Major Clinical Trials in Diabetic Retinopathy

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Diabetic Retinopathy

How are the present treatment choices shaped by results of past clinical trials?

What are important questions yet to be answered by new clinical trials?
Diabetic Retinopathy

- Major cause of legal blindness
- Two Types: Non-proliferative, proliferative
- Intense glucose control results in reduction in diabetic retinopathy
- Laser surgery for retinopathy is most effective before visual loss occurs
Diabetic Retinopathy

Five multicenter clinical trials have established the basis for the management of diabetic retinopathy

- Diabetes Control and Complications Trial
- United Kingdom Prospective Diabetes Study
- Early Treatment Diabetic Retinopathy Study
- Diabetic Retinopathy Study
- Diabetic Retinopathy Vitrectomy Study
Non-Proliferative Diabetic Retinopathy

Does intense glucose control reduce diabetic retinopathy?

- Diabetes Control and Complications Trial
- United Kingdom Prospective Diabetes Study
Non-Proliferative Diabetic Retinopathy:

- Microaneurysms
- Edema
- Hard exudates
- Intraretinal hemorrhages
Diabetes Control and Complications Trial (DCCT) 1983-1993

- 1441 Patients
  - Absence of hypertension, hypercholesterolemia, and severe diabetic complications

- 2 groups
  - Type 1 diabetes and no diabetic retinopathy
  - Type 1 diabetes and mild to moderate diabetic retinopathy

Study questions
- Primary prevention study:
  - Will intensive blood glucose control slow the development of progression to diabetic retinopathy?
- Secondary prevention study:
  - Will intensive blood glucose control slow progression of diabetic retinopathy?
DCCT: 1983-1993

Primary prevention group: Type 1 Diabetes with no retinopathy (726 patients)

Secondary prevention group: Type 1 Diabetes with mild to moderate NPDR (715 patients)

Patients randomized to conventional treatment or intensive treatment groups.
DCCT: 1983-1993

Conventional Treatment Group
- Insulin injections (once or twice a day)
- Daily self monitoring of glucose
- Clinic visits every 3 months
- Diet and exercise education

Intensive Treatment Group
- Insulin pump or 3 or more insulin shots a day
- Self monitoring of blood glucose four or more times a day
- Diet and exercise plan
- Initial hospitalization to implement treatment
- Weekly to monthly clinic visits
DCCT Results: Primary Prevention Group

Intensive blood sugar control 27% reduction in development of Diabetic Retinopathy and 78% reduction in progression of Diabetic Retinopathy, with a mean follow-up 6.5 years.
Intensive blood sugar control had a 54% reduction in progression of Diabetic retinopathy. 47% reduction in Proliferative Diabetic Retinopathy and severe Non-Proliferative Diabetic Retinopathy, 56% reduction in Pan Retinal Laser Photocoagulation, 23% reduction in macular edema, with a mean follow-up of 6.5 years.
United Kingdom Prospective Diabetes Study (UKPDS): 1977-1999

4209 Patients:

- Cohort 1: Newly Diagnosed type 2 Diabetes Mellitus with no diabetic retinopathy
- Cohort 2: Newly Diagnosed type 2 Diabetes Mellitus with mild diabetic retinopathy
United Kingdom Prospective Diabetes Study (UKPDS): 1977-1999

Study questions:

- Will intensive control of blood glucose with type 2 diabetes reduce the risk of retinopathy progression?
- Will intensive control of blood pressure in patients with type 2 diabetes reduce the risk of retinopathy progression?
UKPDS: 1977-1999

 Patients randomized to conventional or intensive treatment groups

- Conventional treatment
  - Diet control followed by sulphonylurea, insulin, metformin

- Intensive treatment
  - Sulphonylurea, Insulin, or if overweight Metformin
UKPDS Conclusions:

Intensive blood glucose control slowed progression of retinopathy with average follow-up of 10 years.

- 27% Reduction in clinically meaningful retinopathy
- 29% Reduction in need for Laser
- 23% Reduction in vitreous hemorrhage
- 16% Reduction in Legal Blindness
UKPDS Conclusions:

Intensive blood pressure control independently slowed progression of retinopathy and reduced the risk of other microvascular complications of diabetes. No difference was found between Angiotensin Converting Enzyme inhibitors and Beta blockers.
Diabetic Macular Edema

Standard Care: Focal Laser Treatment
Macular edema

Before

After
Early Treatment Diabetic Retinopathy Study (ETDRS): 1979-1990

Eligible patients:
Diabetic patients with VA $\geq 20/400$ with mild to severe non-proliferative diabetic retinopathy and/or non high-risk proliferative diabetic retinopathy ± macular edema.

