Management of Diabetic Retinopathy
A Systematic Review

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Context Diabetic retinopathy (DR) is the leading cause of blindness in the working-aged population in the United States. There are many new interventions for DR, but evidence to support their use is uncertain.

Objective To review the best evidence for primary and secondary intervention in the management of DR, including diabetic macular edema.

Evidence Acquisition Systematic review of all English-language articles, retrieved using a keyword search of MEDLINE (1966 through May 2007), EMBASE, Cochrane Collaboration, the Association for Research in Vision and Ophthalmology database, and the National Institutes of Health Clinical Trials Database, and followed by manual searches of reference lists of selected major review articles. All English-language randomized controlled trials (RCTs) with more than 12 months of follow-up and meta-analyses were included. Delphi consensus criteria were used to identify well-conducted studies.

Evidence Synthesis Forty-four studies (including 3 meta-analyses) met the inclusion criteria. Tight glycemic and blood pressure control reduces the incidence and progression of DR. Pan-retinal laser photocoagulation reduces the risk of moderate and severe visual loss by 50% in patients with severe nonproliferative and proliferative retinopathy. Focal laser photocoagulation reduces the risk of moderate visual loss by 50% to 70% in eyes with macular edema. Early vitrectomy improves visual recovery in patients with proliferative retinopathy and severe vitreous hemorrhage. Intravitreal injections of steroids may be considered in eyes with persistent loss of vision when conventional treatment has failed. There is insufficient evidence for the efficacy or safety of lipid-lowering therapy, medical interventions, or antivascular endothelial growth factors on the incidence or progression of DR.

Conclusions Tight glycemic and blood pressure control remains the cornerstone in the primary prevention of DR. Pan-retinal and focal retinal laser photocoagulation reduces the risk of visual loss in patients with severe DR and macular edema, respectively. There is currently insufficient evidence to recommend routine use of other treatments.

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DIABETES MELLITUS AFFECTS 200 million people worldwide,[1] including 20 million in the United States alone.[2] Diabetic retinopathy (DR), a specific microvascular complication of diabetes, is the leading cause of blindness in working-aged persons in the United States.[2] The prevalence of DR increases with duration of diabetes,[3] and nearly all persons with type 1 diabetes and more than 60% of those with type 2 have some retinopathy after 20 years. The major risk factors for DR have been reported from epidemiologic studies[3,4] and are summarized in the BOX.

Diabetic retinopathy can be classified into 2 stages: nonproliferative and proliferative. The earliest visible signs in nonproliferative DR are microaneurysms and retinal hemorrhages (FIGURE, A). Progressive capillary nonperfusion is accompanied by development of cotton-wool spots, venous beading, and intraretinal microvascular abnormalities. Proliferative DR occurs with further retinal ischemia and is characterized by the growth of new blood vessels on the surface of the retina or the optic disc (Figure, B). These abnormal vessels may bleed, resulting in vitreous hemorrhage, subsequent fibrosis, and tractional retinal detachment. Diabetic macular edema (DME), which can occur at any stage of DR, is characterized by increased vascular permeability and the deposition of hard exudates at the central retina (Figure, A). Diabetic macular edema is now the principal cause of vision loss in persons with diabetes.

Primary interventions, such as intensive glycemic and blood pressure control, can reduce the incidence of DR, while secondary interventions, such as laser photocoagulation, may

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prevent further progression of DR and vision loss. There are many new interventions, but the evidence to support their use is uncertain. This article provides a systematic review of the literature to determine the best evidence for primary and secondary interventions for DR.

EVIDENCE ACQUISITION

Data Sources

We conducted a literature search to identify English-language randomized controlled trials (RCTs) or meta-analyses evaluating interventions for DR. Articles were retrieved using MEDLINE (1966 through May 2007), EMBASE, Cochrane Collaborations, the Association for Research in Vision and Ophthalmology database, and the National Institutes of Health Clinical Trials Database through May 2007. Search terms included variations of keywords for retinopathy, diabetes, DR, DME, retinal neovascularization, controlled clinical trial, and randomized controlled trial (RCT). This was supplemented by hand searching the reference lists of major review articles. As we were primarily interested in longer-term outcomes, we excluded studies with less than 12 months of follow-up and those failing to separate data of different retinal conditions (eg, macular edema from diabetes vs retinal vein occlusion). We also excluded secondary complications of proliferative DR such as rubeotic glaucoma and tractional detachments, as they were beyond the scope of this review.

We used the Delphi consensus criteria list to select well-conducted studies.[21] Studies were evaluated on a standardized data extraction form for (1) valid method of randomization, (2) concealed allocation of treatment, (3) similarity of groups at baseline regarding the most important prognostic indicators, (4) clearly specified eligibility criteria, (5) masking of outcome assessor, (6) masking of care provider, (7) masking of patient, (8) reporting of point estimates and measures of variability for outcomes, (9) intention-to-treat analysis, and (10) acceptable loss to follow-up rate unlikely to cause bias. Studies were scored out of a maximum of 10, and studies with a score greater than 5 were considered higher-quality studies. For each intervention, we graded the overall strength of evidence as levels I, II, or III and the ratings for clinical recommendations as levels A, B, and C, using previously reported criteria.[22]

Outcome Measures

For primary interventions, outcome measures included incidence of new DR and rate of adverse effects of intervention. For secondary interventions, measures included progression of DR, changes in visual acuity and macular thickness, and rates of legal blindness and adverse effects. Emphasis was given to studies in which best-corrected visual acuity was measured in a masked fashion using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. For some RCTs, both primary (incidence of DR) and secondary (progression of DR) interventions were evaluated.

Studies used different methods to ascertain retinopathy, including clinical ophthalmoscopy, retinal photography, and/or fluorescein angiography.[23] Studies also classified DR differently, with most using the Airlie House classification[24] with some modifications.[25] This gold-standard assessment involves the grading of seven 30° stereoscopic images of the retina (7 standard fields), with each image compared with standard photographs. A score is then assigned to each eye, ranging from 10 (no retinopathy) to 85 (advanced proliferative DR), and the grades for both eyes are combined into a stepped scale. DME was usually classified as absent or present. Definitions for progression of DR also varied. The Diabetes Control and Complications Trial (DCCT)[26,27] defined progression as at least 3 steps worsening from baseline, while the United Kingdom Prospective Diabetes Study (UKPDS)[28] defined progression as a 2-step change from baseline. Other studies used increases in number of microaneurysms or the need for laser photocoagulation as indicators of progression.

