Review of Medical Risk Factors Associated with Diabetic Retinopathy

Emily Y. Chew, MD
National Eye Institute/National Institutes of Health

FDA meeting of the Endocrinologic and Metabolic Drugs Advisory Committee
October 18, 2017

No Financial Disclosures
Review of Risk Factors Associated with Diabetic Retinopathy

• Diabetic retinopathy classification

• Risk factors
  – Observational studies
  – Clinical Trials
ETDRS Classification of Diabetic Retinopathy-based on photos
ETDRS Classification of Diabetic Retinopathy-based on 7 stereoscopic fields
Diabetic Retinopathy

5 pathologic retinal processes:

- formation of microaneurysms
- excessive vascular permeability
- vascular occlusions
- proliferation of new vessels
- contraction of fibrovascular proliferation
Classification of Diabetic Retinopathy

- No apparent retinopathy
  (No abnormalities)
- Mild nonproliferative (NPDR)
  (Microaneurysms only)
- Moderate nonproliferative (NPDR)
  (More than just microaneurysms but less than severe nonproliferative)
Diabetic Retinopathy: Trypsin Digestion Preparation

Normal
Microaneurysm Formation

-earliest clinical sign of retinopathy
-minimal impact on vision at this stage
Excessive Vascular Permeability

Clinically significant macular edema

20/63 20/63
Excessive Vascular Permeability

Fluorescein angiography
Excessive Vascular Permeability

- with increasing number of microaneurysms

- signs **hard exudates**
  - mainly lipids
  - scattered or circinate ring
  - accompanies retinal edema
Diabetic Retinopathy: Trypsin Digestion Preparation

Microaneurysm
Classification of Diabetic Retinopathy

- Severe & very severe nonproliferative (SNPDR)
  - Signs of nonperfusion
  - High risk of progression to proliferative diabetic retinopathy

![Retina Images]
Proliferation of new vessels (NV)

Vitreous hemorrhage

Proliferative DR-some High-Risk
### Classification of Diabetic Retinopathy

**Early Treatment Diabetic Retinopathy Study (ETDRS)**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Scale step</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/10</td>
<td>No DR</td>
<td>1</td>
</tr>
<tr>
<td>20/&lt;20</td>
<td>Microaneurysms only, one eye</td>
<td>2</td>
</tr>
<tr>
<td>20/20</td>
<td>Microaneurysms only, both eyes</td>
<td>3</td>
</tr>
<tr>
<td>35/&lt;35</td>
<td>Mild NPDR, one eye</td>
<td>4</td>
</tr>
<tr>
<td>35/35</td>
<td>Mild NPDR, both eyes</td>
<td>5</td>
</tr>
<tr>
<td>43/&lt;43</td>
<td>Moderate NPDR, one eye</td>
<td>6</td>
</tr>
<tr>
<td>43/43</td>
<td>Moderate NPDR, both eyes</td>
<td>7</td>
</tr>
<tr>
<td>47/&lt;47</td>
<td>Moderately severe NPDR, one eye</td>
<td>8</td>
</tr>
<tr>
<td>47/43</td>
<td>Moderately severe NPDR, both eyes</td>
<td>9</td>
</tr>
<tr>
<td>53/&lt;53</td>
<td>Severe or very severe NPDR, one eye</td>
<td>10</td>
</tr>
<tr>
<td>53/53</td>
<td>Severe or very severe NPDR, both eyes</td>
<td>11</td>
</tr>
<tr>
<td>60 or 61/&lt;60</td>
<td>Mild PDR and/or SPC, one eye</td>
<td>12</td>
</tr>
<tr>
<td>60 or 61/60 or 61</td>
<td>Mild PDR and/or SPC, both eyes</td>
<td>13</td>
</tr>
<tr>
<td>65/&lt;65</td>
<td>Moderate PDR, one eye</td>
<td>14</td>
</tr>
<tr>
<td>65/65</td>
<td>Moderate PDR, both eyes</td>
<td>15</td>
</tr>
<tr>
<td>71+/&lt;71</td>
<td>High risk PDR, one eye</td>
<td>16</td>
</tr>
<tr>
<td>71+/71+</td>
<td>High risk PDR, both eyes</td>
<td>17+</td>
</tr>
</tbody>
</table>
Medical Risk Factors Impact on Diabetic Retinopathy

- Blood Glucose
- Blood Pressure
- Blood Lipids
Diabetes Control and Complications Trial (DCCT)
Diabetes Control and Complications Trial

Study Design

DCCT Patients
N=1441

Subgroup

Primary Prevention
Intensive N=348
Conventional N=378

Secondary Intervention
Intensive N=363
Conventional N=352
DCCT Study Design

Study Question

Primary Prevention

• Will Intensive Insulin Therapy Prevent the Development and Subsequent Progression of Retinopathy?
DCCT Study Design

Study Question

Secondary Prevention

• Will intensive insulin therapy prevent the progression of retinopathy?
Diabetes Control and Complications Trial

