	Conventional	Intensive	*P*
n	61	357		171	163		229	34	
Cohort			0.7118			0.6596			0.6353
Primary prevention	28 (45.9)	173 (48.5)		87 (50.9)	79 (48.5)		111 (48.5)	15 (44.1)	
Secondary intervention	33 (54.1)	184 (51.5)		84 (49.1)	84 (51.5)		118 (51.5)	19 (55.9)	
Age (years)	27.8 ± 6.5	28.1 ± 6.6	0.5863	27.5 ± 6.4	25.8 ± 7.8	0.0508	26.8 ± 6.8	20.8 ± 6.2	0.0000
Adolescents	3 (4.9)	28 (7.8)	0.5982*	13 (7.6)	35 (21.5)	0.0003	28 (12.2)	14 (41.2)	0.0000
Phase 3	52 (85.2)	289 (81.0)	0.4240	147 (86.0)	130 (79.8)	0.1316	177 (77.3)	20 (58.8)	0.0205
Duration of treatment (years)	6.2 (1.5)	6.5 (1.6)	0.0672	6.3 (1.5)	6.4 (1.7)	0.7694	6.5 (1.7)	7.2 (1.7)	0.0380
Caucasian	61 (100.0)	347 (97.2)	0.3699*	168 (98.2)	155 (95.1)	0.1065	219 (95.6)	31 (91.2)	0.2279*
Duration of type 1 diabetes (years)	6.4 ± 4.6	5.8 ± 4.2	0.4378	6.0 ± 4.3	5.6 ± 4.1	0.4012	5.5 ± 4.1	5.3 ± 3.5	0.8448
Male sex	35 (57.4)	186 (52.1)	0.4455	88 (51.5)	73 (44.8)	0.2222	134 (58.5)	19 (55.9)	0.7715
A1C at eligibility (%)	7.9 (1.0)	9.0 (1.4)	0.0000	8.2 (1.0)	9.6 (1.4)	0.0000	9.0 (1.5)	10.6 (1.7)	0.0000
DCCT updated mean A1C (%)†	7.1 (0.3)	7.0 (0.3)	0.0155	8.0 (0.3)	7.9 (0.3)	0.0011	9.0 (0.3)	8.9 (0.3)	0.1395
MBG at baseline (mmol/l)	10.4 (3.4)	12.8 (4.4)	0.0001	11.3 (3.8)	13.2 (4.4)	0.0000	12.5 (4.0)	16.4 (4.8)	0.0000
DCCT updated MBG (mmol/l)	9.8 (1.6)	8.3 (1.1)	0.0000	11.3 (1.5)	9.5 (1.4)	0.0000	12.5 (1.8)	10.2 (1.9)	0.0000
Baseline retinopathy			0.8987*			0.5078			0.1224*
No retinopathy	28 (45.9)	173 (48.5)		87 (50.9)	79 (48.5)		111 (48.5)	15 (44.1)	
Micro-aneurysm	21 (34.4)	120 (33.6)		50 (29.2)	59 (36.2)		64 (27.9)	15 (44.1)	
Very mild NPDR	8 (13.1)	47 (13.2)		24 (14.0)	18 (11.0)		42 (18.3)	2 (5.9)	
≥Moderate NPDR	4 (6.6)	17 (4.8)		10 (5.8)	7 (4.3)		12 (5.2)	2 (5.9)	
Nephropathy			0.5444*			0.0228			1.0000*
AER <40	57 (93.4)	339 (95.0)		168 (98.2)	152 (93.3)		218 (95.2)	33 (97.1)	
(40≤AER<300)	4 (6.6)	18 (5.0)		3 (1.8)	11 (6.7)		11 (4.8)	1 (2.9)	
Presence of clinical neuropathy	3 (5.5)	19 (6.0)	1.0000*	20 (13.2)	15 (10.9)	0.5514	30 (15.2)	5 (17.9)	0.7797*

Data are *n* (%) and means ± SE. **P* values from Fisher's exact test, where noted. Otherwise, χ^2 test for proportions or Wilcoxon's rank-sum test for individual quantitative variables. Longitudinal normal error models were used for the updated MBG and updated mean A1C. †For each subject the mean over all quarterly follow-up visits was computed. Then the group mean was computed from the subject means. ‡From a 1-day, seven-point capillary collection.

