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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We encourage authors to submit papers for consideration as a Clinical Review. Please contact Michael S. Lauer, MD, at michael.lauer@jama-archives.org.
MANAGEMENT OF DIABETIC RETINOPATHY

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

Consistent Risk Factors
- Duration of diabetes
- Hyperglycemia/glycated hemoglobin value
- Hypertension
- Hyperlipidemia
- Pregnancy
- Nephropathy/renal disease

Less Consistent Risk Factors
- Obesity
- Smoking
- Moderate alcohol consumption
- Physical inactivity

Primary Interventions

Glycemic Control. Early epidemiologic studies have shown showed a consistent relationship between glycated hemoglobin (HbA1c) levels and the incidence of DR. 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 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 HbA1c, 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 HbA1c, 9.1%).

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.

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. 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.

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. Studies also classified DR differently, with most using the Airlie House classification with some modifications. 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) defined progression as at least 3 steps worsening from baseline, while the United Kingdom Prospective Diabetes Study (UKPDS) 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.

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903
The UKPDS 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. These findings have been replicated in other studies, including a meta-analysis prior to the DCCT (Table 1).

Long-term observational DCCT data showed that despite gradual equalization of HbA1c values after study termination, the rate of DR progression in the formerly intensively treated group remained significantly lower than in the former conventional group. Emphasizing the importance of instituting tight glycemic control early in the course of diabetes. This concept is supported by the results of another RCT, in which participants initially assigned to intensive glucose control vs conventional treatment had lower 10-year incidence of severe retinopathy.

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. 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. Participants at risk of this early worsening had higher HbA1c levels at baseline and a more rapid reduction of HbA1c levels in the first 6 months, suggesting that physicians should avoid rapid reductions of HbA1c levels where possible. Second, tight glycemic control is a known risk factor for hypoglycemic episodes and diabetic ketoacidosis. A meta-analysis of 14 RCTs, including the DCCT, 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, 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. 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 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, 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
### Table 1. Randomized Controlled Trials Evaluating Role of Glycemic Control in Diabetic Retinopathy

