Summary of the DCCT/EDIC Study

The Diabetes Control and Complications Trial (DCCT, 1982-93) and the Epidemiology of Diabetes Interventions and Complications (EDIC, 1994-2006) follow-up study have been ongoing for more than twenty years. (22-25) After a mean follow-up of approximately 16 years, the cohort remains remarkably complete with 94% of the original cohort being actively followed. In concert, the clinical trial and subsequent follow-up have provided more information regarding the relationship among glycemia, other risk factors and long-term complications, and the effects of glycemic therapy, than any other study.

The DCCT was a multicenter, randomized clinical trial designed to compare intensive with conventional diabetes therapy with regard to their effects on the development and progression of the early vascular and neurologic complications of insulin-dependent diabetes mellitus.

The goal of the EDIC follow-up was to examine the longer term effects of the original DCCT interventions, especially as they apply to complications, such as cardiovascular and more advanced stages of retinal and renal disease, that require a longer period of time to develop. (24) The EDIC study has been remarkably fruitful in discovering the long term "imprinting" effects (metabolic memory) of the previous intensive and conventional therapies, and in delineating the interactions among risk factors, with regard to microvascular complications. (25-27) In addition, EDIC established, for the first time, the role of intensive therapy and chronic glycemia with regard to atherosclerosis. (28,29)

The following is a summary of the DCCT/EDIC Study results.

Background. Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (T1D). We examined whether intensive treatment (IT) with the goal of maintaining blood glucose concentrations close to the normal range could decrease the development and progression of these complications.

The DCCT (1983-93, mean follow-up of 6.5 years) demonstrated the beneficial effects of IT, aimed at achieving glycemic levels as close to the non-diabetic range as safely possible, compared with CT on retinopathy, nephropathy, and neuropathy. (23, 30-35) (Table 1.1) In addition, the relative costs and risks of intensive therapy (36,37) and its effects on neurocognitive function (38), quality of life (39), and cardiovascular disease (40) were delineated. The relationship among glycemic levels, other risk factors, and diabetic complications were also established. (41,42)

The DCCT represented a landmark study in many ways. Not only did the DCCT clearly define the role of glucose control in the development and progression of the long-term complications of diabetes mellitus, it demonstrated the strength of the randomized controlled clinical trial. The DCCT established the metabolic goals of diabetes care and the means to achieve those goals.

The primary goal of the EDIC study was to determine the long-lasting effects of the previously assigned therapies, based on an intention-to-treat analysis, on diabetic complications. Those complications that require longer time to develop than the original DCCT period of follow-up, including more advanced microvascular complications and cardiovascular disease, were of particular interest.

Table 1.1
Reduction in Risk for Microvascular Complications with Intensive Therapy, Compared with Conventional Therapy, during DCCT and EDIC (Combined Primary Prevention and Secondary Intervention Cohorts)

	Percent Reduction	
Complication	**During DCCT**	**During EDIC**
Retinopathy		
3-step change	63	72
Proliferative	47	76
Macular edema	26*	77
Laser therapy	51	77
Nephropathy		
Microalbuminuria (> 28mg/min)	39	53
Clinical albuminuria (> 208mg/min)	54	82
Neuropathy+	60	

*P< 0.001 for all reductions, except for macular edema during DCCT, which was ns.
+EDIC assessment of neuropathy different than DCCT assessment, precluding comparison of DCCT and EDIC results