Study questions:
- Is focal laser treatment effective in treating diabetic macular edema?
- Is pan retinal laser photocoagulation effective for slowing the progression of diabetic retinopathy?
ETDRS: 1979-1990

- 3711 patients
  - One eye of each patient assigned to early photocoagulation and the other to close monitoring.
ETDRS: 1979-1990

 Defined Clinically Significant Macular Edema as any one of the following:

- Retinal edema at or within 500 microns of the center of the macula
- Hard exudates at or within 500 microns of the center if associated with thickening of adjacent retina
- A zone of thickening larger than 1 disc area if located within 1 disc diameter of the center of the macula
Macular edema

Before

After
ETDRS Conclusions: Macular Edema

Focal photocoagulation for diabetic macular edema reduced the risk of moderate vision loss by $\geq 50\%$ and increased the chance of small improvement in visual acuity and reduced retinal thickening.
ETDRS

Defined Mild Non-Proliferative Diabetic Retinopathy:

At least one microaneurysm
ETDRS: Moderate Diabetic Retinopathy
ETDRS

Defined Severe Non-Proliferative Diabetic Retinopathy as any one of the following:

- 4 quadrants of diffuse intraretinal hemorrhages and microaneurysms
- 2 quadrants of venous beading
- 1 quadrant of intraretinal microvascular abnormalities
ETDRS

Defined Very Severe Non-Proliferative Diabetic Retinopathy as any two of the following:

- 4 quadrants of diffuse intraretinal hemorrhages and microaneurysms
- 2 quadrants of venous beading
- 1 quadrant of intraretinal microvascular abnormalities
ETDRS

Defined Proliferative Diabetic Retinopathy as any of the following:

- Retinal Neovascularization
- Disc Neovascularization
- Vitreous Hemorrhage
- Fibrous Tissue Proliferation
Progression to PDR

- **Severe NPDR** had a 15% chance of progression to high-risk PDR within 1 year and 60% progression in 5 years.

- **Very Severe NPDR** (any 2 criteria for severe NPDR) had a 45% chance of progression to high-risk PDR within 1 year and 75% progression in 5 years.
ETDRS Conclusion: Early Pan Retinal Laser Photocoagulation

Early Pan Retinal Laser Photocoagulation is not indicated for mild to moderate Non-Proliferative Diabetic Retinopathy, but should be considered for those with severe or very severe Non-Proliferative Diabetic Retinopathy.

Pan Retinal Laser Photocoagulation should be performed in eyes with high-risk characteristics of proliferative diabetic retinopathy and
ETDRS: High-Risk Proliferative Diabetic Retinopathy

- Any disc neovascularization with vitreous hemorrhage

- >=1/3 disc area of disc neovascularization with or without vitreous hemorrhage

- >=1/2 disc area of retinal neovascularization with vitreous hemorrhage

+ Pan Retinal Laser Photocoagulation
ETDRS

 Defined Severe Non-Proliferative Diabetic Retinopathy as any one of the following:

- 4 quadrants of diffuse intraretinal hemorrhages and microaneurysms
- 2 quadrants of venous beading
- 1 quadrant of intraretinal microvascular abnormalities

+/- Pan Retinal Laser Photocoagulation
ETDRS

Defined Very Severe Non-Proliferative Diabetic Retinopathy as any two of the following:

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- 1 quadrant of intraretinal microvascular abnormalities

+/- Pan Retinal Laser Photocoagulation
PAN RETINAL Laser
PHOTOCOAGULATION

- 1000 to 3000 burns
- Outpatient procedure
- 1 to 3 sessions
- Standard Treatment for
  Proliferative Diabetic Retinopathy
Diabetic Retinopathy Study (DRS): 1971-1975

First multi-centered, randomized, clinical trial in Ophthalmology, and provided evidence for treatment of proliferative diabetic retinopathy with pan retinal laser photocoagulation.
Diabetic Retinopathy Study

Eligibility

- Proliferative diabetic retinopathy or bilateral severe nonproliferative diabetic retinopathy with visual acuity $\geq 20/100$ in each eye.

