Published in final edited form as:
*J Urol*. 2011 May ; 185(5): 1828–1834. doi:10.1016/j.juro.2010.12.098.

# EFFECT OF INTENSIVE GLYCEMIC THERAPY ON ERECTILE FUNCTION IN MEN WITH TYPE 1 DIABETES IN THE DIABETES CONTROL AND COMPLICATIONS TRIAL/EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS STUDY

**Hunter Wessells, M.D.**[1], **David F. Penson, M.D.**[2], **Patricia Cleary, M.S.**[3], **Brandy N. Rutledge, Ph.D.**[3], **John M. Lachin, Sc.D.**[3], **Kevin T. McVary, M.D.**[4], **David S. Schade, M.D.**[5], **Aruna V. Sarma, Ph.D**[6], and **the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group**[*]

[1]Department of Urology and Diabetes Endocrinology Research Center, University of Washington School of Medicine 1959 Pacific Avenue NE, Seattle, Washington 98195

[2]Department of Urologic Surgery, Vanderbilt University, 2525 West End Avenue, Suite 600 Nashville, Tennessee

[3]The Biostatistics Center, The George Washington University, 6110 Executive Blvd Suite 750, Rockville, MD 20852

[4]Northwestern University, Department of Urology, Tarry Building Rm 11-725, 303 East Chicago Avenue, Chicago IL 60611-3010

[5]University of New Mexico, School of Medicine, Department of Med/Div. of Endocrinology & Metabolism, 2211 Lomas Blvd NE, Albuquerque, NM 87131

[6]University of Michigan, Departments of Urology and Epidemiology, 3875 Taubman Center, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0330

## Abstract

**OBJECTIVE—**To determine whether intensive glycemic therapy reduces the risk of erectile dysfunction (ED) in men with type 1 diabetes enrolled in the Diabetes Control and Complications Trial (DCCT).

**MATERIALS AND METHODS—**DCCT randomized 761 males with type 1 diabetes to intensive or conventional glycemic therapy in 28 sites between 1983–1989, of whom 366 had diabetes for 1–5 years and no microvascular complications (primary prevention cohort) and 395 for 1–15 years with non-proliferative retinopathy or microablbuminuria (secondary intervention cohort). Subjects were treated until 1993 and followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study. In 2003, we conducted an ancillary study using a validated assessment of ED in 571 men (80% participation rate); 291 in the primary cohort and 280 in the secondary cohort.

**RESULTS—**Twenty-three percent of participants reported ED. The prevalence was significantly lower in the intensive versus conventional treatment group in the secondary cohort (12.8% versus 30.8%, p=0.001); but not the primary cohort (17% versus 20.3%, p=0.49). The risk of ED in both

Corresponding Author: Hunter Wessells, M.D., Department of Urology Box 359868, Harborview Medical Center, 325 Ninth Avenue, Seattle Washington 98104, Tel: 206-731-3205, Fax: 206-731-4709, wessells@u.washington.edu.

[*]A complete list of investigators and members of the Research Group appears in N Engl J Med 2005; 353(25):2643-53 and is listed in an electronic appendix.

primary and secondary cohorts was directly associated with mean HbA1c during DCCT and EDIC combined. Age, peripheral neuropathy, and lower urinary tract symptoms were other risk factors.

**CONCLUSIONS—**A period of intensive therapy significantly reduced the prevalence of ED ten years later among those in the secondary intervention cohort, but not the primary prevention cohort; higher HbA1c was significantly associated with risk in both cohorts. These findings provide further support for early implementation of intensive insulin therapy in young men with type 1 diabetes.

### Keywords

Glycemic Control; Diabetes; Erectile Dysfunction; Risk

## INTRODUCTION

One in five men over 20 years of age in the United States report ED. Of all co-morbid medical conditions, diabetes mellitus imparts the greatest risk of ED and its onset is associated with a reduction in health related quality of life[1] and an increase in depressive symptoms.[2] With diabetes, ED begins 10–15 years earlier than in the general population[3] and is less responsive to oral pharmacological therapy.[4] Although its pathogenesis is not completely understood, ED in diabetes is associated with peripheral neuropathy, nephropathy and retinopathy.[5, 6]

Longitudinal and cross-sectional studies have demonstrated an association between glycemic control and ED in men with diabetes;[7–10] those with “poor” control having 2–5 fold increased risk of ED compared to those with “good” control. One small clinical trial, in men with type 2 diabetes and ED, showed reductions in HbA1c and blood pressure led to improvements in erectile function.[11] However, no controlled clinical study has shown that the risk of ED could be lowered by reductions in glycemia.

