

## Analysis Dataset from the Four Year Adolescent Retinopathy Paper\*

(\*DCCT/EDIC Research Group (2001). Beneficial effects of intensive therapy of diabetes during adolescence: Outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *The Journal of Pediatrics*. 139:804-812)

**Format:** Three data sets are stored in **SAS** export library.

**EDICADO4:** Adolescent retinopathy and nephropathy data;

**EDAD4HYP:** Adolescent DCCT hypoglycemia data;

**EDAD4ADL:** Adult and adolescent retinopathy/nephropathy/EDIC hypoglycemia data (for table 6).

### **Structure:**

1) **EDAD4:** One record per patient (171 patients who were adolescents when randomized at DCCT entry, and had retinopathy or nephropathy data at EDIC year 4 were included). Note that retinopathy data is reported only for patients who had fundus photo data at EDIC year 4, and nephropathy data is reported only for those who had renal data at EDIC year 3 or 4.

2) **EDAD4HYP:** One record per patient (195 patients who were adolescents when randomized at DCCT entry were included).

3) **EDAD4ADL:** One record per patient (1129 adults and 171 adolescents with retinopathy or renal data at EDIC year 4 were reported).

**Contents:** A complete SAS contents listing is attached.

**Summary Statistics:** A complete summary statistics (mean/std for continuous variables, frequency for categorical variables) is attached separately.

### **Data Collection:**

Fundus photo data were collected in the full cohort at DCCT closeout and EDIC year 4.

Renal data were collected in the full cohort at DCCT closeout, and every other year during EDIC. EDIC year 3 and year 4 renal data were combined as year 4 renal data.

Hypoglycemia data were collected annually.

### **Method:**

#### **Assessment of Diabetic Retinopathy**

Seven-field stereoscopic color fundus photographs were taken on each eye of the 1441 patients by certified photographers every 6 months and were graded according to the Early Treatment Diabetic Retinopathy Study (**ETDRS**) scale of diabetic retinopathy severity for individual eyes. Photographs from baseline and annual follow-up visits were graded independently by two graders, with grades that differed by one step averaged and those that differed by two or more steps adjudicated by a senior grader, who assigned the final grade. Photographs from non-annual follow-up visits underwent a single grading. Grades for the various lesions were used to derive overall retinopathy severity levels for each patient according to the **ETDRS** interim and final scales.

Table 1 below provides an abbreviated summary of the **ETDRS** final scale for individual eyes. Both the interim and final scales were based on an earlier scale that had only 3 steps in the 30-50 range, designated levels 3, 4, & 5. In order to reflect rough correspondence with the earlier scale, the level designations were expanded to 2 digits and in order to avoid confusion between the interim and final scales, different numbers were used. Thus, levels 35, 43, 47, & 53 in the final scale correspond to levels 30, 41, 45, & 51 plus 55 in the interim scale. Levels 10, 20, & 61 and above are essentially identical in the two scales.

The severity levels for the two eyes of a patient are combined as shown in table 2 to give a level for the patient. A patient is classified first by the more severely involved eye, with this category divided into two according to the severity level of the second eye, e.g. 20/20 designates a patient with microaneurysm in each eye, 20/<20 a patient with microaneurysm only in one eye and a lesser level in the other (in this case level 10, no retinopathy, is the only lower level, but in other cases, all lower levels are pooled). As shown in table 2, the final scale has two fewer steps than the interim level, because it has only one level, rather than two, in the 50's range of the eye scale.

Variables in the dataset that represent **ETDRS** scores (either interim or final) take on as values the ordinal steps listed in table 2.

**Table 1:** Abbreviated summary of **ETDRS** Final Scale of Diabetic Retinopathy Severity for Individual Eyes

| <u>Level</u> | <u>Severity</u>                                     | <u>Definition</u>  |
|--------------|---|--|
| 10           | No retinopathy                                      | Diabetic retinopathy absent  |
| 20           | Very mild <b>NPDR</b>                               | Microaneurysms ( <b>Ma</b> ) only  |
| 35           | Mild <b>NPDR</b>                                    | Ma plus hard exudates ( <b>HE</b> ), soft exudates (cotton-wool spots) and/or mild retinal hemorrhages                                       |
| 43           | Moderate <b>NPDR</b>                                | Ma plus mild <b>IRMA</b> or moderate retinal hemorrhages   |
| 47           | Moderate <b>NPDR</b>                                | More extensive <b>IRMA</b> , severe retinal hemorrhages, or venous beading in one quadrant only  |
| 53           | Severe <b>NPDR</b>                                  | Severe retinal hemorrhages in 4 quadrants or venous beading in at least 2 quadrants, or moderately severe <b>IRMA</b> in at least 1 quadrant |
| 61           | Mild <b>PDR</b>                                     | <b>NVE</b> < 1/2 disc area in 1 or more quadrants  |
| 65           | Moderate <b>PDR</b>                                 | <b>NVE</b> ≥ 1/2 disc area in 1 or more quadrants, or <b>NVD</b> < 1/4-1/3 disc area   |
| 71-75        | High-risk <b>PDR</b>                                | <b>NVD</b> ≥ 1/4-1/3 disc area and/or vitreous hemorrhage  |
| 81-85        | Advanced <b>PDR</b><br>fundus partially<br>Obscured |  |
| 90           | Ungradable Quality (Photograph)                     |  |