Study question

- Is photocoagulation (argon or xenon arc) effective for treating proliferative diabetic retinopathy?
Diabetic Retinopathy Study: 1971-1975

Eligibility

- Proliferative diabetic retinopathy or bilateral severe nonproliferative diabetic retinopathy with visual acuity \( \geq 20/100 \) in each eye.

Study question

- Is photocoagulation (argon or xenon arc) effective for treating diabetic retinopathy?
Design features – 1742 patients

- One eye of each patient was assigned to randomly to photocoagulation (scatter for new vessels), and focal (for macular edema).
- Other eye assigned to monitoring without laser.
- Eye assigned to treatment was randomly given argon laser or xenon arc photocoagulation.
DRS Results

50% or greater reduction in the rates of severe vision loss in eyes treated with Pan Retinal Laser Photocoagulation compared to untreated control eyes over 5 years of follow-up.
VITRECTOMY

- To remove vitreous hemorrhage
- To treat or prevent retinal detachment
Diabetic Retinopathy Vitrectomy Study (DRVS): 1979-1990,

Group 1: Recent severe vitreous hemorrhage (within 5 months) from PDR with VA $\leq 5/200$, macula attached.

Group 2: Advanced very severe PDR VA $\geq 10/200$ with extensive neovascular or fibrovascular proliferations, macula attached.
Diabetic Retinopathy Vitrectomy Study (DRVS): 1979-1990

Study questions

- What is the benefit of early (1-6 months after onset of vitreous hemorrhage) versus late (at 1 year) vitrectomy in eyes with severe vitreous hemorrhage and visual loss.

- What is the role of vitrectomy in managing eyes with very severe PDR?
DRVS Results

Group 1 (617 Eyes): Recent severe vitreous hemorrhage
- Chance of visual acuity ≥ 10/20 increased by early vitrectomy in patients with type 1 diabetes, younger and had more severe proliferative diabetic retinopathy.

Group 2 (370 Eyes): Very severe PDR with useful vision group
- Chance of visual acuity ≥ 10/20 increased by early vitrectomy only in eyes with very severe new vessels.
Advances in vitreoretinal surgical techniques have changed some of the recommendations of the DRVS.

- Patients with preexisting complete PRP with vitreous hemorrhage can have a longer observation period.

- Patients who have not had prior PRP or incomplete PRP should have early intervention if vitreous hemorrhage is secondary to PDR regardless of the type 1 or 2 diabetes.
The Diabetic Retinopathy Clinical Research Network

A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide to Focal/Grid Photocoagulation for Diabetic Macular Edema

Sponsored by the National Eye Institute, National Institutes of Health, U.S. Department of Health and Human Services.
Primary Study Objective

- To compare the efficacy and safety of preservative-free IVT (1 mg or 4 mg) with focal/grid laser
Study Design

Multicenter, randomized clinical trial

Major Eligibility Criteria Assessed:

• >18 years old
• Type 1 or type 2 diabetes
• Center-involved DME (with OCT CSF ≥250 µm)
• VA letter score 73 to 24 (20/40 to 20/320)

Eligible eyes randomized
Subjects with 2 study eyes assigned alternative treatment in 2\textsuperscript{nd} eye

Focal/Grid Laser

1 mg IVT

4 mg IVT
Median Visual Acuity in Laser and 4 mg IVT Treated Eyes

Visual Acuity Score

- 20/80
- 20/50
- 20/32
- 20/40
- 20/63

Months

0 4 8 12 16 20 24
Median Central Subfield Thickness in Laser and 4mg Treated Eyes

Central Subfield Thickness (microns)

Months

Laser

4 mg
Discussion

- Visual acuity benefit in 4 mg IVT group at 4 months consistent with published case series
- No visual acuity differences by 1 year
- Greater visual acuity benefit and fewer side effects (IOP and cataract) in laser group at 2 years
- OCT results mirrored visual acuity results
- Laser or IVT likely improves VA over 2 years compared with expected untreated course
Consistency in Subgroups

