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What are the Clinical, Quality-of-Life, and Cost Consequences of 30 Years of Excellent vs. Poor Glycemic Control in Type 1 Diabetes?

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Abstract

Objective: The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy for type 1 diabetes delayed the development of microvascular and neuropathic complications compared to conventional therapy. At the end of DCCT, all participants were trained in intensive therapy, care was transferred to community providers, and the difference in HbA1c between treatment groups narrowed and disappeared. Our objective was to describe the outcomes and the quality-of-life and costs associated with those outcomes in participants who maintained excellent vs. poor glycemic control over 30 years.

Research Design and Methods: We assessed the incidence of retinopathy, nephropathy, neuropathy, cardiovascular disease, acute metabolic complications, death, quality-of-life, and costs in the tertile of DCCT intensive therapy participants who achieved a mean updated HbA1c of <7.2% (55 mmol/mol) and the tertile of DCCT conventional therapy participants (n=240) who achieved a mean updated HbA1c of >8.8% (73 mmol/mol) over 30 years.

Results: Thirty years of excellent vs. poor glycemic control substantially reduced the incidence of retinopathy requiring laser therapy (5% vs. 45%), end-stage renal disease (0% vs. 5%), clinical neuropathy (15% vs. 50%), myocardial infarction (3% vs. 5%), stroke (0.4% vs. 2%), and death (6% vs. 20%). It also resulted in a gain of ~1.62 quality-adjusted life-years and averted ~\$90,900 in costs of complications per participant.

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Conclusions: Thirty years of excellent vs. poor glycemic control for T1DM can substantially reduce the incidence of complications, comorbidities, and death, improve quality-of-life, and reduce costs. These estimates represent the benefits that may be achieved with excellent glycemic control.

Keywords

Type 1 diabetes; hemoglobin A1c; diabetic complications; quality-adjusted life-years

The Diabetes Control and Complications Trial (DCCT) demonstrated that over 6.5 years, intensive diabetes therapy (mean HbA1c ~7% (53 mmol/mol)) compared to conventional diabetes therapy (mean HbA1c ~9% (75 mmol/mol)) delayed the onset and slowed the progression of the microvascular and neuropathic complications of type 1 diabetes (T1DM).

¹ At the end of DCCT, all participants were taught intensive therapy and referred to community providers for their diabetes care. Thereafter, 96% of the original DCCT cohort were enrolled in the Epidemiology of Diabetes Interventions and Complications (EDIC), an observational follow-up of DCCT.² The resources used for diabetes care by former intensive therapy participants decreased and the resources used for diabetes care by the former conventional therapy participants increased during EDIC follow-up, and the difference in HbA1c between the treatment groups observed at the end of DCCT narrowed and disappeared (mean HbA1c ~8% (64 mmol/mol)). Nevertheless, the benefits of prior intensive therapy on microvascular complications persisted. In addition, prior intensive therapy was associated with reductions in cardiovascular complications and all-cause mortality.^{3–5}

Despite publication of the results of the DCCT in 1993, glycemic control among patients with type 1 diabetes in the U.S. remains suboptimal. In 2005–2010, the mean HbA1c among U.S. adults 20–44 years of age with treated diabetes was 8.1% (65 mmol/mol).⁶ Similarly, between 2013 and 2014, the mean HbA1c among >16,000 patients with type 1 diabetes participating in the T1D Exchange Clinic Registry was 8.4% (68 mmol/mol).⁷

Our objective was to assess clinical outcomes (retinopathy, nephropathy, neuropathy, cardiovascular disease, acute metabolic complications, and death), quality-of-life, and costs in patients with type 1 diabetes that might have been observed if the DCCT had been continued and the HbA1c separation achieved during the randomized trial had been maintained for 30 years. In a companion manuscript, we perform analyses to assess the cost-effectiveness of achieving and maintaining excellent vs. poor glycemic control over 30 years using both the therapies employed during DCCT and those that might be employed today.⁸

RESEARCH DESIGN AND METHODS

Participants and Treatments

Between 1983 and 1989, the DCCT randomized 1,441 participants with T1DM.⁹ The primary prevention cohort included 726 participants 13–39 years of age with diabetes duration of 1–5 years, no retinopathy, and urinary albumin excretion rate (UAER) <40 mg/24 hr. The secondary intervention cohort included 715 participants 13–39 years of age with diabetes duration of 1–15 years, mild non-proliferative diabetic retinopathy, and UAER

200 mg/24 hr. In 1994, 1,375 participants (96% of the surviving cohort) consented to participate in EDIC.¹⁰ In 2014, 92% of the surviving cohort remained active in EDIC.

