Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Intensive Diabetes Therapy and Ocular Surgery in Type 1 Diabetes

The Diabetes Control and Complications Trial (DCCT)-Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group*

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2. Schedule of Retinal Examinations

During EDIC, approximately, but not exactly, one-quarter of subjects had a retinal examination. To be precise, each patient had the retinal examination on the 4th year multiple anniversary of their year of enrollment into the DCCT. Thus, for example, a patient randomized in 1987 had subsequent retinal examinations in EDIC (starting in 1994) during 1995 (8th anniversary), 1999 (12th anniversary) etc. In addition, all subjects had the exam in 1997 (EDIC year 4) and 2003 (year 10).

3. Supplemental Tables and Figures

Figure S1 presents the distribution (median and upper and lower quartiles) of HbA1c values during DCCT followed by the values at each successive year of EDIC.

Table S1 presents the characteristics of subjects at baseline (entry into the DCCT 1983-1989), the end (closeout) of the DCCT (1993) that also marks EDIC baseline, and at year 17 of EDIC (2010).

Table S2 presents the costs of ocular surgeries in DCCT-EDIC

Table S3 presents the incidence of ocular surgery within the DCCT intensive and conventional groups separately within the primary prevention cohort and the secondary intervention cohort.

Table S4 presents the hazard ratios for the conventional versus intensive group separately among males and females.

Table S5 presents the effects of covariates on the risk of surgeries and the proportion of the treatment group effect explained by each covariate separately for cataract surgery and for vitrectomy and/or retinal detachment surgery.

Table S1. Clinical characteristics of DCCT-EDIC participants at DCCT baseline, DCCT closeout, and EDIC year 17.

	DCCT Baseline (1983-1989) (N=1441)		End of DCCT (1993) (N=1418) *		EDIC Year 17 (~2010) (N=1226) *	
	INT	**CONV**	**INT**	**CONV**	**INT**	**CONV**
N	711	730	699	719	628	598
Medical history						
Age (years)	27.1 (7.1)	26.5 (7.1)	33.4 (7.0)	32.8 (7.0) †	51.3 (6.9)	50.4 (6.8) †
Female (%)	48.5	45.9	49.1	46.2	48.6	45.9
Diabetes duration (years)	6.0 (4.2)	5.7 (4.1)	12.1 (4.9)	11.7 (4.8)	29.7 (4.9)	29.2 (4.9)
DCCT primary cohort (%)	49.0	51.8	49.2	51.7	48.7	50.8
Hypertension (%) ‖	3.1	2.1	5.0	4.9	65.6	66.2
Hyperlipidemia (%) **	22.8	23.3	26.2	30.0	65.3	63.2
Current Cigarette smoking (%)	18.6	18.4	20.4	19.6	12.9	11.0
Medical treatment						
Glucose management						
Pump or multiple daily injections (≥3) (%)	0	0	97.4	5.0‡	97.3	96.8
Glucose monitoring ≥ 4 times a day (%)	0	0	52.8	3.8‡	67.3	70.2
RAAS (ACEI or ARB) use (%) §	0	0	0	0	56.1	57.2
Physical examination						
Body mass index (kg/m^2)	23.4 (2.7)	23.5 (2.9)	26.6 (4.3)	25.0 (3.1) ‡	29.4 (13.0)	28.3 (4.7)
Overweight (%)	26.3	29.6	58.6	47.1‡	73.6	74.6
Systolic blood pressure (mmHg)	114.5 (11.3)	114.6 (11.4)	116.5 (11.5)	116.6 (11.9)	122.1 (14.7)	121.2 (14.9)
Diastolic blood pressure (mmHg)	73.1 (8.2)	72.9 (8.7)	74.8 (8.7)	74.4 (8.9)	72.5 (9.1)	72.3 (8.8)
Laboratory values						
Hemoglobin A1c (%) ††	9.1 (1.6)	9.1 (1.6)	7.2 (0.9)	9.1 (1.3) ‡	8.0 (1.1)	8.0 (1.0)
Plasma lipids (mg/dL)						
Total Cholesterol	177.1 (32.8)	175.7 (33.6)	180.3 (30.5)	184.0 (37.6)	173.5 (35.7)	172.3 (40.0)