Box. Summary of Risk Factors for Diabetic Retinopathy Identified in Epidemiologic/Cohort Studies

Consistent Risk Factors

Duration of diabetes[3,5,6]

Hyperglycemia/glycated hemoglobin value[3,5-7]

Hypertension[3,8-10]

Hyperlipidemia[8,11-13]

Pregnancy[14]

Nephropathy/renal disease[15,16]

Less Consistent Risk Factors

Obesity[8]

Smoking[17]

Moderate alcohol consumption[18,19]

Physical inactivity[20]

EVIDENCE SYNTHESIS

A total of 782 citations were accessed, of which 44 studies (including 3 meta-analyses) of interventions for DR met our inclusion criteria

Primary Interventions

Glycemic Control. Early epidemiologic studies have shown showed a consistent relationship between glycated hemoglobin (HbA_{1c}) levels and the incidence of DR.[5,7] This important observation has been confirmed in large RCTs demonstrating that tight glycemic control reduces both the incidence and progression of DR (TABLE 1). The DCCT,[26,27,29,45] conducted between 1983 and 1993, randomized 1441 patients with type 1 diabetes to receive intensive glycemic or conventional therapy. Over 6.5 years of follow-up, intensive treatment (median HbA_{1c}, 7.2%) reduced the incidence of DR by 76% (95% confidence interval [CI], 62%-85%) and progression of DR by 54% (95% CI, 39%-66%), as compared with conventional treatment (median HbA_{1c}, 9.1%).[26,27,29,45]

The UKPDS[31] reported similar findings in type 2 diabetes. The UKPDS randomized 3867 persons newly diagnosed as having type 2 diabetes to receive intensive or conventional therapy. Intensive therapy reduced microvascular end points by 25% (95% CI, 7%-40%) and the need for laser photocoagulation by 29%. Data from a subgroup of participants' retinal photographic grading showed a similar association.[17] These findings have been replicated in other studies,[33,46] including a meta-analysis prior to the DCCT[34] (Table 1).

Long-term observational DCCT data showed that despite gradual equalization of HbA_{1c} values after study termination, the rate of DR progression in the former intensively treated group remained significantly lower than in the former conventional group,[27,30] emphasizing the importance of instituting tight glycemic control early in the course of diabetes. This concept is supported by the results of another RCT,[47] in which participants initially assigned to intensive glucose control vs conventional treatment had lower 10-year incidence of severe retinopathy.[48]

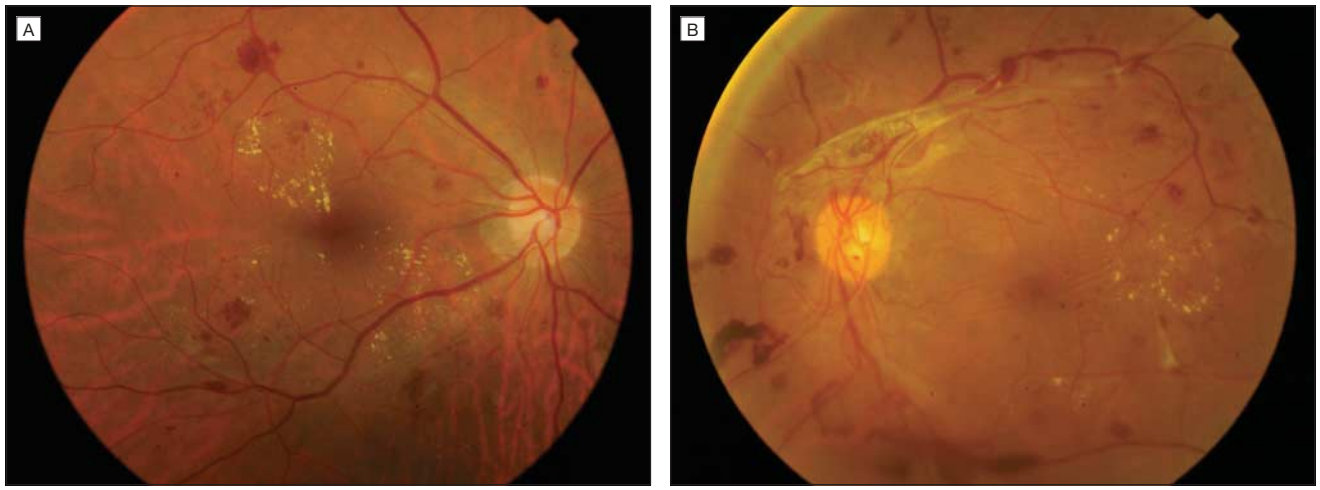
Tight glycemic control has two clinically important adverse effects. First, there is risk of early worsening of DR. In the DCCT, this occurred in 13.1% of the intensive vs 7.6% of the conventional treatment group.[49] However, this effect was reversed by 18 months, and no case of early worsening resulted in serious visual loss. Similar adverse event rates were reported in a meta-analysis.[35] Participants at risk of this early worsening had higher HbA_{1c} levels at baseline and a more rapid reduction of HbA_{1c} levels in the first 6 months, suggesting that physicians should avoid rapid reductions of HbA_{1c} levels where possible. Second, tight glycemic control is a known risk factor for hypoglycemic episodes and diabetic ketoacidosis.[34] A meta-analysis of 14 RCTs, including the DCCT,[50] indicated that intensive treatment is associated with a 3-fold risk of hypoglycemia and 70% higher risk of ketoacidosis as compared with conventional treatment. The risk of ketoacidosis was 7-fold higher among patients exclusively using insulin pumps,[50] suggesting that multiple daily insulin injection might be a safer strategy.

Blood Pressure Control. Epidemiologic studies have not found blood pressure to be a consistent risk factor for DR incidence and progression.[8,9,51,52] Evidence from RCTs, however, indicates that tight control of blood pressure is a major modifiable factor for the incidence and progression of DR (**TABLE 2**). The UKPDS[28] randomized 1048 patients with hypertension to receive tight blood pressure control (target systolic/diastolic pressure, <150/<85 mm Hg) or conventional control (target, <180/<105 mm Hg). After 9 years of follow-up, patients having tight control had a 34% reduction (99% CI, 11%-50%) in DR progression, 47% reduction (99% CI, 7%-70%) in visual acuity deterioration, and 35% reduction in laser photocoagulation compared with those having conventional control.

The UKPDS findings contrast with that of the Appropriate Blood Pressure Control in Diabetes (ABCD) trial,[54,57] which randomized 470 people with type 2 diabetes and hypertension to receive intensive or moderate blood pressure control. Over 5 years, there was no difference in DR progression between the groups. The lack of efficacy in this study may be related to poorer glycemic control, shorter follow-up, and lower blood pressure levels at baseline as compared with the UKPDS. It is unclear if there is a threshold effect beyond which further blood pressure lowering no longer influences DR progression.

The effects of therapy with antihypertensive agents are also apparent among normotensive persons with diabetes. In another group of the ABCD

Figure. Nonproliferative and Proliferative Diabetic Retinopathy



A, Moderate nonproliferative diabetic retinopathy with microaneurysms, retinal hemorrhages, and macular edema characterized by increased vascular permeability and deposition of hard exudates at the central retina. B, Proliferative diabetic retinopathy with new vessels and fibrous tractional bands arising from the optic disc.