HbA1c was measured every 3 months during DCCT and annually during EDIC. Over 30 years of follow-up, there were 37,563 HbA1c measurements during DCCT and 28,875 measurements during EDIC. Time-weighted mean HbA1c levels were calculated using weights of 0.25 for HbA1c levels obtained during quarterly DCCT visits and 1.0 for values obtained during annual EDIC visits in order to describe the total glycemic exposure during DCCT/EDIC. We used empiric data from the tertile of DCCT intensive therapy participants (N=233) who achieved mean updated HbA1c levels of less than 7.2% (55 mmol/mol) and the tertile of DCCT conventional therapy participants (N=240) who achieved mean updated HbA1c levels of greater than 8.8% (73 mmol/mol) over 30 years of combined DCCT/EDIC follow-up. In these subgroups, we identified the frequency, quality-of-life impact, and cost of complications, comorbidities, and death.⁹ Detailed descriptions of how retinopathy, nephropathy, neuropathy, cardiovascular disease, acute metabolic complications, and death were defined and ascertained have been published.^{9–13} We defined the time of onset of each complication, comorbidity, and death as the annual visit at which it was reported or diagnosed.

Between 2005 and 2006, we assessed health utility scores once in 1,262 EDIC participants using the Quality of Well-Being Self-Administered Index (QWB-SA).¹⁴ We found no significant differences in utility scores between former DCCT intensive and conventional therapy participants after adjusting for complications and comorbidities. Therefore, we assumed that intensive and conventional therapies were not associated with different health utility scores. We combined the treatment groups and grouped all participants into one of twelve mutually exclusive groups based on their most severe complication or comorbidity and calculated mean health utility scores for each group. Death was assigned a utility score of 0. Participants with multiple complications and comorbidities were assigned to the category with the lowest utility score. We subsequently used health utility scores to calculate quality-adjusted life-years (QALYs). QALYs adjust length-of-life for quality-of-life. Mathematically, QALYs are calculated as the sum of the product of the number of years of life and the utility scores in each of those years.

We estimated the costs of complications and comorbidities from the literature and considered separately the costs incurred during the first year that a complication occurred (the event cost) and each subsequent year after the complication occurred (ongoing cost).^{15–24} We also included the costs of death.²⁵ To estimate the costs of complications, comorbidities, and death, we applied the event cost and ongoing cost of each outcome to the numbers of outcomes observed over 30 years in the groups with excellent and poor glycemic control. We added the annual costs of complications, comorbidities, and death for the excellent and poor glycemia groups to calculate the cumulative per person direct medical costs of complications over 30 years.

We adopted a healthcare sector perspective and considered only direct medical costs. We adjusted costs with the general consumer price index so that all costs were expressed in 2014 U.S. dollars. All DCCT/EDIC sites received Institutional Review Board approval for DCCT/

EDIC and all subjects provided written informed consent. Excel and SAS 9.1 were used for data management and analysis.

RESULTS

The time-weighted mean HbA1c of the subgroup of 233 DCCT intensive therapy participants who maintained the lowest tertile of HbA1c over 30 years was $6.8 \pm 0.4\%$ (mean $\pm$ SD) (51 ± 2 mmol/mol). The median was 6.8% (51 mmol/mol) and the interquartile range was 6.5% to 7.1% (48 to 54 mmol/mol). The time-weighted mean HbA1c of the subgroup of 240 DCCT conventional therapy participants who maintained the highest tertile of HbA1c over 30 years was $9.8 \pm 0.8\%$ (84 ± 4 mmol/mol). The median was 9.6% (81 mmol/mol) and the interquartile range was 9.2% to 10.1% (77 to 87 mmol/mol). The coefficient of variation of the time-weighted mean HbA1c for both the intensive and conventional therapy subgroups was 0.06, indicating that the within individual HbA1c levels varied only slightly between 6.4 and 7.2% and 9.2 and 10.4%, respectively.

The characteristics of the subgroups did not differ at baseline with respect to age, sex, race, cohort, level of retinopathy, albuminuria, neuropathy, or systolic or diastolic blood pressure (Table 1). The participants who achieved and maintained excellent glycemic control were at potentially higher risk of adverse outcomes in that they had significantly longer duration of diabetes at baseline, but were at potentially lower risk in that they were less likely to be current smokers. The participants who achieved and maintained excellent glycemic control also had slightly lower body mass index, lower HbA1c, and slightly lower total cholesterol, LDL-cholesterol, and triglyceride levels at baseline.

