Original Investigation

# Effects of Prior Intensive Insulin Therapy and Risk Factors on Patient-Reported Visual Function Outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Cohort

Writing Team for the DCCT/EDIC Research Group

**IMPORTANCE** Preservation of vision in patients with diabetes mellitus is critical. Interventions to improve glycemic control through early intensive treatment of diabetes reduce rates of severe retinopathy and preserve visual acuity.

**OBJECTIVE** To assess the effects of prior intensive insulin treatment and risk factors on patient-reported visual function in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort.

**DESIGN, SETTING, AND PARTICIPANTS** Cohort study of 1184 participants with type 1 diabetes from the DCCT/EDIC study (randomized clinical trial followed by an observational follow-up study) who completed the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) during EDIC years 17 through 20 (September 1, 2009, through April 30, 2014) in 28 institutions across the United States and Canada.

**MAIN OUTCOMES AND MEASURES** The primary outcome was the composite NEI-VFQ-25 score. Secondary outcomes were visual acuity (measured by the Early Treatment Diabetic Retinopathy Study protocol), retinopathy level (determined by masked grading of stereoscopic color fundus photographs), and NEI-VFQ-25 subscale scores. The composite NEI-VFQ-25 scale and its subscales were scored 0 to 100, corresponding to poor to excellent function, respectively.

**RESULTS** The overall average NEI-VFQ-25 score for 1184 DCCT/EDIC participants (mean [SD] age, 52.3 [6.9] years; 48% female) with a 30-year duration of diabetes was high (all participants: median, 91.7; interquartile range [IQR], 89.7-96.9; intensive treatment [n = 605]: median, 94.7; IQR, 91.0-97.2; conventional treatment [n = 579]: median, 94.0; IQR, 88.4-96.1; $P = .006$ for intensive vs conventional). After adjustment for sex, age, hemoglobin $A_{1c}$ level, and retinopathy level at DCCT baseline, the former intensive treatment group had a significant, albeit modest, improvement in overall NEI-VFQ-25 score compared with the former conventional diabetes treatment group (median difference, −1.0; 95% CI, −1.7 to −0.3; $P = .006$). This beneficial treatment effect was fully attributed to the prior glycemic control in DCCT (explained treatment effect: 100%). Those with visual acuity worse than 20/100 reported the largest decline in visual function (median difference, −21.0; 95% CI, −40.5 to −1.6; $P = .03$).

**CONCLUSIONS AND RELEVANCE** In the DCCT/EDIC cohort, patient-reported visual function remains high in both treatment groups, comparable to previous reports of overall health-related quality of life. Intensive diabetes therapy modestly improved NEI-VFQ-25 score 30 years after the start of the DCCT, the benefit underestimated owing to more nonparticipants from the conventional treatment group. Visual acuity had the greatest effect on patient-reported visual function from among all risk factors.

**TRIAL REGISTRATION** clinicaltrials.gov Identifiers: NCT00360815 and NCT00360893

*JAMA Ophthalmol*. 2016;134(2):137-145. doi:10.1001/jamaophthalmol.2015.4606
Published online November 19, 2015.

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The National Eye Institute Visual Function Questionnaire (NEI-VFQ) has been used to assess the relationship of diabetic retinopathy severity and visual acuity (VA) with patient-reported visual function.[1-12] Data from previous studies have shown that severe retinopathy and poorer VA adversely affect self-report of visual function and that interventions that improve VA, such as vitrectomy and laser photocoagulation, have a beneficial effect as measured by the NEI-VFQ. To our knowledge, the long-term effect of intensive glycemic control on the patient-reported visual function in a controlled clinical trial in type 1 diabetes mellitus has not been examined. In the Diabetes Control and Complications Trial (DCCT), intensive insulin treatment of type 1 diabetes reduced the risk of development and progression of diabetic retinopathy compared with conventional diabetes treatment. The salutary effects of intensive vs conventional treatment were maintained during the Epidemiology of Diabetes Interventions and Complications (EDIC) observational follow-up of the DCCT cohort.[13,14] The purpose of this study is to assess the long-term effects of prior intensive treatment and risk factors on patient-reported visual function, using the 25-item NEI-VFQ (NEI-VFQ-25), 30 years after the start of the DCCT.

**At a Glance**

- The purpose of this study is to assess the effects of prior intensive treatment and risk factors on patient-reported visual function in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) cohort.
- The DCCT/EDIC patients report high visual function.
- Prior intensive diabetes treatment resulted in a modest benefit in reported visual function outcomes.
- Decline in visual acuity had the greatest effect on patient-reported visual function.