Table 1. Randomized Controlled Trials Evaluating Role of Glycemic Control in Diabetic Retinopathy

Source	No.	Diabetes Type	Intervention	Follow-up, y	Outcome	Comments
DCCT[26,27,29,30]	1441	Type 1 DM (726 with no DR, 715 with mild/moderate NPDR)	Intensive vs conventional treatment	6.5	Median HbA_{1c}, 7.2% vs 9.1% ($P < .001$) With intensive treatment, 76% (95% CI, 62%-85%) decreased risk of developing DR; 54% (95% CI, 39%-66%) decreased risk of DR progression; 23% decreased risk of maculopathy[a]; 47% decreased risk of severe NPDR/PDR; 51% decreased risk of laser photocoagulation for macular edema or PDR	With intensive treatment, 43 extra episodes of hypoglycemia requiring assistance per 100 patient-y, with 3.4 extra cases of overweight per 100 patient-y
UKPDS[31,32]	3867	Newly diagnosed type 2 DM	Intensive (sulfonylurea or insulin, aiming for fasting plasma glucose <6 mmol/L) vs conventional (fasting plasma glucose <15 mmol/L) treatment	10	Mean HbA_{1c}, 7% vs 7.9% With intensive treatment, 25% (95% CI, 7%-40%) decreased risk in microvascular end points; 29% decreased risk of retinal photocoagulation; 17% decreased risk of DR progression; 23% decreased risk of vitreous hemorrhage[a]; 16% decreased risk of legal blindness[a]	
Kumamoto Study,[33] 2000	110	Japanese patients with type 2 DM (55 with no DR, 55 with NPDR)	Intensive vs conventional treatment	8	Mean HbA_{1c}, 7.2% vs 9.4% With intensive treatment, 32% decreased risk of developing DR; 32% decreased risk of DR progression; decreased progression to pre-PDR and PDR (1.5 vs 3.0 events/100 patient-y for intensive vs conventional treatment)	No patient in the primary cohort developed pre-PDR or PDR
Wang et al[34,35b]	529	Type 1 DM	Intensive vs conventional treatment	2-5	Mean HbA_{1c}, for intensive treatment groups, 7%-10.5% across included RCTs With intensive treatment, 51% decreased risk of DR progression; 56% decreased risk of progression to PDR or changes requiring laser treatment Trend toward progression of DR after 6-12 mo of intensive treatment, which was reversed by 2-5 y of intensive treatment	Hypoglycemia episodes requiring assistance, 9.1 extra cases per 100 patient-y with intensive treatment
Lauritzen et al,[36c] 1985	30	Type 1 DM with advanced NPDR	CSII vs conventional treatment	2	PDR developed in 4 vs 5 patients[a] Trend toward more frequent improvement of retinal morphology (47% vs 13%)[a]	Small numbers, study underpowered for any firm conclusion
Kroc Collaborative Study Group[37,38c]	70	Type 1 DM with low C-peptide level and NPDR	CSII vs conventional injection treatment	8 mo, 2 y	Mean HbA_{1c}, 8.1% vs 10.0% Increased retinopathy in both groups Trend toward DR progression (increased soft exudates and IRMAs) with CSII in first 8 mo[a], reversed by 2 y	Study continued after initial 8 mo, with 23/34 (CSII) and 24/34 (conventional treatment) followed up for a further 16 mo
Beck-Nielsen et al,[39] 1990 Olsen et al,[40] 1987[c,d]	24	Type 1 DM without proteinuria, with minimal or no DR	CSSI with portable pump vs conventional insulin treatment	5	Mean HbA_{1c}, 7.4% vs 8.6% ($P < .01$) Trend for DR progression in conventional insulin treatment group ($P > .10$)	Small sample; 1 loss to follow-up in CSII group
Stockholm Diabetes Intervention Study,[41] 1991	96	Type 1 DM with NPDR	Intensive vs conventional treatment	5	Median HbA_{1c}, 7.2% vs 8.7% Increased retinopathy in both groups ($P < .001$) Odds ratio for serious retinopathy with intensive treatment vs conventional treatment, 0.4 ($P = .04$)	Hypoglycemia, 242 vs 98 episodes ($P < .05$) With intensive treatment, 58% increased BMI
Oslo Study[42-44]	45	Type 1 DM	CSII vs multiple insulin injections (5-6/d) vs conventional treatment (twice-daily injections)	2	Decreased retinal microaneurysms and hemorrhages with CSII and multiple insulin injections vs conventional treatment ($P < .01$).	Transient increase in microaneurysms and hemorrhages at 3 mo in CSII group

Abbreviations: BMI, body mass index; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; DM, diabetes mellitus; DR, diabetic retinopathy; HbA_{1c}, glycated hemoglobin; IRMA, intraretinal microvascular abnormalities; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; RCT, randomized clinical trial; UKPDS, United Kingdom Prospective Diabetes Study.

SI conversion factor: To convert glucose values to mg/dL, divide by 0.0555.

[a] Effect was not statistically significant.

[b] Meta-analysis.

[c] Included in meta-analysis by Wang et al.[34]

[d] Three-year results.

trial,[57] among 480 nonhypertensive patients with type 2 diabetes, intensive blood pressure control significantly reduced DR progression over 5 years as compared with moderate control. The EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID)[56] evaluated the effects of the angiotensin-converting enzyme (ACE) inhibitor lisinopril on DR progression in normotensive, normoalbuminuric patients with type 1 diabetes. Over 2 years, lisinopril reduced the progression of DR by 50% (95% CI, 28%-89%) and progression to proliferative DR by 80%.[56] EUCLID was limited by differences in baseline glycemic levels between groups (the treatment group had lower HbA_{1c} levels) and a short follow-up of 2 years. This study, along with another smaller RCT,[58] suggested that ACE inhibitors may have an additional benefit on DR progression independent of blood pressure lowering. However, data from the UKPDS[53] and the ABCD study[54,57] did not find ACE inhibitors to be superior to other blood pressure medications.

Whether newer blood pressure medications have additional beneficial effects is unclear. A recent small RCT (n=24) with short follow-up (4 months) reported a worsening of DME among patients treated with the angiotensin II receptor blocker losartan, compared with controls.[59] Two large RCTs are currently ongoing. The Action in Diabetes and Vascular Disease (ADVANCE) study will evaluate the effect of a perindopril-indapamide combination on the incidence of DR,[60] while the Diabetic Retinopathy Candesartan Trial (DIRECT) will evaluate the angiotensin II receptor blocker candesartan.[61]

Lipid-Lowering Therapy. Observational studies suggest that dyslipidemia increases the risk of DR, particularly DME.[8,11] A small RCT conducted among 50 patients with DR found a nonsignificant trend in visual acuity improvement in patients receiving simvastatin treatment,[62] while another study reported a reduction in hard exudates but no improvement in visual acuity in those with clinically significant DME treated with clofibrate.[63]

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (**TABLE 3**),[64] among 9795 participants with type 2 diabetes, those treated with fenofibrate were less likely than controls to need laser treatment (5.2%

Table 2. Randomized Controlled Trials Evaluating Role of Blood Pressure Control in Diabetic Retinopathy

Source	No.	Diabetes Type	Intervention	Follow-up, y	Outcome	Comments
UKPDS,[53] 2004	1148	Type 2 DM with hypertension (mean BP of 160/94 mm Hg)	Tight BP control (<150/85 mm Hg) vs less tight control (<180/105 mm Hg) Randomized to β-blocker or ACE inhibitor	8.4	With intensive treatment, 34% (99% CI, 11%-50%) decreased risk of DR progression (≥2 ETDRS steps) (P = .004); 47% (99% CI, 7%-70%) decreased risk of visual acuity loss (3 ETDRS lines) (P = .004); 35% decreased risk of laser photocoagulation (P = .02); decreased risk of >5 microaneurysms (RR, 0.66; P < .001), hard exudates (RR, 0.53; P < .001), and cotton-wool spots (RR, 0.53; P < .001) at 7.5 y	Observational data suggest 13% decrease in microvascular complications for each 10-mm Hg decrease in mean systolic BP No difference in outcome between ACE inhibitor and β-blocker
ABCD,[54] 2000	470	Hypertensive type 2 DM (mean baseline diastolic BP >90 mm Hg)	Intensive BP control (aiming for diastolic BP of 75 mm Hg) vs moderate control (diastolic BP of 80-89 mm Hg)	5.3	No difference in progression of DR between intensive (mean BP, 132/78 mm Hg) and moderate (mean BP, 138/86 mm Hg) control	No difference in DR progression with nisoldipine vs enalapril
ABCD,[55] 2002	480	Normotensive type 2 DM (BP <140/90 mm Hg)	Intensive BP control (10 mm Hg below baseline diastolic BP) vs moderate control (80 to 89 mm Hg)	5.3	Decreased DR progression Mean BP, 128/75 mm Hg vs 137/81 mm Hg; P = .019	Results the same regardless of initial antihypertensive agent used
EUCLID,[56] 1998		Normotensive and normoalbuminuric type 1 DM	Lisinopril treatment	2	With lisinopril, 50% (95% CI, 28%-89%) decreased DR progression (2 ETDRS steps); 80% decreased progression to PDR	Concern about possibility of inadequate randomization (lisinopril group had lower HbA_{1c} levels)

