Risk Factors for Retinopathy in Type 1 Diabetes: The DCCT/EDIC Study

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OBJECTIVE

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy reduced the development and progression of retinopathy in type 1 diabetes (T1D) compared with conventional therapy. The Epidemiology of Diabetes Interventions and Complications (EDIC) study observational follow-up showed persistent benefits. In addition to glycemia, we now examine other potential retinopathy risk factors (modifiable and nonmodifiable) over more than 30 years of follow-up in DCCT/EDIC.

RESEARCH DESIGN AND METHODS

The retinopathy outcomes were proliferative diabetic retinopathy (PDR), clinically significant macular edema (CSME), and ocular surgery. The survival (event-free) probability was estimated using the Kaplan-Meier method. Cox proportional hazards models assessed the association between risk factors and subsequent risk of retinopathy. Both forward- and backward-selection approaches determined the multivariable models.

RESULTS

Rate of ocular events per 1,000 person-years was 12 for PDR, 14.5 for CSME, and 7.6 for ocular surgeries. Approximately 65%, 60%, and 70% of participants remained free of PDR, CSME, and ocular surgery, respectively. The greatest risk factors for PDR in descending order were higher mean HbA_{1c}, longer duration of T1D, elevated albumin excretion rate (AER), and higher mean diastolic blood pressure (DBP). For CSME, risk factors, in descending order, were higher mean HbA_{1c}, longer duration of T1D, and greater age and DBP and, for ocular surgeries, were higher mean HbA_{1c}, older age, and longer duration of T1D.

CONCLUSIONS

Mean HbA_{1c} was the strongest risk factor for the progression of retinopathy. Although glycemic control is important, elevated AER and DBP were other modifiable risk factors associated with the progression of retinopathy.

Retinopathy is a major complication of type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) demonstrated that a mean of 6.5 years of intensive diabetes therapy with a mean HbA_{1c} of ~7% substantially reduced microvascular complications, including retinopathy, compared with conventional therapy with a mean HbA_{1c} of ~9% (1). Thereafter, observational follow-up of DCCT participants continued in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (1994 to present) (2). Over the first 4 years of EDIC, the former DCCT intensive

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therapy group experienced a lower incidence of further progression of retinopathy than did the former conventional group, despite similar HbA_{1c} levels in both groups (3). This "metabolic memory" persisted after 10 years of EDIC, albeit to a lesser degree (4). By year 18 of EDIC, the effect of "metabolic memory" had largely faded, with no further divergence of retinopathy rates, but the former intensive group continued to have fewer ocular complications, including a substantially lower risk of advanced retinopathy outcomes (5).

HbA_{1c} was the primary variable for risk of progression of retinopathy studied in the DCCT. In the current analyses, we examined multiple risk factors (modifiable and nonmodifiable) to determine if additional modifiable factors could broaden preventive interventions. The goal of these analyses was to identify risk factors for retinopathy outcomes in the context of a multicenter study with a well-characterized cohort of individuals with type 1 diabetes (T1D) after 30 years of follow-up. Risks for proliferative diabetic retinopathy (PDR), clinically significant macular edema (CSME), and ocular surgery were examined.

RESEARCH DESIGN AND METHODS

Subjects

The DCCT and EDIC protocols were approved by the institutional review boards of all participating centers, and all participants provided written informed consent. The methods of the DCCT and EDIC study have been described in detail (2,6). In brief, the DCCT (1983–1993) was a controlled clinical trial that evaluated whether intensive versus conventional diabetes therapy reduced the risk of complications of diabetes. A total of 1,441 patients with T1D were randomly assigned to receive either intensive (n = 711) or conventional diabetes therapy (n = 730). Intensive therapy was aimed at achieving glycemic control as close to the nondiabetic range as safely possible, whereas conventional therapy was aimed at preventing symptoms of hypo- or hyperglycemia but with no specific glucose targets.

At DCCT baseline, the study cohort consisted of a primary prevention cohort (n = 726) with 1–5 years diabetes duration, no retinopathy based on fundus photography, and $<$40 mg of albuminuria per 24 h; and a secondary intervention cohort (n = 715) with 1–15 years duration, minimal to moderate nonproliferative retinopathy, and $<$200 mg of albuminuria per 24 h (6). Exclusion criteria included neuropathy sufficiently severe to require therapy, hypertension ($\geq$140/90 mmHg or medication), and hyperlipidemia (LDL cholesterol [LDLc] $>$130 mg/dL or medication).

