SUPPLEMENTARY DATA

Details of Complication Ascertainment in the Epidemiology of Diabetes Complications (EDC) Study

Participants were followed for 25 years to ascertain incidence of complications, including proliferative diabetic retinopathy (PDR), microalbuminuria (MA), overt nephropathy (ON), end-stage renal disease (ESRD), coronary artery disease (CAD), and confirmed distal symmetric polyneuropathy (CDSP). The assessment of PDR has been described in detail elsewhere (Klein, 1986). Stereoscopic color fundus photographs of three standard fields (1, 2, and 4) with a Zeiss camera (Carl Zeiss, Oberkochen, Germany), taken after pupil dilation. Photos were graded using a modification of the Early Treatment Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie House classification of PDR (ETDRS Reports 10 and 12, 1991). Grading of stereoscopic fundus photographs was performed at the Fundus Photograph Reading Center at the University of Wisconsin-Madison. PDR was defined as ETDRS score ≥60 or laser photocoagulation for PDR.

Urinary albumin was measured by immunonephelometry (Ellis, 1977). Albumin excretion rate (AER) was calculated for each of three timed urine samples (24-hour, overnight, and 4-hour collections obtained over a two-week period). MA was defined as albumin excretion rate (AER) >20 μg/min in 2 of 3 timed urine samples, renal failure, or renal transplantation and ON was defined as AER >200 μg/min in 2 of 3 timed urine samples, renal failure, or renal transplantation. ESRD was ascertained by self-report of dialysis or renal transplantation.

CAD was defined as the first instance of CVD death, nonfatal myocardial infarction (MI, including clinical events and subclinical myocardial infarction on ECG, i.e. Minnesota code 1.1 or 1.2), coronary revascularization procedure, blockage ≥50%, ischemic EGC at EDC study visit (Minnesota codes 1.3, 4.1-4.3, 5.1-5.3, 7.1), or EDC physician-diagnosed angina. Fatal events were ascertained using medical records, death certificates, autopsy reports, and/or interview with next of kin and classified according to the Diabetes Epidemiology Research International (DERI) system (DERI Mortality Study Group, 1991). Nonfatal MI, stroke, coronary revascularization, and blockage were confirmed with medical records.

CDSP was defined as experiencing at least two out of three of the following: symptoms consistent with distal symmetric polyneuropathy; sensory and/or motor signs; and absent/reduced tendon reflexes based on the Diabetes Control and Complications Trial clinical examination protocol (Feldman, 1994), in addition to an abnormal age-specific vibratory threshold using the Vibratron II Tester (Physitemp Instruments, Clifton, NJ, USA).

References:

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Ellis D, Buffone GJ. New approach to evaluation of proteinuric states. Clin Chem. 1977;23(4):666–70.

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Klein R, Klein BE, Magli YL, Brothers RJ, Meuer SM, Moss SE, et al. An alternative method of grading diabetic retinopathy. Ophthalmology. 1986;93(9):1183–7.

SUPPLEMENTARY DATA

Weibull Regression: Additional Details

To determine whether the published cumulative incidences of proliferative retinopathy, overt nephropathy, and cardiovascular disease in DCCT/EDIC differ from what would be expected based on A1c Months exposure, we estimated the cumulative incidence of each complication across the range of A1c months using Weibull regression within the DCCT-comparable subgroup of the EDC cohort. The Weibull distribution is a commonly used distribution for parametric modeling of survival data. In our models, A1c months was used as the time scale, rather than diabetes duration or follow-up time. The Weibull distribution has the property that the log-log of survival is linear with the log of time. Thus, we confirmed than this assumption held for each complication by plotting log-log survival curves against log (A1c Months) using PROC LIFETEST in SAS 9.4 (SAS Institute Inc., Cary, NC). Weibull accelerated failure time models were then fit for each complication, with A1c Months as the time scale, using PROC LIFEREG (SAS 9.4, SAS Institute Inc., Cary, NC). Using the regression coefficients, the estimated cumulative incidence of each complication was calculated at 534 and 729 A1c Months (the means observed in the DCCT/EDIC Intensive and Conventional treatment arms, respectively, at EDIC Year 8) and compared to the published cumulative incidences at 20 years' diabetes duration in DCCT/EDIC (DCCT/EDIC Research Group, 2009). As the published DCCT/EDIC results were based on unadjusted models, we have also not adjusted for covariates in the current analyses.

Reference:

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration. Arch Intern Med. 2009; 169(14): 1307-16.