Abbreviations: ABCD, Appropriate Blood Pressure Control in Diabetes; ACE, angiotensin-converting enzyme; BP, blood pressure; CI, confidence interval; DM, diabetes mellitus; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; EUCLID, EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus; HbA_{1c}, glycated hemoglobin; PDR, proliferative diabetic retinopathy; RR, relative risk; UKPDS, United Kingdom Prospective Diabetes Study.

vs 3.6%, $P < .001$). However, the severity of DR, indications for laser treatment, and type of laser treatment (focal or pan-retinal) were not reported.

The Collaborative Atorvastatin Diabetes Study (CARDS), an RCT of 2830 patients with type 2 diabetes, did not find atorvastatin to be effective in reducing DR progression.[75,76] The study was limited by substantial missing data (only 65% of patients had retinopathy status recorded at baseline) and lack of pho-

Table 3. Randomized Controlled Trials of Medical Interventions in Diabetic Retinopathy

Source	No.	Diagnosis	Intervention	Follow-up	Outcome	Comments
FIELD,[64] 2005	9795	Type 2 DM (total cholesterol 3-6.5 mmol/L and no lipid-lowering drugs at baseline)	Fenofibrate vs placebo	5 y	With fenofibrate, decreased reported need for retinal laser photocoagulation (5.2% vs 3.6%, $P = .0003$)	Not main end point; large loss of data; severity of DR indication for laser treatment, and type of laser (focal or pan-retinal) not reported
ETDRS,[65] 1991 Chew et al,[66] 1995	3711	Mild to severe NPDR or early PDR	Aspirin (650 mg/d) vs placebo	3 y	Vitreous hemorrhage in 32% vs 30% ($P = .48$) No difference in the severity of vitreous/preretinal hemorrhages ($P = .11$) or rate of resolution ($P = .86$)	Aspirin had no effect on DR incidence/progression, vitreous hemorrhage, or need for vitrectomy
DAMAD,[67] 1989	475	Early diabetic retinopathy (type 1 and type 2 DM)	Aspirin (330 mg 3 times/d) alone vs aspirin + dipyridamole (75 mg 3 times/d) vs placebo	3 y	With aspirin alone and aspirin + dipyridamole, decreased mean yearly increases in microaneurysms on FFA (aspirin alone, 0.69 [SD, 5.1]; aspirin + dipyridamole, 0.34 [SD, 3.0]; placebo, 1.44 [SD, 4.5]) ($P = .02$)	Loss to follow-up in 10% of patients
TIMAD,[68] 1990	435	NPDR	Ticlopidine hydrochloride (antiplatelet agent) vs placebo	3 y	Decreased yearly microaneurysm progression on FFA (0.23 [SD, 6.66] vs 1.57 [SD, 5.29]; $P = .03$) and decreased progression to PDR ($P = .056$)	Adverse reactions included neutropenia (severe in 1 case), diarrhea, and rash
Cullen et al,[63] 1974		Exudative diabetic maculopathy	Clofibrate	1 y	Decreased hard exudates but no statistical improvement in visual acuity	Lacked power
PKC-DRS,[69] 2005	252	Moderately severe to very severe NPDR (ETDRS severity level between 47B and 53E; visual acuity ≥20/125 and no previous scatter photocoagulation)	Ruboxistaurin (8, 16, or 32 mg/d) vs placebo	36-46 mo	No significant effect on DR progression Ruboxistaurin (32 mg) delayed occurrence of MVL ($P = .038$) and SVL ($P = .226$) In multivariable Cox proportional hazard analysis, ruboxistaurin (32 mg) decreased risk of MVL vs placebo (HR, 0.37 [95% CI, 0.17-0.80]; $P = .012$)	Decrease of SVL by ruboxistaurin observed only in eyes with definite DME at baseline (10% ruboxistaurin vs 25% placebo, $P = .017$)
PKC-DRS2,[70] 2006	685	Moderately severe to very severe NPDR (ETDRS severity level between 47B and 53E; visual acuity ≥20/125 and no previous scatter photocoagulation)	Ruboxistaurin (32mg/d) vs placebo	3 y	No significant effect on DR progression Treatment decreased risk of sustained MVL (5.5% treated vs 9.1% placebo, $P = .034$)	
PKC-DME,[71] 2007	686	DME >300 µm from center (ETDRS severity level 20-47A, visual acuity ≥75 ETDRS letters, and no previous laser treatment)	Ruboxistaurin (32md/d)	3 y	No significant effect on progression to sight-threatening DME or need for focal laser treatment	Variation in application of focal laser between centers Ruboxistaurin reduced progression of DME vs placebo in secondary analysis ($P = .054$, unadjusted)
Sorbinil Retinopathy Trial,[72] 1990	497	Type 1 diabetes	Oral sorbinil (250 mg) vs placebo	41 mo	No significant effect on DR progression (28% vs 32%, $P = .344$)	Hypersensitivity reaction in 7% of sorbinil-treated group
Gardner et al,[73] 2006	63	DME (no previous macular photocoagulation)	Astemizol (antihistamine) vs placebo	1 y	No effect on retinal thickening or hard exudates (photographs graded by modified ETDRS protocol)	54/63 patients (86%) completed 1 y of follow-up
Grant et al,[74] 2000	23	Severe NPDR or early non–high-risk PDR	Maximum tolerated doses of octreotide (200-5000 µg/d subcutaneously) vs conventional treatment	15 mo	Octreolide decreased progression to high-risk PDR needing PRP (1/22 vs 9/24 eyes, $P < .006$) and decreased DR progression (27% vs 42%; $P = .0605$)	Thyroxine replacement therapy needed in all treated patients

Abbreviations: CI, confidence interval; DM, diabetes mellitus; DME, diabetic macular edema; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; FFA, fundus fluorescein angiography; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; HR, hazard ratio; MVL, moderate visual loss; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, pan-retinal laser photocoagulation; SVL, severe visual loss; TIMAD, Ticlopidine Microangiopathy of Diabetes.
SI conversion factor: To convert total cholesterol values to mg/dL, divide by 0.0259.

tographic grading for DR. Several ongoing RCTs, such as the Atorvastatin Study for Prevention of Coronary Endpoints in NIDDM (ASPEN),[77] will also evaluate the effects of atorvastatin on DR.

Secondary Interventions

Medical Interventions. *Antiplatelet Agents*. The ETDRS showed that aspirin (650 mg/d) had no beneficial effect on DR progression or loss of visual acuity in patients with DME or severe nonproliferative DR during 9 years of follow-up (Table 3).[65,66] Aspirin treatment was not associated with an increased rate of vitrectomy.[65,66] A smaller RCT evaluating aspirin alone and in combination with dipyridamole reported a reduction in microaneurysms on fluorescein angiograms in both groups as compared with placebo.[67] A similar trend was observed in a small RCT[68] evaluating ticlopidine, although results were not statistically significant.