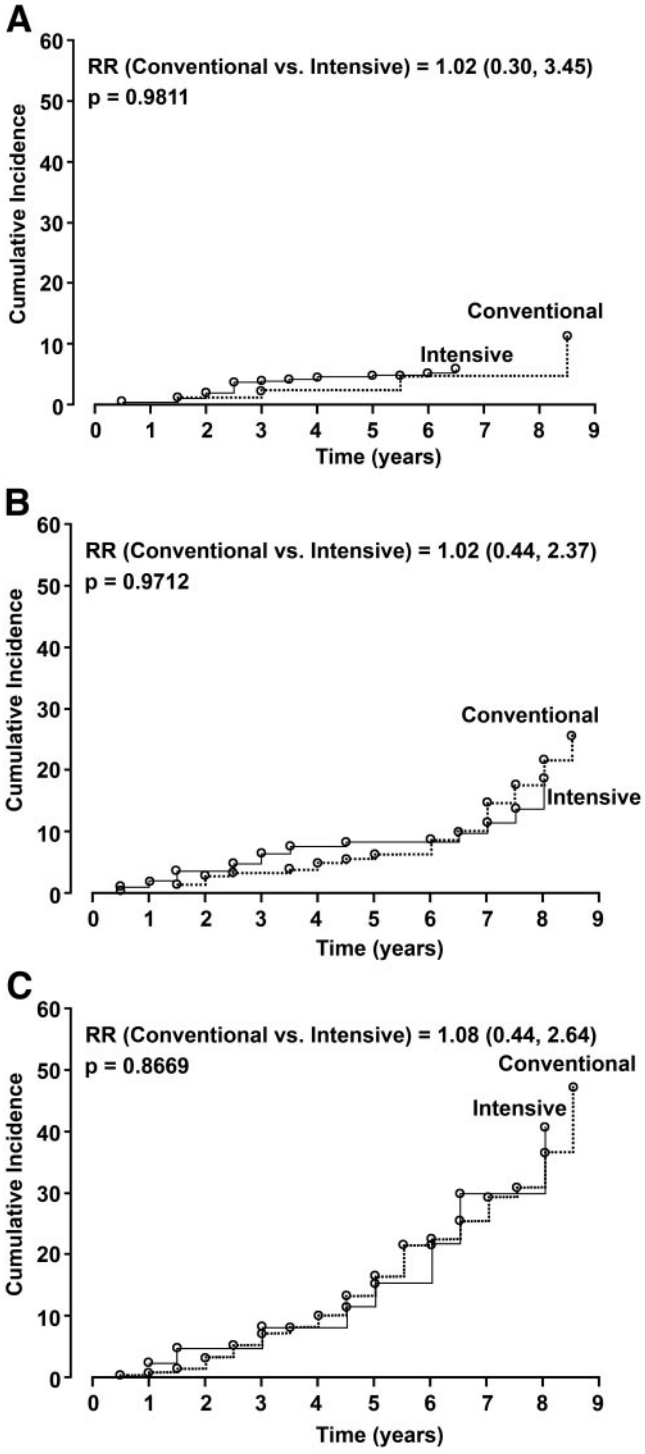

FIG. 2. Cumulative incidence of sustained retinopathy progression within the intensive and conventional treatment groups obtained from a PH regression model among subjects with a mean A1C during the DCCT within specific ranges: 6.5–7.49% (*A*), 7.5–8.49% (*B*), and 8.5–9.49% (*C*). Each model is adjusted for the updated current mean A1C over time and the other covariates shown in Table 3 that are significantly different between groups at $P \leq 0.05$.

However, when examined in combination with the A1C, such factors can only explain a small part of the differences in risk between the intensive and conventional groups during the DCCT. Whether glucose variability via oxidative stress could contribute to or mediate the difference between treatment groups in the risk of complications, independent of A1C, is speculative (2,3).

Furthermore, the adjustment for the updated mean A1C in these analyses provides an estimate of the treatment group difference in the risk of a complication under the hypothetical assumption that there is no difference in A1C. For all of the outcomes assessed in Table 2, the A1C-adjusted group effect is small and not statistically significant. These results show that the initial DCCT analyses presented in Fig. 1 are incorrect.

However, the total glycemic exposure (A1C and duration of diabetes) explains only ~11% of the variation in retinopathy risk in the complete cohort (Table 9 of ref. 1), so that other factors may presumably explain the remaining 89% of the variation in risk among subjects independent of A1C. Thus, other mechanisms, including environmental and genetic factors, may be additional determinants, independent of the A1C, of the overall risk of complications in individual subjects, regardless of the treatment group assignment.

