

Guidelines for diabetic retinopathy and maculopathy management

CONTENTS

Acknowledgment	2
Abbreviations	2
Glossary	3
Executive Summary	5
Introduction	6
Purpose of the guidelines	6
Scope of the guidelines	7
Target audience	7
Methods	7
Evidence assessment	7
Recommendations	11
Remarks on treatment	14
Updates	16
Research Gaps	16
Clinical indications for monitoring	16
Appendix: major study results	17
References	27

ACKNOWLEDGEMENTS

The Ophthalmology Committee of National Egyptian Guidelines, Ministry of Health and Ophthalmology

Chair of the committee: Prof. Hany S. Nasr.

Committee members professors: A. Farag, A. Alghoneimy, E. El-Toukhy, K. Rizk, M. Maher, M. Zaatat, M. Mourad, R. Zaki, W. Ahmad

ABBREVIATIONS

Anti-VEGF: See Anti-vascular endothelial growth factor.

BCVA: best corrected visual acuity

CI-DME: center-involving macular edema

CSME: clinically significant macular edema

DME: diabetic macular edema

DR: diabetic retinopathy

ERM: epiretinal membrane

ETDRS: Early Treatment for Diabetic Retinopathy Study

FFA: fundus fluorescein angiography

IRMA: Intraretinal microvascular abnormalities.

IVI: intravitreal injections

NCI-DME: non center-involving macular edema

NPDR: non proliferative diabetic retinopathy

OCT: optical coherence tomography

PDR: proliferative diabetic retinopathy

PRP: pan retinal photocoagulation

VEGF: vascular endothelial growth factor

GLOSSARY

Anti-vascular endothelial growth factor (anti-VEGF): Substances that inhibit the action of vascular endothelial growth factor protein.

Clinically significant macular edema (CSME): Retinal thickening at or within 500 μm of the center of the macula; and/or hard exudates at or within 500 μm of the center of the macula, if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening 1 disc area in size, any part of which is within 1 disc diameter of the center of the macula.

Diabetes mellitus: According to the American Diabetes Association Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, the criteria for the diagnosis of diabetes mellitus are as follows.

- Fasting plasma glucose equal to or exceeding 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.
- or
- Symptoms of hyperglycemia and a casual plasma glucose concentration equal to or exceeding 200 mg/dL (11.1 mmol/L). “Casual” is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss. or
 - A plasma glucose measurement at 2 hours postload equal to or exceeding 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. However, the expert committee has recommended against oral glucose tolerance testing for routine clinical use. (Source: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2008;31 (suppl):55-60.)

Diabetic macular edema: The accumulation of fluid in the macula due to leaky blood vessels.

Early proliferative diabetic retinopathy (i.e., proliferative retinopathy without DRS high-risk characteristics): New vessels that do not meet the criteria of high-risk proliferative retinopathy.

Focal photocoagulation: A laser technique directed to abnormal blood vessels with specific areas of focal leakage (i.e., microaneurysms) to reduce chronic fluid leakage in patients with macular edema.

Grid photocoagulation: A laser technique in which a grid pattern of scatter burns is applied in areas of diffuse macular edema and nonperfusion. Typically, fluorescein angiograms of these areas show a diffuse pattern rather than focal leakage.

High-risk proliferative diabetic retinopathy: New vessels on or within 1 disc diameter of the optic disc about one-quarter to one-third disc area, with or without vitreous or preretinal hemorrhage; or vitreous and/or preretinal hemorrhage accompanied by new vessels either on the optic disc less than $\frac{1}{4}$ disc area, or new vessels elsewhere equaling or exceeding one-quarter disc area.

Intraretinal microvascular abnormalities: Tortuous intraretinal vascular segments, varying in caliber from barely visible to 31 μ m in diameter (one-quarter the width of a major vein at the disc margin); they occasionally can be larger. Intraretinal microvascular abnormalities may be difficult to distinguish from neovascularization.

Macular edema: Thickening of the retina within 1 or 2 disc diameters of the center of the macula. (See Clinically significant macular edema.) Any other thickening of the macula not within this area is non-CSME.

Mild nonproliferative diabetic retinopathy: At least 1 microaneurysm and less than moderate nonproliferative diabetic retinopathy.

Moderate nonproliferative diabetic retinopathy: Hemorrhages and/or microaneurysms greater than standard photograph 2A, and/or soft exudates, venous beading, or IRMA present but less than severe nonproliferative retinopathy.

Moderate visual loss: The loss of 15 or more letters on the ETDRS visual acuity chart, or doubling of the visual angle (e.g., 6/6 to 6/12 etc.).

New vessels at the optic disc: New vessels at the optic disc; neovascularization on or within 1 disc diameter of the optic disc.

New vessels elsewhere in the retina: New vessels elsewhere in the retina; neovascularization elsewhere in the retina and greater than 1 disc diameter from the optic disc margin.

New vessels on the iris: New vessels on the iris; neovascularization of the iris.

Nonproliferative diabetic retinopathy: The phases of diabetic retinopathy with no evidence of retinal neovascularization.

Optical coherence tomography: A diagnostic test using low energy lasers that takes a cross-section image of the retina. Used mostly to determine if there are membranes on the surface of the macula or fluid within or beneath it.

Panretinal photocoagulation: A type of laser surgery used for patients with PDR. The surgery is delivered in a scatter pattern throughout the peripheral fundus and is intended to lead to a regression of neovascularization.

Proliferative diabetic retinopathy: Advanced disease characterized by NVD and/or new vessels elsewhere in the retina.

Retinal hard exudate: Protein and lipid accumulation within the retina.

Refractory DME: in which the patient received 3 monthly doses of antiVEGF with poor anatomical and functional response.

Scatter photocoagulation: See Panretinal photocoagulation.

Severe nonproliferative diabetic retinopathy: Using the 4-2-1 rule, the presence of at least one of the following features: (1) severe intraretinal hemorrhages and microaneurysms, in 4 quadrants; (2) venous beading in 2 or more quadrants; or (3) moderate IRMA in 1 or more quadrants.

Severe visual loss: Occurrence of visual acuity worse than 5/200 at any two consecutive visits scheduled at 4-month intervals.

EXECUTIVE SUMMARY

In PDR and severe NPDR

Severe non proliferative DR

- *compliant patient without diabetic maculopathy: regular follow up*

Recommendation: *conditional*

- *non-compliant patient without diabetic maculopathy: laser PRP*

Recommendation: *Strong*

PDR and high risk PDR without diabetic maculopathy and no abundant fibrosis

- *Non-compliant patient: laser PRP*

Recommendation: *strong*

- *Compliant patient: Laser PRP or antiVEGF injection within 4 weeks;*

Recommendation: *strong*

PDR and high risk PDR with diabetic maculopathy

- *Compliant patient: antiVEGF before PRP*

Recommendation: *moderate*

Non compliant patient: laser PRP with focal/grid laser for the macula

Recommendation: *moderate*

NCI-DME:

- *Vision 6/12 or better in compliant patients: observe with control of risk factors.*

Recommendation: *strong*

- *Vision 6/12 or better in non-compliant patients: laser treatment based on angiography and OCT*

Recommendation: *strong*

- *Vision less than 6/12: no treatment and investigate to exclude ischemic maculopathy, if present,IVI of anti VEGF or steroids*

Recommendation: *consensous*

CI-DME

- *Vision better than 6/12 compliant patient: observe with control of risk factors*

Recommendation: *Conditional*

- *Vision better than 6/12 non compliant patient: laser treatment*

Recommendation: *strong*

- *Vision less than 6/12 in compliant patient: AntiVEGF*

Recommendation: *strong*

- *Vision less than 6/12 in non compliant patient: laser*

Recommendation: *strong*

- *Vision less than 6/12 with signs of vitreo-retinal traction: Vitrectomy +/-AntiVEGF*

Recommendation: *strong*

- *Refractory DME: received a minimum of three monthly injections of AntiVEGF with poor anatomical and functional response in compliant patient: intra vitreal steroids/vitreotomy only in places with subspecialty retinal service.*

Recommendation: strong

Introduction:

Diabetes mellitus (DM) is an alarming public health issue globally and its prevalence is increasing heavily in developing countries [1-4]. The number of diabetics between 20 and 79 years of age is estimated to be 415 million people in the world and is expected to rise to 642 million in 2040.[5] In Egypt, DM is a dilemma and a fast-expanding concern. According to the International Diabetes Federation (IDF), the prevalence of DM among Egyptian adults is 15.2%, which may be an underestimation [6]. Diabetic retinopathy (DR) is one of the major complications of diabetes and leading cause of visual impairment or blindness. One of the most devastating complications of diabetes is diabetic retinopathy, which can be potentially blinding [7-14]. Evidence through the years reveals that almost all type I and around 60% of type II diabetic patients develop some degree of retinopathy within 20 years after diagnosis [15]. Given the increasing number of diabetics worldwide, developing countries are expected to receive the greatest toll [14].