## Methods

The DCCT/EDIC has been described in detail in previous reports.[15,16] Between 1983 and 1989, 1441 participants with type 1 diabetes, aged 13 to 39 years, provided written informed consent and were enrolled in the DCCT, an institutional review board–approved multicenter clinical trial comparing the effects of intensive treatment, aimed at lowering glycemia as close to the nondiabetic range as safely possible, with those of conventional treatment. Intensive treatment, which aimed for hemoglobin $A_{1c}$ ($HbA_{1c}$) levels lower than 6.05% of total hemoglobin (to convert to proportion of total hemoglobin, multiply by 0.01), used 3 or more daily insulin injections or treatment with insulin pumps, with dose selection guided by frequent self-monitoring of blood glucose level. Conventional treatment had no numeric blood glucose targets but aimed for the absence of symptoms of hyperglycemia and hypoglycemia with 1 or 2 daily injections of insulin, the standard therapy at the time. The trial included 2 cohorts. The primary prevention cohort had diabetes for 1 to 5 years, an albumin excretion rate (AER) less than 40 mg/24 hours, and no retinopathy. The secondary intervention cohort had diabetes for 1 to 15 years, very mild to moderate nonproliferative retinopathy, and an AER equal to or lower than 200 mg/24 hours. After study end, the conventionally treated participants were instructed in intensive treatment and all patients were encouraged to implement and instructed in the use of intensive treatment. All participants were then referred to their health care professionals for ongoing diabetes care.[16] In 1994, 1375 of the 1428 surviving cohort members (96.3%) agreed to participate in the EDIC follow-up study, which included annual examinations and periodic evaluation of diabetic complications. To assess the long-term effect of prior intensive treatment and risk factors on patient-reported visual function in this cohort, 1184 EDIC participants completed the 25-item NEI-VFQ (NEI-VFQ-25) during EDIC years 17 through 20 (September 1, 2009, through April 30, 2014), a maximum of 30 years after the start of the DCCT.

This study was approved the Clinical Coordinating Center Institutional Review Board at Case Western Reserve University as well as the local institutional review board at each clinical center.

### Patient-Reported Visual Function Outcomes

Beginning in 2004, EDIC administered the NEI-VFQ-25 among one-quarter of the cohort every year. The NEI-VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related domains including general vision, ocular pain, near vision, distance vision, limitation on social functioning, mental health symptoms due to vision, role difficulties, dependency on others, driving difficulty, limitation with color vision, and limitation with peripheral vision, plus an additional single-item general health domain question. Subscale scores ranging from 0 to 100 (with 100 indicating highest function) were generated for each of the 12 domains. The main outcome in our analysis is the composite NEI-VFQ-25 score, which is an average of the 11 vision-related subscale scores. A composite quality-of-life (QOL) score was also examined, which comprises all of the 12 subscales including general health.

### Visual Acuity

Measurement of VA was performed by certified EDIC VA examiners every 4 years in EDIC based on the Early Treatment Diabetic Retinopathy Study (ETDRS) charts and procedures. The VA was determined for each eye individually and tested first at the 4-m distance. If the number of letters read correctly at 4 m was less than 20, the test was repeated at 1 m. If the number of letters read correctly at 1 m was 0, then the patient's ability to count fingers, detect hand motion, or have light perception was evaluated. For each eye, the best-corrected VA was recorded as the number of letters read correctly from 0 through 2 (worse than 20/800) to 98 through 100 (20/10). For each participant, the better eye was based on comparison of the best-corrected VA of each eye tested.[17]

### Retinopathy and Ocular Surgery

During EDIC, retinopathy was assessed by standardized 7-field fundus photography in one-quarter of the cohort each year and in the entire cohort at EDIC years 4 and 10. All photographs were



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graded centrally, with graders masked to the former DCCT therapy assignment, using the final ETDRS grading scale and DCCT methods.[13,18] Retinopathy level was classified as no retinopathy (ETDRS grade 10 in both eyes), microaneurysms only (grade 20 in either eye), mild nonproliferative diabetic retinopathy (grade 35 in either eye), moderate nonproliferative diabetic retinopathy (grade 43 in either eye), severe nonproliferative diabetic retinopathy (grade 53 in either eye), and proliferative diabetic retinopathy (grade 61 or greater in either eye).

Clinically significant macular edema was based on the detailed grading of fundus photographs and was defined as the presence of any 1 of the following: retinal thickening at or within 500 µm of the center of the macula; hard exudates at or within 500 µm of the center of the macula if associated with thickening of the adjacent retina; or a zone or zones of retinal thickening 1 disc area in size, at least part of which was within 1 disc diameter of the center.[19]

Panretinal and focal photocoagulation was assessed by patient annual report and confirmed by grading of photocoagulation scars in fundus photographs. Ocular surgery, including cataract extraction, vitrectomy, glaucoma-related surgery, corneal-related surgery, capsulotomy, and eye enucleation, were reported annually in DCCT and EDIC.