Table 2 shows the numbers of complications, comorbidities, and deaths and the number of participants with excellent and poor glycemic control who experienced the events over 30 years of combined DCCT/EDIC follow-up. Events occurred substantially less frequently in the group with excellent vs. poor glycemic control. Five percent of participants who maintained excellent glycemic control received laser therapy for retinopathy versus 45% of participants who maintained poor glycemic control. Corresponding rates were 0% vs. 5% for end-stage renal disease, 15% vs. 50% for clinical neuropathy, 3% vs. 5% for myocardial infarction, 0.4% vs. 2% for stroke, and 6% vs. 20% for death.

Table 3 shows the QWB-SA-derived health utility scores for EDIC participants. The score for participants with no complications or only minimal asymptomatic complications was 0.68. The QWB-SA-derived health utility scores were 0.52 for participants who survived strokes and 0.54 for participants who underwent amputations. Over 30 years, participants with excellent glycemic control accrued on average 18.58 QALYs and those with poor glycemic control accrued 16.96 QALYs, a difference of 1.62 QALYs over 30 years.

Table 4 shows the event costs and ongoing costs of complications, comorbidities, and death. End-stage renal disease (ESRD), amputations, cardiovascular events, cardiovascular procedures, and death were the most expensive events. Ongoing costs were greatest for ESRD and stroke.

Figure 1 shows the cumulative per participant costs of complications, comorbidities, and death for participants who maintained excellent vs. poor glycemic control. The cost curves separate at approximately 6 years of combined DCCT/EDIC follow-up and continue to diverge thereafter. The costs of complications, comorbidities, and death over 30 years were \$118,257 in participants with poor glycemic control and \$27,369 in participants with excellent glycemic control, a difference of ~\$90,900 over 30 years.

DISCUSSION

Based on this *post hoc* analysis of DCCT/EDIC, long-term therapy for T1DM that maintains HbA1c levels of approximately 7% (53 mmol/mol) compared to therapy that maintains HbA1c levels of approximately 9% (75 mmol/mol) over 30 years would substantially reduce the incidence of microvascular and macrovascular complications and death. Over 30 years, individuals who maintain excellent glycemic control might gain as much as 1.62 QALYs and have costs of complications, comorbidities, and death as much as \$90,900 lower than individuals who maintain poor glycemic control.

There are a number of limitations to our analyses. First, the characteristics of the DCCT/EDIC subgroups with excellent vs. poor glycemic control differed modestly at baseline (Table 1). It is possible that differences contributed to the differences in the incidence of complications, comorbidities, and death independent of long-term glycemic control. Nevertheless, it must be remembered that the meticulously collected and remarkably complete outcome data from DCCT/EDIC provide the most comprehensive picture of the relationship between glycemic control and complications in type 1 diabetes. Selecting subgroups of participants randomized to DCCT intensive and conventional therapies who maintained HbA1c levels during EDIC that were close to those achieved during DCCT was necessary to simulate the complications, comorbidities, and deaths that might have occurred if the randomized trial had been continued for 30 years and the difference in HbA1c achieved during DCCT were maintained for the duration of follow-up. Although HbA1c levels varied over time within both groups, the low coefficients of variation of the time-weighted mean HbA1c levels indicate that both those with excellent control and poor control maintained HbA1c levels within 0.4 to 0.6% of their time-weighted mean levels. Nevertheless, the reduction in complications, comorbidities, and death that we report (Table 2) should probably be regarded as the upper limits of the benefits that might be achieved with 30 years of excellent vs. poor glycemic control.

Second, we may have underestimated the quality-of-life differences between the treatment and complication states (Table 3). When we administered the QWB-SA in 2005/2006, participants had already lived with T1DM for 20–35 years. Health utility scores for participants without complications or comorbidities were almost certainly lower than they would have been had we measured utility scores at DCCT randomization. This might result in smaller apparent quality-of-life difference between participants without and with complications and comorbidities. If the quality-of-life differences are larger than we estimated, the difference in quality-of-life might be even greater than we estimated between patients with poor vs. excellent glycemic control.

Third, our estimates for the costs of complications/comorbidities/death may be low, given that they were based largely on estimates for patients with type 2 diabetes in the year 2000 (Table 4). Although we inflated the costs to reflect year 2014 U.S. dollars, the introduction of new treatments and technologies may have increased costs more than captured by a simple inflation adjustment. If the costs of complications, comorbidities, and death are greater than we estimated, the difference in costs would be greater than we estimated between patients with poor vs. excellent glycemic control.