The DCCT, a randomized controlled trial comparing conventional and intensive therapy for glycemic control in type 1 diabetes (T1DM), and its observational follow-up, the EDIC Study, convincingly demonstrated that intensive therapy aimed at near normal levels of glycemic control reduces the risk of retinopathy, nephropathy, neuropathy, and cardiovascular disease. [12] As part of the *UroEDIC* ancillary study of urologic complications, we assessed erectile function to determine whether intensive glycemic therapy during DCCT, and improved glycemic control during DCCT/EDIC, lowered the risk of prevalent ED ten years after the close of the DCCT.

## METHODS

### Subjects

The DCCT randomly assigned 761 males with T1DM to intensive or conventional therapy, with a mean of 6.5 years of treatment during 1983–1993.[13] The 378 primary prevention cohort males had no retinopathy or nephropathy and 1–5 years of diabetes. The 383 secondary intervention cohort males had mild to moderate non-proliferative retinopathy, microalbuminuria and 1–15 years of diabetes. Individuals with hypertension, symptomatic ischemic heart disease, or symptomatic peripheral neuropathy requiring treatment were excluded from enrollment in DCCT at baseline.

Figure 1 shows the flow of participants through the trial. Of the 761 men enrolled, 746 completed DCCT closeout in 1993. Of these, 720 (97%) enrolled in EDIC in 1994.[14] Of the 713 men still active in EDIC year 10, 591 (83%) agreed to participate in *UroEDIC*. Of these,

571 (80%) men provided data on erectile function and comprise the study cohort for the current analyses. The institutional review board approved the study, and the Federal Government issued a Certificate of Confidentiality.

## DCCT Intervention and Other Therapies

Intensive therapy was aimed at achieving near normal levels of HbA1c using multiple daily insulin injections or continuous subcutaneous insulin infusion with dose adjustments based on frequent self-monitoring of glucose. Conventional therapy was aimed at maintaining clinical well-being with 1–2 daily insulin injections with no glucose targets.

At the end of DCCT, conventional group subjects were trained in intensive therapy and all subjects were returned to their own physicians for diabetes management with the recommendation to implement intensive therapy. By EDIC year 10, 97% of intensive and 94% of conventional group subjects were implementing intensive therapy, and mean HbA1c in the two groups had equalized.[15, 16]

## Assessment of Erectile Dysfunction

We administered the International Index of Erectile Function (IIEF), a widely used reliable, validated multi-dimensional self report instrument for the evaluation of male sexual dysfunction, at EDIC year 10.[17] Because 20% of participants responded “Did not attempt intercourse” on questions 1–5 of the Erectile Function (EF) domain, we created a proxy item to assess erectile function in the entire cohort regardless of sexual activity and presence or absence of a partner. IIEF Question 15 asks participants: “Over the past 4 weeks, how would you rate your confidence that you get and keep your erection?” Those who answered ‘Very Low’ or ‘Low’ were classified as having ED. Those who answered ‘Moderate’, ’High’, or ‘Very High’ were classified as not having ED. Among the men who engaged in sexual intercourse during the preceding four weeks, this definition of ED correlated strongly with EF domain scores ($r=0.77$, $p<0.001$) and ED bother ($r= 0.80$, $p<0.001$).

## Measurement of Other Factors

HbA1c was measured at baseline, quarterly during DCCT, and annually in EDIC. Therefore, mean HbA1c over DCCT/EDIC weighted each DCCT value by 0.25, and EDIC value by 1.[16]

Peripheral neuropathy was defined during the DCCT by the presence of distal symmetrical polyneuropathy and an abnormal nerve conduction study; or during EDIC by >6 positive responses to the Michigan Neuropathy Screening Instrument (MNSI) *or* a score >2 on the examination.[18] Retinopathy was assessed using fundus photographs that were centrally graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale.[19] Albumin excretion rate (AER) was measured in half of the cohort annually. Nephropathy was defined as microalbuminuria (AER 40–300 mg/24hr) or albuminuria (AER >300 mg/24hr).