Purpose of the guidelines:

Identifying the stages of diabetic retinopathy and maculopathy

Initiate an appropriate management plan for all stages of diabetic retinopathy and maculopathy

Scope of guidelines:

Methodology for treating diabetic retinopathy and maculopathy

Target audience:

Ophthalmologists - Pediatricians – Family doctors - High nurses.

Methods

A comprehensive search for guidelines was undertaken to identify the most relevant guidelines to consider for adaptation.

The inclusion/exclusion criteria followed in the search and retrieval of guidelines to be adapted:

- *Selecting only evidence-based guidelines (guideline must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence)*
- *Selecting peer reviewed publications only*
- *Selecting guidelines written in English language*
- *Excluding guidelines written by a single author not on behalf of an organization in order to be valid and comprehensive, a guideline ideally requires multidisciplinary input*
- *Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations*

The following characteristics of the retrieved guidelines were summarized in a table:

- *Developing organization/authors*
- *Date of publication, posting, and release*
- *Country/language of publication*
- *Date of posting and/or release*
- *Dates of the search used by the source guideline developers*

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least two members. the panel decided a cut-off point or rank the guidelines (any guideline scoring above 50% on the rigour dimension was retained). This guideline was adapted from the Indian, Iranian guidelines and preferred practice in the American ophthalmological society as well as the royal college of ophthalmology [15-18].

Evidence assessment

According to WHO handbook for Guidelines (5) we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because they represent internationally agreed standards for making transparent recommendations. Detailed information on GRADE is available on the following sites:

- *GRADE working group: <http://www.gradeworkinggroup.org>*
- *GRADE online training modules: <http://cebgrade.mcmaster.ca/>*
- *GRADE profile software: <http://ims.cochrane.org/revman/gradepro>*

Table 1 Quality of evidence in GRADE

Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

WHO guideline reporting tool - V1.5, December 2021

Table 2 Significance of the four levels of evidence

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 3 Factors that determine how to upgrade or downgrade the quality of evidence

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

WHO guideline reporting tool - V1.5, December 2021

The strength of the recommendation

The strength of a recommendation communicates the importance of adherence to this recommendation.

Strong recommendations

With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations

These are made when there is greater uncertainty about the four factors mentioned in table 3 or if local adaptation has to account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations

When there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

Recommendations

Severe non proliferative DR

- *compliant patient without diabetic maculopathy: regular follow up*

Recommendation: *conditional*

Evidence level: high [19-21]

- *non-compliant patient without diabetic maculopathy: laser PRP*

Recommendation: *Strong*

Evidence level: high [19-21]

PDR and high risk PDR without diabetic maculopathy and no abundant fibrosis

- *Non-compliant patient: laser PRP*

Recommendation: *strong*

Evidence level: high [22-27]

- *Compliant patient: Laser PRP or antiVEGF injection within 4 weeks;*

Recommendation: *strong*

Evidence level: high [28-121]

PDR and high risk PDR with diabetic maculopathy

- *Compliant patient: antiVEGF before PRP*

Recommendation: *moderate*

Evidence level: moderate

Non compliant patient: laser PRP with focal/grid laser for the macula

Recommendation: moderate

Evidence level: high [22-121]

NCI-DME:

- Vision 6/12 or better in compliant patients: observe with control of risk factors.

Recommendation: conditional

Evidence level: high [22-121]

- Vision 6/12 or better in non-compliant patients: laser treatment based on angiography and OCT

Recommendation: strong

Evidence level: high [22-121]

- Vision less than 6/12: no treatment and investigate to exclude ischemic maculopathy, if present, IVI of anti VEGF or steroids

Recommendation: consensous

Evidence level: low [22-121]

CI-DME

- Vision better than 6/12 compliant patient: observe with control of risk factors

Recommendation: Conditional

Evidence level: low [28-121]

- Vision better than 6/12 non compliant patient: laser treatment

Recommendation: strong

Evidence level: high [28-121]

- *Vision less than 6/12 in compliant patient: AntiVEGF*

Recommendation: strong

Evidence: high [28-121]

- *Vision less than 6/12 in non compliant patient: laser*

Recommendation: strong

Evidence: low [28-121]

- *Vision less than 6/12 with signs of vitreo-retinal traction: Vitrectomy +/-AntiVEGF*

Recommendation: strong

Evidence: very low [22-118]

Refractory DME: received a minimum of three monthly injections of AntiVEGF with poor anatomical and functional response in compliant patient: intra vitreal steroids/vitrectomy only in places with subspecialty retinal service.

Recommendation: strong

Evidence level: low [22-118]

Remarks on treatment

1. Laser PRP :

- Laser for mild PDR (neovessels less than 1/3 DD) should be between 1200-1800 shot 500um size, moderate PDR (NVD: greater than third of disc diameter, and forward NVD extending beyond the disc margin or NVE: complexes in all quadrants, forward NVE in any quadrant) 2000-2500 shot, severe PDR (Large, NVE complexes in any quadrant, NVE with tractional retinal detachment, large, forward NVD covering whole optic disc surface, NVD with tractional retinal detachment. These cases are high risk of continued traction and haemorrhagic complications following PRP) full PRP 3000 shots
Evidence level: high [22-118]

- If possible, PRP should be delivered on the same day of the diagnosis of high-risk PDR and if not, within 2 weeks from the time of diagnosis.

Evidence level moderate [22-118]

- PRP should be postponed until clinically significant macular edema (CSME) is treated.

Evidence level moderate [22-118]

- Coexisting high-risk PDR and CSME should be treated with combined PRP plus intravitreal anti-vascular endothelial growth factor (VEGF) injection or macular laser photocoagulation (MPC).

Evidence level: very low [22-118]

- In cases with fresh vitreous hemorrhage, PRP is usually applied after intravitreal injection of anti-VEGF when the ocular media is clear.

Evidence level: very low [22-118]

- In patients with florid type DR, PRP may be applied with shorter intervals (3-5 days between PRP sessions instead of 1-4 weeks).

Evidence level: very low [22-118]

Recommendations for follow up laser therapy:

- First follow up should be at three to four months – ideally at two months

Evidence level: high [22-118]

- PDR: Retreatment is required if vessels have not regressed, or further new vessels develop [22-121]

2. AntiVEGF monotherapy for PDR

- Frequent, regular, follow up i.e., every two to three months for at least a year is an essential prerequisite for the treatment of PDR with AntiVEGF agents.
- Repeat injections, if required. [119-120]

3. Vitrectomy

Recommendations for treatment

- Early vitrectomy (within three months) is indicated for people with Type 1 DM who develop severe vitreous haemorrhage in whom severe PDR is suspected

Evidence level: high [123-127]

- Consider early vitrectomy in eyes where PDR does not respond to extensive and aggressive laser PRP

Evidence level: moderate [123-127]

- Consider vitreoretinal surgery to relieve vitreoretinal traction if the macular is detached or threatening to detach, to salvage some vision

Evidence level: very low [123-127]

- Consider combined cataract surgery / vitrectomy in eyes with DR and/or DME with lens opacities, to enable subsequent management of PDR and/or DME.

Evidence: moderate [123-127]

Recommendations for practice

- Counselling patients before treatment, regarding improving the control of their diabetes and comorbidities is essential.

The procedure should be explained, including the likely outcome as well as the need for and timing and frequency of follow up, the likelihood of repeat treatment and the need for lifelong care. [123-127]

Intravitreal injection before vitrectomy

- Patients with PDR and active neovascularization who have been planned for vitrectomy may receive intravitreal anti-VEGF injection within one week before surgery to minimize intraoperative and early postoperative bleeding.

Evidence level: high [123-127]

- Patients with advanced DR and active fibrovascular tissue who are vitrectomy candidates may receive intravitreal anti-VEGF injection within one week before the surgery to minimize the risk of bleeding during and after the surgical procedure.