At the end of the DCCT, after an average follow-up of 6.5 years, all participants were taught intensive therapy and were referred to their health care providers for subsequent diabetes care. In 1994, EDIC enrolled 98% of the surviving DCCT cohort, and 94% of the surviving cohort still actively participates after more than 20 years of additional follow-up.

Risk Factors

The potential risk factors were assessed by standardized methods at periodic visits during DCCT and EDIC (6,7). HbA_{1c} was measured quarterly during DCCT and annually during EDIC (8). Fasting lipid levels (triglycerides and total and HDL cholesterol [HDLc]) were measured annually during DCCT and every other year during EDIC. LDLc was calculated using the Friedwald equation. Albuminuria was measured annually during DCCT and every other year during EDIC, alternating with the fasting lipids, and serum creatinine was measured annually. Albumin-to-creatinine ratio values obtained after 1 August 2012 were converted to albumin excretion rate (AER) levels as previously described (9). Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using serum creatinine levels, age, sex, and race (10). All laboratory measurements were performed in the DCCT/EDIC central biochemistry laboratory, with standardized methods and controls in place to guard against long-term drift.

As previously described (11), candidate risk factors were grouped into the following 11 blocks (described in detail in Supplementary Table 1): design (treatment group and cohort), physical (sex, age, weight, and BMI), behavioral (smoking, drinking, and exercise), family history (family history of hypertension, myocardial infarction, and type 1 or type 2 diabetes), traditional blood pressure/pulse (systolic blood pressure [SBP] and diastolic blood pressure [DBP] and pulse rate), medication use (ACE inhibitors, angiotensin receptor blockers, β-adrenergic blockers, lipid-lowering agents, and calcium channel blockers), traditional lipid levels (total cholesterol, triglycerides, LDLc, and HDLc), diabetes specific (duration of diabetes at enrollment, stimulated C-peptide, insulin dose, and estimated glucose disposal rate), renal complications (eGFR $<$60 mL/min and AER $\geq$30 mg/24 h), hypoglycemia events (coma/seizure and/or required assistance), and glycemia (HbA_{1c} at eligibility and HbA_{1c} during follow-up).

A risk factor could be included in the model as a fixed or baseline covariate (B), or as a time-dependent covariate, using either the current (most recent) measurement (C) or as the updated mean of all follow-up values since randomization (M) (Supplementary Table 1). The updated mean accounts for the different measurement frequencies during DCCT and EDIC by weighting each value by the time interval since the last measurement. For example, the mean updated HbA_{1c} value of a participant at year 10 is the weighted average of the HbA_{1c} values up to and including year 10 for that particular individual.

Retinopathy Assessments

Standardized stereoscopic seven-field fundus photographs were obtained every 6 months during the DCCT, and every 4th year (staggered from the start of the EDIC follow-up period) during EDIC. In addition, photographs were obtained in the full cohort at EDIC study years 4 and 10. The photographs were graded centrally using the final Early Treatment of Diabetic Retinopathy Study (ETDRS) severity grading scale (12), and graders were masked to treatment assignment and other risk factors.

Outcomes

PDR was defined by neovascularization observed on fundus photograph grading or evidence of scatter photocoagulation. CSME was defined using fundus photography grading or the presence of focal photocoagulation scars. Ocular surgical interventions were self-reported at annual visits and were captured based on structured interviews conducted by study staff. Ocular surgery is a composite outcome that included cataract extraction, vitrectomy and/or retinal detachment surgery, glaucoma-related surgery (including laser treatment, filtering

surgery, cyclocryotherapy, or other operative procedures to lower intraocular pressure), cornea or lens-related surgery (including corneal transplant or yttrium aluminum garnet [YAG] posterior capsulotomy), or enucleation (13).

Statistical Analysis

Risk factor modeling in a Cox proportional hazards (PH) model using 100 conventional group outcome case subjects and ~150 case subjects in the full cohort (i.e., intensive and conventional combined), allowing for an R^2 = 0.35 for the association of up to 10 adjusting covariates with a given risk factor of interest, and using a test at the 0.01 level (two sided), provided 97% power to detect a 30% risk reduction per SD change in a factor (14).

For each outcome (PDR, CSME, and ocular surgery), the analysis was based on the time to that outcome. The survival (event-free) probability was estimated using the Kaplan-Meier method. Semiparametric Cox PH models assessed the association between fixed and time-dependent covariates and the risk of an outcome (15). For quantitative risk factors, hazard ratios (HRs) are reported per 1 unit change in the risk factor. If HR denotes the HR per 1 unit change in a quantitative risk factor, then the HR per x units change in that risk factor is calculated as HR^x (HR to the power x). The functional form for the effect of the weighted mean HbA_{1c} on the empirical log hazards of each outcome was investigated using smoothing splines (16).