Protein Kinase C Inhibitors. Hyperglycemia induces synthesis of diacylglycerol in vascular cells, leading to activation of protein kinase C (PKC) isozymes. Excessive PKC activation may be involved in the pathophysiology of DR. Ruboxistaurin, an orally active PKC inhibitor, was evaluated in the Protein Kinase C Diabetic Retinopathy Study (PKC-DRS) (Table 3),[69] which randomized 252 patients with moderate to severe nonproliferative DR to receive ruboxistaurin (8, 16, or 32 mg) or placebo. No significant difference in DR progression was observed after 36 months of follow-up, although patients treated with 32 mg of ruboxistaurin had a significant reduc-

Table 4. Randomized Controlled Trials of Laser Treatment in Nonproliferative and Proliferative Diabetic Retinopathy and Diabetic Macular Edema

Source	No.	Retinopathy Severity	Intervention	Follow-up	Outcome	Comments
Nonproliferative and Proliferative Diabetic Retinopathy						
Rohan et al,[87] 1989[a]	2243	NPDR/PDR (with/without DME)	Peripheral PRP with/without focal laser treatment vs observation	1-5 y	PRP decreased risk of blindness in eyes with PDR by 61% (combined "best estimate" based on 5 RCTs including DRS and BMS)	Criteria for study inclusion, quality assessment, baseline comparability, and adverse effects of included studies not described
DRS,[88] 1981	1742	Severe NPDR (bilateral) or PDR (with/without DME)	Peripheral PRP with/without focal laser treatment vs observation	5 y	PRP decreased risk of SVL by 52% at 2 y; 90/650 treated (14%) vs 171/519 observed (33%) (RR, 0.42; 95% CI, 0.34-0.53) Eyes with "high risk" features had most benefit (57% decreased risk of SVL)	Decreased visual acuity and constriction of peripheral visual field in some eyes
ETDRS,[89,90]	3711	Mild to severe NPDR or early PDR (with/without DME in both eyes)	1 eye of each patient assigned to early PRP with/without focal laser treatment vs treatment deferral	5 y	SVL in 2.6% vs 3.7%; PRP decreased risk of vitrectomy (2.3% vs 4%); 4% decreased risk of SVL or vitrectomy with early photocoagulation vs 6% with deferral	Eyes assigned to deferral of PRP did not receive any focal laser treatment for any coexistent DME until positive results of macular treatment were released
BMS[91] 1984	107	PDR (bilateral symmetrical)	Xenon-arc laser photocoagulation vs observation	5-7 y	Decreased risk of blindness, 5% vs 17% (RR, 0.29; 95% CI, 0.11-0.77) Patients with NVD at entry had greatest difference; treated eyes that became blind had less treatment than those that retained vision	Large loss to follow-up (28%) Only 77 completed 5-y follow-up No intention-to-treat analysis
BMS,[92] 1983	99	NPDR	Peripheral xenon arc laser vs observation	5 y	Decreased visual deterioration, 32% vs 55% (RR, 0.49; 95% CI, 0.32-0.74)	Large loss to follow-up No intention-to-treat analysis
Hercules et al[93] 1977	94	Symmetrical PDR involving optic disc	PRP vs observation	3 y	Decreased risk of blindness, 7% (7/94) vs 38% (36/94) (RR, 0.19; 95% CI, 0.09-0.41)	Incomplete masking No individual treatment assessment
Patz et al[94] 1973	66	NPDR with DME	PRP vs observation	26 mo	Decreased visual deterioration, 6% vs 63% (RR, 0.10; 95% CI, 0.04-0.26)	Poorly specified criteria Loss not specified
Lövestam-Adrian et al,[95] 2003	81	Severe NPDR and PDR in patients with type 1 diabetes	All participants treated with PRP (1 randomly selected eye per patient entered into study)	2.9 ± 1.5 y	14/40 eyes (35%) treated for severe NPDR developed neovascularization Vitreous hemorrhage less frequent in treated eyes with severe NPDR vs PDR (2/40 vs 12/41, $P = .007$) Decreased vitrectomy for vitreous hemorrhage in eyes treated for severe NPDR (1/40 vs 6/41, $P = .052$) Decreased visual impairment in eyes treated for severe NPDR vs PDR (4/40 vs 10/40, $P = .056$)	Time for PRP not randomly assigned Adverse outcomes not assessed Inclusion/exclusion criteria, blinding, intention-to-treat analysis not specified Coexistent CSME treated with macular laser

(continued)

Table 4. Randomized Controlled Trials of Laser Treatment in Nonproliferative and Proliferative Diabetic Retinopathy and Diabetic Macular Edema (cont)

Source	No.	Retinopathy Severity	Intervention	Follow-up	Outcome	Comments
Diabetic Macular Edema						
ETDRS,[96] 1985	2244	Bilateral DME (mild to moderate NPDR)	Focal argon laser (754 eyes) vs observation (1490 eyes)	3 y	Treatment decreased moderate visual loss (RR, 0.50; 95% CI, 0.47-0.53) Benefits most marked in eyes with CSME, particularly if the center of the macula was involved or imminently threatened (subgroup analysis)	
DRCR Network,[97] 2007	323	DME with no previous treatment	Modified ETDRS laser (162 eyes) vs mild grid laser (161 eyes)	1 y	No significant difference in central macular thickness (on OCT) or visual acuity (treatment decreased CMT by 88 μm in the modified ETDRS group vs 49 μm in the mild macular grid laser group, $P = .04$)	
Blankenship,[98] 1979	39	Bilateral symmetrical DME (moderate to severe NPDR)	Grid argon laser vs observation	2 y	Visual deterioration in 7/30 eyes (23%) with laser vs 13/30 (43%) with no treatment (RR, 0.54; 95% CI, 0.25-1.16)	
Olk,[99] 1986	92	Diffuse DME with/without CSME	Modified grid argon laser vs observation	2 y	Treatment decreased risk of moderate visual loss by 50%-70% Loss of visual acuity reduced compared with no treatment at 1 y (RR, 0.84) and at 2 y (RR, 0.78; 95% CI, 0.60-0.96)	
Multicenter controlled study interim report,[100] 1975	76	Bilateral symmetrical DME	Xenon-arc laser vs observation	3 y	Blindness in 8 treated vs 18 control eyes Prognosis was best in those with initial visual acuity ≥6/24	Only 44 patients at 2 y; 25 after 3 y
Ladas and Theodossiadis,[101] 1993	42	Diffuse DME (NPDR)	Modified grid argon laser vs observation	3 y	Trend for improved visual acuity with treatment at 1 and 2 y; no difference in visual acuity at 3 y[b]	No masking Poor characterization of groups

Abbreviations: BMS, British Multicenter Study; BP, blood pressure; CI, confidence interval; CMT, central macular thickness; CSME, clinically significant macular edema; DME, diabetic macular edema; DRCR, Diabetic Retinopathy Clinical Research; DRS, Diabetic Retinopathy Study; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, nonproliferative diabetic retinopathy; NVD, neovascularization of the disc; OCT, ocular coherence tomography; PDR, proliferative diabetic retinopathy; PRP, pan-retinal laser photocoagulation; RCT, randomized controlled trial; RR, risk reduction; SVL, severe visual loss.
[a] Review/meta-analysis of 5 trials.
[b] Not significant.

tion in the risk of moderate visual loss. Treatment was well tolerated with few adverse events, largely mild gastrointestinal symptoms. A larger study, the PKC-DRS2, which randomized 685 patients, showed similar results.[70]

The PKC-DMES Study (Table 3) reported no significant reduction in progression of DR or incidence of DME in 686 patients with mild to moderate nonproliferative DR and no prior laser therapy.[71,78] There was a trend for a reduction in clinically significant DME among patients treated with 32 mg of ruboxistaurin ($P = .04$), with a larger effect when patients with HbA_{1c} levels of 10% or greater were excluded ($P = .02$).