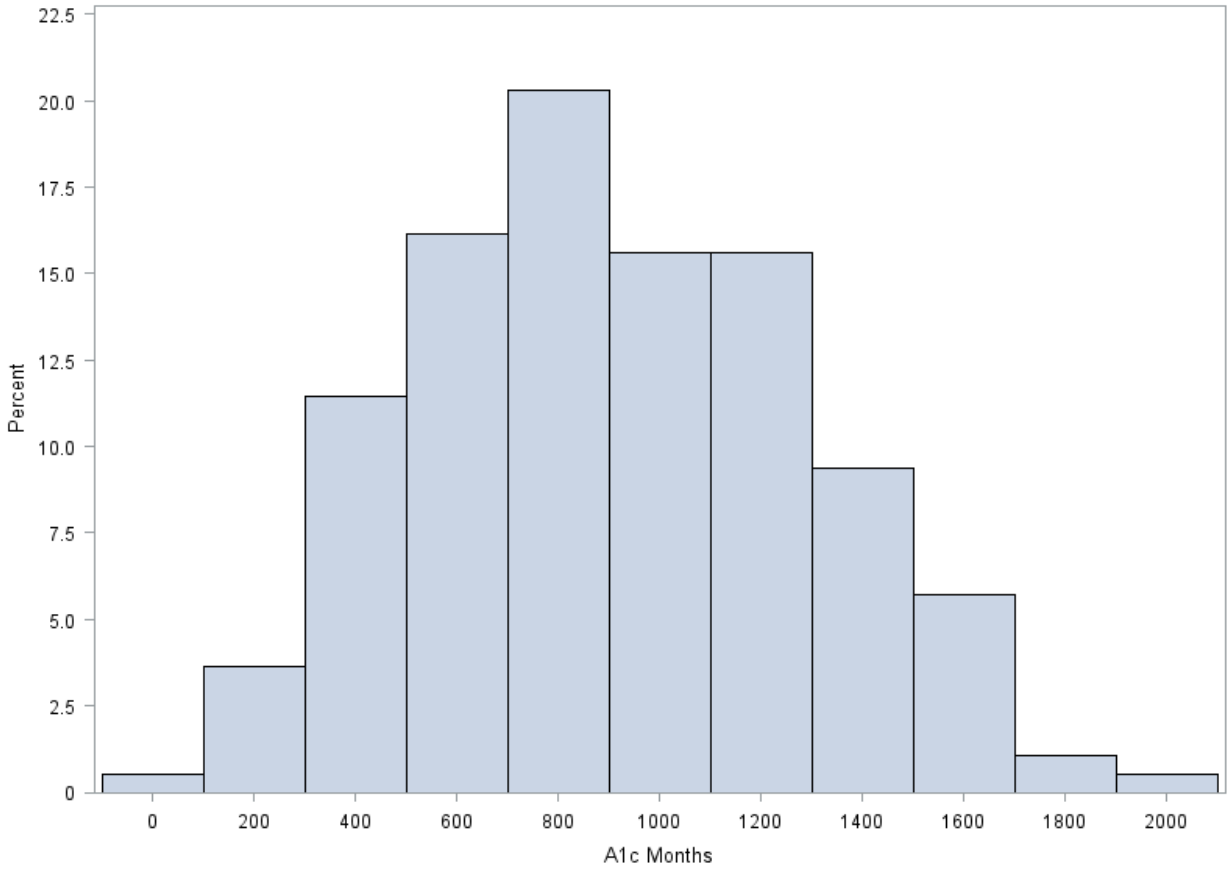
SUPPLEMENTARY DATA

Supplementary Figure 1. Example A1c months calculations in three EDC participants from the 1965-1980 diagnosis cohort

Participant A Lower glycemic exposure for longer period (control improved over time) 20 Years T1D Duration at Baseline	HbA1c (%)	8.94	6.70	7.86	6.86	7.36	7.28	6.57	5.15
	Excess HbA1c (>6.1)	2.84	0.60	1.76	0.76	1.26	1.18	0.47	0
	Length of Interval (Years)	21.4	2.1	2.0	1.9	2.0	2.1	5.6	1.7
	A1c Months	729	744	787	804	834	864	895	895
Participant B Lower glycemic exposure for longer period (control worsened over time) 19 Years T1D Duration at Baseline	HbA1c (%)	7.61	7.86	9.19	9.60	8.19	8.27	8.11	9.22
	Excess HbA1c (>6.1)	1.51	1.76	3.09	3.50	2.09	2.17	2.01	3.12
	Length of Interval (Years)	19.9	2.2	2.1	2.0	2.1	2.0	5.0	1.5
	A1c Months	361	407	485	569	622	673	799	855
Participant C Higher glycemic exposure for shorter period 8 Years T1D Duration at Baseline	HbA1c (%)	8.19	9.77	12.01	10.68	10.18	10.1	7.62	8.48
	Excess HbA1c (>6.1)	2.09	3.67	5.91	4.58	4.08	4.00	1.52	2.38
	Length of Interval (Years)	9.3	3.0	2.4	1.2	1.7	2.2	6.2	1.2
	A1c Months	233	365	535	601	684	792	905	939

SUPPLEMENTARY DATA

Supplementary Figure 2. Distribution of A1c Months at proliferative retinopathy incidence



SUPPLEMENTARY DATA

Supplementary Table 1. Time to 900 A1c Months by Degree of HbA1c Excess

Excess HbA1c	**Time**
1% above normal	75 years
2% above normal	38 years
3% above normal	25 years
4% above normal	19 years
5% above normal	15 years