Hemoglobin A₁C

HgbA₁C mg%

Conventional

Intensive

Years
Diabetes Control and Complications Trial

Primary Intervention - 3 Step Worsening

Tight Control

Standard Care

Percent With Event

Years

P < 0.02

0 0.5 1

0 0.5 1

2.5

2

1.5

1

0.5

0
Diabetes Control and Complications Trial

Primary Intervention - 3 Step Worsening

- Tight Control
- Standard Care

Percent With Event vs. Years

P < 0.01
Diabetes Control and Complications Trial
Secondary Intervention - 3 Step Worsening

Percent With Event

Years

P < 0.02

Tight Control

Standard Care

0 1 2
Diabetes Control and Complications Trial

Primary Intervention - 3 Step Change

Percent With Event

Years

Standard Care

Tight Control

p<0.001

Diabetes Control and Complications Trial

Secondary Intervention - 3 Step Change

![Graph showing the comparison between Standard Care and Tight Control over 10 years. The graph indicates that Tight Control has a lower percent with event compared to Standard Care, with a significance level of p<0.001.]


28
DCCT Summary

Results of Intensive Therapy:

Early worsening (1st to 2nd year)
Then Reduction in Retinopathy

• Clinically Important Retinopathy (34-76%)
• Photocoagulation (34%)
• First Appearance of Retinopathy (27%)

Early worsening of diabetic retinopathy in the DCCT.

- To document:
  - the frequency, importance of, and risk factors for "early worsening" of diabetic retinopathy in the Diabetes Control and Complications Trial (DCCT).
- "early" = occurring between baseline and 12 month visit.
- q 6 month study visits

Early worsening of diabetic retinopathy in the DCCT

- Early worsening was observed at the 6- and/or 12-month visit in 13.1% of 711 patients assigned to intensive treatment and in 7.6% of 728 patients assigned to conventional treatment (odds ratio, 2.06; \( P < .001 \))

- Recovery had occurred at the 18-month visit in 51% and 55% of these groups, respectively (\( P = .39 \))
KROC Study of Diabetic Retinopathy

Original Contributions

Diabetic Retinopathy After Two Years of Intensified Insulin Treatment
Follow-up of The Kroc Collaborative Study

The Kroc Collaborative Study Group

- Randomized to Continuous Subcutaneous Insulin Infusion (CSII) or Unchanged Conventional Injection Treatment
- 68 participants with diabetic retinopathy
Kroc Study of Diabetic Retinopathy

months of the study. During those first eight months, substantial lowering of blood glucose concentration had been achieved in the CSII group, unexpectedly associated with evidence of accelerated progression of retinopathy compared with the conventional injection treatment group. Glycemic separation was maintained at two years between the two groups continuing to receive the assigned treatment; during this time the mean retinopathy level deteriorated with conventional injection treatment and improved with CSII. At two years the degree of retinopathy in the two treatment groups was indistinguishable, with some trend to lesser overall deterioration with CSII. It is concluded that, in diabetics with mild to moderate nonproliferative retinopathy, the acceleration in activity associated with tightened control is not sustained and does not initiate vasoproliferative deterioration in retinopathy.

- With intensive glycemic control 8 months, accelerated progression of diabetic retinopathy
- Diabetic retinopathy almost similar in both arms by 2 years

JAMA 1988;260:37–41
EDIC/DCCT Study

Epidemiology of Diabetes Intervention & Complications Study

- extension of the DCCT study
- natural history study of DCCT patients
- beneficial effects persist for additional 4-23 yrs (Legacy effect or metabolic memory)
### DCCT/EDIC Study

#### Hemoglobin A₁C results

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>DCCT</th>
<th>EDIC</th>
<th>EDIC</th>
<th>EDIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.5 yrs</td>
<td>4 yrs</td>
<td>8 yrs</td>
<td>10 yrs</td>
</tr>
<tr>
<td>Conventional</td>
<td>9.1%</td>
<td>8.2%</td>
<td>8.2%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Intensive Rx</td>
<td>7.2%</td>
<td>7.9%</td>
<td>8.0%</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

P-values:
- Conventional Rx: P<0.001
- Intensive Rx: P<0.04
- P<0.83
- P<0.20
## EDIC Study Results at 4 years

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression of Retinopathy</td>
<td>75%</td>
</tr>
<tr>
<td>Development of PDR* or SNPDR*</td>
<td>69%</td>
</tr>
<tr>
<td>Macular edema development</td>
<td>58%</td>
</tr>
<tr>
<td>Photocoagulation</td>
<td>52%</td>
</tr>
</tbody>
</table>

*PDR=Proliferative or *SNPDR=severe nonproliferative diabetic retinopathy
φAdjusted odds reduction
Further Retinopathy Progression from the Level at DCCT Closeout

Adjusted For DCCT Closeout Level
Reduction in risk of diabetic retinopathy progression associated with intensive glycemic control in DCCT/EDIC