Fourth, we did not perform analyses from a societal perspective or consider costs from the informal healthcare sector (e.g., patient- and caregiver-time costs) or from the non-healthcare sector (e.g., productivity losses arising from disease-related absence from work, long-term disability, and premature death). To the extent that complications that cause disability and premature mortality occur more frequently with poor glycemic control, we might have underestimated the costs of poor control.

Finally, 30 years may not be enough time to see the full benefits of excellent glycemic control, especially given that the cumulative risk of expensive complications including ESRD accelerate after 20 years of T1DM.²⁶ In Figure 1, the cumulative per participant cost of complications, comorbidities, and death continue to diverge between the poor and excellent glycemic control groups at 30 years. Longer follow-up may further amplify the difference in complication costs between patients with poor vs. excellent glycemic control.

In summary, this 30-year economic analysis informed by the results of DCCT/EDIC suggests that 30 years of excellent vs. poor glycemic control has the potential to substantially reduce the incidence of complications, comorbidities, and death, improve health-related quality-of-life, and reduce costs. These results provide the best empiric data to date regarding the long-term benefits of excellent vs. poor glycemic control for type 1 diabetes and provide the basis for an assessment of the long-term cost-effectiveness of interventions for type 1 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A complete list of participants in the DCCT/EDIC Research Group is presented in the Supplementary Material published with this article.

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Abbreviations:

DCCT	Diabetes Control and Complications Trial
EDIC	Epidemiology of Diabetes Interventions and Complications
HbA1c	Hemoglobin A1c
QALY	Quality-adjusted life-year

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Figure 1.
Cumulative per person cost of complications, comorbidities, and death for type 1 diabetic patients with poor glycemic control and excellent glycemic control over 30 years

Table 1.

Baseline characteristics of the subgroup of DCCT conventional therapy participants who maintained HbA1c greater than 8.8% (73 mmol/mol) and the subgroup of DCCT intensive therapy participants who maintained HbA1c less than 7.2% (55 mmol/mol) over 30 years of combined DCCT/EDIC follow-up

	Conventional therapy subgroup (N=240)	Intensive therapy subgroup (N=233)	P-value ^a
Demographic characteristics			
Age (yrs)	26 ± 8	27 ± 7	0.2372
Sex (%)	46	43	0.4662
Race (% white)	94	98	0.0520
Diabetes duration (yrs)	5.0 ± 3.8	6.3 ± 4.5	0.0013
Primary prevention cohort (%)	53	47	0.1542
Current cigarette smoking (%)	26	15	0.0141
Physical examination			
Body mass index (kg/m ²)	23.6 ± 3.0	22.9 ± 2.5	0.0107
Systolic blood pressure (mm Hg)	114 ± 12	115 ± 12	0.8308
Diastolic blood pressure (mm Hg)	73 ± 9	73 ± 9	0.8506
Laboratory examinations			
HbA1c (%)	9.8 ± 1.6	8.5 ± 1.4	<0.0001
mmol/mol	84 ± 18	69 ± 15	
Lipids (mg/dl)			
HDL cholesterol	50 ± 12	51 ± 12	0.2095
LDL cholesterol	112 ± 30	106 ± 28	0.0084
Total cholesterol	180 ± 35	172 ± 33	0.0073
Triglycerides	90 ± 65	76 ± 41	0.0008
Complications			
Retinopathy levels (%)			
No retinopathy	53	27	0.0831
Microaneurysm only	25	36	
Mild NPDR	12	11	
Moderate NPDR	10	7	
Renal function			
Albumin excretion rate (mg/24 hr)	17.0 ± 17.8	17.6 ± 23.9	0.1419
AER 30 (%)	11	12	0.9080
Neuropathy			
Confirmed clinical neuropathy (%)	7	5	0.2765

Data are mean ± standard deviation or %. Abbreviations: AER, albumin excretion rate; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; eGFR, estimated glomerular filtration rate; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

^aP-value was derived using the Wilcoxon rank-sum test or the chi-square test to compare the two groups.

Table 2.