Aldose Reductase Inhibitors. Aldose reductase is the rate-controlling enzyme in the polyol pathway of glucose metabolism and is involved in pathogenesis of DR. Two aldose reductase inhibitors, sorbinil (Pfizer, New York, New York) and tolrestat (Wyeth-Ayerst, St Davids, Pennsylvania), showed no statistically significant effect in reducing DR incidence or progression in RCTs of 3 to 5 years' duration.[72]

Growth Hormone/Insulinlike Growth Factor Inhibitors. Observations of improvements in DR following surgical hypophysectomy[79,80] and of increased serum and ocular levels of insulinlike growth factor in patients with severe DR led to studies investigating the use of agents inhibiting the growth hormone/insulinlike growth factor pathway for prevention of DR.[81] A small RCT conducted over 15 months among 23 patients reported reduction in retinopathy severity with octreotide, a synthetic analogue of somatostatin that blocks growth hormone,[74] but another RCT conducted over 1 year among 20 patients[82] evaluating continuous subcutaneous infusion of octreotide found no significant benefits. Two larger RCTs currently evaluating long-acting–release octreotide injection[83,84] have reported inconclusive preliminary results,[85] with significant adverse effects (eg, diarrhea, cholelithiasis, hypoglycemic episodes).

Laser and Surgical interventions for Severe Nonproliferative and Proliferative DR. *Pan-Retinal Laser Photocoagulation*. Pan-retinal laser photocoagulation (PRP), in which laser burns are placed over the entire retina, sparing the central macula, is an established technique for treating severe nonproliferative and proliferative DR[86] (TABLE 4).

The strongest evidence comes from 2 related RCTs in the 1970s and 1980s, the

Diabetic Retinopathy study (DRS)[86,88] and the ETDRS.[102] The DRS randomized 1758 patients with proliferative DR in least 1 eye or bilateral severe nonproliferative DR to receive PRP or no treatment. At 2 years, severe visual loss (visual acuity <5/200 on 2 successive visits) was observed in 6.4% of treated vs 15.9% of untreated eyes, with the greatest benefit in eyes with high-risk characteristics (new vessels at the optic disc or vitreous hemorrhage with new vessels

Table 5. Randomized Controlled Trials of Surgical Interventions in Proliferative Diabetic Retinopathy and Diabetic Macular Edema

Source	No.	Diagnosis	Intervention	Follow-up, y	Outcome	Comments
Proliferative Diabetic Retinopathy						
Diabetic Retinopathy Vitrectomy Study[107,108]	616 eyes	Recent severe diabetic vitreous hemorrhage reducing visual acuity to ≤5/200 for at least 1 mo	Early vitrectomy vs deferral of vitrectomy for 1 y	4	Increased recovery of visual acuity to ≥10/20 (25% vs 15%) Trend for more frequent loss of light perception with early surgery (25% vs 19%) Greatest benefit (visual acuity increased to 10/20) in type 1 DM with more severe PDR (36% vs 12%), and proportion losing light perception was similar (28% vs 26%)	
	370 eyes	Advanced PDR with fibrovascular proliferation and visual acuity ≥10/200	Early vitrectomy vs conventional treatment	4	Increased proportion of eyes with visual acuity ≥10/20 (44% vs 28%) No difference in proportion with loss of vision to light perception or less	Most benefit in patients with very advanced PDR; no benefit in group with less severe neovascularization
Diabetic Macular Edema						
Gillies et al,[109] 2006	43 (69 eyes)	DME and impaired vision that persisted or recurred after laser treatment	Intravitreal triamcinolone acetonide injections (4 mg) vs subconjunctival saline placebo	2	Best-corrected visual acuity increased by ≥5 letters (56% vs 26%, $P = .006$) Mean visual acuity increased by 5.7 letters (95% CI, 1.4-9.9) vs placebo IOP increase of ≥5 mm Hg in 23/34 (68%) eyes vs 3/30 (10%) ($P < .0001$) Cataract surgery in 54% vs 0% ($P < .0001$) 2 treated eyes required trabeculectomy 1 case of infectious endophthalmitis	Data for 60 of 69 eyes (87%) (in 35 of 41 patients [85%])
Pearson et al,[110] 2006	197	DME	Sustained-release fluocinolone acetonide intravitreal implant (Retisert) vs standard care (randomized 2:1 ratio)	3	Implant decreased DME (no edema in 58% vs 30%; $P < .001$) Implant increased >2 improvement in CMT (45% vs 24%) Trend for increased visual acuity with implant (visual acuity increased by ≥3 lines in 28% vs 15%, $P < .05$) Cataract surgery in 95% of phakic implanted eyes	Increased IOP in 35%; 28% required a filtering procedure, and 5% explanted to manage IOP
Yanyali et al,[111] 2006	20 eyes of 10 patients	Bilateral DME unresponsive to grid laser photocoagulation	Vitrectomy with removal of the ILM randomly in 1 eye	1	CMT decreased by 165.8 (SD, 114.8) μm vs 37.8 (SD, 71.2) μm ($P = .016$) Vitrectomy increased visual acuity by ≥2 lines in 4 (40%) vs 1 (10%)[a]	
Thomas et al,[112] 2005	40 eyes	DME (visual acuity ≤6/12) unresponsive to laser treatment with no associated traction	Vitrectomy + ILM peel vs further macular laser	1	CMT decreased by 73 μm (20%) vs 29 μm (10.7%) Vitrectomy decreased mean best-corrected visual acuity by 0.05 logMAR vs increased by 0.03 logMAR in controls[a]	18% loss to follow-up
Dhingra et al,[113] 2005	20 eyes (20 patients)	DME (visual acuity ≤6/12) unresponsive to laser treatment with no associated traction or ischemia	Vitrectomy + ILM peel vs observation	1	Vitrectomy decreased mean CMT (250.6 [SD, 56.8] μm vs 450 [SD, 40] μm) No significant change in logMAR visual acuity	Masking unclear
Bahadir et al,[114] 2005	58 eyes of 49 patients	Diffuse CSME	Vitrectomy + ILM peel (17 eyes) vs vitrectomy without ILM peel (41 eyes total)	1	No significant difference between groups in visual acuity Visual acuity increased in both groups (0.391 [SD, 0.335] in vitrectomy + ILM peel and 0.393 [SD, 0.273] logMAR, $P > .01$).	Randomization and masking unclear HbA_{1c} and baseline BP not reported

Abbreviations: BP, blood pressure; CI, confidence interval; CMT, central macular thickness; CSME, clinically significant macular edema; DM, diabetes mellitus; DME, diabetic macular edema; HbA_{1c}, glycated hemoglobin; ILM, internal limiting membrane; IOP, intraocular pressure; logMAR, logarithmic minimal angle resolution; PDR, proliferative diabetic retinopathy.
[a]Not significant.

elsewhere [Figure, B]), in which the risk of severe visual loss was reduced by 50%.[86]

The ETDRS[102] randomized 3711 patients with less severe DR and visual acuity greater than 20/100 to early PRP or deferral (4-month observation and treatment if high-risk proliferative DR developed). Early PRP treatment decreased the risk of high-risk proliferative DR by 50% as compared with deferral, although the incidence of severe visual loss was low in both the early treatment and the deferral groups (2.6% vs 3.7%). Other RCTs[91-93] and a meta-analysis with combined data of 2243 patients[87] have confirmed the effectiveness of PRP.