Continuous variables were described using medians and first and third quartiles, and discrete variables were described using counts and percentages. The risk factor variable selection approach has been previously described (11). In brief, both forward- and backward-selection approaches were used. The forward-selection procedure added variables into the Cox PH model one block at a time, and at each step, factors were eliminated to yield the best subset model based on statistical significance (i.e., P values), the minimum (best) Akaike information criterion (17), and a penalized likelihood (lasso method) (18). The next block of variables was then entered, and the process continued until a final model was reached. The backward-selection approach used the lasso and, separately, selected the model with the best (smallest) Akaike information criterion, both starting with all the variables included in the model. Interaction terms with sex were used to investigate sex differences in the effect of covariates on risk of retinopathy.

Because any z statistic with absolute value of 3.89 or larger has $P < 0.0001$, and z values as high as ~16 are observed, the z value better represents the significance of the covariate effect in the model than does the designation "$P < 0.0001$." Moreover, the z statistic is independent of the measurement unit used and therefore allows comparisons across risk factors.

RESULTS

A total of 379 participants reached PDR over an average follow-up of 22 years (rate of 12 events per 1,000 person-years), 431 participants reached CSME over an average follow-up of 21.2 years (rate of 14.5 events per 1,000 person-years), and 280 participants had ocular surgeries over an average follow-up of 25.7 years (rate of 7.6 cases per 1,000 person-years). Moreover, 261 participants reached both PDR and CSME during the follow-up, 156 participants reached CSME and had ocular surgery, and 178 participants reached PDR and had ocular surgery, whereas 127 participants reached both PDR and CSME and had ocular surgery over the follow-up period (Fig. 1). Approximately 65% of the cohort remained free of PDR, ~60% remained free of CSME, and ~70% remained free of ocular surgery after 30 years of follow-up (Supplementary Fig. 1).

Baseline Characteristics

At DCCT baseline, 53% of the participants were male, 51% were assigned to the conventional therapy, and 50% were in the primary prevention cohort; the participants had a median (quartiles) age of 27 years (22, 32), duration of diabetes of 4.3 years (2.3, 9.1), HbA_{1c} of 8.7% (7.8, 9.9), and 18% were smokers. Compared with subjects without PDR, those with PDR were more likely to be in the conventional group and in the original secondary intervention cohort (Table 1). They also had higher baseline BMI, DBP, pulse rate, total cholesterol, triglycerides, LDLc, AER, and HbA_{1c} levels and longer duration of T1D. Higher risk of CSME was associated with conventional therapy and secondary intervention cohort; male sex; older age; family history of T1D; higher BMI, DBP, pulse rate, total cholesterol, triglycerides, LDLc, AER, and HbA_{1c} levels; and longer duration of T1D (Supplementary Table 2). Higher risk of ocular surgery was associated with conventional treatment group and secondary intervention cohort; older age; currently smoking; higher weight, BMI, pulse rate, triglycerides, and HbA_{1c} levels; and longer duration of T1D (Supplementary Table 3).

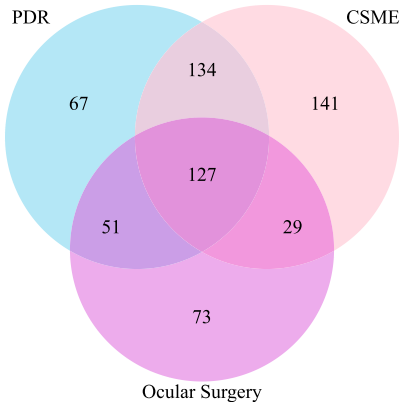

Figure 1—The joint distribution of the number of participants with PDR, CSME, and ocular surgery over the follow-up.

Unadjusted and Minimally Adjusted Time-Dependent Models

Similar patterns were observed when these risk factors were considered over the entire follow-up period as time-dependent variables (Table 2 and Supplementary Tables 4–6). When adjusted for age and mean updated HbA_{1c}, higher risk of PDR was associated with original DCCT cohort (secondary intervention vs. primary prevention), adult versus adolescent status at baseline, lower weight gain in females, higher SBP and DBP, higher pulse rate, presence of hypertension, higher lipids, higher AER, any macroalbuminuria, and higher HbA_{1c} at baseline. Similarly, higher risk of CSME was observed in participants in the secondary intervention cohort and in males and was associated with higher weight, mean BMI, blood pressure, pulse rate, total cholesterol, LDLc, and triglyceride levels; alcohol use; lack of lipid-lowering medication use; either higher or lower HDLc; longer duration of T1D; any eGFR <60 mL/min; and the presence of macroalbuminuria. Higher risk of ocular surgery was observed in participants in the secondary intervention cohort, in males and in participants enrolled as adults, and was