Subclinical atherosclerosis was assessed by the sum of the standardized common and internal carotid artery intima-media thickness on centrally graded carotid ultrasonography[20] at EDIC years 1 and 6; and by the presence of coronary artery calcification on centrally graded computed tomography conducted during EDIC year 8.[21] Lipid profiles were measured in half of the cohort annually.

We used the American Urological Association Symptom Index (AUASI) to assess urinary symptoms of nocturia, frequency, urgency, weak urinary stream, intermittency, straining, and the sensation of incomplete emptying.[22] Lower urinary tract symptoms (LUTS), were

defined as an AUASI ≥ 8. Other drug treatments were assessed during DCCT/EDIC with a yearly drug inventory.

### Statistical Methods

The Wilcoxon rank-sum test assessed differences between groups in quantitative variables, and the contingency Chi-square test, or Fisher Exact test as appropriate, assessed categorical variables. Effects nominally significant at $p \leq 0.05$ are cited. All analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

A multivariable logistic regression model estimated the associations between several covariates and the presence of ED at EDIC year 10 using odds ratios (OR) and 95% confidence intervals. Probabilities of ED by treatment group were calculated separately for primary and secondary cohorts after adjustment for age, HbA1c levels at DCCT eligibility and duration of diabetes. Odds of ED as a function of HbA1c levels were estimated from separate multivariable logistic regression models using the log of DCCT mean HbA1c and time-weighted DCCT/EDIC mean HbA1c nested within primary and secondary cohort and adjusted for age, HbA1c levels at DCCT eligibility, duration of diabetes and duration of treatment/follow-up in the DCCT**. The treatment group by cohort interaction was also adjusted for other covariates in a model that included a cohort by covariate interaction, i.e. allowing for different covariate effects within each cohort.**

A separate multivariable logistic regression model examined the association of clinical risk factors with ED in the combined (intensive plus conventional) cohort. Variables nominally significant at the $p \leq 0.05$ level in bivariate analyses were included in the model. **Throughout, nominal p-values are presented with no adjustment for multiple tests of significance.**

## RESULTS

Figure 1 shows the history of the 761 males who entered the DCCT. Of these, 735 survived and were eligible to participate in the UroEDIC assessment at the EDIC year 10 visit, 713 attended the EDIC year 10 visit, 591 (84.5%) completed the UroEDIC questionnaire, and 571 answered the erectile function question. Of these, 23% fulfilled the criteria for ED (i.e. reported “Very Low” or “Low” confidence).

Characteristics of the 571 men in UroEDIC (Supplemental Table) revealed that at DCCT baseline, diabetes duration was significantly shorter in the conventional vs. intensive treatment group ($p=0.03$); at EDIC year 10, the proportion of participants with nephropathy, retinopathy, peripheral neuropathy, and hypertension were all lower in the intensive treatment group, reflecting the previously described benefits of intensive therapy.[13, 15] Sildenafil citrate use was reported by 30 subjects (12 with ED and 18 without), representing about 5% of those in each treatment group and 9% of those reporting ED.

### DCCT Treatment and Erectile Dysfunction

More conventional treatment group participants expressed “Very low” (17.5%) or “Low” (8.9%) confidence in erection than in the intensive treatment group (11.1% and 8.6%, respectively). Overall, ED was present in 26.5% and 19.6% of the former conventional and intensive groups, respectively.

Table 1 presents the effects of DCCT intensive versus conventional treatment, separately within the primary and secondary cohorts, on the prevalence of ED after adjustment for age, HbA1c at DCCT eligibility and duration of diabetes. Within the primary cohort, DCCT treatment group had no significant effect (OR=1.24, 95%CI=0.68, 2.28), with an adjusted

prevalence of 20.3% versus 17% in the conventional versus intensive treatment group. Conversely, in the secondary cohort, DCCT treatment group had a substantial effect (OR=0.33, 95%CI=0.18, 0.60) with an adjusted prevalence of 30.8% versus 12.8% in the conventional versus intensive group.

The treatment group effect in the primary cohort differed significantly from that in the secondary cohort (p=0.003). Increasing age and increased DCCT baseline HbA1c also had strong effects on the prevalence of ED. Results were unchanged in analyses including all 30 sildenafil users as having ED, or excluding them entirely.