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Methods. The DCCT studied a cohort of 1,441 subjects between 13 and 39 years old with type 1 diabetes mellitus (T1DM) for 1-15 years. (22,23) All participants were relatively healthy except for diabetes and were free of severe diabetes-related complications. The Primary Prevention cohort consisted of 726 subjects with T1DM for 1-5 years and no diabetes-related complications (no microaneurysms on fundus photography and urine albumin excretion <40 mg/day). The Secondary Intervention Cohort consisted of 715 subjects with T1DM for 1-15 years and mild to moderate nonproliferative retinopathy and a urinary albumin excretion rate <200 mg/day. Subjects were randomized to conventional (CT) or intensive diabetes therapy (IT). The intent of IT was to achieve blood glucose levels of 70-120 mg/dL in the morning and before meals, <180 mg/dL after meals, and an HbA1c in the non-diabetic range (<6.05%). Although it was not feasible to achieve these glycemic targets consistently in the majority of the subjects assigned to the IT group (fewer than 5% maintained an average HbA1c <6.05%), there was a substantial difference in glycemic control between the IT and the CT groups. The CT group maintained an average HbA1c of about 9.0% (similar to their baseline value) throughout the 3-9 (mean 6.5) years of follow-up. Those in the IT group lowered their HbA1c to about 7.0% and maintained this for the duration of the study (Figure 1.1).

Following the end of the DCCT in 1993, and a transitional period during which the conventional treatment group was taught intensive therapy and the clinical care of all of the subjects was transferred to their own health care providers, an observational study of the DCCT cohort, entitled Epidemiology of Diabetes Interventions and Complications, was launched. (24) During the transition from the DCCT clinical trial to the EDIC observational study, the difference in glycemic control, measured by HbA1c, that had been approximately 2% during the DCCT (7.2% in the intensive treatment group compared with 9.1% in the conventional treatment group) narrowed (7.9% vs. 8.1% in IT and CT groups, respectively). (23,25) The difference in mean HbA1c between the two original treatment groups has become statistically indistinguishable during the most recent six years of EDIC follow-up. (Figure 1.1)

Phase 1 of the EDIC follow-up study spanned twelve years. The total mean follow-up of the original cohort was approximately 16 (range 13-20) years. Retention of the DCCT cohort

remained outstanding. Ninety-six percent of the surviving DCCT cohort joined EDIC in 1994 and 94% of the original cohort (n= 1357 of 1441) remained active throughout the first phase of EDIC. The demographics of the EDIC study population at closeout are shown in Table 1.2.