Evidence level: high[123-127]

- Extensive fibrovascular tissue increases the risk of traction retinal detachment following intravitreal injection of anti-VEGF drugs; the time interval between the injection and vitrectomy should be not more than 2-3 days in such cases.

Evidence level: moderate [123-127]

Updates:

To keep these recommendations up to date and ensure its validity it will be periodically updated. This will be done whenever new strong evidence is available and necessitates updating.

Research Gaps:

It is recommended to have high quality randomised controlled studies from combining different types of antiVEGF and concomitant use of laser.

Clinical indications for monitoring:

1. History of vascular occlusions, and associated conditions.
2. Blood sugar level.
3. Corrected visual acuity in all visits.
4. Detailed fundus biomicroscopy.
5. Prior to treatment, fundus fluorescein angiography or OCTA and OCT macula.
6. OCT macula after one month at the end of initial loading doses.
7. According to retreatment protocol OCT in each visit has to be presented with measurement of visual acuity.

Appendix 1

Major study results

DIABETIC RETINOPATHY STUDY (1972-1979)

The Diabetic Retinopathy Study (DRS) was designed to investigate the value of laser photocoagulation surgery for patients with severe nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). The results are shown in Table A4-1.

TABLE A3-1 VISUAL OUTCOME FOR LASER PHOTOCOAGULATION FROM THE DIABETIC RETINOPATHY STUDY

Baseline Severity of Retinopathy	Duration of Follow-up (Years)	Control Patients (% with Severe Visual Loss)	Treated Patients (% with Severe Visual Loss)
Severe nonproliferative	2	3	3
	4	13	4
Mild proliferative	2	7	3
	4	21	7
High-risk proliferative	2	26	11
	4	44	20

NOTE: Severe visual loss was defined as worse than 5/200 visual acuity at two or more consecutive completed visits (scheduled at 4-month intervals).

WISCONSIN EPIDEMIOLOGIC STUDY OF DIABETIC RETINOPATHY (1979)

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) began in 1979. It was initially funded by the National Eye Institute, which is part of the National Institutes of Health. The purpose of the WESDR is to describe the frequency and incidence of complications associated with diabetes (eye complications such as diabetic retinopathy and visual loss, kidney complications such as diabetic nephropathy, and amputations), and to identify risk factors (such as poor glycemic control, smoking, and high blood pressure) that may contribute to the development of these complications.

EARLY TREATMENT DIABETIC RETINOPATHY STUDY (1985-1990)

The Early Treatment Diabetic Retinopathy Study (ETDRS) investigated the value of photocoagulation surgery for patients with NPDR or PDR without high-risk characteristics. The results for eyes with macular edema are shown in Table A4-2. Visual loss was defined as at least doubling of the visual angle (e.g., 20/20 to 20/40, or 20/50 to 20/100).

TABLE A3-2 VISUAL OUTCOME FOR LASER PHOTOCOAGULATION TREATMENT FROM THE EARLY TREATMENT DIABETIC RETINOPATHY STUDY

Extent of Macular Edema	Duration of Follow-up (Years)	Control Patients (% with Visual Loss)	Treated Patients (% with Visual Loss)
CSME (center of macula not involved)	1	8	1
	2	16	6
	3	22	13
CSME (center of macula involved)	1	13	8
	2	24	9
	3	33	14

CSME = clinically significant macular edema

NOTE: Visual loss was defined as at least doubling of the visual angle.

Results of Early Scatter Laser Treatment in ETDRS

In eyes with NPDR or non-high-risk PDR, early panretinal photocoagulation (PRP) was compared with deferral of photocoagulation, and although there was a beneficial treatment effect, the outlook for maintaining vision was good in both groups. The 5-year rates of severe visual loss or vitrectomy ranged from 2% to 6% in eyes assigned to early photocoagulation and from 4% to 10% in eyes assigned to deferral. Early PRP was associated with side effects (small decreases in visual acuity and visual field) in some eyes, and the ETDRS concluded that deferral of photocoagulation was preferable at least until retinopathy was approaching the high-risk stage. Eyes approaching that stage had a 50% risk of reaching it within 12 to 18 months. Eyes in this category had very severe NPDR or non-high-risk PDR characterized by NVD less than one-quarter to one-third disc area and/or NVE, without vitreous or preretinal hemorrhage.

Recent additional analyses of visual outcome in ETDRS patients with severe NPDR to nonhigh-risk PDR suggest that the recommendation to consider PRP before the development of high-risk PDR is particularly appropriate for patients with type 2 diabetes. The risk of severe vision loss or vitrectomy was reduced by 50% in patients who were treated early compared with those who deferred treatment until high-risk PDR developed.

For patients with type 1 diabetes, the timing of the PRP will depend on the compliance with follow-up, status and response to treatment of the fellow eye, impending cataract surgery, and/or pregnancy status.

DIABETIC RETINOPATHY VITRECTOMY STUDY (1983-1987)

The Diabetic Retinopathy Vitrectomy Study (DRVS) investigated the role of vitrectomy in managing eyes with very severe PDR. The benefit of early vitrectomy for severe vitreous hemorrhage (defined as

hemorrhage obscuring the macula or major retinal vessels for 3 disc diameters from the macular center) was seen in type 1 patients, but no such advantage was found in type 2 patients, who did not benefit from earlier surgery. Early vitrectomy was beneficial among patients with visual acuity of 5/200 or worse and severe vitreous hemorrhage with reduced vision for at least 1 month and without previous treatment or complications such as retinal detachment or neovascularization of the iris. Overall, at 2 years after surgery, 25% of the early vitrectomy group and 15% of the deferral group had visual acuity of 20/40 or better. The advantage was most pronounced in patients with type 1 diabetes (36% vs. 12% for early vitrectomy versus deferral of vitrectomy, respectively) and was not statistically significant for patients with type 2 diabetes.

The DRVS showed that early vitrectomy was beneficial for patients with visual acuity of 20/400 or better plus 1 of the following: (1) severe neovascularization and fibrous proliferation; (2) fibrous proliferation and moderate vitreous hemorrhage; or (3) moderate neovascularization, severe fibrous proliferation, and moderate vitreous hemorrhage. Among such patients, 44% with early vitrectomy and 28% in the observation group had visual acuity of 20/40 or better at 4 years of follow-up.

The results of the DRVS should be interpreted in light of subsequent advances in vitreoretinal surgery, such as the introduction of small-gauge vitrectomy technology, endoscopic and indirect ophthalmoscopic laser photocoagulation surgery, and advanced instrumentation. The use of longacting intraocular gases such as sulfur hexafluoride (SF₆) and perfluoropropane (C₃F₈), the use of viscodissection, and the use of heavier-than-water liquids such as perfluoro-octane are advances in vitreoretinal surgery that developed after the DRVS. Thus, the results may actually be better than those reported in the DRVS. Early vitrectomy should be considered for selected patients with type 2 diabetes, particularly those in whom severe vitreous hemorrhage prohibits laser therapy photocoagulation of active neovascularization.

FENOFIBRATE INTERVENTION AND EVENT LOWERING IN DIABETES (FIELD) STUDY (2005)

The FIELD study was a randomized controlled trial that evaluated long-term fenofibrate therapy for the reduction of cardiovascular events in 9795 patients with type 2 diabetes mellitus. Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce total cardiovascular events, mainly due to fewer nonfatal myocardial infarctions and revascularizations. The higher rate of starting statin therapy in patients allocated to receive placebo might have masked a moderately larger treatment benefit.