Is there excess risk with conventional therapy over time? In the prior publication (1), absolute risk (Poisson regression) models (Fig. 6 of ref. 1, Fig. 1 herein) suggested that at the same constant level of A1C over time, conventional treatment group subjects had a higher risk of complications than those in the intensive treatment group. However, those analyses did not directly compare subjects in the two treatment groups with similar levels of A1C over time, nor did they account for the multitude of factors on which subjects in the two groups differed at the same level of A1C. Thus, further analyses were conducted to assess the differences between groups using PH (relative risk) models in subgroups of subjects with mean A1C values over the duration of the DCCT in the ranges of 6.5–7.49, 7.5–8.49, and 8.5–9.49%.

Within the first two A1C strata, there were no differences in risk of sustained retinopathy progression between the treatment groups without or with adjustment for other covariates (Fig. 2*A* and *B*). Within the 8.5–9.49% stratum, there was a nonsignificant ($P = 0.15$) 1.7-fold greater risk among the 229 conventional group subjects than among the 34 intensive group subjects. However, there were substantial differences between these two treatment groups of subjects within this A1C stratum (Table 3), including a 0.1% higher mean level of A1C over time and 2.3 mmol/l higher mean capillary glucose over time in the conventional group. A higher fraction of intensive subjects entered during phase 2, while a higher fraction of conventional group subjects entered in phase 3. Phase 2 was the feasibility phase of subjects entered during 1983–1984 with potential follow-up from 9–10 years before study closeout in 1993; phase 3 was the full-scale recruitment from 1985–1989 with potential follow-up of 4–8 years. Finally, the intensive group subjects in this A1C stratum were significantly younger and had a higher percentage of adolescents. After adjusting for all of these factors, there was no meaningful difference in risk (Fig. 2*C*, relative risk 1.08, $P = 0.8669$).

Recently, Kilpatrick (9), in an independent analysis of the publicly available DCCT data, showed that conventional treatment DCCT subjects had consistently higher MBG concentrations than intensive treatment subjects at any given A1C value. The authors suggested that this might explain the purportedly higher risk of complications with conventional versus intensive therapy at given levels of A1C suggested in Fig. 6 of ref. 1. However, other analyses have shown that mean blood glucose does not add sub-

stantially to the predictive risk above and beyond that provided by the A1C (10,11).

Glycemic variation and complications. Brownlee and Hirsch (2), among others, have suggested that glycemic variation, or diurnal excursions in blood glucose, may explain a portion of the risk of complications independent of that contributed by the mean A1C. Indeed, the DCCT authors interpreted the original Fig. 6 of the prior publication (1) to imply that such mechanisms might exist. However, the analyses herein show that such mechanisms could account for very little, if any, of the difference between intensive versus conventional treatment on risk of complications above and beyond that explained by the A1C. Furthermore, Service and O'Brien (10) and Kilpatrick et al. (11) have conducted additional, independent analyses of the DCCT data to relate measures of variation in quarterly blood glucose profiles to the risk of developing complications. Neither analysis was able to demonstrate an independent effect of glucose variation on the risk of complications in the DCCT; however, both studies showed the risk to increase with MBG, though not independently of the A1C.

In conclusion, the apparent differences over time in risk of retinopathy between the DCCT intensive and conventional treatment groups at the same level of A1C suggested in Fig. 6 of the prior article (1) are an artifact of the Poisson regression model assumptions and reflect, in part, a cohort effect among those followed to 8 or more years versus those followed for less than 8 years (online-only appendix). The differences between the intensive and conventional treatment groups in the levels of A1C explain virtually all of the treatment group effect on complications. While other components of hyperglycemia, such as glucose variation, may contribute to the risk of complications in those with type 1 diabetes, such factors can only explain a small part of the differences in risk between intensive and conventional therapy over time. Furthermore, when subsets of subjects at similar levels of A1C are compared between groups, there is little difference in risk after adjusting for those factors in which the subsets of subjects differ between groups. Thus, our prior suggestion (1) that subjects treated conventionally have a higher risk of complications over time than those treated intensively at the same level of A1C is incorrect.

Although the prior analyses of the effects of A1C over time in ref. 1 were flawed, it is important to emphasize that the prior analysis of the effects of the mean A1C itself on complications in ref. 1 are indeed correct, as verified by parallel analyses using PH regression models in ref. 1, and through model-free analyses as described in ref. 12. The dominant determinant of the reduction in the risk of progression of complications in the DCCT with intensive versus conventional therapy is the difference between groups in the mean level of A1C. Thus, the original recommendations of the DCCT still apply—that subjects with type 1 diabetes should be treated intensively, as early and as safely as possible, with the goal of maintaining levels of glycemia as close to normal as safely possible

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