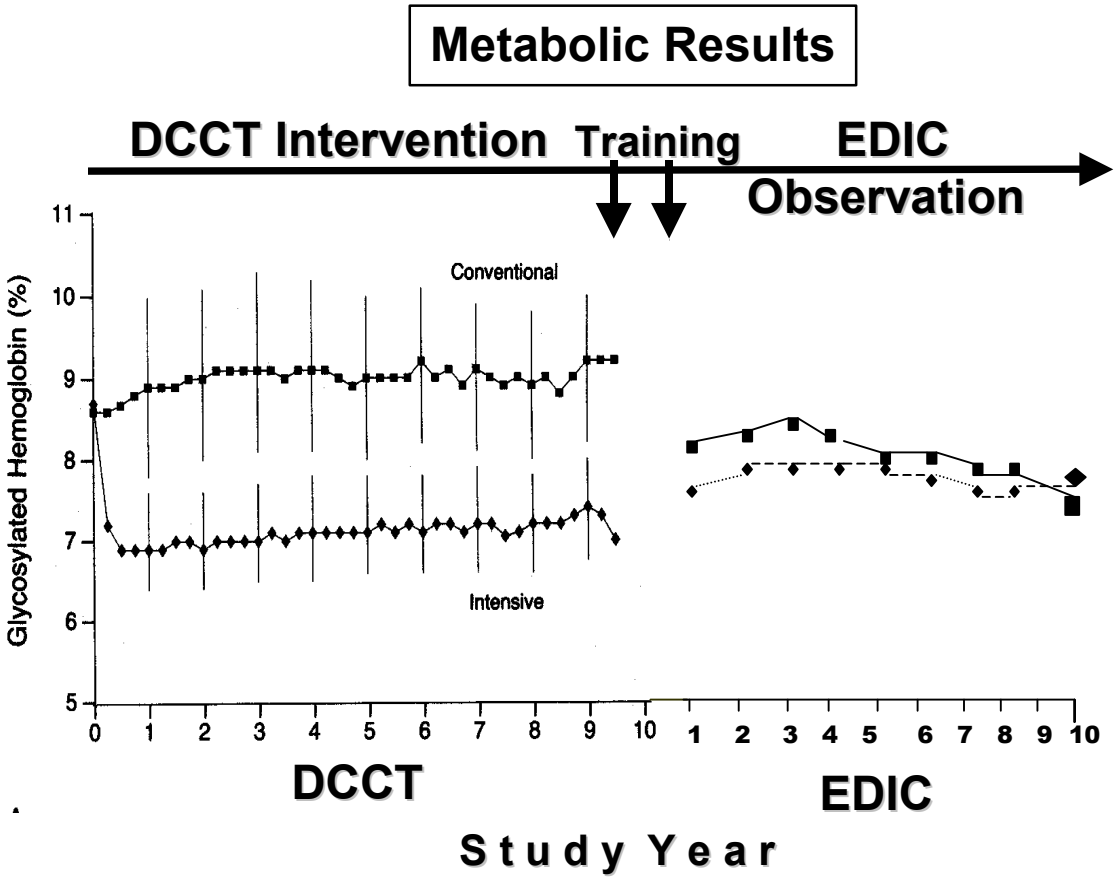

Figure 1.1: Glycemic Levels during DCCT/EDIC as measured by glycosylated hemoglobin (HbA1c). Medians with 25th to 75th percentiles shown.

Table 1.2
Characteristics of DCCT/EDIC Study Population 2003 (EDIC 10 year followup)
Original Cohorts

	Primary Prevention n= 638	Secondary Intervention n= 638	All 1276
Attained age (years)	43	45	44
Gender (% males)	52	53	53
Diabetes Duration (years)	19	26	22
Race (% Caucasian)	96	97	97
Retinopathy (%)			
None	2	0	1
Mild NPDR or Worse	55	77	63
Moderate NPDR or Worse	25	44	34
Severe NPDR or Worse	9	30	19
Proliferative DR or Worse	8	27	18
HRC[#] or Worse	7	20	13
CSME[#]	13	25	19
Laser therapy (all)	8	21	8
For macular edema	7	11	15
For proliferative DR	7	18	8
VA < 20/200 (both eyes)	0	0	0
Nephropathy (%)			
No microalbuminuria	70	55	62
> 40 mg/24 h	30	45	38
> 300 mg/24 h	7	13	10
Severe renal*	2.1	2.5	2.3

*Cr > 2.0, dialysis, or renal transplant.
[#]NPDR—nonproliferative diabetic retinopathy.
CSME—clinically significant macular edema.
HRC—high risk characteristics.

Results. In the primary-prevention cohort, intensive therapy reduced the adjusted mean risk for the development of retinopathy by 76 percent (95 percent confidence interval, 62 to 85 percent), as compared with conventional therapy. In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54 percent (95 percent confidence interval, 39 to 66 percent) and reduced the development of proliferative or severe non-proliferative retinopathy by 47 percent (95 percent confidence interval, 14 to 67 percent). In the two cohorts combined, intensive therapy reduced the occurrence of microalbuminuria (urinary albumin excretion of ≥40 mg per 24 hours) by 39 percent (95 percent confidence interval, 21 to 52 percent), that of albuminuria (urinary albumin excretion of ≥300 mg per 24 hours) by 54 percent (95 percent confidence interval, 19 to 74 percent), and that of clinical neuropathy by 60 percent (95 percent confidence interval, 38 to 74 percent). In addition, there was a 41% decrease (95 percent confidence interval, -10 to 68) in macrovascular events although not statistically significant in the intensive treatment group. The chief adverse event associated with intensive therapy was a two- to three-fold increase in severe hypoglycemia.