DIABETIC RETINOPATHY CLINICAL RESEARCH NETWORK (DRCR.NET) (2002–PRESENT)

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network dedicated to facilitating multicenter clinical research of diabetic retinopathy, diabetic macular edema (DME), and associated conditions. The DRCR.net supports the identification, design, and implementation of multicenter clinical research initiatives focused on diabetes-induced retinal disorders. Principal emphasis is placed on clinical trials, but epidemiologic outcomes and other research may be supported as well. The DRCR.net was formed in 2002 and currently includes over 115 participating sites (offices) with over 400 physicians throughout the United States. The DRCR.net is funded by the National Eye Institute (NEI), which is a part of the National Institutes of Health, the branch of government that funds medical research. The DRCR.net has completed multiple clinical trials evaluating the role of anti-vascular endothelial growth factor (anti-VEGF), laser treatment, and corticosteroids in DME, anti-VEGF efficacy in PDR and vitreous hemorrhage, and even diabetes education effectiveness on DME (See Table A3-3). Most importantly, DRCR.net Protocol T (Comparative Effectiveness Study of Intravitreal Aflibercept, Bevacizumab, and Ranibizumab for Diabetic Macular Edema) compared the effectiveness of ranibizumab, aflibercept, and bevacizumab in the treatment of DME.⁹⁶ This study found that all three drugs resulted in improvement in visual acuity at 1 year with similar safety profiles. However, the mean visual acuity using aflibercept was better for eyes with visual acuity of 20/50 or worse at 1 year. At 2 years, the mean visual acuity in the aflibercept was no longer superior to ranibizumab, although it remained superior to bevacizumab. Another important treatment comparison was done in Protocol I: Intravitreal Ranibizumab for Diabetic Macular Edema with Prompt vs. Deferred Laser Treatment. Three-year results were reported in 2012. The study utilized ranibizumab monthly until improvement no longer occurred (with resumption if the condition worsened) and random assignment to focal/grid laser treatment promptly or deferred (≥ 24 weeks). The 3-year results suggest that focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better, and worse for vision outcomes, than deferring laser treatment for ≥ 24 weeks in eyes with DME involving the fovea and with vision impairment.⁹⁴

A previous publication from Protocol I results confirmed the 1-year results that intravitreal ranibizumab with prompt or deferred laser was more effective through 2 years compared with prompt laser alone for the treatment of DME involving the central macula. Laser was not associated with endophthalmitis, the rare but potentially devastating complication of injecting ranibizumab. In pseudophakic eyes, results with intravitreal triamcinolone plus prompt laser appeared similar to results in the ranibizumab arms and were more effective than laser alone, but the triamcinolone plus prompt laser arm had an increased risk of IOP elevation.¹⁸⁹

Most recently, the DRCR.net Protocol S evaluated the effects of anti-VEGF versus PRP.²⁹¹ In a randomized, multicenter, noninferiority trial, 394 eyes of 305 adults with PDR were randomized to receive either PRP or anti-VEGF therapy. Ranibizumab 0.5 mg was given at baseline and as frequently as every 4 weeks based on a structured retreatment design. Eyes in both groups were allowed ranibizumab if DME was present. In eyes with PDR, ranibizumab was not inferior to PRP in terms of visual acuity outcomes at 2 years. Mean visual

TABLE A3-3 DIABETIC RETINOPATHY CLINICAL RESEARCH NETWORK STUDIES

Protocol	Study Name	End Date	Study Conclusions
A	A Pilot Study of Laser Photocoagulation for Diabetic Macular Edema	01/31/2009	In eyes with DME, an MMG photocoagulation technique was less effective at reducing OCT-measured retinal thickening over 12 months than the standard focal photocoagulation technique modified from the ETDRS.
B	A Randomized Control Trial Comparing Intravitreal Triamcinolone Acetonide and Laser Photocoagulation for Diabetic Macular Edema	10/03/2008	Over 2 years, focal/grid photocoagulation for center-involved DME was more effective and had fewer adverse effects than 1-mg or 4-mg doses of preservative-free intravitreal triamcinolone.
C	Temporal Variation in Optical Coherence Tomography Measurements of Retinal Thickening in Diabetic Macular Edema	05/20/2005	Although retinal thickening decreases slightly over the day on average, most eyes with DME have little meaningful change in OCT CST or visual acuity between the hours of 8 AM and 4 PM. A change in CST>11% is likely to be real.
D	Evaluation of Vitrectomy for Diabetic Macular Edema Study	02/26/2009	Vitrectomy reduces retinal thickening in most eyes with DME and vitreomacular traction. Although visual acuity outcomes improved by 10 or more letters in 38% of eyes, 22% lost 10 or more letters after vitrectomy
E	A Pilot Study of Peribulbar Triamcinolone Acetonide for Diabetic Macular Edema	11/01/2007	In cases of DME where the patient has good visual acuity, peribulbar triamcinolone, with or without focal photocoagulation, is unlikely to be of substantial benefit.
F	An Observational Study of the Development of Diabetic Macular Edema Following Scatter Laser Photocoagulation	01/31/2008	Clinically meaningful differences in OCT thickness or visual acuity are not substantially different when PRP is applied in 1 sitting compared with 4 sittings.
G	Subclinical Diabetic Macular Edema Study	04/22/2009	Approximately one-quarter to one-half of eyes diagnosed with subclinical DME will progress to more definite thickening or be judged to need treatment for DME within 2 years. Because CST is greater in men than in women, studies involving comparisons of retinal thickness to expected norms should consider different mean values for men and women.
H	A Phase 2 Evaluation of Anti-VEGF Therapy for Diabetic Macular Edema: Bevacizumab (Avastin)	02/29/2008	Intravitreal bevacizumab can reduce DME in some eyes, but this preliminary study was not designed to definitively determine whether the treatment was beneficial.

acuity improvement was +2.8 letters for ranibizumab and +0.2 letters for PRP-treated eyes ($P<0.001$). When the totality of the visual acuity data was included (area under the curve analysis), eyes given ranibizumab had overall better visual acuity outcomes than eyes treated with PRP. There was less mean reduction in peripheral visual field (-23 dB vs. -422 dB; $P<0.001$) with ranibizumab than with PRP treatment. The rates for vitrectomy were more frequent (15% vs. 4%; $P<0.001$), and DME development was more frequent (28% vs. 9%; $P<0.001$) in the PRP group than in the ranibizumab group. Moreover, rates of active neovascularization or rates of regression of neovascularization were similar between the two groups.

I	Intravitreal Ranibizumab or Triamcinolone Acetonide in Combination with Laser Photocoagulation for Diabetic Macular Edema	12/31/2013	At 2 years, intravitreal ranibizumab with prompt or deferred (≥ 24 weeks) focal/grid laser photocoagulation is more effective in increasing visual acuity compared with focal/grid laser treatment alone or intravitreal triamcinolone with laser photocoagulation for the treatment of center-involved DME. Focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better, and possibly worse, for vision outcomes than deferring laser treatment for 24 weeks or more in eyes with center-involved DME with vision impairment.
J	Intravitreal Ranibizumab or Triamcinolone Acetonide as Adjunctive Treatment to Panretinal Photocoagulation for Proliferative Diabetic Retinopathy	07/07/2010	The addition of 1 intravitreal triamcinolone injection or 2 intravitreal ranibizumab injections in eyes receiving focal/grid laser photocoagulation for DME and PRP is associated with better visual acuity outcomes and decreased macular edema by 14 weeks.
K	The Course of Response to Focal Photocoagulation for Diabetic Macular Edema	06/19/2008	Eyes that demonstrate a definite reduction in, but not complete resolution of, central DME at 16 weeks after focal/grid laser photocoagulation have a 23%-63% likelihood of continuing to improve without additional treatment.
L	Evaluation of Visual Acuity Measurements in Eyes with Diabetic Macular Edema	11/06/2010	Across nationwide sites using a variety of autorefractors, visual acuity tended to be worse and more variable with autorefraction than manual refraction, suggesting that autorefraction is not a good substitute for manual refraction for clinical trials with improved visual acuity outcomes as a primary endpoint.
M	Effect of Diabetes Education During Retinal Ophthalmology Visits on Diabetes Control	12/31/2014	Use of a personalized intervention at ophthalmology visits, including HbA _{1c} measurement and counseling about the importance of glycemic control in reducing diabetic complications was not effective in improving HbA _{1c} levels.
N	An Evaluation of Intravitreal Ranibizumab for Vitreous Hemorrhage Due to Proliferative Diabetic Retinopathy	12/21/2012	Intravitreal ranibizumab versus saline did result in significantly different rates of vitrectomy by 16 weeks in eyes with vitreous hemorrhage from PDR. However, ranibizumab treatment resulted in improved short-term secondary outcomes including visual acuity improvement, increased panretinal photocoagulation completion rates, and reductions in recurrent vitreous hemorrhage.
O	Comparison of Time-Domain OCT and Spectral-Domain OCT Retinal Thickness Measurement in Diabetic Macular Edema	01/31/2013	This study of eyes with no to minimal nonproliferative diabetic retinopathy developed conversion equations to transform CST values obtained on a spectral-domain OCT to a time-domain OCT scale for group comparisons. In addition, values were established for machine and gender-specific thresholds to determine DME presence in diabetic eyes.