HDL Cholesterol	50.8 (12.3)	50.3 (12.3)	51.0 (12.9)	51.8 (13.1)	61.6 (19.0)	60.8 (17.8)
LDL Cholesterol	110.3 (28.7)	109.1 (29.4)	112.5 (27.1)	114.9 (32.0)	95.9 (29.6)	95.3 (29.8)
Triglycerides	80.8 (43.3)	81.8 (51.3)	84.2 (52.6)	88.6 (51.4) †	80.0 (45.8)	81.3 (74.6)
Complications						
Eye						
Retinopathy levels				‡		‡
No Retinopathy (10/10)	49.0	51.8	28.4	17.1	9.4	4.9
MA Only (20/(<)20)	35.0	27.8	39.5	32.3	40.1	27.6
Mild NPDR (35/(<)35)	11.5	15.2	21.5	28.6	23.1	17.9
Moderate/Severe NPDR (43/<43 – 53/53)	4.5	5.2	8.3	15.8	18.2	25.4
PDR (60/60 +)	0	0	2.4	6.3	9.2	24.3
CSME (%)	0	0	3.4	6.8‡	12.6	21.2‡
Visual acuity in the worse eye				‡		†
≤20/20	83.8	84.4	86.7	82.5	66.6	60.4
>20/20 - < 20/40	16.2	15.6	12.9	16.0	29.0	32.8
20/40 - < 20/100	0	0	0.4	1.3	2.6	4.7
≥20/100	0	0	0	0.3	1.9	2.2
Renal						
Sustained AER ≥ 30 mg/24hr (%)	5.2	4.3	7.6	14.6‡	11.2	18.4‡
AER ≥ 300 mg/24 hr (%)	0	0	1.4	3.2†	4.0	6.5†
eGFR (mL/min/1.73m^2)	126.0 (13.9)	126.2 (14.6)	116.0(13.0)	117.8(13.7) ‡	94.1 (18.0)	93.0 (19.5)
Sustained eGFR<60 mL/min/1.73m^2 (%)	0	0	0.1	0.4	3.3	4.9
Neuropathy						
Confirmed clinical neuropathy	6.8	5.6	9.3	17.5‡	24.2	31.9‡

Values are reported as either mean (SD) or %.

* Ocular surgery was ascertained in 1418 subjects at DCCT closeout and 1,227 subjects at EDIC year 17. If a characteristic was not assessed at EDIC year 17, the value from the most recent visit was employed.

† $p<0.05$ by the Wilcoxon rank-sum test for group differences in quantitative or ordinal characteristics, or by the chi-square test for categorical variables.
‡ $p<0.01$ by the Wilcoxon rank-sum test for group differences in quantitative or ordinal characteristics, or by the chi-square test for categorical variables.
|| Hypertension was defined by a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medications.
** Hyperlipidemia was defined by an LDL cholesterol level ≥130 mg per deciliter (3.4 mmol per liter) or the use of lipid-lowering agents.
†† End of DCCT hemoglobin A1c is the mean of the quarterly hemoglobin A1c values throughout the DCCT. EDIC Year 17 hemoglobin A1c is the mean of the annual EDIC hemoglobin A1c values. DCCT-EDIC weighted mean hemoglobin A1c is the time-averaged HbA1c of DCCT quarterly values (weight ¼) and EDIC annual values (weight 1), with mean (SD) values 7.8% (0.9%) and 8.3% (1.0%) among participants assigned to intensive and conventional diabetes therapy, respectively.
§ Medication data were not collected during the DCCT. ACE inhibitors were prohibited during the DCCT. At EDIC year 1, ACEI use was 5.6% in INT and 6.9% in CONV. ARBs were not available until later during EDIC.
Abbreviations: DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications Study; INT = intensive diabetes therapy; CONV = conventional diabetes therapy; RAAS = renin-angiotensin-aldosterone system; ACEI = angiotensin receptor blocker; ARB = angiotensin II receptor blocker; HDL = high density cholesterol; LDL = low density cholesterol.