### HbA1c Measures and Erectile Dysfunction

DCCT mean HbA1c levels were substantially higher among those with ED versus those without in the secondary cohort, but with an attenuated difference in the primary cohort. (Table 2) For every 10% higher mean DCCT HbA1c level (e.g. 8.8% versus 8%), the adjusted odds of ED increased by 55% (p<0.0001) in the secondary cohort, and by 21.5% (p=0.04) in the primary cohort. The difference in the HbA1c effect between cohorts approached significance (p=0.07). For every 10% increase in DCCT/EDIC mean HbA1c, the odds of ED increased by 97% in the secondary cohort versus 74% in the primary cohort, p<0.0001 for each.

### Erectile Dysfunction Risk Factors at EDIC Year 10

Table 3 compares clinical characteristics of the 132 men with ED to the 439 without ED. In unadjusted analyses, a number of factors were nominally associated with ED including age, DCCT therapy group, measures of HbA1c, presence of microvascular complications, cardiovascular factors, LUTS, and cigarette smoking, among others.

In adjusted analyses, increasing age had the strongest effect on prevalence of ED ($\chi^2$=29, p<0.0001, 13% greater odds per year of age, 95% CI=8.5, 20%), followed by DCCT/EDIC mean HbA1c ($\chi^2$=14.7, p=0.0002, 60% greater odds per 10% higher mean HbA1c, 95% CI=25, 105%). While retinopathy and nephropathy were not significant after adjusting for mean HbA1c, there remained a higher adjusted proportion with ED among those with peripheral neuropathy and LUTS versus not (33 vs. 17%, p=0.02) and (31 vs. 19%, p=0.04), respectively.

## DISCUSSION

In the largest most extensive prospective study of T1DM in the world, men randomized to intensive glycemic therapy during DCCT had a significantly lower prevalence of subsequent ED *in the secondary intervention cohort with limited microvascular complications at baseline.* Although no difference was noted between treatment groups in the primary prevention cohort of men without diabetic complications at baseline, in both cohorts the risk of ED increased with increasing levels of HbA1c over the average of 17.5 years of the DCCT and EDIC combined. HbA1c at eligibility for DCCT, at the very outset of the trial, also influenced the odds of subsequent ED. Thus, cumulative glycemic exposure over a long period of time is required before diabetes-related ED becomes clinically apparent. To place the findings in context, a mean HbA1c of 8.8% over the course of DCCT and EDIC imparted a 1.5 to 2 fold greater odds of ED compared to a mean HbA1c of 8.0%. This confirms other reports of increased ED risk associated with poor glycemic control.[7–10] The DCCT/EDIC provides the novel additional insight that, *in the secondary cohort*, lowering of HbA1c via intensive glycemic control reduced the odds of ED by 63%.

An important question is why we only saw the effect of intensive glycemic control in the secondary cohort. The primary cohort contained more adolescents, shorter diabetes duration,

lower baseline HbA1c, shorter treatment duration, lower age and diabetes duration at EDIC year 10, and a lower prevalence of ED. Nevertheless, analyses accounting for all of these factors **in a cohort by covariate interaction model** failed to explain the diminished treatment group difference in prevalence of ED within the primary cohort.

The accumulation of advanced glycation end products (AGEs), a consequence of long-term hyperglycemia, is thought to mediate many diabetic complications.[23] AGEs have also been implicated in impairment of neurogenic and endothelium dependent relaxation of the corpus cavernosum.[24–26] In the case of other diabetic complications, including retinopathy and nephropathy, the term “metabolic memory” has been used to explain the persistent protective effect of intensive therapy well beyond the time frame of the DCCT.[12–16] Although intensive therapy during DCCT did reduce the incidence of hypertension, the cohort overall is similar to T1D patients in general with a point prevalence of hypertension in excess of 45% at year 10 of EDIC. An important future question is whether the reduced risk of ED associated with intensive therapy in the secondary cohort will persist.

Even though T1DM greatly increases the risk of ED, age is an independent risk factor for ED in the DCCT/EDIC, and in the general population.[1, 27] Peripheral neuropathy and LUTS were the only diabetic complications associated with ED in adjusted analyses. It is possible these complications are surrogate markers of autonomic neural dysfunction, an important proposed mechanism of diabetes-associated ED.