P	A Pilot Study in Individuals with Center-Involved DME Undergoing Cataract Surgery	11/12/2010	This small, observational study of eyes with DME undergoing cataract surgery revealed only a small percentage of eyes experienced substantial visual acuity loss or definitive worsening of DME after surgery.
Q	An Observational Study in Individuals with Diabetic Retinopathy without Center-Involved DME Undergoing Cataract Surgery	05/19/2011	A history of DME treatment and presence of non-center-involved DME are risk factors for development of center-involved DME after cataract surgery in eyes with diabetic retinopathy and no center-involved DME prior to surgery.
R	A Phase II Evaluation of Topical NSAIDs in Eyes with Non Central Involved DME	12/18/2013	At 1-year follow-up in eyes with non-center-involved DME, this study did not identify a difference between the effect of topical nepafenac 0.1% and placebo drops on OCT parameters or visual acuity.
S	Prompt Panretinal Photocoagulation versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy	--	Ranibizumab injections are an effective alternative to panretinal photocoagulation in treating PDR. At 2 years, visual acuity outcomes were noninferior to ranibizumab, while average visual acuity over the 2-year period was better and there was less peripheral field loss, reduced rates of DME onset, and fewer eyes that underwent vitrectomy.
T	A Comparative Effectiveness Study of Intravitreal Aflibercept, Bevacizumab and Ranibizumab for Diabetic Macular Edema	10/18/2018	The 2-year clinical trial compared 3 drugs used to treat DME and found that gains in vision were greater for participants receiving the drug aflibercept than for those receiving bevacizumab, but only among participants starting treatment with 20/50 or worse visual acuity. At 1 year, aflibercept had superior gains to ranibizumab in this vision subgroup; however, a difference could not be identified at 2 years. The 3 drugs yielded similar gains in vision for patients with 20/32 or 20/40 visual acuity at the start of treatment.
U	Short-term Evaluation of Combination Corticosteroid + Anti-VEGF Treatment for Persistent Central-Involved Diabetic Macular Edema Following Anti-VEGF Therapy	06/01/2017	In eyes with persistent DME and visual impairment despite previous anti-VEGF therapy, the dexamethasone + ranibizumab group experienced greater reduction of DME but no greater improvement in vision than sham + ranibizumab group over 6 months.

CST = central subfield thickness; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA_{1c} = hemoglobin A_{1c}; MMG = modified macular grid; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy
 Data from Diabetic Retinopathy Clinical Research Network (DRCR.net) website; www.drcr.net. Accessed March 15, 2018.

(Adapted with permission from the American Academy of Ophthalmology Basic and Clinical Science Course Subcommittee. Basic and Clinical Science Course. Retina and Vitreous: Section 12, 2018-2019. San Francisco, CA: American Academy of Ophthalmology; 2018)

STUDY OF RANIBIZUMAB INJECTION IN SUBJECTS WITH CLINICALLY SIGNIFICANT DIABETIC MACULAR EDEMA WITH CENTER INVOLVEMENT SECONDARY TO DIABETES MELLITUS (RISE AND RIDE)

The RISE and RIDE trials were parallel phase III multicenter double-masked sham injection– controlled randomized studies conducted at private and university-based retina specialty clinics in the United States and South America. (See Glossary.)

The phase III results for both studies were published in 2012. The studies utilized monthly intravitreal ranibizumab (0.5 or 0.3 mg) or sham injections, with macular laser available if needed. The study concluded that ranibizumab rapidly and sustainably improved vision, reduced the risk of further vision loss, and improved macular edema in patients with DME, with low rates of ocular and nonocular side effects.

RANIBIZUMAB FOR EDEMA OF THE MACULA IN DIABETES (READ-2)

READ-2 was a phase II multicenter randomized controlled trial that compared 0.5 mg injections of ranibizumab versus focal laser treatment over 2 years in patients with type 1 or type 2 diabetes mellitus and DME. Patients randomized to one arm of the trial received ranibizumab at baseline, and at 1, 3 and 5 months after baseline; a second arm received laser treatment at baseline and at 3 months (if needed); the third arm received both ranibizumab and laser treatment at baseline and 3 months. From month 5, all subjects received ranibizumab every 2 months and/or maintenance laser treatment every 3 months.

At 24 months, differences between the groups were not statistically significant, and all groups experienced improved visual acuity. Patients receiving combined ranibizumab and laser treatment required fewer injections than patients receiving ranibizumab alone.

BEVACIZUMAB OR LASER THERAPY (BOLT) STUDY

BOLT was a phase II 2-year randomized controlled trial that compared intravitreal 1.25 mg bevacizumab injections and focal laser treatment in patients with persistent DME and visual impairment. Bevacizumab patients received an injection every 6 weeks, whereas laser patients were treated every 4 weeks.

At 2 years, visual acuity results were substantially better in the bevacizumab group compared with the laser group, with significant differences in the proportions of patients gaining 10 letters and 15 letters. No patients lost 10 or more letters in the bevacizumab group, compared with 14% of patients treated with laser.

DIABETIC MACULAR EDEMA AND VASCULAR ENDOTHELIAL GROWTH FACTOR TRAP-EYE: VIVID AND VISTA

These studies compared the efficacy and safety of intravitreal aflibercept injection (IAI) with macular laser photocoagulation surgery for DME. Visual improvement were observed in the IAI treatment regimens over laser control at 52, 100 and 148 weeks. Incidence of adverse events was consistent with the known safety profile of IAI.

COMPARISON OF DRUGS

The DRCR.net compared the efficacy and safety of bevacizumab, ranibizumab, and aflibercept in a multicentered, randomized clinical trial. At the primary endpoint at 1 year, the mean change in vision was greater for aflibercept than for either of the other two drugs. However, the mean visual acuity changes were dependent on the baseline visual acuity. For eyes with milder visual acuity loss, the drugs resulted in similar visual outcomes (8.0 with aflibercept, 7.5 with bevacizumab, and 8.3 with ranibizumab; $P>0.50$ for each pairwise comparison). However, for eyes with 20/50 or worse vision, the mean visual acuity in eyes treated with aflibercept had greater improvements in vision (18.9 with aflibercept, 11.8 with bevacizumab, and 14.2 with ranibizumab; $P<0.001$ for aflibercept vs. bevacizumab, $P=0.003$ for aflibercept vs. ranibizumab, and $P=0.21$ for ranibizumab vs.

bevacizumab). There were no significant differences in rates of adverse events. However, at 2 years, the mean visual acuity results were similar for ranibizumab and aflibercept, although aflibercept results remained significantly better than bevacizumab results. There was a slightly higher rate of Antiplatelet Trialists' Collaboration (APTIC) events with ranibizumab compared with the other two drugs at the 2-year endpoint. All three drugs improved visual acuity at 2 years, and the number of injections decreased in year 2 compared to year 1.