- No clear benefit of intravitreal triamcinolone over laser:
  - With or without prior laser
  - Across baseline OCT thickness
  - Across baseline visual acuities
Results re-affirm importance of laser in management of DME

It was widely believed that the ETDRS showed laser reduces vision loss, but did not improve VA... however... majority of eyes in ETDRS were better than 20/40 (no room for substantial improvement)
Future Studies Needed

- Determine whether combining focal/grid and intravitreal triamcinolone results in better outcomes for DME
- Determine whether other treatments (e.g., anti-VEGF), with or without focal/grid, results in better outcomes for DME
**Lucentis™**
*(ranibizumab, rhuFab V2)*

- Humanized Antibody
- Monoclonal Antibody
- Human
- Monoclonal Antibody
- Mouse

**Preparation of Fab**

- Humanization

**Improved Version**

- V1 -> V2

**Avastin™**

- Presta...Ferrara
- Cancer Res. 47: 4593-4599,
  1997

**Lucentis™**

- Chen, et al. Journal of Molecular Biology,
  Vol. 293, No. 4( 865-881) Nov 1999

- Humanized Antibody

- Monoclonal Antibody

- Mouse

**Monoclonal Antibody**

- A.4.6.1

- Kim...Rosenfeld Nature 362,
  841-844.(1993)

- Humanized Antibody

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- Mouse

**Preparation of Fab**

- rhuFab

**Improved Version**

- V1 -> V2

**Lucentis™**

- Chen, et al. Journal of Molecular Biology,
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## Study Summary

| Trials | Two Phase III studies, double-masked, three randomized arms in each study  
Study 1: RIDE  
Study 2: RISE |
|--------|------------------------------------------------------------------|
| Duration: | 36 Months for safety  
24 Months for primary efficacy endpoint |
| Population | CSME-CI secondary to diabetes mellitus  
Type I/Type II |
| Treatment assignment | Arm 1: 0.5 mg ranibisumab (N 122)  
Arm 2: 0.3 mg ranibizumab (N 122)  
Arm 3: Sham injection (N 122) |
| Sample size | 366 per trial |
Laser-Ranibizumab-Triamcinolone for DME Study
Diabetic Clinical Research Network Protocol I
Randomization to one of the following 4 groups:

- **Group A:** *Sham injection + focal laser*

- **Group B:** 0.5 mg injection of intravitreal *Ranibizumab + focal laser*

- **Group C:** 0.5 mg injection of intravitreal *Ranibizumab + deferred focal laser*

- **Group D:** 4 mg injection of intravitreal *Triamcinolone + focal laser*
Intravitreal Ranibizumab or Triamcinolone Acetonide as Adjunctive Treatment to Panretinal Photocoagulation for Proliferative Diabetic Retinopathy (Diabetic Retinopathy Research Network Protocol J)
Protocol J: Treatment Groups

All groups receive focal photocoagulation and panretinal photocoagulation.

Randomization to one of the following 3 groups:
- Intravitreal injection of 0.5 mg ranibizumab (Lucentis™) at baseline and 4 weeks
- Intravitreal injection of 4 mg triamcinolone acetonide at baseline and sham injection at 4 weeks
- Sham injection at baseline and 4 weeks
Diabetic Retinopathy

- Review indications and results of focal laser treatment for diabetic macular edema
- Review indications and results of pan retinal laser photocoagulation for severe non-proliferative diabetic retinopathy and for proliferative diabetic retinopathy
Diabetic Retinopathy

- Review the results of mono-therapy comparing focal laser treatment and intravitreal triamcinolone

- Discussions on new clinical trials
Questions?
DIABETIC RETINOPATHY AND CADIOVASCULAR DISEASE

- PDR risk indicator for MI, stroke, amputation
- PDR elevates risk of developing diabetic nephropathy
- Elevated serum lipid levels associated with retinal hard exudates
PREGNANCY AND DIABETIC RETINOPATHY

- Discuss risks before conception
  - Retinopathy may worsen
  - Regular ophthalmologic exam advised
SCREENING GUIDELINES:
DIABETES Dx < AGE 30

- Annual ophthalmologic exams starting 5 years after Dx
- Ophthalmoscopy by PCP for signs at other intervals
SCREENING GUIDELINES:
DIABETES Dx > AGE 30