**NPDR**=nonproliferative diabetic retinopathy;

**PDR**=proliferative diabetic retinopathy;

**IRMA**=intraretinal microvascular abnormalities;

**NVD**=new vessels on or within 1 disc diameter of optic disc;

**NVE**=new vessels elsewhere

**CSME**: Presence of Clinically Significant Macular Edema

**Table 2:** Abbreviated summary of **ETDRS** Final Scale of Diabetic Retinopathy Severity for Persons

| <u>Step</u> | <b>Final Scale</b>                  | <u>Step</u> | <b>Interim Scale</b>                |
|-------------|-------------------------------------|-------------|-------------------------------------|
|             | <u>Level (worse eye/better eye)</u> |             | <u>Level (worse eye/better eye)</u> |

|       |                   |       |                   |
|-------|-------------------|-------|-------------------|
| 1     | 10/10             | 1     | 10/10             |
| 2     | 20/<20            | 2     | 20/<20            |
| 3     | 20/20             | 3     | 20/20             |
| 4     | 35/<35            | 4     | 30/<30            |
| 5     | 35/35             | 5     | 30/30             |
| 6     | 43/<43            | 6     | 41/<41            |
| 7     | 43/43             | 7     | 41/41             |
| 8     | 47/<47            | 8     | 45/<45            |
| 9     | 47/47             | 9     | 45/45             |
| 10    | 53/<53            | 10    | 51/<51            |
| 11    | 53/53             | 11    | 51/51             |
| 12-23 | 61/<61 or greater | 12    | 55/<55            |
|       |                   | 13    | 55/55             |
|       |                   | 14-25 | 61/<61 or greater |

### **Definition of Main Outcomes and Terms**

- 3-Step Change:** A 3-step change relative to the DCCT baseline level is defined to have occurred if there is an increase by 3 steps or more in the **ETDRS** score compared to the **ETDRS** level at DCCT BASELINE. For example, a patient who is in step 1 (see Table 2) at DCCT baseline is defined to have experienced a 3-step change, at say the 2<sup>nd</sup> EDIC year, if patient's **ETDRS** score is 4 or above.
- Further 3-Step Change:** A further 3-step change relative to the DCCT closeout level is defined to have occurred if there is an increase by 3 steps or more in the **ETDRS** score compared to the **ETDRS** level at DCCT CLOSEOUT.
- Level of retinopathy at DCCT closeout:**
  - None: level 10/10 (DCCT10=1)
  - Microaneurysms Only: Level 20/<20 or 20/20 (DCCT20=1)
  - Mild Nonproliferative retinopathy: Level 35/<35 or 35/35 (DCCT30=1)
  - Moderate or Severe nonproliferative retinopathy: Level 43/<43, 43/43, 47/<47, 47/47 (DCCT40=1) OR level 53/<53, 53/53(DCCT50=1).
- Albumin Excretion Rate (AER).** Four-hour timed collection at the annual visit.

The **AER** data are presented as the unit of mg/24hrs. They can be transformed to ug / min

The formula is:

$$(\text{mg}/24\text{hrs}) * (1000 \text{ ug}/\text{mg} / (60\text{min}/\text{hour} * 24\text{hrs})) = (\text{ug} / \text{min}) \text{ or } (\text{mg}/24\text{hrs}) / 1.44 = (\text{ug} / \text{min})$$

Example:

AER = 40 mg/ 24hrs equals AER = 28 ug/ min. (rounded up to the closest integer)

AER = 300 mg/24 hrs equals AER= 208 ug/min.

### **Assessment of Hypoglycemia**

All hypoglycemia events were based on the Annual Medical History and Physical Examination (Form 2) and confirmed by Notification and Further Details of Severe Hypoglycemia Requiring Assistance (Form 42). The EDIC events reported include only those that occur in three months prior to the annual visit as confirmed by Form 42. Severe hypoglycemia was defined as hypoglycemia that required assistance, including but not limited to coma or seizure.

**De-identification:**

1. Replaced Patient ID with MASK Patient ID.
2. Stripped obvious identifier, like CLINIC, INITIALS, RACE, DOB, etc.