REFERENCES

1. Nanditha A, Ma RC, Ramachandran A, Snehalatha C, Chan JC, Chia KS, et al. Diabetes in Asia and the Pacific: Implications for the global epidemic. *Diabetes Care* 2016;39:472-485.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:4-14.
3. Prevention of blindness from diabetes mellitus: report of a WHO consultation in Geneva, Switzerland, 9-11 November 2005. Available from: <http://www.who.int/blindness/Prevention%20of%20Blindness%20from%20Diabetes%20Mellitus-with-coversmall.pdf>. [Last accessed on 2015 Dec 27].
4. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract* 2014;103:137-49.
5. International Diabetes Federation. IDF Diabetes Atlas. 6th ed., 2015. Available from: <http://www.diabetesatlas.org/component/attachments/?task=download&id=116>. [Last accessed on 2016 Jan 25].
6. Katibeh M, Pakravan M, Yaseri M, Pakbin M, Soleimanizad R. Prevalence and causes of visual impairment and blindness in central Iran; The Yazd Eye Study. *J Ophthalmic Vis Res* 2015;10:279-285.
7. Dehghan MH, Katibeh M, Ahmadi H, Nourinia R, Yaseri M. Prevalence and risk factors for diabetic retinopathy in the 40 to 80 year-old population in Yazd, Iran: The Yazd Eye Study. *J Diabetes* 2015;7:139-141.
8. Judah G, Vlaev I, Gunn L, King D, King D, Valabhji J, et al. Incentives in Diabetic Eye Assessment by Screening (IDEAS): Study protocol of a three-arm randomized controlled trial using financial incentives to increase screening uptake in London. *BMC Ophthalmol* 2016;16:28.
9. Klein BE. Overview of epidemiologic studies of diabetic retinopathy. *Ophthalmic Epidemiol* 2007;14:179-183.
10. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ* 2004;82:844-851.
11. Moss SE, Klein R, Klein BE. The 14-year incidence of visual loss in a diabetic population. *Ophthalmology* 1998;105:998-1003.
12. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet* 2010;376:124-136.
13. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 1984;102:527-532.
14. Hatef E, Fotouhi A, Hashemi H, Mohammad K, Jalali KH. Prevalence of retinal diseases and their pattern in Tehran: The Tehran eye study. *Retina* 2008;28:755-762.
15. Gilbert C, Gordon I, Mukherjee CR, Govindhari V. Guidelines for the prevention and management of diabetic retinopathy and diabetic eye disease in India: A synopsis. *Indian J Ophthalmol* 2020;68:S63-6.
16. Indian Institute of Public Health, Hyderabad, 2019. Guidelines for the Prevention and Management of Diabetic Retinopathy and Diabetic Eye Disease in India. Hyderabad, India: Indian Institute of Public Health.

17. Rajavi Z, Safi S, Javadi MA, Azarmina M, Moradian S, Entezari M, et al. Diabetic retinopathy clinical practice guidelines: Customized for Iranian population. *J Ophthalmic Vis Res* 2016;11:394-414.
18. Flaxel CJ, Adelman RA, Bailey ST, Fawzi A, Lim JJ, Vemulakonda A, Ying G, Diabetic retinopathy preferred practice pattern, DOI:<https://doi.org/10.1016/j.optha.2019.09.025> Royal college of ophthalmologists, Diabetic retinopathy guidelines.
19. Ferris F. Early photocoagulation in patients with either type I or type II diabetes. *Trans Am Ophthalmol Soc.* 1996;94: 505-37.
20. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology.* 1991;98(5 Suppl): 766-85.
21. Early Treatment Diabetic Retinopathy Study research Group. Photocoagulation for diabetic macular edema. Study report number 1. *Arch Ophthalmol.* 1985;103(12): 1796-806.
22. Lövestam-Adrian M, Agardh CD, Torffvit O, Agardh E. Type 1 diabetes patients with severe non-proliferative retinopathy may benefit from panretinal photocoagulation. *Acta Ophthalmol Scand* 2003;81:221-225.
23. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 1987;94:761-774.
24. Diabetic Retinopathy Study Research Group. Indications for photocoagulation treatment of diabetic retinopathy: Diabetic Retinopathy Study Report number 14. *Int Ophthalmol Clin* 1987;27:239-253.
25. Zaluski S, Marcil G, Lamer L, Lambert J. Study of the visual field using automated static perimetry following panretinal photocoagulation in the diabetic. *J Fr Ophtalmol* 1986;9:395-401.
26. Buckley SA, Jenkins L, Benjamin L. Fields, DVLC and panretinal photocoagulation. *Eye (Lond)* 1992;6(Pt 6):623-625.
27. Pahor D. Visual field loss after argon laser panretinal photocoagulation in diabetic retinopathy: Full-versus mild-scatter coagulation. *Int Ophthalmol* 1998;22:313-319.
28. Diabetic Retinopathy Clinical Research Network (DRCR.net), Beck RW, Edwards AR, Aiello LP, Bressler NM, Ferris F, et al. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Arch Ophthalmol* 2009;127:245-251.
29. Gillies MC, Simpson JM, Gaston C, Hunt G, Ali H, Zhu M, et al. Five-year results of a randomized trial with open-label extension of triamcinolone acetonide for refractory diabetic macular edema. *Ophthalmology* 2009;116:2182-2187.
30. Lam DS, Chan CK, Mohamed S, Lai TY, Lee VY, Liu DT, et al. Intravitreal triamcinolone plus sequential grid laser versus triamcinolone or laser alone for treating diabetic macular edema: Six-month outcomes. *Ophthalmology* 2007;114:2162-2167.
31. Gillies MC, McAllister IL, Zhu M, Wong W, Louis D, Arnold JJ, et al. Pretreatment with intravitreal triamcinolone before laser for diabetic macular edema: 6-month results of a randomized, placebo-controlled trial. *Invest Ophthalmol Vis Sci* 2010;51:2322-2328.
32. Diabetic Retinopathy Clinical Research Network, Chew E, Strauber S, Beck R, Aiello LP, Antoszyk A, et al. Randomized trial of peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: A pilot study. *Ophthalmology* 2007;114:1190-1196.

33. Gillies MC, Simpson JM, Billson FA, Luo W, Penfold P, Chua W, et al. Safety of an intravitreal injection of triamcinolone: Results from a randomized clinical trial. *Arch Ophthalmol* 2004;122:336-340.
34. Quiram PA, Gonzales CR, Schwartz SD. Severe steroid-induced glaucoma following intravitreal injection of triamcinolone acetonide. *Am J Ophthalmol* 2006;141:580-582.
35. Haller JA, Kuppermann BD, Blumenkranz MS, Williams GA, Weinberg DV, Chou C, et al. Randomized controlled trial of an intravitreal dexamethasone drug delivery system in patients with diabetic macular edema. *Arch Ophthalmol* 2010;128:289-296.
36. Campochiaro PA, Hafiz G, Shah SM, Bloom S, Brown DM, Busquets M, et al. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. *Ophthalmology* 2010;117:1393-1399.e3.
37. Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology* 2012;119:2125-2132.
38. Adamis AP, Miller JW, Bernal MT, D'Amico DJ, Folkman J, Yeo TK, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol* 1994 15;118:445-450.
39. Cunningham ET Jr., Adamis AP, Altaweel M, Aiello LP, Bressler NM, D'Amico DJ, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. *Ophthalmology* 2005;112:1747-1757.
40. Nguyen QD, Shah SM, Heier JS, Do DV, Lim J, Boyer D, et al. Primary end point (Six Months) results of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. *Ophthalmology* 2009;116:2175-2181.e1.
41. Nguyen QD, Shah SM, Khwaja AA, Channa R, Hatf E, Do DV, et al. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. *Ophthalmology* 2010;117:2146-2151.
42. Massin P, Bandello F, Garweg JG, Hansen LL, Harding SP, Larsen M, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): A 12-month, randomized, controlled, double-masked, multicenter phase II study. *Diabetes Care* 2010;33:2399-2405.
43. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, et al. The RESTORE study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;118:615-625.
44. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010;117:1064-1077.e35.
45. Goyal S, Lavalley M, Subramanian ML. Meta-analysis and review on the effect of bevacizumab in diabetic macular edema. *Graefes Arch Clin Exp Ophthalmol* 2011;249:15-27.
46. Yilmaz T, Cordero-Coma M, Gallagher MJ, Teasley LA. Systematic review of intravitreal bevacizumab injection for treatment of primary diabetic macular oedema. *Acta Ophthalmol* 2011;89:709-717.
47. Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, Quhill F, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: Report 2. *Ophthalmology* 2010;117:1078-1086.e2.