Table S2. Cost Estimate of Ocular Surgeries in DCCT and EDIC by Treatment Group in 2010 dollars without and with adjustment for inflation (discounting) at 3% per year. [19,20]

	Total Cost ($)	
Ocular Surgery Category	**Intensive**	**Conventional**
Cataract surgery - 2010 prices	227,355	296,550
Cataract surgery - inflation adjusted prices	199,444	263,405
Vitrectomy/Retinal detachment surgery - 2010 prices	269,619	473,655
Vitrectomy/Retinal detachment surgery - inflation adjusted prices	225,244	364,732
Glaucoma related surgery - 2010 prices	5,280	8,096
Glaucoma related surgery - inflation adjusted prices	4,781	6,789
Total cost of ocular surgery - 2010 prices	502,254	778,301
Total cost of ocular surgery - inflation adjusted prices	429,469	634,925

Table S3. Count of ocular surgeries during DCCT and EDIC follow-up among the 726 participants in the primary cohort on entry and 715 participants in the secondary cohort. A test of the interaction between cohort and treatment group in any complication-related surgery (i.e. a test of homogeneity) is not significant (p=0.65)

A. Primary Prevention Cohort

	Number (%) of Subjects with Ocular Surgeries		Incidence Rate Per 1000 Patient-years		Risk Reduction (%, 95% CI)*	P value
	Intensive Diabetes Therapy (N=348)	Conventional Diabetes Therapy (N=378)	Intensive Diabetes Therapy	Conventional Diabetes Therapy		
Any diabetes-related ocular surgery	20 (5.7%)	32 (8.5%)	2.60	3.98	45.3 (3.8, 68.9)	**0.04**
Cataract surgery	10 (2.9%)	19 (5.0%)	1.29	2.34	56.0 (5.5, 79.5)	**0.04**
Vitrectomy or retinal detachment surgery	13 (3.7%)	14 (3.7%)	1.68	1.72		
Glaucoma-related surgery	1 (0.3%)	6 (1.6%)	0.13	0.73		
Corneal-related surgery	1 (0.3%)	1 (0.3%)	0.13	0.12		
Eye enucleation	0 (0%)	0 (0%)	0	0		
YAG posterior capsulotomy	1 (0.3%)	2 (0.5%)	0.13	0.24		
N (%) of subjects with						
0 ocular surgeries	328 (94.3%)	346 (91.5%)				
1 surgery type	15 (4.3%)	26 (6.9%)				
2 surgery types	5 (1.4%)	4 (1.1%)				
3 surgery types	0 (0%)	2 (0.5%)				
Trend P value	0.19					

B. Secondary Intervention Cohort

	Number (%) of Subjects with Ocular Surgeries		Incidence Rate Per 1000 Patient-years		Risk Reduction (%, 95% CI) †	P value
	Intensive Diabetes Therapy (N=363)	Conventional Diabetes Therapy (N=352)				
Any diabetes-related ocular surgery	43 (11.8%)	66 (18.8%)	5.21	8.60	51.0 (27.5,66.9)	**<0.001**
Cataract surgery	32 (8.8%)	42 (11.9%)	3.83	5.29	45.7 (11.5,66.6)	**0.02**
Vitrectomy or retinal detachment surgery	16 (4.4%)	36 (10.2%)	1.91	4.62	59.8 (27.4,77.8)	**0.003**
Glaucoma-related surgery	8 (2.2%)	8 (2.3%)	0.95	0.99		
Corneal-related surgery	1 (0.3%)	2 (0.6%)	0.12	0.25		
Eye enucleation	1 (0.3%)	1 (0.3%)	0.12	0.12		
YAG posterior capsulotomy	2 (0.6%)	2 (0.6%)	0.24	0.25		
N (%) of subjects with						
0 ocular surgeries	320 (88.2%)	286 (81.3%)				
1 surgery type	32 (8.8%)	47 (13.4%)				
2 surgery types	7 (1.9%)	16 (4.6%)				
3 surgery types	4 (1.1%)	3 (0.9%)				
Trend P value	0.024					

*Time to the first of any complication-related ocular surgery was the primary study outcome. For those patients with multiple ocular surgery types, time to the onset of the first surgery of each type was used. All of the surgeries occurred in EDIC except for 6 during DCCT including 1 glaucoma-related surgery (intensive), 2 cataract extraction (conventional), 2 vitrectomy surgeries (conventional), and 1 enucleation (conventional).