Table 1—Baseline characteristics of DCCT/EDIC participants according to the presence or absence of PDR over the course of the DCCT/EDIC study

		Any PDR				
	Overall	No	Yes	HR	95% CI	*P* value
n	1,440	1,061	379			
Treatment group (% conventional)	51	46	65	2.151	1.741, 2.657	**<0.0001**
Cohort (% secondary)	50	44	66	2.158	1.743, 2.671	**<0.0001**
Sex (% males)	53	52	54	1.103	0.901, 1.351	0.3402
Age (years)	27 (22, 32)	27 (22, 32)	26 (21, 32)	0.99	0.977, 1.005	0.1825
Adult vs. adolescent (<18 years)	86	87	84	0.821	0.625, 1.079	0.1577
Weight males (kg)	75 (68, 82)	75 (68, 82)	75 (68, 82)	1.001	0.988, 1.014	0.9044
Weight females (kg)	62 (56, 69)	62 (56, 68)	63 (57, 70)	1.012	0.996, 1.029	0.1367
BMI males (kg/m^2)	24 (22, 25)	23 (22, 25)	24 (22, 26)	1.053	1, 1.108	**0.0495**
BMI females (kg/m^2)	23 (21, 25)	23 (21, 25)	24 (21, 25)	1.07	1.016, 1.125	**0.0098**
Smoking (%)	18	19	18	1.016	0.782, 1.321	0.9041
Drinking (% occasional or regular vs. no)	29	29	31	1.121	0.9, 1.394	0.3078
Exercise (% moderate or strenuous)	82	81	84	1.245	0.945, 1.64	0.1200
Family history of HT (%)	56	55	59	1.157	0.942, 1.42	0.1641
Family history of MI (%)	49	49	49	0.986	0.806, 1.206	0.8881
Family history of T1D (%)	14	13	17	1.245	0.95, 1.631	0.1128
Family history of T2D (%)	9	9	9	0.969	0.678, 1.385	0.8629
SBP (mmHg)	114 (108, 122)	112 (108, 122)	116 (108, 123)	1.007	0.998, 1.016	0.1032
DBP (mmHg)	72 (68, 80)	72 (68, 78)	74 (70, 80)	1.024	1.012, 1.037	**0.0001**
Pulse pressure (mmHg)	40 (36, 48)	40 (36, 48)	40 (34, 46)	0.992	0.982, 1.003	0.1501
Pulse (bpm)	76 (68, 84)	76 (68, 82)	76 (72, 84)	1.023	1.014, 1.032	**<0.0001**
HT (%)	3	2	3	1.21	0.664, 2.205	0.5329
Total cholesterol (mg/dL)	174 (153, 196)	173 (152, 195)	177 (156, 202)	1.005	1.002, 1.008	**0.0017**
Triglycerides (mg/dL)	73 (55, 93)	71 (54, 89)	80 (58, 103)	1.73	1.402, 2.134	**<0.0001**
HDLc (mg/dL)	49 (42, 57)	50 (42, 58)	46 (40, 56)	0.993	0.985, 1.002	0.1115
LDLc (mg/dL)	107 (91, 127)	106 (89, 125)	109 (93, 131)	1.005	1.002, 1.009	**0.0024**
Duration of T1D (years)	4.3 (2.3, 9.1)	3.8 (2.2, 8.3)	6.6 (3.1, 10.9)	1.087	1.061, 1.113	**<0.0001**
C-peptide among those with T1D duration <5 years (per 100 nmol/L)	13 (4, 25)	13 (4, 26)	10 (3, 24)	0.991	0.979, 1.003	0.1542
C-peptide among those with T1D duration >5 years (per 100 nmol/L)	3 (3, 4)	3 (3, 4)	3 (3, 3)	0.982	0.943, 1.022	0.3645
Log AER (mg/24 h)	2.4 (2.0, 2.9)	2.3 (1.8, 2.8)	2.6 (2.0, 3.1)	1.388	1.226, 1.571	**<0.0001**
HbA_{1c} (%)	8.7 (7.8, 9.9)	8.4 (7.6, 9.5)	9.4 (8.4, 10.7)	1.349	1.277, 1.426	**<0.0001**

Data are included for 1,440 patients who had at least two fundus photographs. Data are medians (first quartile, third quartile) or % unless otherwise indicated. HRs and *P* values are generated using a Cox PH model with no adjustment for other factors. Values in boldface type indicate $P < 0.05$. HT, hypertension; MI, myocardial infarction.

associated with higher pulse rate, mean SBP, pulse pressure, mean triglycerides, eGFR, AER, HbA_{1c} at baseline, and current HbA_{1c} value; history of hypertension; longer duration of T1D; use of ACE inhibitors; and use of any β and calcium channel blockers. The association between use of ACE inhibitors and use of any β blockers and calcium channel blockers and higher risk of ocular surgery likely represents an indication bias due to hypertension.