### Biomedical and Clinical Evaluations

Demographic characteristics, marital status, education, unemployment status, and history of smoking were assessed by annual questionnaires. Blood pressure and $HbA_{1c}$ level were measured quarterly during DCCT and annually during EDIC.[20] The AER and plasma lipid concentrations were measured yearly during DCCT and every 2 years during EDIC.[21] The serum creatinine level was measured annually in DCCT and EDIC. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine level, age, sex, and race using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[22]

Nephropathy outcomes reported in the current analysis are a single or sustained eGFR lower than 60 mL/min/1.73 $m^2$, an AER greater than 300 mg/24 hours, or a sustained AER greater than 30 mg/24 hours on 2 consecutive visits.[22] Clinical neurologic assessment, nerve conduction study, and cardiac autonomic neuropathy testing were conducted at EDIC years 13 and 14.[23,24] Cardiac autonomic neuropathy testing was repeated at EDIC years 16 and 17. Confirmed clinical neuropathy was defined as the presence of definite clinical neuropathy (the presence of signs and symptoms consistent with distal symmetrical polyneuropathy based on examination by a board-certified neurologist) and confirmed by abnormal nerve conduction (≥1 abnormal attribute in ≥2 anatomically distinct nerves among the sural, peroneal, or median nerves).[24] Cardiac autonomic neuropathy was defined as either an R-R variation less than 15 or an R-R variation between 15 and 19.9 in combination with a Valsalva ratio of 1.5 or lower or a decrease of more than 10 mm Hg in diastolic blood pressure on postural testing.[23]

### Diabetes-Related QOL

The diabetes-related QOL (DQOL) questionnaire was administered annually in DCCT and at every other year during EDIC. The DQOL questionnaire is a self-administered, multiple-choice, 46-item questionnaire assessing different aspects of QOL including satisfaction, impact, diabetes worry, and social or vocational worry.[25]

### Psychiatric Events

Psychiatric history was reported annually during EDIC. Presence of a psychiatric event was defined as at least 1 occurrence of nervousness or anxiety, affective disorder, or suicide attempt, with inpatient or outpatient treatment for the event during the year in which it was reported.

### Statistical Analysis

Clinical characteristics were compared using Wilcoxon rank sum test for quantitative or ordinal variables and $\chi^2$ test for categorical variables. The composite NEI-VFQ-25 score or QOL scale score used in the analyses was a weighted average of the subscales with an equal weight assigned to each of the 11 (excluding general health) or 12 (including general health) subscales rather than to each of the 25 questions. Internal consistency reliability among the NEI-VFQ-25 subscales was assessed with Cronbach α.[26] Spearman correlation was used to evaluate the strength of the association among the NEI-VFQ-25 subscales and of the NEI-VFQ-25 with each risk factor.

Between-group comparisons in composite and subscale scores were conducted by Wilcoxon rank sum test. For subscale comparisons, to adjust for multiple tests, the Benjamini and Hochberg method was used to control the false discovery rate at the .05 level.[27] Owing to the ordinal scoring and a skewed distribution of the NEI-VFQ-25 scores, quantile regression was used to assess the effect of former DCCT treatment groups and risk factors on median NEI-VFQ-25 composite score.[28,29] Robust confidence intervals and *P* values were generated with Huber sandwich estimates to incorporate any data that were not identically or independently distributed.[30] The proportion of the treatment group effect explained by each covariate was calculated as the percentage of reduction in the magnitude of the *t* value for the treatment group effect before and after adjustment for the covariate.

All analyses were performed using SAS version 9.3 statistical software (SAS Institute, Inc).

## Results

### Clinical Characteristics

The characteristics of the 1184 DCCT/EDIC participants (at the time of survey completion: mean [SD] age, 52.3 [6.9] years; 48% female) who completed the NEI-VFQ-25 in EDIC years 17 through 20 are described in **Table 1**, by original DCCT treatment group (intensive treatment, n = 605; conventional treatment, n = 579). At DCCT entry, there was a marginally significant difference between treatment groups in age. During the DCCT and by study design, the intensive treatment group had a significantly lower mean $HbA_{1c}$ level than the conventional treatment group (7.2% vs 9.0% of total hemoglobin, respectively; $P < .001$). During EDIC, the mean $HbA_{1c}$ for both the intensive and conventional treatment groups converged (approximately 8.0% of total hemoglobin for both groups; $P = .59$).



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Table 1. Clinical Characteristics of the 1184 Participants With 25-Item National Eye Institute Visual Function Questionnaire Evaluation During EDIC Years 17 Through 20 by Treatment Group