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Diabetes Type</th>
<th>Intervention</th>
<th>Follow-up, y</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCC26,27,29,30</td>
<td>1441</td>
<td>Type 1 DM (726 with no DR, 715 with mild/moderate NPD)</td>
<td>Intensive vs conventional treatment</td>
<td>6.5</td>
<td>Median HbA1c, 7.2% vs 9.1% (P &lt; .001)</td>
<td>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</td>
</tr>
<tr>
<td>UKPDS31,32</td>
<td>3867</td>
<td>Newly diagnosed type 2 DM</td>
<td>Intensive (sulfonylurea or insulin, aiming for fasting plasma glucose &lt;5 mmol/L) vs conventional (fasting plasma glucose &lt;15 mmol/L) treatment</td>
<td>10</td>
<td>Mean HbA1c, 7% vs 7.9% With intensive treatment, 25% (96% 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; 16% decreased risk of legal blindness</td>
<td>No patient in the primary cohort developed pre-PDR or PDR</td>
</tr>
<tr>
<td>Kumamoto Study,41</td>
<td>110</td>
<td>Japanese patients with type 2 DM</td>
<td>Intensive vs conventional treatment</td>
<td>8</td>
<td>Mean HbA1c, 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</td>
<td>Hypoglycemia episodes requiring assistance, 9.1 extra cases per 100 patient-y with intensive treatment</td>
</tr>
<tr>
<td>Wang et al44,45</td>
<td>529</td>
<td>Type 1 DM</td>
<td>Intensive vs conventional treatment</td>
<td>2-5</td>
<td>Mean HbA1c, 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</td>
<td>Hypoglycemia episodes, 58% decrease in microaneurysms and IRMAs, and 23% decrease in PDR</td>
</tr>
<tr>
<td>Lauritzen et al,36,37</td>
<td>30</td>
<td>Type 1 DM with advanced NPDR</td>
<td>CSII vs conventional treatment</td>
<td>2</td>
<td>PDR developed in 4 vs 5 patientsa Trend toward more frequent improvement of retinal morphology (47% vs 13%)</td>
<td>Small numbers, study underpowered for any firm conclusion</td>
</tr>
<tr>
<td>Kroc Collaborative Study Group,37,38,39</td>
<td>70</td>
<td>Type 1 DM with low C-peptide level and NPD</td>
<td>CSII vs conventional injection treatment</td>
<td>8 mo, 2 y</td>
<td>Mean HbA1c, 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, reversed by 2 y</td>
<td>Study continued after initial 8 mo, with 23/34 (CSII) and 24/34 (conventional treatment) followed up for a further 16 mo</td>
</tr>
<tr>
<td>Beck-Nielsen et al,40,41,46</td>
<td>24</td>
<td>Type 1 DM without proteinuria, with minimal or no DR</td>
<td>CSII with portable pump vs conventional insulin treatment</td>
<td>5</td>
<td>Mean HbA1c, 7.4% vs 8.6% (P &lt; .01) Trend for DR progression in conventional insulin treatment group (P &gt; .10)</td>
<td>Small sample; 1 loss to follow-up in CSII group</td>
</tr>
<tr>
<td>Stockholm Diabetes Intervention Study,41</td>
<td>96</td>
<td>Type 1 DM with NPD</td>
<td>Intensive vs conventional treatment</td>
<td>5</td>
<td>Median HbA1c, 7.2% vs 8.7% Increased retinopathy in both groups (P &lt; .001) Odds ratio for serious retinopathy with intensive treatment vs conventional treatment, 0.4 (P = .04)</td>
<td>Hypoglycemia, 242 vs 98 episodes (P &lt; .05) With intensive treatment, 58% increased BMI</td>
</tr>
<tr>
<td>Oslo Study42,43</td>
<td>45</td>
<td>Type 1 DM</td>
<td>CSII vs multiple insulin injections (5-6/d) vs conventional treatment (twice-daily injections)</td>
<td>2</td>
<td>Decreased retinal microaneurysms and hemorrhages with CSII and multiple insulin injections vs conventional treatment (P &lt; .01)</td>
<td>Transient increase in microaneurysms and hemorrhages at 3 mo in CSII group</td>
</tr>
</tbody>
</table>

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; HbA1c, glycosylated hemoglobin; IRMAs, intraretinal microvascular abnormalities; NPD, 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.

aEffect was not statistically significant.
bMeta-analysis.
cIncluded in meta-analysis by Wang et al44.
dThree-year results.
trial, 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) 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%. EUCLID was limited by differences in baseline glycemic levels between groups (the treatment group had lower HbA1c levels) and a short follow-up of 2 years. This study, along with another smaller RCT, suggested that ACE inhibitors may have an additional benefit on DR progression independent of blood pressure lowering. However, data from the UKPDS and the ABCD study 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. 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, while the Diabetic Retinopathy candesartan Trial (DIRECT) will evaluate the angiotensin II receptor blocker candesartan.