Multivariable Models

Table 3 reports the final multivariable Cox models for PDR, CSME, and ocular surgery, with variables presented in order of significance (i.e., larger absolute *z* values first). Using HbA_{1c} as an example of a time-dependent covariate, we used "baseline HbA_{1c}" to denote the HbA_{1c} at baseline and "mean HbA_{1c}" to denote the mean updated HbA_{1c} value, whereas the current (most recent) HbA_{1c} value was referred to as "HbA_{1c}." In the model for PDR (Table 3*A*), a higher mean HbA_{1c} (HR = 2.1539 per 1% higher [95% CI 1.9597, 2.3673], $z = 15.9155$, $P < 0.0001$), longer duration of T1D (HR = 1.1135 per year [95% CI 1.0757, 1.1525], $z = 6.1194$, $P < 0.0001$), AER (HR = 1.0310 per 20% increase [95% CI 1.0177, 1.0445], $z = 4.6223$, $P < 0.0001$), and higher mean DBP (HR = 1.0448 per 1 mmHg [95% CI 1.0255, 1.0645], $z = 4.6141$, $P < 0.0001$) were the most significant factors. Other significant factors associated with higher risk of PDR were higher pulse rate ($z = 2.9705$, $P = 0.0029$), being in the secondary intervention versus primary prevention cohort ($z = 2.3797$, $P = 0.0173$), higher HbA_{1c} at baseline ($z = 2.2629$, $P = 0.0236$), and older age ($z = 1.9611$, $P = 0.0498$), whereas use of lipid-lowering medication was protective (HR 0.6786, $z = -2.3842$, $P = 0.0171$).

In the model for CSME (Table 3*B*), mean HbA_{1c} (HR = 1.8257 per 1% increase

Table 2—Cox models, minimally adjusted for age and the updated mean HbA_{1c}, for individual time-dependent covariates with PDR, CSME, and ocular surgery