There are several limitations to this study. First, 25% of the original cohort failed to participate in the UroEDIC study due to losses-to-follow-up over time and non-response. Second, the absence of data on serum testosterone is a potential limitation of the study, although hypogonadism is not prevalent in T1DM[28] and its contribution to ED remains controversial.[29] Third, the use of a single item as opposed to the full EF domain of the IIEF may have reduced our ability to detect milder degrees of ED severity, as might our dichotomous definition of ED that excluded “moderate” responses. Patients who used sildenafil were counted as having ED in the primary analyses only if they reported “very low” or “low” confidence in erection. This also may have underestimated ED prevalence in the study population. However, the results of the study were unchanged when all subjects using sildenafil were counted as having ED, or if they were excluded from the analysis. Finally, ED was assessed at a single point in time in the history of diabetes for these subjects. Characterization of baseline ED status and assessment over a period of years to describe the evolution of ED and the growth (or waning) of treatment group effects would be optimal.[30]

## CONCLUSIONS

Men with diabetes who received intensive glycemic therapy during the DCCT had a significantly lower prevalence of ED ten years later in EDIC, principally among those enrolled into the secondary intervention cohort. The prevalence of ED was also strongly associated with the levels of HbA1c during the DCCT and later in EDIC. These results from an extremely well characterized longitudinal cohort study provide further strong support for early implementation of intensive therapy in young men with established T1DM and limited microvascular complications, for whom tight glycemic control could reduce the burden of ED.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

A complete list of participants in the DCCT/EDIC research group can be found in Archives of Ophthalmology, 2008;126(12):1713.

Contributors of free or discounted supplies and/or equipment: Lifescan, Roche, Aventis, Eli Lilly, OmniPod, Can-Am, B-D, Animas, Medtronic, Medtronic Minimed, Bayer (donation one time in 2008), Omron.

Funding/Support: The DCCT/EDIC project is supported by contracts with the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, National Eye Institute, National Institute of Neurological Disorders and Stroke, the General Clinical Research Centers Program and the Clinical and Translational Science Awards Program, National Center for Research Resources, and by Genentech through a Cooperative Research and Development Agreement with the National Institute of Diabetes and Digestive and Kidney Diseases.

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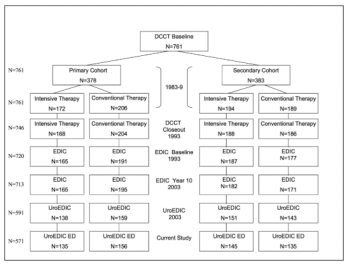


**Figure 1.**

Flow of male participants through DCCT and EDIC to UroEDIC showing time line of enrollment and number of participants* unavailable owing to inactive study status or death. ED=Erectile Dysfunction

* EDIC has an “open door” policy regarding participation, allowing inactive participants to return to the study. Thus, the number of subjects in a given year may be greater than in a previous one.

## Table 1

Multivariable logistic regression model* examining the difference between DCCT intensive versus conventional glycemic therapy in the prevalence of erectile dysfunction at EDIC year 10 follow-up after trial completion separately within the primary prevention and secondary intervention cohorts, adjusted for other baseline factors.

| Variable | OR (95%CI) | p-value† |
|---|---|---|
| DCCT Intervention (Intensive v Conventional Glycemic Therapy)‡ | | |
| In the Primary Prevention Cohort | 1.24 (0.68, 2.28) | 0.49 |
| In the Secondary Intervention Cohort | 0.33 (0.18, 0.60) | <0.001 |
| HbA1c at Eligibility (per HbA1c%) | 1.36 (1.19, 1.56) | <0.001 |
| Diabetes Duration (per month) | 1.00 (0.99, 1.01) | 0.87 |
| Age (per year) | 1.13 (1.09, 1.17) | <0.001 |

Note: OR=Odds Ratio, CI=Confidence Interval

*Multivariable logistic regression model with erectile dysfunction as the dependent variable and the following independent variables: HbA1c at DCCT eligibility, diabetes duration, age and DCCT treatment group nested within cohort. All variables adjusted for all others in model. The multivariable model was based on 571 subjects, 132 with erectile dysfunction.

†P-value based on Likelihood Ratio Chi-square test

‡p=0.003 for test of DCCT treatment group by primary vs. secondary cohort interaction. No other two-way interactions approached significance among any pair of variables in the model.