| Characteristic | DCCT Baseline[a] | | EDIC Years 17-20 | | |
|---|---|---|---|---|---|
| | Intensive (n = 605) | Conventional (n = 579) | Intensive (n = 605) | Conventional (n = 579) | *P* Value |
| Age, mean (SD), y | 27.5 (7.1) | 26.7 (7.0) | 52.8 (6.9) | 51.8 (6.9) | .02 |
| Female, % | 49.8 | 46.1 | 49.8 | 46.1 | .21 |
| Primary prevention cohort, % | 47.4 | 50.6 | 47.4 | 50.6 | .28 |
| Duration of diabetes, mean (SD), y | 6.1 (4.3) | 5.7 (4.1) | 30.5 (5.0) | 29.9 (5.0) | .07 |
| Unemployed or retired, % | 1.3 | 0.5 | 14.4 | 11.6 | .15 |
| Married, % | 49.3 | 51.1 | 72.7 | 73.1 | .90 |
| College education or higher, % | 73.6 | 73.1 | 90.1 | 90.2 | .97 |
| Smoking, % | 19.2 | 18.7 | 10.9 | 11.2 | .86 |
| Arterial pressure, mean (SD), mm Hg[b] | 86.0 (8.8) | 86.8 (8.7) | 87.6 (9.9) | 87.1 (9.3) | .36 |
| Hypertension, %[c] | 3.3 | 3.1 | 65.0 | 69.1 | .13 |
| DQOL score, mean (SD)[d] | 1.9 (0.3) | 1.9 (0.3) | 75.1 (10.8) | 74.5 (10.4) | .23 |
| Depression or psychiatric event, %[e] | ... | ... | 28.2 | 27.6 | .84 |
| Eye complications | | | | | |
| Retinopathy, % | | | | | |
| No retinopathy | 47.5 | 50.6 | 10.7 | 5.2 | <.001 |
| MA only | 35.8 | 29.5 | 38.7 | 26.1 | |
| Mild NPDR | 12.3 | 14.9 | 22.0 | 24.2 | |
| Moderate or severe NPDR | 4.5 | 5.0 | 17.9 | 19.7 | |
| PDR or worse | 0 | 0 | 10.7 | 24.9 | |
| CSME, % | 0 | 0 | 16.4 | 25.2 | <.001 |
| Visual acuity, % | | | | | |
| Worse eye | | | | | |
| ≤20/20 | 85.1 | 85.2 | 60.3 | 53.9 | .048 |
| >20/20 to <20/40 | 14.9 | 14.9 | 34.7 | 38.5 | |
| 20/40 to <20/100 | 0 | 0 | 3.0 | 5.5 | |
| ≥20/100 | 0 | 0 | 2.0 | 2.1 | |
| Better eye | | | | | |
| ≤20/20 | 95.9 | 96.7 | 81.3 | 76.2 | .049 |
| >20/20 to <20/40 | 4.1 | 3.3 | 17.9 | 21.9 | |
| 20/40 to <20/100 | 0 | 0 | 0.5 | 1.7 | |
| ≥20/100 | 0 | 0 | 0.3 | 0.2 | |
| Any prior ocular surgery in DCCT/EDIC, %[f] | 0 | 0 | 8.6 | 14.9 | <.001 |
| Renal complications, % | | | | | |
| Any AER >300 mg/24 h or sustained eGFR <60 mL/min/1.73 $m^2$ | 0 | 0 | 8.4 | 16.6 | <.001 |
| Any sustained AER >30 mg/24 h or single eGFR <60 mL/min/1.73 $m^2$ | 5.3 | 3.5 | 27.3 | 36.8 | <.001 |
| Neuropathy complications, % | | | | | |
| Abnormal autonomic response | 3.8 | 5.4 | 35.3 | 40.2 | .09 |
| Confirmed clinical neuropathy | 7.0 | 5.4 | 23.6 | 32.8 | <.001 |
| Glycemic control, $HbA_{1c}$, mean (SD), % of total Hb | 9.0 (1.6) | 8.9 (1.6) | 8.0 (1.2) | 7.9 (1.2) | .33 |
| DCCT[g] | ... | ... | 7.2 (0.8) | 9.0 (1.2) | <.001 |
| EDIC[g] | ... | ... | 8.0 (1.0) | 8.0 (1.0) | .59 |

Abbreviations: AER, albumin excretion rate; CSME, clinically significant macular edema; DCCT, Diabetes Control and Complications Trial; DQOL, diabetes-related quality of life; EDIC, Epidemiology of Diabetes Interventions and Complications; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; $HbA_{1c}$, hemoglobin $A_{1c}$; MA, microaneurysm; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; ellipses, not applicable.

SI conversion factor: To convert $HbA_{1c}$ to proportion of total hemoglobin, multiply by 0.01.

[a] There were not significant treatment group differences at DCCT baseline with the exception of a marginally significant difference in age ($P < .05$).

[b] Mean arterial pressure was defined as one-third systolic blood pressure plus two-thirds diastolic blood pressure.

[c] Hypertension was defined by a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, documented hypertension, or the use of antihypertensive agents. Medication data were not collected during the DCCT.

[d] The DQOL questionnaire is a self-administered, multiple-choice, 46-item assessment of different aspects of quality of life used by the DCCT.

[e] Depression or psychiatric event is defined as at least 1 occurrence of nervousness or anxiety, affective disorder, or suicide attempt in EDIC accompanied by hospitalization or outpatient treatment including tranquilizers.

[f] Other ocular surgery includes glaucoma-related surgery, corneal-related surgery, YAG capsulotomy, and eye enucleation.

[g] The DCCT or EDIC mean $HbA_{1c}$ values are time averaged throughout the DCCT or EDIC.

The overall DCCT/EDIC updated mean $HbA_{1c}$ level remained statistically lower in the intensive treatment group (7.8% vs 8.2% of total hemoglobin, respectively; $P < .001$).