Adverse effects of PRP include visual field constriction (with implications for driving[103,104]), night blindness, color vision changes, inadvertent laser burn, macular edema exacerbation, acute glaucoma, and traction retinal detachment.[105] There is also the possibility of visual loss immediately following PRP. The DRS reported vision loss of 2 to 4 lines within 6 weeks of PRP in 10% to 23% of patients vs 6% of controls.[106]

Surgical Vitrectomy for Vitreous Hemorrhage and Proliferative DR. Vitrectomy has been used for treatment of eyes with advanced DR, including proliferative DR with nonclearing vitreous hemorrhage or fibrosis, areas of traction involving or threatening the macula, and, more recently, persistent DME with vitreous traction (**TABLE 5**).[115] The Diabetic Retinopathy Vitrectomy Study (DRVS) randomized 616 eyes with recent vitreous hemorrhage and visual acuity of 5/200 or less for at least 1 month to undergo early vitrectomy within 6 months or observation.[107,108,116,117] After 2 years' follow-up, 25% of the early vitrectomy group vs 15% of the observation group had 20/40 or greater vision, with the benefits maintained at 4 years and longer in individuals with type 1 diabetes. Vitreoretinal surgery has advanced considerably since the DVRS. These advances include intraoperative fundal imaging and laser treatment and bimanual instrumentation to manipulate the retina. These have widened the indications of vitrectomy and may improve outcomes.[118]

Laser and Surgical Interventions for Diabetic Macular Edema. *Focal Laser Treatment*. Like PRP, there is good evidence that focal laser treatment preserves vision in eyes with DME. The ETDRS[96] randomized 1490 eyes with DME to receive focal laser treatment or observation. At 3 years, treatment significantly reduced moderate visual loss as compared with observation,[96] with the greatest benefits in eyes with clinically significant DME.[119] There is limited evidence that laser type (argon, diode, dye, krypton) or method used influences outcomes.[97,120-122] Adverse effects include inadvertent foveal burn, central visual field defect, color vision abnormalities, retinal fibrosis, and spread of laser scars.[105,106]

Surgical Vitrectomy for Diabetic Macular Edema. Widespread or diffuse DME that is nonresponsive to focal laser treatment may benefit from vitrectomy.[123-126] However, the few RCTs to date have had small sample sizes and short follow-up, with inconsistent results (Table 5). An RCT of 28 patients with diffuse DME reported reduced macular thickness and improved visual acuities at 6 months after vitrectomy vs observation.[127] Vitrectomy was superior to focal laser treatment in 1 RCT[128] but not in others.[112,113] Complications of vitrectomy include recurrent vitreous hemorrhage, retinal tears and detachment, cataract formation, and glaucoma. The presence of vitreous traction and macular edema—now readily documented with optical coherence tomography—in association with visual impairment is currently a common indication for vitrectomy.

Intravitreal Corticosteroids. Corticosteroids have potent anti-inflammatory and antiangiogenesis effects. Intravitreal triamcinolone (IVTA)—ie, injection of triamcinolone acetonide into the vitreous cavity[129]—has been used for treatment of DME,[130-132] with a number of RCTs demonstrating significant improvements in DME and visual acuity.[133-138] Many of these, however, had small participant numbers and short follow-up. Additionally, there were substantial adverse effects, include infection, glaucoma, and cataract formation.[109,139-142]

In the largest RCT having the longest follow-up yet reported, eyes with persistent DME were randomized to receive 4 mg of IVTA or sham injection (saline injection into the subconjunctival space).[109] After 2 years, 19 of 34 IVTA-treated eyes (56%) had a visual acuity improvement of 5 letters or more compared with 9 of 35 placebo-treated eyes (26%) ($P=.007$). Overall, IVTA-treated eyes had twice the chance of improved visual acuity and half the risk of further loss. However, many eyes required repeated injections (mean, 2.2), and there was significant intraocular pressure elevation (≥5 mm Hg in 68% of treated eyes vs 10% of controls). Cataract surgery was required in 55% of IVTA-treated eyes. Thus, while this study demonstrated significant efficacy of IVTA in persistent DME, larger RCTs are needed to provide further data on long-term benefits and safety.[143] Additionally, the ideal dose of triamcinolone remains unclear.[144]

More recently, intravitreal or retinal implants have been developed, allowing extended drug delivery. A surgically implanted intravitreal fluocinolone acetonide (Retisert; Bausch & Lomb, Rochester, New York) was evaluated in 97 patients with DME randomized to receive either implantation or standard care (laser treatment or observation).[110] At 3 years, 58% of implanted eyes vs 30% of controls had resolution of DME ($P<.001$) and associated improvement in visual acuity. However, adverse effects included a substantially higher risk of cataract formation and glaucoma than that observed in eyes receiving IVTA, with 5% requiring implant removal to control glaucoma.[110] An injectable, biodegradable intravitreal dexamethasone extended-release implant (Posurdex; Allergan, Irvine, California) was evaluated in an RCT, with reported improvements in visual acuity and macular thickness.[145]

This study, however, also included eyes with macular edema from other causes (retinal vein occlusion, uveitis, and following cataract surgery) and had relatively short follow-up. A larger RCT of Posurdex for DME is currently under way.

Intravitreal Antiangiogenesis Agents. Several RCTs are currently evaluating 3 agents that suppress vascular endothelial growth factor (VEGF) for treatment of DME. Pegaptanib (Macugen; Pfizer, New York, New York) targets the 165 isoform of VEGF for treatment of neovascular age-related macular degeneration (AMD). An RCT of 172 patients with DME randomized to receive repeated intravitreal pegaptanib or sham injections showed that treated eyes were more likely to have improvement in visual acuity of 10 letters or more (34% vs 10%, $P=.03$), macular thickness ($P=.02$), and need for focal laser treatment ($P=.04$) at 36 weeks.[146] Serious infection occurred in 1 of 652 injections (0.15%) and was not associated with severe visual loss.[146] Retrospective data analysis of 16 eyes with proliferative DR also showed regression of neovascularization.[147]

Ranibizumab (Lucentis; Genentech, South San Francisco, California) is another anti-VEGF agent used for treatment of neovascular AMD[148,149] and may also be useful for DR and DME.[150] A phase 2 RCT (the RESOLVE study) is currently evaluating ranibizumab in DME. Finally, bevacizumab (Avastin, Genentech) is an anti-VEGF agent similar to ranibizumab that is approved for the treatment of disseminated colorectal cancer and not licensed for intraocular use. However, bevacizumab appears to show similar efficacy for treatment of neovascular AMD and may also be effective for DME and proliferative DR.[151-154] Bevacizumab has attracted interest because of its low cost, but systemic safety is a concern.[155] An ongoing RCT sponsored by the US National Eye Institute is comparing the ef-