**Table 2**

Mean HbA1c levels by erectile dysfunction status at EDIC year 10 by primary and secondary cohort and adjusted odds of erectile dysfunction per 10% higher HbA1c levels.

| | No Erectile Dysfunction | | Erectile Dysfunction | | | |
|---|---|---|---|---|---|---|
| | **N** | **Mean±SD** | **N** | **Mean±SD** | **% Increase in Odds per 10% Higher HbA1c(95% CI)*** | **Adjusted P value*** |
| **A. DCCT HbA1c** (1983–1993) | | | | | | |
| **Primary Prevention Cohort** | 230 | 8.06±1.34 | 61 | 8.68±1.67 | 21.5% (1.2, 46.0%) | 0.04 |
| **Secondary Intervention Cohort** | 209 | 7.89±1.25 | 71 | 8.63±1.30 | 55.0% (27.4, 88.5%) | <0.0001 |
| **B. DCCT/EDIC HbA1c** (1983–2003) | | | | | | |
| **Primary Prevention Cohort** | 230 | 7.94±0.99 | 60 | 8.73±1.32 | 74.4% (34.4, 126%) | <0.0001 |
| **Secondary Intervention Cohort** | 209 | 7.90±1.00 | 69 | 8.56±1.04 | 97% (51.2, 256%) | <0.0001 |

*Odds of erectile dysfunction, 95%CI and p-value from separate multivariable logistic regression models using either the log of DCCT mean HbA1c or of the time-weighted DCCT/EDIC mean HbA1c nested within primary and secondary cohort and adjusted for the HbA1c at DCCT eligibility, diabetes duration, age, and the duration of treatment/follow-up in the DCCT. For log(HbA1c) coefficient β, the percent increase in the odds of erectile dysfunction per 10% higher HbA1c is computed as $100*(1.1^{\beta} - 1)$.

## Table 3

Distribution of clinical characteristics by erectile dysfunction status at EDIC year 10 follow-up after trial completion.

| CHARACTERISTIC | No Erectile Dysfunction (n=439) | Erectile Dysfunction (n=132) | Unadjusted p-value | Jointly Adjusted p-value |
|---|---|---|---|---|
| **Sociodemographic** | | | | |
| Attained Age(yr) | 43.5(6.4) | 48.0(5.9) | <0.001 | <0.001 |
| Race No.(%) | | | | |
| White, not of Hispanic Origin | 423(96.4) | 128(97.0) | | |
| Black, not of Hispanic Origin | 9(2.1) | 1(0.8) | 0.69 | |
| Hispanic | 4(0.9) | 2(1.5) | | |
| Asian or Pacific Islander | 3(0.7) | 1(0.8) | | |
| Married No. (%) | 334(78.0) | 97(75.8) | 0.59 | |
| Graduate Education No. (%) | 108(25.1) | 20(15.6) | 0.03 | 0.29 |
| Cigarette Smoker No. (%) | 52(12.0) | 26(20.2) | 0.02 | 0.94 |
| Depression* No. (%) | 42(9.6) | 30(22.7) | <0.001 | 0.10 |
| Antidepressant Use† No. (%) | 40(9.9) | 29(23.6) | <0.001 | |
| Body Mass Index (kg/m2) | 27.9(4.1) | 28.3(4.4) | 0.08 | |
| Waist-Hip Ratio | 0.91(0.06) | 0.92(0.07) | 0.02 | 0.63 |
| Sildenafil citrate use‡ No. (%) | 18(4.1) | 12(9.1) | 0.02 | 0.10 |
| **Diabetes Treatment and Control** | | | | |
| Intervention No. (%) | | | 0.05 | |
| Intensive therapy | 225 (51.3) | 55 (41.7) | | |
| Conventional therapy | 214 (48.7) | 77 (58.3) | | |
| Diabetes Duration (yr) | 22.0(4.8) | 22.5(4.7) | 0.29 | |
| Cohort No. (%) | | | 0.21 | |
| Primary | 230(52.4) | 61(46.2) | | |
| Secondary | 209(47.6) | 71(53.8) | | |
| HemoglobinA1c at DCCT baseline (%) | 8.6(1.5) | 9.0(1.6) | 0.003 | 0.43 |
| DCCT mean HbA1c | 8.0(1.3) | 8.6(1.5) | <0.001 | |
| Time weighted DCCT/EDIC mean HbA1c | 7.9(1.0) | 8.6(1.2) | <0.001 | 0.0002 |
| Insulin dose (units/kg/day) | 0.69(0.26) | 0.74(0.23) | 0.02 | 0.86 |
| **Microvascular Complications** | | | | |
| Retinopathy§ No.(%) | | | <0.001 | 0.19 |
| Nonproliferative or None | 286(65.1) | 54(40.9) | | |
| Proliferative | 153(34.9) | 78(59.1) | | |
| Nephropathy No. (%) | | | | |
| None (AER¶<40) | 338(77.0) | 73(55.3) | | |
| Microalbuminuria(40≤AER<300) vs. none | 73(16.6) | 29(22.0) | < 0.001 | 0.79 |
| Albuminuria (AER≥300) vs. none | 28(6.4) | 30(22.7) | < 0.001 | 0.64 |
| Creatinine Clearance, mean(SD), mL/min per 1.73m$^2$ | 121.2(28.6) | 115.0(28.8) | 0.11 | 0.41 |