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

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

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

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Diabetes Type</th>
<th>Intervention</th>
<th>Follow-up, y</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS, 2004</td>
<td>1148</td>
<td>Type 2 DM with hypertension (mean BP of 160/94 mm Hg)</td>
<td>Tight BP control (&lt;150/85 mm Hg) vs less tight control (&lt;180/105 mm Hg) Randomized to β-blocker or ACE inhibitor</td>
<td>8.4</td>
<td>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 &gt;5 microaneurysms (RR, 0.66; P &lt; .001), hard exudates (RR, 0.53; P &lt; .001), and cotton-wool spots (RR, 0.53; P &lt; .001) at 7.5 y</td>
<td>Observational data suggest 13% decrease in microvascular complications for each 10-mm Hg decrease in mean systolic BP</td>
</tr>
<tr>
<td>ABCD, 2000</td>
<td>470</td>
<td>Hypertensive type 2 DM (mean baseline diastolic BP &gt;90 mm Hg)</td>
<td>Intensive BP control (aiming for diastolic BP of 75 mm Hg) vs moderate control (diastolic BP of 80-89 mm Hg)</td>
<td>5.3</td>
<td>No difference in progression of DR between intensive (mean BP, 132/78 mm Hg) and moderate (mean BP, 138/66 mm Hg) control</td>
<td>No difference in DR progression with nisoldipine vs enalapril</td>
</tr>
<tr>
<td>ABCD, 2002</td>
<td>480</td>
<td>Normotensive type 2 DM (BP &lt;140/90 mm Hg)</td>
<td>Intensive BP control (10 mm Hg below baseline diastolic BP) vs moderate control (80 to 89 mm Hg)</td>
<td>5.3</td>
<td>Decreased DR progression Mean BP, 128/75 mm Hg vs 137/81 mm Hg; P = .019</td>
<td>Results the same regardless of initial antihypertensive agent used</td>
</tr>
<tr>
<td>EUCLID, 1998</td>
<td>2</td>
<td>Normotensive and normoalbuminuric type 1 DM</td>
<td>Lisinopril treatment</td>
<td>With lisinopril, 50% (95% CI, 28%-89%) decreased DR progression (2 ETDRS steps); 80% decreased progression to PDR</td>
<td>Concern about possibility of inadequate randomization (lisinopril group had lower HbA1c levels)</td>
<td></td>
</tr>
</tbody>
</table>

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; HbA1c, glycated hemoglobin; PDR, proliferative diabetic retinopathy; RR, relative risk; UKPDS, United Kingdom Prospective Diabetes Study.
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.73,76 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

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Diagnosis</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIELD,64 2005</td>
<td>3711</td>
<td>Mild to severe NPDR or early PDR</td>
<td>Aspirin (650 mg/d) vs placebo</td>
<td>3 y</td>
<td>Vitrine hemorrhage in 32% vs 30% (P = .48)</td>
<td>Aspirin had no effect on DR incidence/progression, vitreous hemorrhage, or need for vitrectomy</td>
</tr>
<tr>
<td>TIMAD,68 1990</td>
<td>435</td>
<td>Type 2 DM</td>
<td>Ticlopidine hydrochloride (antiplatelet agent) vs placebo</td>
<td>3 y</td>
<td>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)</td>
<td>Adverse reactions included neutropenia (severe in 1 case), diarrhea, and rash</td>
</tr>
<tr>
<td>PKC-DRS,62 2005</td>
<td>686</td>
<td>Type 2 DM</td>
<td>Ruboxistaurin (8, 16, or 32 mg/d) vs placebo</td>
<td>36-46 mo</td>
<td>No significant effect on DR progression</td>
<td>Decrease of SVL by ruboxistaurin observed only in eyes with definite DME at baseline (10% vs placebo, P = .917)</td>
</tr>
<tr>
<td>PKC-DPS2,71 2006</td>
<td>688 DME &gt;300 µm from center ETDRS severity level 20-47A, visual acuity ≥5 ETDRS letters, and no previous laser treatment</td>
<td>Ruboxistaurin (32mg/d) vs placebo</td>
<td>3 y</td>
<td>No significant effect on DR progression Treatment decreased risk of sustained MVL (5.3% treated vs 8.1% placebo, P = .034)</td>
<td>Variation in application of focal laser between centers Ruboxistaurin reduced progression of DME vs placebo in secondary analysis (P = .054, unadjusted)</td>
<td></td>
</tr>
<tr>
<td>Sorbinil Retinopathy Trial,72 1990</td>
<td>497 Type 1 diabetes</td>
<td>Oral sorbinil (250 mg) vs placebo</td>
<td>41 mo</td>
<td>No significant effect on DR progression (28% vs 32%, P = .344)</td>
<td>Hyposensitivity reaction in 7% of sorbinil-treated group</td>
<td></td>
</tr>
<tr>
<td>Gardner et al,73 2006</td>
<td>63 DME (no previous macular photocoagulation)</td>
<td>Astemizol (antihistamine) vs placebo</td>
<td>1 y</td>
<td>No effect on retinal thickening or hard exudates (photographs graded by modified ETDRS protocol)</td>
<td>54/63 patients (86%) completed 1 y of follow-up</td>
<td></td>
</tr>
<tr>
<td>Grant et al,74 2000</td>
<td>23 Severe NPDR or early non-high-risk PDR</td>
<td>Maximum tolerated doses of ocrelizum (200-5000 µg/d subcutaneously) vs conventional treatment</td>
<td>15 mo</td>
<td>Ocrelizum decreased progression to high-risk PDR needing PPR (1/22 vs 9/24 eyes, P &lt; .006) and decreased DR progression (27% vs 42%; P = .0865)</td>
<td>Thyroxine replacement therapy needed in all treated patients</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DM, diabetes mellitus; DME, diabetic macular edema; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; FFA, 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; PPR, pan-retinal laser photocoagulation; SVL, severe visual loss; TIMAD, Ticlopidine Microangiopathy of Diabetes.
tographic grading for DR. Several ongoing RCTs, such as the Atorvastatin Study for Prevention of Coronary Endpoints in NIDDM (ASPEN), 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). Aspirin treatment was not associated with an increased rate of vitrectomy. A smaller RCT evaluating aspirin alone and in combination with dipiridamole reported a reduction in microaneurysms on fluorescein angiograms in both groups as compared with placebo. A similar trend was observed in a small RCT 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) isoenzymes. 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), 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