	PDR				CSME				Ocular surgery			
	HR	LL	UL	*P* value	HR	LL	UL	*P* value	HR	LL	UL	*P* value
Cohort (secondary vs. primary)	2.7107	2.1848	3.3631	<0.0001	1.8580	1.5291	2.2578	<0.0001	1.7128	1.3407	2.1883	<0.0001
Male vs. female					1.3358	1.1019	1.6195	0.0031	0.7738	0.6117	0.9788	0.0325
Adult vs. adolescent	1.5370	1.0427	2.2656	0.0299					0.5804	0.3525	0.9555	0.0324
Weight (kg)					1.0074	1.0013	1.0135	0.0161				
Mean weight (kg)					1.0088	1.0017	1.0160	0.0147				
Mean BMI (kg/m^2)					1.0316	1.0029	1.0611	0.0304				
Weight gain females (kg)	0.9799	0.9649	0.9951	0.0098								
Drinking (occasional or regular vs. no)					1.2150	1.0017	1.4736	0.0479				
SBP (mmHg)	1.0162	1.0087	1.0239	<0.0001	1.0129	1.0057	1.0201	0.0003				
DBP (mmHg)	1.0319	1.0201	1.0439	<0.0001	1.0300	1.0190	1.0411	<0.0001				
SBP	1.0197	1.0107	1.0289	<0.0001	1.0123	1.0036	1.0210	0.0050	1.0157	1.0049	1.0267	0.0042
Mean SBP (mmHg)	1.0279	1.0151	1.0408	<0.0001	1.0272	1.0154	1.0390	<0.0001	1.0261	1.0117	1.0408	0.0003
Mean DBP (mmHg)	1.0605	1.0413	1.0801	<0.0001	1.0524	1.0344	1.0706	<0.0001				
Mean pulse (bpm)	1.0323	1.0170	1.0479	<0.0001	1.0144	1.0012	1.0279	0.0324	1.0448	1.0254	1.0647	<0.0001
Pulse pressure (mmHg)									1.0132	1.0038	1.0227	0.0055
Hypertension	1.4137	1.1115	1.7981	0.0047					1.4281	1.0931	1.8659	0.0089
History of hypertension (yes vs. no)									1.6208	1.1512	2.2820	0.0056
Any ACE (yes vs. no)									1.4008	1.0974	1.7879	0.0067
Any β blockers (yes vs. no)									1.5584	1.1182	2.1721	0.0088
Lipid lowering (yes vs. no)					0.6565	0.4851	0.8884	0.0064				
Calcium channel blockers (yes vs. no)									1.5800	1.0937	2.2827	0.0148
Total cholesterol (mg/dL)	1.0034	1.0007	1.0061	0.0121	1.0052	1.0027	1.0077	<0.0001				
Triglycerides (log) (mg/dL)	1.4359	1.1907	1.7315	0.0001	1.6188	1.3634	1.9220	<0.0001				
LDLc (mg/dL)	1.0038	1.0007	1.0070	0.0162	1.0058	1.0028	1.0088	0.0001				
HDLc (mg/dL)	0.9915	0.9843	0.9987	0.0217	0.9932	0.9866	0.9998	0.0450				
Mean cholesterol (mg/dL)					1.0054	1.0020	1.0089	0.0017				
Mean triglycerides (log) (mg/dL)	1.6398	1.2919	2.0813	<0.0001	1.7128	1.3746	2.1343	<0.0001	1.3805	1.0421	1.8287	0.0245
Mean LDLc (mg/dL)					1.0053	1.0015	1.0092	0.0060				
Duration (years)	1.1511	1.1241	1.1801	<0.0001	1.0977	1.0731	1.1228	<0.0001	1.0990	1.0680	1.1295	<0.0001
Stimulated C-peptide among those with T1D duration <5 years (nmol/L)	0.2573	0.0698	0.9473	0.0412								
eGFR (mL/min/1.73 m^2)					1.0105	1.0026	1.0184	0.0084	0.9936	0.9881	0.9991	0.0241
Any eGFR <60									1.8229	1.2629	2.6312	0.0013
AER (mg/24 h)	1.0002	1.0000	1.0003	0.0024					1.0001	1.0000	1.0002	<0.0001
Any macroalbuminuria (yes vs. no)	1.8899	1.3716	2.6040	<0.0001	1.5364	1.0848	2.1761	0.0155	1.7932	1.3185	2.4393	0.0001
HbA_{1c} at baseline (%)	1.0843	1.0189	1.1539	0.0107					1.1129	1.0329	1.1991	0.0049
HbA_{1c} (%)									0.8153	0.7307	0.9097	0.0002

If HR denotes the HR per 1 unit change in a quantitative risk factor (such as duration of T1D), the HR per *x* units change in that risk factor is HR^x, where ^ denotes the "to the power of." Only values for covariates significant at $P < 0.05$ are shown. Complete results are presented in Supplementary Tables 2–4. LL, 95% CI lower limit; UL, 95% CI upper limit.

[95% CI 1.6840, 1.9795], $z = 14.5977$, $P < 0.0001$) was again the strongest risk factor, followed by duration of T1D (HR = 1.0912 per 1 year [95% CI 1.0654, 1.1161], $z = 7.4741$, $P < 0.0001$), age (HR = 1.0562 per 1 year [95% CI 1.0399, 1.0728], $z = 6.9031$, $P < 0.0001$), and DBP (HR = 1.0260 per 1 mmHg [95% CI 1.0150, 1.0371], $z = 4.6653$, $P < 0.0001$). Other significant risk factors associated with higher risk of CSME were higher AER ($z = 3.6024$, $P = 0.0003$), higher eGFR ($z = 3.5133$, $P = 0.0004$), higher mean triglycerides ($z = 3.0883$, $P = 0.0020$), and higher LDLc ($z = 1.9995$, $P = 0.0455$), whereas use of lipid-lowering medication was again protective ($z = -2.5272$, $P = 0.0114$).