By EDIC years 17 through 20, the original DCCT intensive treatment group, as compared with the conventional treatment group, had significantly less overall retinopathy severity ($P < .001$), a lower prevalence of clinically significant macular edema (16.4% vs 25.2%, respectively; $P < .001$), better VA in the better eye ($P = .049$) and worse eye ($P = .048$), and a decreased incidence of ocular surgery (8.6% vs 14.9%, respectively; $P < .001$).[31]

The intensive treatment group also demonstrated a significantly lower incidence of renal complications in DCCT/EDIC including an AER greater than 300 mg/24 hours or sustained eGFR less than 60 mL/min/1.73 $m^2$ (8.4% vs 16.6%, respectively; $P < .001$) and sustained AER greater than 30 mg/24 hours or single eGFR less than 60 mL/min/1.73 $m^2$ (27.3% vs 36.8%, respectively; $P < .001$), as well as a significantly lower prevalence of confirmed clinical neuropathy (23.6% vs 32.8%, respectively; $P < .001$). Notably, after 30 years, the DQOL and the number of psychiatric events were similar between the 2 treatment groups.



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Table 2. Scores on the 25-Item National Eye Institute Visual Function Questionnaire During Epidemiology of Diabetes Interventions and Complications Years 17 Through 20

| Domain | Intensive Treatment (n = 605) | | Conventional Treatment (n = 579) | | P Value[a] |
|---|---|---|---|---|---|
| | Mean (SD) | Median (IQR) | Mean (SD) | Median (IQR) | |
| General health | 62.5 (22.3) | 75.0 (50.0-75.0) | 60.4 (23.4) | 50.0 (50.0-75.0) | .22 |
| Subscale | | | | | |
| General vision | 79.7 (13.9) | 80.0 (80.0-80.0) | 78.0 (15.0) | 80.0 (80.0-80.0) | .05 |
| Ocular pain | 92.6 (12.4) | 100.0 (87.5-100.0) | 92.4 (12.3) | 100.0 (87.5-100.0) | .61 |
| Difficulty with near activities | 86.7 (14.3) | 91.7 (83.3-100.0) | 85.1 (16.0) | 91.7 (75.0-100.0) | .23 |
| Difficulty with distance activities | 92.6 (11.3) | 100.0 (91.7-100.0) | 89.5 (14.9) | 91.7 (83.3-100.0) | .001[b] |
| Limitation on social functioning | 98.6 (5.8) | 100.0 (100.0-100.0) | 97.6 (9.0) | 100.0 (100.0-100.0) | .03[c] |
| Mental health symptoms due to vision | 90.1 (12.2) | 93.8 (87.5-100.0) | 88.0 (13.6) | 93.8 (87.5-93.8) | <.001[b] |
| Role difficulties due to vision | 94.0 (14.0) | 100.0 (100.0-100.0) | 92.7 (15.0) | 100.0 (87.5-100.0) | .04[c] |
| Dependency on others due to vision | 98.0 (8.1) | 100.0 (100.0-100.0) | 97.1 (11.1) | 100.0 (100.0-100.0) | .31 |
| Driving difficulty | 91.7 (11.3) | 91.7 (83.3-100.0) | 89.1 (13.3) | 91.7 (83.3-100.0) | <.001[b] |
| Limitation with color vision | 98.2 (7.2) | 100.0 (100.0-100.0) | 97.3 (9.8) | 100.0 (100.0-100.0) | .10 |
| Limitation with peripheral vision | 95.3 (12.7) | 100.0 (100.0-100.0) | 93.6 (16.4) | 100.0 (100.0-100.0) | .22 |
| Composite | | | | | |
| Overall QOL, including general health item | 90.0 (8.2) | 92.1 (87.7-94.8) | 88.4 (10.1) | 91.0 (85.6-94.5) | .005 |
| Overall vision-related subscales, without general health item | 92.5 (7.9) | 94.7 (91.0-97.2) | 90.9 (10.0) | 94.0 (88.4-96.9) | .006 |

Abbreviations: IQR, interquartile range; QOL, quality of life.

[a] *P* values are from between-group comparisons using Wilcoxon rank sum test. For subscale comparisons, the Benjamini and Hochberg false discovery rate α adjustment for multiple tests was also conducted to control the overall false discovery rate at the .05 level.

[b] Remained significant after Benjamini and Hochberg false discovery rate α adjustment (difficulty with distance activities, *P* = .002; mental health symptoms due to vision, *P* = .006; and difficulty driving, *P* = .001).

[c] Lost significance after Benjamini and Hochberg false discovery rate α adjustment (*P* > .05).

Comparing clinical characteristics from DCCT baseline, those who did not complete the NEI-VFQ-25 part of the examination (n = 257, including 99 who were deceased) were more likely to be smokers, have poor VA, and have worse glycemic control than those who did participate (eTable 1 in the Supplement). Participants and nonparticipants in the NEI-VFQ-25 did not differ in retinopathy status.

