

Analysis Dataset from the Four Year Retinopathy Paper*

(*DCCT/EDIC Research Group (2000). Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *The New England Journal of Medicine*. 342:381-389)

Format: Two data sets are stored in **SAS** export library and named **EDICRET4** (retinopathy data) and **EDICREN4** (renal data).

Structure:

1) EDICRET4: One record per visit (EDIC years 0 - 4) per patient. 1352 patients with fundus photo data at any time during DCCT closeout (EDIC year 0) and EDIC years 1-4 are included. Among whom, 1208 patients with DCCT closeout and EDIC year 4 fundus photo were included in the year 4 prevalence analysis, indexed by Y4ANAL=1.

2) EDICREN4: One record per patient (1302 patients with DCCT closeout and EDIC year 4 AER data were reported).

Contents: A complete SAS contents listing is attached as Appendix A.

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, and a quarter of the cohort during EDIC years 1, 2 and 3.

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.

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 NPDR	Microaneurysms (Ma) only
35	Mild NPDR	Ma plus hard exudates (HE), soft exudates (cotton-wool spots) and/or mild retinal hemorrhages
43	Moderate NPDR	Ma plus mild IRMA or moderate retinal hemorrhages
47	Moderate NPDR	More extensive IRMA , severe retinal hemorrhages, or venous beading in one quadrant only
53	Severe NPDR	Severe retinal hemorrhages in 4 quadrants or venous beading in at least 2 quadrants, or moderately severe IRMA in at least 1 quadrant
61	Mild PDR	NVE < ½ disc area in 1 or more quadrants
65	Moderate PDR	NVE ≥ ½ disc area in 1 or more quadrants, or NVD < ¼-½ disc area
71-75	High-risk PDR	NVD ≥ ¼-½ disc area and/or vitreous hemorrhage
81-85	Advanced PDR	
	fundus partially 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>	Final Scale		<u>Step</u>	Interim Scale	
	<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

1. **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 2nd EDIC year, if patient's **ETDRS** score is 4 or above.

2. **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.

3. **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).

4. **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:

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

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.

5. **Creatinine Clearance:** < 70 ml/min/1.73 m² as an event.

6. DCCT closeout is the same as EDIC entry or EDIC year 0.

Naming Conventions

1. **ANY_XXX:** Indicates an occurrence of a specific event during at any time from DCCT baseline to the visit date, with the value 1 indicating the occurrence of the specific event, and 0 indicating the non-occurrence of the event.

Note:

In Table 1 of the NEJM paper, “Nephropathy at EDIC entry” was misconstrued by the editor to “Nephropathy at EDIC year 3 or 4”. So the renal data in table 1 is the DCCT closeout / EDIC entry record, not EDIC year 3 or 4 record.

De-identification:

1. Replaced Patient ID with MASK Patient ID.
2. Stripped obvious identifier, like CLINIC, INITIALS, RACE, DOB, etc.
3. Shifted all the dates to days since DCCT randomization date.