In the model for ocular surgery (Table 3*C*), mean HbA_{1c} (HR = 1.8065 per 1% increase [95% CI 1.6011, 2.0383], $z =$

Table 3—A multivariable Cox model for PDR (*A*), CSME (*B*), and ocular surgery (*C*) as a function of fixed (baseline) and time-dependent covariates, the latter either the current value or mean from baseline

	HR	LL	UL	*z*	*P* value
A. PDR (Akaike information criterion = 4,629.176, χ^2 = 625.3039, df = 9)					
Mean HbA_{1c} (per 1%)	2.1539	1.9597	2.3673	15.9155	<0.0001
Duration of T1D (per 1 year)	1.1135	1.0757	1.1525	6.1194	<0.0001
AER* (per 1 mg/24 h)	1.0310	1.0177	1.0445	4.6223	<0.0001
Mean DBP (per 1 mmHg)	1.0448	1.0255	1.0645	4.6141	<0.0001
Pulse (per 1 bpm)	1.0141	1.0047	1.0235	2.9705	0.0029
Use of lipid-lowering medication (yes vs. no)	0.6786	0.4934	0.9333	−2.3842	0.0171
Cohort (secondary vs. primary)	1.4356	1.0658	1.9337	2.3797	0.0173
HbA_{1c} at baseline (per 1%)	1.0806	1.0104	1.1557	2.2629	0.0236
Age (per 1 year)	1.0143	1.0000	1.0288	1.9611	0.0498
B. CSME (Akaike information criterion = 5,542.11, χ^2 = 439.7664, df = 9)					
Mean HbA_{1c} (per 1%)	1.8257	1.6840	1.9795	14.5977	<0.0001
Duration of T1D (per 1 year)	1.0912	1.0654	1.1161	7.4741	<0.0001
Age (per 1 year)	1.0562	1.0399	1.0728	6.9031	<0.0001
DBP (per 1 mmHg)	1.0260	1.0150	1.0371	4.6653	<0.0001
AER* (per 1 mg/24 h)	1.0249	1.0113	1.0388	3.6024	0.0003
eGFR (per 1 mL/min/1.73 m^2)	1.0138	1.0060	1.0216	3.5133	0.0004
Mean triglycerides* (per 1 mg/dL)	1.0726	1.0259	1.1214	3.0883	0.0020
Use of lipid-lowering medication (yes vs. no)	0.6701	0.4912	0.9140	−2.5272	0.0114
LDLc (per 1 mg/dL)	1.0032	1.0000	1.0064	1.9995	0.0455
C. Ocular surgery (Akaike information criterion = 3,558.252, χ^2 = 289.5059, df = 7)					
Mean HbA_{1c} (per 1%)	1.8065	1.6011	2.0383	9.6041	<0.0001
Age (per 1 year)	1.0660	1.0466	1.0858	6.8259	<0.0001
Duration of T1D (per 1 year)	1.0886	1.0591	1.1188	5.9957	<0.0001
AER* (per 1 mg/24 h)	1.1567	1.0702	1.2502	3.6706	0.0002
Mean pulse (per 1 bpm)	1.0274	1.0072	1.0481	2.6776	0.0074
Sex (males vs. females)	0.7071	0.5449	0.9175	−2.6079	0.0091
Mean SBP (per 1 mmHg)	1.0169	1.0010	1.0331	2.0856	0.0370

If HR denotes the HR per 1 unit change in a quantitative risk factor (such as duration of T1D), the HR per *x* units change in that risk factor is HR^*x*, where ^ denotes the "to the power of." LL, 95% CI lower limit; UL, 95% CI upper limit. *Per 20% increase.

9.6047, $P < 0.0001$) was the strongest risk factor, followed by age (HR = 1.0660 per 1 year [95% CI 1.0466, 1.0858], z = 6.8259, $P < 0.0001$) and duration of T1D (HR = 1.0886 per 1 year [95% CI 1.0591, 1.1188], z = 5.9957, $P < 0.0001$). Other significant risk factors associated with higher risk of ocular surgery were higher AER (z = 3.6706, P = 0.0002), higher mean pulse (z = 2.6776, P = 0.0074), and higher mean SBP (z = 2.0856, P = 0.0370), whereas males had lower risk than females (z = −2.6079, P = 0.0091).

Interaction terms with sex in the final multivariable models for PDR and ocular surgery were not significant. For CSME, there were significant interactions between sex and age, and sex and DBP. The association between age and CSME was higher in females (HR = 1.07 per 1 year, z = 5.85) than in males (HR = 1.04 per 1 year, z = 3.64), whereas the association between DBP and CSME was only significant in males (HR = 1.04 per 1 mmHg, z = 5.36) but not in females (HR = 0.003 per 1 mmHg, z = 0.33).