## Effect of Intensive Diabetes Management on Patient-Reported Visual Function

The distributions of scores on the NEI-VFQ-25 and its subscales are presented in **Table 2.** The overall NEI-VFQ-25 score in both treatment groups was high (all participants: median, 91.7; interquartile range, 89.7-96.9; intensive treatment: median, 94.7; interquartile range, 91.0-97.2; conventional treatment: median, 94.0; interquartile range, 88.4-96.9; *P* = .006 for intensive vs conventional). Few participants had scale scores at or near 0, while a sizable proportion had scale scores of 100. Subscale scores for general health and general vision were lowest (ie, median score ≤80). The intensive treatment group had significantly higher subscale scores in the visual health domains of difficulty with distance activities (*P* = .001), mental health symptoms due to vision (*P* < .001), and driving difficulty (*P* < .001). Multivariate analyses of treatment group effect on patient-reported visual function (not including general health) after adjustment for age, sex, $HbA_{1c}$ level at DCCT screening, and retinopathy level at DCCT baseline demonstrated a modest, yet statistically significant, lower NEI-VFQ-25 score in the conventional treatment group compared with the intensive treatment group (median difference, −1.0; 95% CI, −1.7 to −0.3; *P* = .006) (**Table 3**). These differences, while statistically significant, were not in the range usually considered clinically meaningful.[32-35] The treatment group effect on patient-reported visual function was largely attributed to the higher DCCT mean $HbA_{1c}$ level and more rapid progression of retinopathy in the conventional treatment group (explained treatment group effect, 100% and 79%, respectively) (**Figure**).

Table 3. Treatment Effect in the DCCT on Overall 25-Item National Eye Institute Visual Function Questionnaire Score Using Quantile Regression

| Risk Factor | Estimated Difference in Median (95% CI) | t Value | P Value |
|---|---|---|---|
| Conventional vs intensive treatment | −1.0 (−1.7 to −0.3) | −2.76 | .006 |
| Female vs male | −1.3 (−2.0 to −0.6) | −3.57 | <.001 |
| Age at DCCT baseline, per 10-y increase | −0.9 (−1.3 to −0.4) | −3.49 | <.001 |
| $HbA_{1c}$ level at DCCT eligibility, per 10% increase | −0.3 (−0.5 to −0.1) | −2.97 | .003 |
| Retinopathy at DCCT baseline | | | |
| MA only vs no retinopathy | −0.2 (−1.1 to 0.6) | −0.65 | .58 |
| Mild NPDR vs no retinopathy | −0.3 (−1.4 to 0.8) | −0.85 | .57 |
| Moderate NPDR vs no retinopathy | −2.4 (−5.6 to 0.7) | −1.46 | .13 |

Abbreviations: DCCT, Diabetes Control and Complications Trial; $HbA_{1c}$, hemoglobin $A_{1c}$; MA, microaneurysm; NPDR, nonproliferative diabetic retinopathy.

All multi-item subscales demonstrated a moderately high internal consistency (Cronbach α = .62-.87) (eTable 2 in the Supplement), similar to those reported in other studies.[1,7,8] The Spearman correlation among the 11 visual-related subscales ranges from 0.13 (between general health and limitation with



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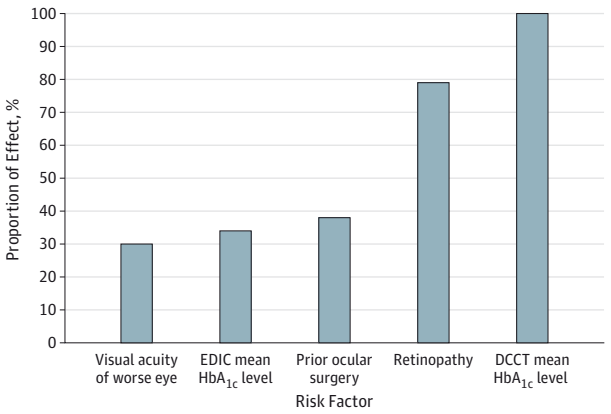
Figure. Proportion of the Effect of Diabetes Control and Complications Trial (DCCT) Treatment Assignment on Patient-Reported Visual Function Outcomes Attributed to Various Risk Factors at Epidemiology of Diabetes Interventions and Complications (EDIC) Years 17 Through 20




Proportion is calculated as the percentage reduction in the magnitude of the *t* value for treatment group (Table 3) before and after adjustment for each risk factor separately. Risk factors explaining 30% or more of the treatment group effect are presented. $HbA_{1c}$ indicates hemoglobin $A_{1c}$.

color vision) to 0.58 (between difficulty with distance activities and driving difficulty) (eTable 3 in the Supplement).