The EDIC follow-up has demonstrated that the differences in outcomes between the IT and CT groups persist for as long as ten years, despite the narrowing of glycemic differences that appeared to explain the vast majority of the treatment differences during the DCCT. (25-27)

The prolonged salutary effects of IT and prolonged deleterious effects of CT have been named "imprinting" or "metabolic memory". During the DCCT, the frequency of cardiovascular events was too low to determine whether the interventions had significantly different effects. (40) During EDIC, two measures of atherosclerosis were employed, ultrasound measurement of carotid intima-media wall thickness (IMT) (28,43) and electron beam (or multidetector) computed tomography of the heart to measure coronary artery calcification. (29) The progression of IMT during EDIC was decreased in the former IT group compared with the former CT group. (28) Similarly, the prevalence of coronary calcification was less in the former intensive treatment group. (29) Both measures were associated with the level of glycemia during the DCCT, independent of other established cardiovascular risk factors. The frequency of major CVD clinical events (defined as any one of the following: fatal and non-fatal myocardial infarctions and stroke, silent myocardial infarctions, angina confirmed by a positive stress test or catheterization, and PTCA or CABG) has increased during EDIC. Preliminary analysis of the clinical events has shown differences between the two original treatment groups that support a benefit of IT on clinical disease as was previously demonstrated for atherosclerosis. Collaboration with investigators centered at Medical University of South Carolina, and supported by an independent Program Project from NHLBI, has explored inflammatory, lipid, hemorheologic and other risk factors for micro- and macrovascular disease during EDIC.

Conclusions. In summary, the DCCT/EDIC Research Group has established the following:

1. Intensive therapy aimed at achieving glycemic levels as close to the non-diabetic range as safely possible reduces the development and progression of all diabetes-specific complications by as much as 76%.

2. Intensive therapy reduces measures of atherosclerosis over time, and probably reduces CVD events as well.

3. Intensive intervention is most effective when implemented early in the course of diabetes; if intensive intervention is delayed, the momentum of complications is harder to slow, as shown by the results of the secondary intervention group.

4. The salutary effects of a 6.5-year mean period of intensive therapy persist for at least 10 years after differences in glycemia between the original intensive and conventional therapy groups have disappeared (metabolic memory).

5. Chronic glycemia and duration of diabetes are the major factors in the pathogenesis of microvascular complications in Type 1 diabetes and play a role in the development of atherosclerosis

1.3 Study Goal

In planning the future study of the DCCT/EDIC cohort, the most extensively phenotyped (and genotyped) population with Type 1 diabetes, we have carefully selected those clinical and scientific questions that can be addressed uniquely through further study, or with additional analyses of collected data, of the DCCT/EDIC cohort. New tools such as imaging methods, proteomics and metabolomics, that have the potential to advance our understanding of Type 1 diabetes and its complications have become available since we added genomic studies to the DCCT/EDIC five years ago.

The studies in the core follow-up described in this protocol continue methods that have been used consistently during DCCT/EDIC and utilize new studies and analyses to address remaining clinical and scientific questions regarding Type 1 diabetes and its complications. The ability to perform the proposed studies in the multicenter environment of DCCT/EDIC and the projected burden on our research volunteer partners has been included in our planning. The success of DCCT/EDIC has largely been predicated on the extraordinary cooperation of our cohort over the past twenty years, and we will not do anything to jeopardize that special relationship.

The core protocol has been designed to provide the resources necessary to continue follow-up of the DCCT/EDIC cohort on an annual basis, as during the past 12 years of EDIC. The core study will include an annual physical examination, interval history, standard questionnaires, and biochemical measurements, as performed previously during EDIC, with the expectation that the retention of participants will remain at the high levels experienced in the past. In addition, those specialized studies that have been central to the DCCT and EDIC, including assessment of retinopathy, nephropathy, neuropathy, and cardiovascular disease are included as part of this core. Continuation of identical, or comparable, methods is a focus of the protocol with the goal of providing a continuous series of interpretable observations and analyses over time.

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