CONCLUSIONS

The total exposure to glycemia as captured by the mean updated HbA_{1c} was by far the strongest risk factor for the three outcomes of PDR (z = 15.9155), CSME (z = 14.5977), and ocular surgery (z = 9.6047). The next most significant factors associated with PDR were duration of T1D (z = 6.1194), AER (z = 4.6223), and mean DBP (z = 4.6141); with CSME were duration of T1D (z = 7.4741), age (z = 6.9031), and DBP (z = 4.6653); and with ocular surgery were age (z = 6.8264) and duration of T1D (z = 5.9957). As explained in RESEARCH DESIGN AND METHODS, we emphasized z values over P values since they better describe strong associations, such as those observed in our analyses, and, similarly to the P values, they are independent of the measurement units used.

Note that other than T1D duration, which was the second strongest risk factor for PDR and CSME and third strongest for ocular surgery, other nonmodifiable risk factors included age for all three outcomes, treatment cohort for PDR, and sex for ocular surgery. Most risk factors for retinopathy disease in T1D identified in our work are modifiable. Intensive glycemia control is of overwhelming importance in decreasing retinopathy progression. However, the additional modifiable risk factors examined suggest that early, vigorous, non–glycemia-related interventions, in addition to controlling glycemia, might further mitigate retinopathy progression and vision loss.

Although we reported these as risk factors, the inverse of the modifiable factors identified can be thought of as preventative strategies. Certainly improved HbA_{1c} control reduces the risk of retinopathy. Our analyses support that blood pressure control and lipid-lowering medication (for PDR and CSME) could also reduce risk of retinopathy progression. Whether optimal control of all modifiable risk factors examined would result in a substantial further decrease of retinopathy progression independent of glycemic control alone would require prospective clinical trials.

The goal of this analysis was to identify risk factors for the three clinically relevant retinopathy outcomes considered in a well-characterized cohort of individuals with T1D. A limitation of our study is the relatively small number of DCCT/EDIC participants with an outcome event (379 PDR, 431 CSME, and 280 ocular surgery); therefore, we did not attempt to develop prediction models. Such prediction models would require additional external cohort(s) with T1D for validation and calibration. Similarly, the prevalence of blindness (visual acuity <20/100 in either eye) remains extremely low in both original treatment groups (<2%), precluding an analysis (5).

In the forward variable selection approach for PDR, the model included the initial DCCT randomization group, mean SBP, LDLc, mean triglycerides, and eGFR, all significant at a *P* value threshold of 0.05 before adding the glycemia block. However, none of those five variables remained significant after adjustment for glycemia, which is likely explained by mediation (e.g., the DCCT group effect on PDR is mediated by its effect on glycemic levels) or causal (e.g., glycemia lowers eGFR) mechanisms. For CSME, the addition of the glycemia block in the forward selection for CSME only resulted in elimination of the initial randomization group and eGFR, and in a reduction of the association between AER and the risk of CSME (from $z = 7.11$ without mean HbA_{1c} to $z = 3.60$ with HbA_{1c}). For ocular surgery, the model before adding the glycemia block included the initial randomization group, smoking, DBP, mean insulin, and use of β blockers, all significant at level 0.05, but none of which remained significant after further adjustment for glycemia (data not shown).

Cox PH models assessed the association between potential risk factors and the risk of retinopathy outcomes. Since these risk factors (such as HbA_{1c}) were measured longitudinally during the follow-up, they were included as time-dependent covariates in the Cox models. There are no established R^2 or area under the curve measures for Cox models with time-dependent covariates. Instead, the Akaike information criterion and the model χ^2 values were used for comparing models. Moreover, since the R^2 measures in other models are directly proportional to the test statistic value (the *z* value), the strength of association between risk factors and outcomes was described using the corresponding *z* values.

Most of the ocular surgeries were cataract extractions (89 in the intensive group and 125 in the conventional group), followed by vitrectomy or retinal detachment (41 and 66, in intensive and conventional, respectively), glaucoma-related surgeries (14 and 19), corneal-related surgeries (5 and 7), YAG capsulotomy (2 and 4), and enucleation (2 and 2) in the intensive and conventional groups, respectively. The small number of individual types of surgeries other than cataract extraction precluded us from investigating them individually, and instead we used a composite outcome defined as any ocular surgery.

In conclusion, long-term exposure to hyperglycemia (as captured by high levels of mean updated HbA_{1c}) was the strongest risk factor for the progression of retinopathy. We found that most risk factors identified were modifiable, with the exception of duration of T1D, age, study cohort (for PDR), and sex. These findings suggest that aggressive glycemic management is key but should also be coupled with aggressive management of several other non–glycemia-related risk factors, such as blood pressure control and control of lipids to reduce the burden of retinopathy in individuals with T1D. The general principles derived from the DCCT/EDIC study most likely apply to current patients with T1D, but the higher rate of overweight and obesity in current patients (19) may lead to additional risk factors.

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