† Risk reduction associated with intensive diabetes therapy is calculated as (1 - hazard ratio of intensive versus conventional diabetes therapy) x 100%. Hazard ratio is generated from a Cox proportional hazards model adjusting for age, gender, diabetes duration, HbA1c and visual acuity level at DCCT baseline.

Table S4. Conventional versus intensive group hazard ratios for any complication-related ocular surgery, cataract surgery, and vitrectomy or retinal detachment surgery by gender, with the p-value from a test of homogeneity (no treatment by gender interaction).

Surgery*	Gender	Hazard Ratio	p value	Homogeneity p-value
Any Surgery	Male	2.560 (1.550, 4.228)	**0.0002**	0.15
	Female	1.584 (1.032, 2.429)	**0.0352**	
Cataract Extraction	Male	2.649 (1.382, 5.077)	**0.0033**	0.23
	Female	1.591 (0.943, 2.687)	0.0821	
Vitrectomy	Male	3.58 (1.69, 7.58)	**0.0009**	0.02
	Female	1.07 (0.58, 1.97)	0.8412	

* Cox proportional hazards models adjusting for age, gender, treatment by gender interaction, diabetes duration, HbA1c, secondary versus primary cohort and visual acuity level at DCCT baseline were used to examine each surgery type.

Table S5. Association of HbA1c and complications as time-dependent covariates with the risk of surgery in separate Cox proportional hazards models. The proportion of the treatment group differences explained by each covariate on the incidence of surgery is also shown. A) cataract surgery; B) vitrectomy and/or retinal detachment surgery.

A. Cataract surgery.

Model*	Time-Dependent Covariate Hazard Ratio (95% CI) †	P value	Risk reduction (%) of intensive diabetes therapy (95% CI) ‡	P value	Proportion of treatment effect explained by each covariate§
Intensive vs. conventional group	---	**---**	48.5 (22.7, 65.7)	**0.001**	
Updated DCCT-EDIC time-weighted mean HbA1c: (Per 10% increase)	1.71 (1.42, 2.04)	**<.001**	8.68 (-44.5, 42.3)	0.70	98.5%
Retinopathy: Moderate NPDR or worse vs Mild NPDR or better	3.40 (2.05, 5.64)	**<.001**	26.0 (-16.0, 52.8)	0.19	83.2%
CSME	2.95 (1.88, 4.65)	**<.001**	36.8 (2.2, 59.1)	**0.04**	58.6%
Visual acuity: ≤ 20/20 vs. >20/20	6.21 (3.78, 10.20)	**<.001**	37.5 (6.1, 58.4)	**0.03**	50.2%
AER	1.03 (1.02, 1.04)	**<.001**	40.5 (9.3, 60.9)	**0.02**	43.2%
Sustained AER>30 mg/24 hr	2.34 (1.47, 3.73)	**0.004**	41.5 (10.6, 61.7)	**0.02**	40.3%
AER>300 mg/24 hr	3.63 (2.04, 6.47)	**<.001**	42.7 (13.0, 62.3)	**0.009**	33.6%
Hypertension	2.79 (1.63, 4.80)	**0.002**	43.0 (14.3, 62.1)	**0.007**	28.9%
RAAS inhibitor use	1.85 (1.13, 3.00)	**0.02**	45.8 (18.2, 64.1)	**0.004**	17.3%
eGFR (per 1 std: 18 mL/min/1.73m^2 increase)	0.71 (0.61, 0.82)	**<.001**	43.8 (14.7, 63.0)	**0.007**	28.5%