48. Arevalo JF, Sanchez JG, Wu L, Maia M, Alezzandrini AA, Brito M, et al. Primary intravitreal bevacizumab for diffuse diabetic macular edema: The Pan-American Collaborative Retina Study Group at 24 months. *Ophthalmology* 2009;116:1488-1497, 1497.e1.
49. Lam DS, Lai TY, Lee VY, Chan CK, Liu DT, Mohamed S, et al. Efficacy of 1.25 MG versus 2.5 MG intravitreal bevacizumab for diabetic macular edema: Six-month results of a randomized controlled trial. *Retina* 2009;29:292-299.
50. Ahmadieh H, Ramezani A, Shoeibi N, Bijanzadeh B, Tabatabaei A, Azarmina M, et al. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial. *Graefes Arch Clin Exp Ophthalmol* 2008;246:483-489.
51. Soheilian M, Ramezani A, Obudi A, Bijanzadeh B, Salehipour M, Yaseri M, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. *Ophthalmology* 2009;116:1142-1150.
52. Solaiman KA, Diab MM, Abo-Elenin M. Intravitreal bevacizumab and/or macular photocoagulation as a primary treatment for diffuse diabetic macular edema. *Retina* 2010;30:1638-1645.
53. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. *Br J Ophthalmol* 2008;92:667-668.
54. Do DV, Nguyen QD, Shah SM, Browning DJ, Haller JA, Chu K, et al. An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema. *Br J Ophthalmol* 2009;93:144-149.
55. Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, et al. One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema. *Ophthalmology* 2012;119:1658-1665.
56. Lanzagorta-Aresti A, Palacios-Pozo E, Menezo Rozalen JL, Navea-Tejerina A. Prevention of vision loss after cataract surgery in diabetic macular edema with intravitreal bevacizumab: A pilot study. *Retina* 2009;29:530-555.
57. Akinci A, Muftuoglu O, Altinsoy A, Ozkilib E. Phacoemulsification with intravitreal bevacizumab and triamcinolone acetate injection in diabetic patients with clinically significant macular edema and cataract. *Retina* 2011;31:755-758.
58. Fard MA, Yazdaneh Abyane A, Malihi M. Prophylactic intravitreal bevacizumab for diabetic macular edema (thickening) after cataract surgery: Prospective randomized study. *Eur J Ophthalmol* 2011;21:276-281.
59. Ishibashi T, Miki K, Sorgente N, Patterson R, Ryan SJ. Effects of intravitreal administration of steroids on experimental subretinal neovascularization in the subhuman primate. *Arch Ophthalmol* 1985;103:708-711.
60. Danis RP, Bingaman DP, Yang Y, Ladd B. Inhibition of preretinal and optic nerve head neovascularization in pigs by intravitreal triamcinolone acetate. *Ophthalmology* 1996;103:2099-2104.
61. Ciulla TA, Criswell MH, Danis RP, Hill TE. Intravitreal triamcinolone acetate inhibits choroidal neovascularization in a laser-treated rat model. *Arch Ophthalmol* 2001;119:399-404.
62. Wang YS, Friedrichs U, Eichler W, Hoffmann S, Wiedemann P. Inhibitory effects of triamcinolone acetate on bFGF-induced migration and tube formation in choroidal microvascular endothelial cells. *Graefes Arch Clin Exp Ophthalmol* 2002;240:42-48.

63. Jonas JB, Hayler JK, Söfker A, Panda-Jonas S. Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative diabetic retinopathy. *Am J Ophthalmol* 2001;131:468-471.
64. Nauck M, Karakiulakis G, Perruchoud AP, Papakonstantinou E, Roth M. Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. *Eur J Pharmacol* 1998;341:309-315.
65. Brooks HL Jr., Caballero S Jr., Newell CK, Steinmetz RL, Watson D, Segal MS, et al. Vitreous levels of vascular endothelial growth factor and stromal-derived factor 1 in patients with diabetic retinopathy and cystoid macular edema before and after intraocular injection of triamcinolone. *Arch Ophthalmol* 2004;122:1801-1817.
66. Jonas JB, Kreissig I, Söfker A, Degenring RF. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. *Arch Ophthalmol* 2003;121:57-61.
67. Jonas JB, Söfker A. Intraocular injection of crystalline cortisone as adjunctive treatment of diabetic macular edema. *Am J Ophthalmol* 2001;132:425-427.
68. Jonas JB. Intravitreal triamcinolone acetate for treatment of intraocular oedematous and neovascular diseases. *Acta Ophthalmol Scand* 2005;83:645-663.
69. Jonas JB, Degenring RF, Kampeter BA. Outcome of eyes undergoing trabeculectomy after intravitreal injections of triamcinolone acetate. *J Glaucoma* 2004;13:261.
70. Kuhn F, Barker D. Intravitreal injection of triamcinolone acetate for diabetic macular edema. *Arch Ophthalmol* 2004;122:1082-1083.
71. Savage H, Roh M. Safety and efficacy of intravitreal triamcinolone. *Arch Ophthalmol* 2004;122:1083.
72. Patelli F, Fasolino G, Radice P, Russo S, Zumbo G, DI Tizio FM, et al. Time course of changes in retinal thickness and visual acuity after intravitreal triamcinolone acetate for diffuse diabetic macular edema with and without previous macular laser treatment. *Retina* 2005;25:840-845.
73. Larsson J, Zhu M, Sutter F, Gillies MC. Relation between reduction of foveal thickness and visual acuity in diabetic macular edema treated with intravitreal triamcinolone. *Am J Ophthalmol* 2005;139:802-806.
74. Massin P, Audren F, Haouchine B, Erginay A, Bergmann JF, Benosman R, et al. Intravitreal triamcinolone acetate for diabetic diffuse macular edema: Preliminary results of a prospective controlled trial. *Ophthalmology* 2004;111:218-224.
75. Avitabile T, Longo A, Reibaldi A. Intravitreal triamcinolone compared with macular laser grid photocoagulation for the treatment of cystoid macular edema. *Am J Ophthalmol* 2005;140:695-702.
76. Sutter FK, Simpson JM, Gillies MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: Three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. *Ophthalmology* 2004;111:2044-2049.
77. Audren F, Leclaire-Collet A, Erginay A, Haouchine B, Benosman R, Bergmann JF, et al. Intravitreal triamcinolone acetate for diffuse diabetic macular edema: Phase 2 trial comparing 4 mg vs 2 mg. *Am J Ophthalmol* 2006;142:794-799.
78. Jonas JB, Kampeter BA, Harder B, Vossmerbaeumer U, Sauder G, Spandau UH. Intravitreal triamcinolone acetate for diabetic macular edema: A prospective, randomized study. *J Ocul Pharmacol Ther* 2006;22:200-207.

79. Audren F, Erginay A, Haouchine B, Benosman R, Conrath J, Bergmann JF, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular oedema: 6-month results of a prospective controlled trial. *Acta Ophthalmol Scand* 2006;84:624-630.
80. Lam DS, Chan CK, Mohamed S, Lai TY, Li KK, Li PS, et al. A prospective randomised trial of different doses of intravitreal triamcinolone for diabetic macular oedema. *Br J Ophthalmol* 2007;91:199-203.
81. Kang SW, Sa HS, Cho HY, Kim JI. Macular grid photocoagulation after intravitreal triamcinolone acetonide for diffuse diabetic macular edema. *Arch Ophthalmol* 2006;124:653-658.
82. Parke DW. Intravitreal triamcinolone and endophthalmitis. *Am J Ophthalmol* 2003;136:918-919.
83. Roth DB, Chieh J, Spirn MJ, Green SN, Yarian DL, Chaudhry NA. Noninfectious endophthalmitis associated with intravitreal triamcinolone injection. *Arch Ophthalmol* 2003;121:1279-1282.
84. Jonas JB, Kreissig I, Spandau UH, Harder B. Infectious and noninfectious endophthalmitis after intravitreal high-dosage triamcinolone acetonide. *Am J Ophthalmol* 2006;141:579-580.
85. Jonas JB, Degenring RF, Kreissig I, Akkoyun I, Kampeter BA. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. *Ophthalmology* 2005;112:593-598.
86. Konstantopoulos A, Williams CP, Newsom RS, Luff AJ. Ocular morbidity associated with intravitreal triamcinolone acetonide. *Eye (Lond)* 2007;21:317-320.
87. Lang Y, Leibu R, Shoham N, Miller B, Perlman I. Evaluation of intravitreal kenalog toxicity in humans. *Ophthalmology* 2007;114:724-731.
88. Bandello F, Polito A, Pognuz DR, Monaco P, Dimastrogiovanni A, Paissios J. Triamcinolone as adjunctive treatment to laser panretinal photocoagulation for proliferative diabetic retinopathy. *Arch Ophthalmol* 2006;124:643-650.
89. Spandau UH, Derse M, Schmitz-Valckenberg P, Papoulis C, Jonas JB. Dosage dependency of intravitreal triamcinolone acetonide as treatment for diabetic macular oedema. *Br J Ophthalmol* 2005;89:999-1003.
90. Jonas JB, Degenring RF, Kampeter BA, Kreissig I, Akkoyun I. Duration of the effect of intravitreal triamcinolone acetonide as treatment for diffuse diabetic macular edema. *Am J Ophthalmol* 2004;138:158-160.
91. Rodriguez-Coleman H, Yuan P, Kim H, Gravlin L, Srivastava S, Csaky KG, et al. Intravitreal injection of triamcinolone for diffuse macular edema. *Arch Ophthalmol* 2004;122:1085-1116.
92. Negi AK, Vernon SA, Lim CS, Owen-Armstrong K. Intravitreal triamcinolone improves vision in eyes with chronic diabetic macular oedema refractory to laser photocoagulation. *Eye (Lond)* 2005;19:747-751.
93. Gibran SK, Cullinane A, Jungkim S, Cleary PE. Intravitreal triamcinolone for diffuse diabetic macular oedema. *Eye* 2006;20:720-724.
94. Jonas JB, Spandau UH, Kampeter BA, Vossmerbaeumer U, Harder B, Sauder G. Repeated intravitreal high-dosage injections of triamcinolone acetonide for diffuse diabetic macular edema. *Ophthalmology* 2006;113:800-804.
95. Kim H, Csaky KG, Gravlin L, Yuan P, Lutz RJ, Bungay PM, et al. Safety and pharmacokinetics of a preservative-free triamcinolone acetonide formulation for intravitreal administration. *Retina* 2006;26:523-530.