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Retinopathy Severity</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rohan et al,1989</td>
<td>2243</td>
<td>NPDR/PDR (with/without DME)</td>
<td>Peripheral PRP with/without focal laser treatment vs observation</td>
<td>1-5 y</td>
<td>Decreased risk of blindness in eyes with PDR by 61% (combined &quot;best estimate&quot; based on 5 RCTs including DRS and BMS)</td>
<td>Criteria for study inclusion, quality assessment, baseline comparability, and adverse effects of included studies not described</td>
</tr>
<tr>
<td>DRS, 1981</td>
<td>1742</td>
<td>Severe NPDR (bilateral) or PDR (with/without DME)</td>
<td>Peripheral PRP with/without focal laser treatment vs observation</td>
<td>5 y</td>
<td>Decreased risk of SVL by 52% at 2 y; 90/650 treated (14%) vs 171/519 observed (33%) (RR, 0.42; 95% CI, 0.34-0.63)</td>
<td>Decreased visual acuity and constriction of peripheral visual field in some eyes</td>
</tr>
<tr>
<td>ETDRS, 1984</td>
<td>3711</td>
<td>Mild to severe NPDR or early PDR (with/without DME in both eyes)</td>
<td>1 eye of each patient assigned to early PRP with/without focal laser treatment vs treatment deferral</td>
<td>5 y</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>BMS, 1984</td>
<td>107</td>
<td>PDR (bilateral symmetrical)</td>
<td>Xenon-arc laser photocoagulation vs observation</td>
<td>5-7 y</td>
<td>Decreased risk of blindness, 5% vs 17% (RR, 0.29; 95% CI, 0.11-0.77)</td>
<td>Patients with NVD at entry had greatest difference; treated eyes that became blind had less treatment than those that retained vision</td>
</tr>
<tr>
<td>BMS, 1983</td>
<td>99</td>
<td>NPDR</td>
<td>Peripheral xenon arc laser vs observation</td>
<td>5 y</td>
<td>Decreased visual deterioration, 32% vs 55% (RR, 0.49; 95% CI, 0.32-0.74)</td>
<td>Large loss to follow-up (28%) No intention-to-treat analysis</td>
</tr>
<tr>
<td>Hercules et al, 1977</td>
<td>94</td>
<td>Symmetrical PDR involving optic disc</td>
<td>PRP vs observation</td>
<td>3 y</td>
<td>Decreased risk of blindness, 7% (7/94) vs 38% (36/94) (RR, 0.19; 95% CI, 0.09-0.41)</td>
<td>Incomplete masking No individual treatment assessment</td>
</tr>
<tr>
<td>Patz et al, 1973</td>
<td>66</td>
<td>NPDR with DME</td>
<td>PRP vs observation</td>
<td>26 mo</td>
<td>Decreased visual deterioration, 6% vs 63% (RR, 0.10; 95% CI, 0.04-0.26)</td>
<td>Poorly specified criteria Loss not specified</td>
</tr>
<tr>
<td>Lövestam-Adrian et al, 2003</td>
<td>81</td>
<td>Severe NPDR and PDR in patients with type 1 diabetes</td>
<td>All participants treated with PRP (1 randomly selected eye per patient entered into study)</td>
<td>2.9 ± 1.5 y</td>
<td>14/40 eyes (35%) treated for severe NPDR developed neovascularization</td>
<td>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</td>
</tr>
</tbody>
</table>