The observed number of events and number of participants experiencing complications, comorbidities, and death over 30 years in the poor and excellent glycemic control groups

	Events (Participants)	
	Poor glycemic control	Excellent glycemic control
Retinopathy		
Severe NPDR	118 (118)	13 (13)
Laser treatment for macular edema or PDR	294 (107)	25 (12)
Any ocular surgery		
Cataract extraction	29 (24)	7 (6)
Vitreotomy or retinal detachment	31 (24)	2 (2)
Glaucoma-related surgeries	4 (4)	1 (1)
Nephropathy		
Sustained microalbuminuria	65 (64)	29 (29)
Proteinuria	123 (123)	13 (13)
End-stage renal disease	22 (11)	0 (0)
Hemodialysis		
Renal transplant		
Neuropathy		
Clinical neuropathy	121 (121)	34 (34)
Lower extremity ulcer	71 (45)	2 (2)
Amputation	20 (13)	1 (1)
Cardiovascular disease		
Angina	19 (13)	2 (2)
Silent myocardial infarction	17 (15)	7 (6)
Myocardial infarction	15 (13)	8 (8)
PTCA	24 (16)	9 (8)
CABG	6 (6)	1 (1)
Myocardial infarction with CABG	5 (5)	1 (1)
Congestive heart failure	5 (5)	0 (0)
Hospitalized arrhythmias (atrial fibrillation)	10 (8)	3 (3)
Transient ischemic attack	1 (1)	1 (1)
Stroke	5 (5)	1 (1)
Acute metabolic complications		
Diabetic ketoacidosis	620 (86)	247 (35)
Hypoglycemia requiring hospitalization	143 (28)	108 (32)
Death		
	48 (48)	15 (15)

Abbreviations: NA, not applicable; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

Table 3.

Health utility scores derived from the Quality of Well-Being Self-Administered (QWB-SA) Index for EDIC population in years 2005–2006

	Utility score (Mean $\pm$ SD)
No complications or severe nonproliferative diabetic retinopathy or microalbuminuria	0.68 $\pm$ 0.15
Laser photocoagulation or proteinuria or confirmed clinical neuropathy	0.66 $\pm$ 0.16
Diabetic ketoacidosis or hypoglycemia requiring hospitalization	0.64 $\pm$ 0.17
Silent myocardial infarction, transient ischemic attack, or hospitalized arrhythmias	0.62 $\pm$ 0.17
Dialysis or renal transplant	0.59 $\pm$ 0.17
Ocular surgery or lower extremity ulcers	0.58 $\pm$ 0.16
Confirmed angina	0.57 $\pm$ 0.19
Myocardial infarction or percutaneous transluminal coronary angioplasty or coronary artery bypass graft	0.57 $\pm$ 0.17
Congestive heart failure	0.57 $\pm$ 0.17
Amputation	0.54 $\pm$ 0.13
Stroke	0.52 $\pm$ 0.18
Death	0.00

Abbreviation: SD, standard deviation.

Table 4.

Event costs and ongoing costs of diabetes complications, comorbidities, and death as derived from the literature

	2014 US dollars ^a		Sources
	Event cost	Ongoing cost	
Retinopathy			
Severe NPDR	103	103	[15]
Laser treatment for macular edema or PDR	1,101	103	[15]
Any ocular surgery			
Cataract extraction	3,093	103	[15,16]
Vitrectomy or retinal detachment	6,841	103	[15,16]
Glaucoma-related surgeries	342	103	[15,17]
Nephropathy			
Sustained microalbuminuria	437	437	[18]
Proteinuria	748	748	[18]
End-stage renal disease			
Hemodialysis	99,046	99,046	[19]
Renal transplant	138,071	44,331	[19]
Neuropathy			
Clinical neuropathy	511	511	[15]
Lower extremity ulcer	3,987	598	[15,20]
Amputation	42,929	1,500	[15]
Cardiovascular disease			
Angina	8,282	2,139	[15]
Silent myocardial infarction	0	2,307	[15]
Myocardial infarction	41,744	2,307	[15]
PTCA	8,282	2,139	[15]
CABG	60,685	2,307	[15]
Myocardial infarction with CABG	60,685	2,307	[15]
Congestive heart failure	34,635	7,620	[21]
Hospitalized arrhythmias (atrial fibrillation)	20,442	2,557	[22,23]
Transient ischemic attack	5,326	195	[15]
Stroke	55,278	18,448	[15]
Acute metabolic complications			
Diabetic ketoacidosis	8,980	NA	[24]
Hypoglycemia requiring hospitalization	7,315	NA	[15]
Death			
	74,776	NA	[25]

Abbreviations: NA, not applicable; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

^a Costs were expressed in year 2014 US dollars using the general Consumer Price Index to reflect inflation.

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