- Annual ophthalmologic exams starting at time of Dx
- Ophthalmoscopy by PCP for signs at other intervals
SCREENING GUIDELINES:
CONCEPTION AND PREGNANCY

- Ophthalmologic exam before conception
- Ophthalmologic exam at 3-month intervals, beginning in first trimester
Ophthalmologic exam follow-up schedule determined by ophthalmologist and primary care physician.
CONCLUSION

- Early treatment may prevent blindness
- Improved screening can ensure early treatment
DIABETIC RETINOPATHY: A PUBLIC HEALTH ISSUE

- Prevalence may rise as % of aged in population rises
- Screening is a cost-effective way to reduce the incidence of blindness
Diabetic Retinopathy Vitrectomy Study (DRVS)

Eligible patients (2 groups)
- Recent severe vitreous hemorrhage (within 5 months) from PDR with VA $\leq 5/200$, macula attached.
- Advanced very severe PDR VA $\geq 10/200$ with extensive neovascular or fibrovascular proliferations, macula attached.

Study questions
- What is the benefit of early (1-6 months after onset of vitreous hemorrhage) versus late (at 1 year) vitrectomy in eyes with severe vitreous hemorrhage and visual loss.
- What is the role of vitrectomy in managing eyes with very severe PDR?
DRVS

Study Design

- Group with severe vitreous hemorrhage from PDR (617 eyes)
  - Eligible eyes assigned randomly to early vitrectomy or conventional management (vitrectomy if center of macula detaches or if vitreous hemorrhage persists for 1 year; photocoagulation if possible)

- Group with severe PDR and useful vision (370 eyes)
  - Eligible eyes assigned randomly to early vitrectomy or conventional management (vitrectomy if center of macula detaches or if vitreous hemorrhage persists for 6 months)
DRVS Results

Recent severe vitreous hemorrhage group
- Chance of visual acuity $\geq 10/20$ increased by early vitrectomy in patients with type 1 diabetes, younger and had more severe proliferative diabetic retinopathy.

Very severe PDR with useful vision group
- Chance of visual acuity $\geq 10/20$ increased by early vitrectomy only in
Advances in vitreoretinal surgical techniques have changed some of the recommendations of the DRVS.

- Patients with preexisting complete PRP with vitreous hemorrhage can have a longer observation period.

- Patients who have not had prior PRP or incomplete PRP should have early intervention if vitreous hemorrhage is secondary to PDR regardless of the type 1 or 2 diabetes.
EDUCATION ISSUES FOR PHYSICIANS AND PATIENTS

- Diabetic eye complication
- Examination schedules
- Treatment options
- Screening guidelines
Research results

Improved screening and treatment

Continuing education program

Ophthalmologist and medical community
Primary care physician
+
Optometrists
+
Ophthalmology
↓
Effective screening
timely treatment
DCCT Results

Intensive blood sugar control reduced risk of developing retinopathy by 76% and slowed progression of retinopathy by 54%.

Intensive blood sugar control also reduced risk of neuropathy by 60% and albuminuria by 54%.
DIABETIC RETINOPATHY: EFFECTIVE SCREENING

- Depends on retinal examination
- $62 million potential saving annually
DIABETIC MACULAR EDEMA: PREVALENCE

- Diabetes Dx ≤ 5 yrs = 5%
- Diabetes Dx ≥ 5 yrs = 15%
Proliferative Diabetic Retinopathy: PREVALENCE

- Age of Diagnosis
- Duration of Diabetes Mellitus
%PATIENT WITH PDR: INSULIN USERS Dx<AGE 30

Years After Diagnosis %

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%PATIENT WITH PDR: INSULIN USERS Dx > AGE 30

Yrs After Dx %

20 20%
Group 1: severe vitreous hemorrhage from PDR (617 eyes)
- Eligible eyes assigned randomly to early vitrectomy or conventional management (vitrectomy if center of macula detaches or if vitreous hemorrhage persists for 1 year; photocoagulation if possible)

Group 2: severe PDR and useful vision (370 eyes)
- Eligible eyes assigned randomly to early vitrectomy or conventional management (vitrectomy if center of macula detaches or if vitreous hemorrhage persists for 6 months)
Inclusion Criteria

Decrease in vision is due to diabetic macular edema and not due to other causes.

Patient is able (in the opinion of the investigator) and willing to return to all visits and assessments.