| CHARACTERISTIC | No Erectile Dysfunction (n=439) | Erectile Dysfunction (n=132) | Unadjusted p-value | Jointly Adjusted p-value |
|---|---|---|---|---|
| Hypertension[#] No. (%) | 179(41.3) | 79(61.2) | <0.001 | 0.54 |
| Antihypertensive[**] Use No. (%) | 168(40.2) | 84(65.6) | <0.001 | |
| Peripheral Neuropathy ever during DCCT and EDIC[††] No. (%) | 117(29.0) | 70(58.8) | <0.001 | 0.01 |
| **Macrovascular Complications** | | | | |
| Coronary Calcification > 0 No. (%) | 145(36.1) | 69(56.6) | <0.001 | |
| Carotid Intima Media Thickness at EDIC yr 1[‡‡] | 0.05(1.40) | 1.16(2.28) | <0.001 | |
| Carotid Intima Media Thickness at EDIC year 6 [‡‡] | 0.05(1.48) | 1.21(2.27) | <0.001 | 0.09 |
| Total Cholesterol (mg/dl) | 178.9(31.9) | 182.8(39.1) | 0.65 | |
| Triglyceride (mg/dl) | 93.7(65.0) | 109.0(69.5) | 0.005 | 0.16 |
| Dorsalis pedis pulse pressure in mmHg. No. (%) | 138.1(20.0) | 142.2(25.4) | 0.10 | 0.81 |
| **Other Complications** | | | | |
| Lower Urinary Tract Symptoms (LUTS) [††] No. (%) Yes | 68(15.5) | 44(33.3) | <0.001 | 0.03 |

All variables are assessed at the time of the URO-EDIC examination except where indicated. All data are expressed as mean (SD) unless noted otherwise. Sample sizes for individual variables may not equal group totals due to missing data. Unadjusted p-values based on Wilcoxon Rank sum for differences in means and Contingency Chi Square for differences in proportions. Jointly adjusted p-values obtained from the Wald test of each covariate in a single multivariate logistic regression model that included the weighted DCCT/EDIC mean HbA1c **with no adjustment for multiple tests of significance**. Coronary calcification and year 1 carotid IMT, though significant in the unadjusted analyses, were not included in the multivariate model due to more missing observations than was the case for other covariates.

[*]Depression was self-reported. If the participant indicated so on an annual review of psychiatric events that occurred in the year(s) since the last evaluation, then the coordinator completed a documentation form to get more information (e.g. where treated, if medication was prescribed, DSM III diagnosis). Additionally if the participant indicated that they regularly took antidepressants they were included in the depression category.

[†]Anti-depressants defined by patient indicating regular usage of anti-depressants on medication form.

[‡]Sildenafil citrate use reported during yearly EDIC drug inventory.

[§]Determined by Early Treatment Diabetic Retinopathy Study <12 Nonproliferative, >=12 Proliferative.

[¶]Albumin Excretion Rate (mg/24hr).

[#]Hypertension is defined as sitting sBP≥140 mm Hg and/or dBP≥90 mm Hg or the use of antihypertensive medication.

[**]Anti-hypertensive medication for any reason including use of ACE inhibitors and angiotensin II receptor blockers.

[††]Defined in DCCT by the presence of definite clinically evident distal symmetrical polyneuropathy and an abnormal nerve conduction study or in EDIC by Michigan Neuropathy Screening Instrument >6 positive responses on the questionnaire **or** a score >2 on the examination.

[‡‡]Sum of the intima media thickness of the standardized common and internal arties.

[§§]The AUASI contains seven questions assessing urinary symptoms of nocturia, frequency, urgency, weak urinary stream, intermittency, straining, and the sensation of incomplete emptying. The AUASI is expressed as a summary score with a score breakdown as follows: <8 (No), ≥ 8 (Yes).