### Risk Factors Affecting NEI-VFQ-25 Scores

Among participants in both treatment groups combined, univariate analysis revealed that the overall NEI-VFQ-25 score was most strongly associated with the following risk factors (eTable 4 in the Supplement): DQOL ($r$ = 0.43), AER ($r$ = −0.41), VA in the worse eye ($r$ = −0.31), VA in the better eye ($r$ = −0.28), DCCT/EDIC $HbA_{1c}$ level ($r$ = −0.26), severity of retinopathy ($r$ = −0.24), EDIC mean $HbA_{1c}$ level ($r$ = −0.24), and ocular surgery ($r$ = −0.23) (AER, $P$ = .004; all others, $P$ < .001). Particularly, those with VA worse than 20/100 reported the lowest NEI-VFQ-25 score, further supporting the validity of the measure. The NEI-VFQ-25 score decreased to a median of 81 when VA was poorer than 20/100 in the worse eye and further declined to 49 if the better eye was similarly impaired.

In multivariate risk factor analyses (**Table 4**), sex, depression or psychiatric events in EDIC, clinically significant macular edema, reduced VA, prior ocular surgery, and higher mean $HbA_{1c}$ level in DCCT/EDIC were associated with significantly lower patient-reported visual function, when adjusted for all other risk factors ($P$ < .05). Those with VA poorer than 20/100 in the worse eye had a 21-point lower median NEI-VFQ-25 score (95% CI, −40.5 to −1.6; $P$ = .03) compared with those with VA 20/20 or better.

Table 4. Multivariate Risk Factor Effect on 25-Item National Eye Institute Visual Function Questionnaire Score Using Quantile Regression

| Risk Factor at EDIC Years 17-20 | Estimated Difference in Median (95% CI) | *t* Value | *P* Value |
|---|---|---|---|
| Age at DCCT baseline, per 10-y increase | −0.4 (−1.0 to 0.1) | −1.94 | .05 |
| Female vs male | −0.9 (−1.6 to −0.3) | −2.84 | .005 |
| Unemployed or retired vs employed | −0.1 (−1.5 to 1.2) | −0.21 | .83 |
| Married vs not married | 0.01 (−0.7 to 0.7) | 0.03 | .98 |
| College or above vs secondary school or below | 0.2 (−0.6 to 1.0) | 0.48 | .63 |
| Hypertension, yes vs no | −0.3 (−0.9 to 0.4) | −0.83 | .41 |
| Depression or psychiatric events in EDIC, yes vs no | −1.3 (−2.0 to −0.6) | −3.76 | <.001 |
| Retinopathy, moderate NPDR or worse vs mild NPDR or less | 0.4 (−0.3 to 1.1) | 1.19 | .24 |
| CSME, yes vs no | −1.1 (−2.2 to −0.1) | −1.98 | .047 |
| VA in worse eye | | | |
| >20/20 to <20/40 vs ≤20/20 | −1.9 (−2.8 to −1.1) | −4.64 | <.001 |
| 20/40 to <20/100 vs ≤20/20 | −4.1 (−6.2 to −2.0) | −3.85 | <.001 |
| ≥20/100 vs ≤20/20 | −21.0 (−40.5 to −1.6) | −2.13 | .03 |
| Prior ocular surgery vs no ocular surgery | −2.1 (−3.1 to −1.1) | −4.19 | <.001 |
| Any AER >300 mg/24 h or sustained eGFR <60 mL/min/1.73 $m^2$ vs never | −1.1 (−3.0 to 0.7) | −1.21 | .23 |
| Cardiac autonomic neuropathy, yes vs no | −0.6 (−1.5 to 0.2) | −1.40 | .16 |
| Confirmed clinical neuropathy at EDIC years 13/14, yes vs no | −0.9 (−1.9 to 0.1) | −1.87 | .06 |
| $HbA_{1c}$ at DCCT eligibility, per 10% increase | 0.04 (−0.2 to 0.2) | 0.42 | .67 |
| DCCT/EDIC weighted mean $HbA_{1c}$, per 10% increase | −0.7 (−1.0 to −0.4) | −4.66 | <.001 |

Abbreviations: AER, albumin excretion rate; CSME, clinically significant macular edema; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; eGFR, estimated glomerular filtration rate; $HbA_{1c}$, hemoglobin $A_{1c}$; NPDR, nonproliferative diabetic retinopathy; VA, visual acuity.

## Discussion

The NEI-VFQ-25 has been shown to be a reliable and valid questionnaire for patients with 5 chronic eye conditions or low vision from any cause.[36] The data presented herein extend these findings to the DCCT/EDIC cohort of persons with long-term type 1 diabetes. Remarkably, after an average duration of diabetes of 30 years, the overall NEI-VFQ-25 score among all questionnaire participants is very high, with a median composite score of 91.7 at EDIC years 17 through 20, almost certainly reflecting the modest degree of eye disease in the DCCT/EDIC cohort. Notably, although both former treatment groups reported relatively high NEI-VFQ-25 scores, intensive management of diabetes during the DCCT still resulted in a statistically significant higher NEI-VFQ-25 composite score, up to 30 years after the start of the DCCT. To our knowledge, this is the first report of a difference (albeit only approximately 1.0 point on average on a median score of approximately 92) (Table 3) in NEI-VFQ-25 scores (not including general health) in conventional compared with intensive diabetes management.