Table 6. Summary of Clinical Recommendations for Primary and Secondary Interventions for Diabetic Retinopathy

Intervention	Evidence Level[a]	Recommendation
Glycemic control	A, I	Any lowering of HbA_{1c} level advantageous in reducing development of new or progression of existing DR In patients with DR, HbA_{1c} level <7% is ideal
BP control	A, I	Any lowering of systolic and/or diastolic BP is advantageous in reducing development and progression of DR In patients with DR, systolic BP <130 mm Hg is ideal
Lipid-lowering therapy	A, II	Lowering of LDL-C levels reduces macrovascular complications of diabetes and may be advantageous in DME
PRP	A, I	Prompt PRP is recommended in patients with PDR, especially if high-risk features are present
	A, II	Early PDR with less severe PDR (flat new vessels elsewhere and no high-risk features) and severe NPDR may be observed closely, but treatment recommended if any difficulty or delay in follow-up is anticipated or there are associated risk factors or signs of progression, especially in patients with type 2 diabetes
Focal laser photocoagulation	A, I	Focal laser therapy recommended in eyes with DME involving the center of macula and reducing visual acuity Treatment should be considered for DME threatening the center of macula, but patients must be warned of potential risks of treatment, especially when vision is 6/6 or better Treatment is ideally guided by a fluorescein angiogram and is unlikely to be beneficial in the presence of significant macular ischemia
Surgical vitrectomy	B, II	Early vitrectomy (within 3 mo) is recommended in patients with type I diabetes with severe vitreous hemorrhage and significant DR Vitrectomy should be considered in eyes with severe PDR not responsive to extensive PRP, associated with traction involving the macula, or both
	B, III	Vitrectomy may be advantageous in selected cases of diffuse severe DME not responsive to other therapies, especially in presence of vitreomacular traction
Intravitreal steroids	B, II	Intravitreal triamcinolone may have a role in diffuse DME unresponsive to focal laser treatment Patients must be warned of high incidence of secondary intraocular pressure increase, cataract, other potential risks, and possible need for repeat treatment
Intravitreal anti-VEGF agents	B, II/III	These agents may have a role in reducing PDR and DME, but patients require repeated treatment and agents have potential adverse effects; currently, there is insufficient evidence to recommend their routine use
Aspirin and other medical treatment	C, I	Aspirin does not reduce risk of developing DR or increase the incidence of retinal or vitreous hemorrhage
	C, II/III	Currently, there is insufficient evidence to recommend routine use of PKC inhibitors, GH antagonists, and other treatments, but they may have a role in some patients

Abbreviations: BP, blood pressure; DME, diabetic macular edema; DR, diabetic retinopathy; GH, growth hormone; HbA_{1c}, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PKC, protein kinase C; PRP, pan-retinal laser photocoagulation; VEGF, vascular endothelial growth factor.

[a] Presented as importance of clinical outcome, strength of evidence. A indicates most important or crucial to a good clinical outcome; B, moderately important to clinical outcome; C, possibly relevant but not critical to clinical outcome. I indicates data providing strong evidence in support of clinical recommendation; II, strong evidence in support of recommendation but evidence lacks some qualities, thereby preventing its justifying the recommendation without qualification; III, insufficient evidence to provide support for or against recommendation or panel/individual expert opinion.

fects of laser treatment, intravitreal bevacizumab, and combined intravitreal bevacizumab and laser or sham injection on DME.[156]

COMMENT

Primary Interventions

There is strong evidence that tight glycemic control reduces the incidence and progression of DR (TABLE 6). For type 1 diabetes, the DCCT showed that each 10% decrease in HbA_{1c} level (eg, 9% to 8%) reduces the risk of DR by 39%, and this beneficial effect persists long after the period of intensive control. In type 2 diabetes, the UKPDS showed that each 10% decrease in HbA_{1c} level reduces the risk of microvascular events, including DR, by 25% (95% CI, 7%-40%).

There also is strong evidence that tight blood pressure control in patients with hypertension and diabetes is beneficial in reducing visual loss from DR. The UKPDS showed that each 10-mm Hg decrease in systolic blood pressure reduces the risk of microvascular complications by 13%, independent of glycemic control. The benefit of blood pressure treatment in normotensive patients with diabetes is less clear.

There remains inconclusive evidence about the benefits of lipid-lowering therapy for DR prevention. There also is little evidence that aspirin, other antiplatelet agents, or aldose reductase inhibitors confer any benefit in reducing progression of DR. The role of PKC and growth hormone inhibitors is currently unclear, and results from ongoing trials are pending.

Secondary Interventions

Proliferative DR. There is strong evidence that PRP significantly reduces the risk of severe vision loss from proliferative DR by at least 50%. The benefits are most marked in those with high-risk proliferative DR, in whom PRP should be commenced without delay.[89] Early vitrectomy should be considered in patients with type 1 diabetes and persistent vitreous hemorrhage or when hemorrhage prevents other treatment. The benefits of vitrectomy are less clear for those with type 2 diabetes. With advances in vitreoretinal surgery, vitrectomy may be indicated earlier in eyes with nonclearing hemorrhage.

Nonproliferative DR. Although there is level I evidence that early PRP reduces the risk of severe visual loss in nonproliferative DR, the absolute risk reduction from early PRP treatment is small, and the risks of deferred treatment are low. In mild to moderate nonproliferative DR, systemic factors such as control of glycemia and blood pressure should be gradually optimized and PRP deferred with careful follow-up. The ETDRS and other RCTs[95] suggest that PRP should be considered in more severe nonproliferative DR, especially in patients with type 2 diabetes. This benefit for PRP should be balanced against the small risk of vision loss. Early PRP is recommended in these patients if regular follow-up examination is not feasible, if there is significant media opacity or cataract that may affect the ability to apply future laser treatment, or if there are concomitant risk factors (eg, pregnancy) for rapid progression.

Diabetic Macular Edema. There is strong evidence that focal laser photocoagulation reduces the risk of moderate vision loss in DME that poses risk to fixation (or clinically significant DME) by at least 50% and increases the chance of visual improvement. In patients with coexistent proliferative DR and DME, focal laser treatment concurrent with or prior to PRP is recommended.[89]

There is moderate evidence that IVTA may be useful in eyes with persistent DME and loss of vision despite conventional treatment, including focal laser treatment and attention to systemic risk factors. Patients should be warned of adverse effects and the need for reinjection. Further studies are warranted to determine the ideal dose and longer-term efficacy and safety. Intravitreal anti-VEGF agents are being evaluated in several clinical trials; until results are available, there is currently insufficient evidence recommending their routine use.

There is weak evidence that vitrectomy may be beneficial in some patients with DME, particularly in eyes with associated vitreomacular traction, but well-conducted studies with longer follow-up are needed.

CONCLUSIONS

Although DR remains the leading cause of preventable blindness in working adults, there are primary and secondary interventions proven effective in limiting visual loss. The indications, efficacy, and safety of newer medical and surgical treatments, however, require further evaluation.

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Study concept and design: Mohamed, Gillies, Wong.
Acquisition of data: Mohamed, Gillies.
Analysis and interpretation of data: Mohamed, Wong.
Drafting of the manuscript: Mohamed, Gillies, Wong.
Critical revision of the manuscript for important intellectual content: Gillies, Wong.
Statistical analysis: Mohamed, Wong.
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Study supervision: Gillies, Wong.
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