Sustained eGFR>60 mL/min/1.73m^2	3.75 (2.02, 6.94)	**<.001**	44.3 (15.3, 63.3)	**0.006**	27.3%
Confirmed clinical neuropathy	2.18 (1.39, 3.40)	**0.006**	45.8 (18.4, 64.0)	**<0.001**	16.4%

B. Vitrectomy and/or retinal detachment surgery.

Model*	Time-Dependent Covariate Hazard Ratio (95% CI) †	P value	Risk reduction (%) of intensive diabetes therapy (95% CI) ‡	P value	Proportion of treatment effect explained by each covariate§
Intensive vs. conventional group	---	**---**	45.4 (12.5, 65.9)	**0.010**	
Updated DCCT-EDIC time-weighted mean HbA1c: (Per 10% increase)	1.71 (1.43, 2.04)	**<.001**	-64.5 (-209.6, 12.5)	0.13	62.3%
Retinopathy: Moderate NPDR or worse vs Mild NPDR or better	31.14 (13.18, 73.56)	**<.001**	-9.1 (-74.8, 31.9)	0.72	97.9%
CSME	9.3 (5.2, 16.6)	**<.001**	23.3 (-23.5, 52.4)	0.28	81.2%
Visual acuity: ≤ 20/20 vs. <> 20/20	6.2 (3.7, 10.3)	**<.001**	35.9 (-2.9, 60.1)	0.07	46.3%
AER	1.05 (1.03, 1.06)	**<.001**	28.3 (-17.2, 56.1)	0.19	72.3%
Sustained AER>30 mg/24 hr	5.11 (3.04, 8.59)	**<.001**	29.7 (-14.9, 57)	0.17	68.8%
AER>300 mg/24 hr	5.20 (2.85, 9.50)	**<.001**	35.6 (-5.9, 60.9)	0.09	52.7%
Hypertension	5.7 (3.2, 10.4)	**<.001**	37.5 (-0.2, 61)	0.06	39.8%
RAAS inhibitor use	3.27 (1.95, 5.48)	**<.001**	39.8 (3.7, 62.3)	**0.04**	29.3%
eGFR (per 1 std: 18 mL/min/1.73m^2 increase)	0.72 (0.60, 0.87)	**0.004**	41.5 (4.9, 64)	**0.04**	25.9%
Sustained eGFR>60 mL/min/1.73m^2	4.11 (1.61, 10.54)	**0.004**	43.1 (7.9, 64.9)	**0.03**	16.7%
Confirmed clinical neuropathy	2.23 (1.21, 4.11)	**0.006**	43.2 (7.9, 65)	**0.03**	17.0%

* Cox proportional hazards models adjusting for age, gender, diabetes duration, HbA1c, secondary versus primary cohort and visual acuity level at DCCT baseline. Separate models examine the adjusted effect of treatment group alone, then each time-dependent covariate individually, one at a time, and then both treatment group and the covariate. All models use the Lin-Wei robust estimate of the covariate standard errors, confidence limits and p-values.

† Hazard ratio is evaluated per 10% increase in updated mean HbA1c, or one standard deviation increase in eGFR (18 mL/min/1.73m^2), or for yes versus no for qualitative covariates.

‡ Risk reduction associated with intensive diabetes therapy is calculated as (1 - hazard ratio of intensive versus conventional diabetes therapy) x 100%. A negative risk reduction estimate corresponds to a non-significant risk increase and designates that all of the treatment group difference is explained by the covariate.

§ The proportion of the treatment group effect explained is the percentage change in the treatment group chi-square test value in the Cox model without and then with adjustment for the covariate.

Abbreviations: DCCT = Diabetes Control and Complications Trial; CI = confidence interval, AER = albumin excretion rate, RAAS = renin-angiotensin-aldosterone system.

Figure S1. Distribution of HbA1c during the DCCT and then annually during each successive year of EDIC through year 17. Presented are the mean (+), median (-),upper and lower quartiles (the box) and the extreme 5 and 95 percentile values (whiskers).