Despite differences in incidence of ocular and systemic complications between the intensive and conventional treatment groups, the difference in the scores for the NEI-VFQ-25, 1.0, is considered not clinically meaningful. A 5-point change in NEI-VFQ-25 score is thought to represent a clinically meaningful change with respect to VA.[32-35] The difference might have



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been higher had we included the nonparticipants who had higher $HbA_{1c}$ levels on entry and throughout the DCCT and more renal and neurological complications related to their diabetes. These were all factors associated with a decline in patient-reported visual function outcomes based on our analyses. Together with the tendency for more nonresponders to be in the conventional treatment group than the intensive treatment group (55.8% vs 44.2%, respectively), this suggests a selection bias to our cross-sectional analysis. This may have influenced our modest treatment group effect and resulted in an underestimation of the beneficial effect of intensive diabetes management on patient-reported visual function.

Another explanation for the relatively high NEI-VFQ-25 scores in both the conventional and intensive treatment groups was the preservation of good VA in both groups (81.3% of participants with intensive treatment and 76.2% of participants with conventional treatment had VA ≥20/20 in the better eye), despite differences in the presence of severe retinopathy between the groups. Projecting forward, the 30% to 50% increases in severe eye disease and macular edema in the conventional treatment group are likely to progress over time, adversely affect VA, and thus more substantially affect the NEI-VFQ-25 score in the conventional treatment group. Supporting this premise, we reported the increase in ocular surgical procedures in the conventional treatment group compared with the intensive treatment group, which were principally complication-related surgical procedures largely performed to improve VA.[31] In the end, the success of these surgical procedures in restoring VA may also help in sustaining high patient-reported visual function.

Preserving VA over time in patients with diabetes remains critical. Analysis of the NEI-VFQ-25 subscales demonstrates a consistent trend in the conventional treatment group: more difficulty with distance activities, such as driving, was reported by the conventional treatment group. Over time, visual impairment and limitations in driving in the aging population can induce feelings of depression and anxiety, a subscale also found to be statistically lower in the conventional treatment group compared with the intensive treatment group.

Not surprisingly, multivariate analysis demonstrated that other known diabetes-related outcomes, such as the presence of clinically significant renal or neurologic disease, and diabetes duration were independently correlated with patient-reported visual function. It is these latter diabetes-related factors, reflecting longer duration of poor control in the conventional treatment group and affecting DQOL, and not hypoglycemia, that likely mitigate the modest association of low DQOL with NEI-VFQ-25 score.

A limitation of this study is the lack of baseline NEI-VFQ-25 score at DCCT entry. However, given that the DCCT was a well-designed randomized clinical trial and that retinopathy, VA, and all the other major risk factors were well balanced between the 2 treatment groups at baseline, we believe that the baseline NEI-VFQ-25 score should also be balanced between the 2 groups and therefore should not substantively bias our study conclusions. Lastly, the tool itself (NEI-VFQ-25) may limit the benefit of intensive treatment as it reflects the patient's impression from the viewpoint of the better eye, giving 2 chances to report adequate visual function.

## Conclusions

In summary, our findings show that in the EDIC cohort patient-reported visual function remains high in both treatment groups, with only a modest benefit accruing to the intensive treatment group. This may reflect, in part, the relatively good VA in this cohort, the factor with greatest effect on patient-reported visual function outcomes from among all risk factors.

ARTICLE INFORMATION

**Submitted for Publication:** June 22, 2015; final revision received September 30, 2015; accepted October 3, 2015.

**Published Online:** November 19, 2015. doi:10.1001/jamaophthalmol.2015.4606.

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**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Das reported serving as a consultant for Regeneron and Teva; serving as a speaker for Novartis; and receiving research support from Genentech, the National Eye Institute, and the Department of Veterans Affairs. Dr Tamborlane reported serving as a consultant for Novo Nordisk, Sanofi, and Medtronic; and receiving personal fees from AstraZeneca, Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi, and Takeda. No other disclosures were reported.

**Funding/Support:** The DCCT/EDIC study has been supported by cooperative agreement grants (1982-1993, 2012-2017) and contracts (1982-2012) with the Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (current grants U01 DK094176 and U01 DK094157) and by the National Eye Institute, the National Institute of Neurological Disorders and Stroke, the General Clinical Research Centers Program (1993-2007), and the Clinical Translational Science Center Program (2006-present). The following industry contributors have provided free or discounted supplies or equipment to support participants' adherence to the study: Abbott Diabetes Care, Animas, Bayer Diabetes Care, Becton Dickinson, Eli Lilly and Co, Extend Nutrition, Insulet Corp, Lifescan, Medtronic Diabetes, Nipro Home Diagnostics, Nova Diabetes Care, Omron, Perrigo Diabetes Care, Roche Diabetes Care, and sanofi-aventis.



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**Role of the Funder/Sponsor:** Representatives of the National Institutes of Health and other federal agencies participated in the design and conduct of the study but had no role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The industry contributors had no role in the DCCT/EDIC study and no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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