96. Pearson P, Levy B, Comstock T, Fluocinolone Acetonide Implant Study Group. Fluocinolone acetonide intravitreal implant to treat diabetic macular edema: 3-year results of a multi-centre clinical trial. *Invest Ophthalmol Vis Sci* 2006;47 5442 [E-abstract 5442].
97. Kuppermann BD, Blumenkranz MS, Haller JA, Williams GA, Weinberg DV, Chou C, et al. Randomized controlled study of an intravitreal dexamethasone drug delivery system in patients with persistent macular edema. *Arch Ophthalmol* 2007;125:309-317.
98. Verma LK, Vivek MB, Kumar A, Tewari HK, Venkatesh P. A prospective controlled trial to evaluate the adjunctive role of posterior subtenon triamcinolone in the treatment of diffuse diabetic macular edema. *J Ocul Pharmacol Ther* 2004;20:277-284.
99. Bakri SJ, Kaiser PK. Posterior subtenon triamcinolone acetonide for refractory diabetic macular edema. *Am J Ophthalmol* 2005;139:290-294.
100. Cardillo JA, Melo LA Jr., Costa RA, Skaf M, Belfort R Jr., Souza-Filho AA, et al. Comparison of intravitreal versus posterior sub-Tenon's capsule injection of triamcinolone acetonide for diffuse diabetic macular edema. *Ophthalmology* 2005;112:1557-1563.
101. Bonini-Filho MA, Jorge R, Barbosa JC, Calucci D, Cardillo JA, Costa RA. Intravitreal injection versus sub-Tenon's infusion of triamcinolone acetonide for refractory diabetic macular edema: A randomized clinical trial. *Invest Ophthalmol Vis Sci* 2005;46:3845-3849.
102. Caldwell RB, Bartoli M, Behzadian MA, El-Remessy AE, Al-Shabrawey M, Platt DH, et al. Vascular endothelial growth factor and diabetic retinopathy: Role of oxidative stress. *Curr Drug Targets* 2005;6:511-524.
103. Zhang SX, Ma JX. Ocular neovascularization: Implication of endogenous angiogenic inhibitors and potential therapy. *Prog Retin Eye Res* 2007;26:1-37.
104. Ng EW, Shima DT, Calias P, Cunningham ET Jr., Guyer DR, Adamis AP. Pegaptanib, a targeted anti-VEGF aptamer for ocular vascular disease. *Nat Rev Drug Discov* 2006;5:123-132.
105. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR; VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004;351:2805-2816.
106. Adamis AP, Altaweel M, Bressler NM, Cunningham ET Jr., Davis MD, Goldbaum M, et al. Changes in retinal neovascularization after pegaptanib (Macugen) therapy in diabetic individuals. *Ophthalmology* 2006;113:23-28.
107. Churchill AJ, Carter JG, Lovell HC, Ramsden C, Turner SJ, Yeung A, et al. VEGF polymorphisms are associated with neovascular age-related macular degeneration. *Hum Mol Genet* 2006 1;15:2955-2961.
108. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432-1444.
109. Chun DW, Heier JS, Topping TM, Duker JS, Bankert JM. A pilot study of multiple intravitreal injections of ranibizumab in patients with center-involving clinically significant diabetic macular edema. *Ophthalmology* 2006;113:1706-1712.
110. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. *Retina* 2006;26:275-278.
111. Avery RL, Pearlman J, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. *Ophthalmology* 2006;113:1695.e1-15.

112. Mason JO 3rd, Nixon PA, White MF. Intravitreal injection of bevacizumab (Avastin) as adjunctive treatment of proliferative diabetic retinopathy. *Am J Ophthalmol* 2006;142:685-688.
113. Oshima Y, Sakaguchi H, Gomi F, Tano Y. Regression of iris neovascularization after intravitreal injection of bevacizumab in patients with proliferative diabetic retinopathy. *Am J Ophthalmol* 2006;142:155-158.
114. Grisanti S, Biester S, Peters S, Tatar O, Ziemssen F, Bartz-Schmidt KU; Tuebingen Bevacizumab Study Group. Intracameral bevacizumab for iris rubeosis. *Am J Ophthalmol* 2006;142:158-160.
115. Avery RL. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. *Retina* 2006;26:352-354.
116. Haritoglou C, Kook D, Neubauer A, Wolf A, Priglinger S, Strauss R, et al. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. *Retina* 2006;26:999-1005.
117. Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, Sanchez JG, Wu L, Maia M, et al. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: Results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. *Ophthalmology* 2007;114:743-750.
118. Yanyali A, Aytug B, Horozoglu F, Nohutcu AF. Bevacizumab (Avastin) for diabetic macular edema in previously vitrectomized eyes. *Am J Ophthalmol* 2007;144:124-126.
119. Isaacs TW, Barry C. Rapid resolution of severe disc new vessels in proliferative diabetic retinopathy following a single intravitreal injection of bevacizumab (Avastin). *Clin Experiment Ophthalmol* 2006;34:802-803.
120. Bakri SJ, Donaldson MJ, Link TP. Rapid regression of disc neovascularization in a patient with proliferative diabetic retinopathy following adjunctive intravitreal bevacizumab. *Eye (Lond)* 2006;20:1474-1475.
121. Diabetic Retinopathy Clinical Research Network, Scott IU, Edwards AR, Beck RW, Bressler NM, Chan CK, et al. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. *Ophthalmology* 2007;114:1860-1867.
122. Zhao LQ, Zhu H, Zhao PQ, Hu YQ. A systematic review and meta-analysis of clinical outcomes of vitrectomy with or without intravitreal bevacizumab pretreatment for severe diabetic retinopathy. *Br J Ophthalmol* 2011;95:1216-1222.
123. Ahmadi H, Shoeibi N, Entezari M, Monshizadeh R. Intravitreal bevacizumab for prevention of early postvitrectomy hemorrhage in diabetic patients: A randomized clinical trial. *Ophthalmology* 2009;116:1943-1948.
124. Rizzo S, Genovesi-Ebert F, Di Bartolo E, Vento A, Miniaci S, Williams G. Injection of intravitreal bevacizumab (Avastin) as a preoperative adjunct before vitrectomy surgery in the treatment of severe proliferative diabetic retinopathy (PDR). *Graefes Arch Clin Exp Ophthalmol* 2008;246:837-842.
125. Yeoh J, Williams C, Allen P, Buttery R, Chiu D, Clark B, et al. Avastin as an adjunct to vitrectomy in the management of severe proliferative diabetic retinopathy: A prospective case series. *Clin Experiment Ophthalmol* 2008;36:449-454.
126. Oshima Y, Shima C, Wakabayashi T, Kusaka S, Shiraga F, Ohji M, et al. Microincision vitrectomy surgery and intravitreal bevacizumab as a surgical adjunct to treat diabetic traction retinal detachment. *Ophthalmology* 2009;116:927-938.

127. Zhang ZH, Liu HY, Hernandez-Da Mota SE, Romano MR, Falavarjani KG, Ahmadieh H, et al. Vitrectomy with or without preoperative intravitreal bevacizumab for proliferative diabetic retinopathy: A meta-analysis of randomized controlled trials. *Am J Ophthalmol* 2013;156:106-115.e2.