<table>
<thead>
<tr>
<th></th>
<th>Relative risk reduction (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Years (EDIC)</td>
<td>53 – 56%</td>
<td>0.001</td>
</tr>
<tr>
<td>First 4 years EDIC</td>
<td>70 - 71%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Reduction in ocular surgical risk associated with intensive glycemic control in DCCT/EDIC (23 years)

<table>
<thead>
<tr>
<th>End Points</th>
<th>Relative risk reduction(%)</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular Surgery</td>
<td>48 (29-63)</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cataract surgery</td>
<td>37 (12-55)</td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Retinal detachment/vitrectomy</td>
<td>45 (12-66)</td>
<td></td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Follow-up of DCCT/EDIC at 30 Years

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview

David M. Nathan, for the DCCT/EDIC Research Group

Diabetes Care 2017; 37:9-16
U K Prospective Diabetes Study

Randomized Clinical Trial

Intensive Blood Glucose Control vs. Conventional Blood Glucose Control

Type 2 Diabetes
UK Prospective Diabetes Study

Intensive Blood Glucose Control

4209 Patients
Randomized

Conventional Treatment
Aim: FPG < 15 mmol/L
N = 1138

- Diet
- Followed by:
  - Sulphonylurea
  - Insulin
  - Metformin

Intensive Treatment
Aim: FPG < 6.0 mmol/L
N = 3071

Randomized

- 1573 - Sulphonylurea
- 1156 - Insulin
- Overweight
- 342 - Metformin
U K Prospective Diabetes Study

Hemoglobin A1C

HgbA1c

Conventional

Intensive
UK Prospective Diabetes Study
Microvascular Endpoints

Event Rate

Photocoagulation/VH
Renal Failure/Death
Myocardial Infarction

Conventional
Intensive

p=0.0099

Years

0% 10% 20% 30%
0 3 6 9 12 15
UK Prospective Diabetes Blood Glucose Study - Retinopathy 2-step progression

Event Rate

Years

Conventional

Intensive

p=0.78  p=0.02  p=0.01  p=0.01

%
### End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Relative risk reduction(%)</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes-related endpoint</td>
<td>2</td>
<td>1-21</td>
<td>0.029</td>
</tr>
<tr>
<td>Any diabetes-related death</td>
<td>10</td>
<td>-11 – 27</td>
<td>0.34</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>6</td>
<td>-10 – 20</td>
<td>0.44</td>
</tr>
<tr>
<td>Microvascular endpoint*</td>
<td>25</td>
<td>7-40</td>
<td>0.0099</td>
</tr>
</tbody>
</table>

*including need for laser photocoagulation

Lancet 1998;352:837-855
UKPDS Blood Pressure Trial

Retinopathy - 2 Step Progression

Event Rate

Years

Less Tight BP Control

More Tight BP Control

P=0.38  P=0.02  P=0.004
ACCORD* Eye Study Trial Goal

To determine whether:
- Intensive glycemic control (<6% vs. 7-7.9%)
- Combination therapy of dyslipidemia with fenofibrate and simvastatin vs. placebo
- Intensive blood pressure control

Affect the progression of diabetic retinopathy in a subset of ACCORD Participants

*Actions to Control Cardiovascular Risk in Diabetes*
### Original ACCORD Eye Study (composite outcome 3-step change)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemia</td>
<td>0.67</td>
<td>(0.51, 0.87)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Lipid</td>
<td>0.60</td>
<td>(0.42, 0.86)</td>
<td>0.0056</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>1.23</td>
<td>(0.84, 1.79)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Mean Glycated Hgb on Follow-up

- Intensive (A1C <6%)
- Standard (A1C 7 to 7.9%)
# ACCORDION Eye Study Retinopathy Progression at 8 years

<table>
<thead>
<tr>
<th>Effect</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemia</td>
<td>0.42</td>
<td>(0.28, 0.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lipid</td>
<td>1.13</td>
<td>(0.71, 1.79)</td>
<td>0.60</td>
</tr>
<tr>
<td>BP</td>
<td>1.21</td>
<td>(0.61, 2.40)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

*Diabetes Care. 2016 Jul;39(7):1089-100*
"Legacy Effect for Intensive Glycemic Control in Type 2 Diabetes"

Intensive glycemic control during the ACCORD trial (3.7 y) reduced the progression of diabetic retinopathy by 1/3.

4 years later (8 years after start of ACCORD), a persistent reduction of ~ 50% in progression of diabetic retinopathy participants previously assigned to intensive glycemic control.
Summary of Medical Risk Factors for Diabetic Retinopathy

- Intensive Glycemic Control
  - Hugh impact on diabetic retinopathy
  - Early worsening is transient and far outweighed by the benefits of tight glycemic control
  - Legacy effect is found in persons with Type 1 and Type 2 diabetes.
Summary of Medical Risk Factors for Diabetic Retinopathy

- Fenofibrate treatment reduced the risk of diabetic retinopathy progression by about 1/3 –no legacy effect
- Intensive Blood Pressure Control
  - Important in the UKPDS for diabetic retinopathy
  - Effect not seen in ACCORD and other studies