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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 HbA1c 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 hypophysectomy79,80 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 patients82 evaluating continuous subcutaneous infusion of octreotide found no significant benefits. Two larger RCTs currently evaluating long-acting release octreotide injection83,84 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 DR76 (Table 4).

The strongest evidence comes from 2 related RCTs in the 1970s and 1980s, the...
Diabetic Retinopathy study (DRS)\textsuperscript{106,108} and the ETDRS.\textsuperscript{102} The DRS randomized 1758 patients with proliferative DR in at 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

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Diagnosis</th>
<th>Intervention</th>
<th>Follow-up, y</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proliferative Diabetic Retinopathy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| diabetic vitreous hemorrhage reducing visual acuity to ≤5/200 for at least 1 mo | 616 eyes | Recent severe | 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%)
| Advanced PDR with fibrovascular proliferation and visual acuity ≥10/200 | 370 eyes | Advanced PDR | 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** | | | | | | |
| DME and impaired vision that persisted or recurred after laser treatment | 43 (69 eyes) | DME and impaired vision | Intravitreal triamcinolone acetate 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 84% vs 6% (\( P < .0001 \))
2 treated eyes required trabeculectomy
1 case of infectious endophthalmitis
| DME | 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
| Bilateral DME unresponsive to grid laser photocoagulation | 20 eyes (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) \( \mu \text{m} \) vs 37.8 (SD, 71.2) \( \mu \text{m} \) (\( P = .016 \)) | Implant improved vision by ≥2 lines in 4 (40%) vs 1 (10%)
| DME (visual acuity ≤6/12) unresponsive to laser treatment with no associated traction | 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 \( \mu \text{m} \) (20%) vs 29 \( \mu \text{m} \) (10.7%) | Vitrectomy improved mean best-corrected visual acuity by 0.05 logMAR vs increased by 0.02 logMAR in controls
18% loss to follow-up
| DME (visual acuity ≤6/12) unresponsive to laser treatment with no associated traction or ischemia | 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] \( \mu \text{m} \) vs 450 [SD, 40] \( \mu \text{m} \)) | No significant change in logMAR visual acuity
| Diffuse CSME | 58 eyes (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 improved in both groups (0.391 [SD, 0.335] vs vitrectomy + ILM peel and 0.393 [SD, 0.273] logMAR, \( P = .31 \))
Randomization and masking unclear
HbA\textsubscript{1c}, 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\textsubscript{1c}, glycated hemoglobin; ILM, internal limiting membrane; IOP, intraocular pressure; logMAR, logarithmic minimal angle resolution; PDR, proliferative diabetic retinopathy.\textsuperscript{a}Not significant.
elsewhere [Figure, B]), in which the risk of severe visual loss was reduced by 50%.36

The ETDRS102 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 RCTs91-93 and a meta-analysis with combined data of 2243 patients97 have confirmed the effectiveness of PRP.

Adverse effects of PRP include visual field constriction (with implications for driving103,104), 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).113 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 DRVS. These advances include intraoperative fundal imaging and laser treatment and bi-manual 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 ETDRS96 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 RCT128 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—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, including infection, glaucoma, and cataract formation.109,110,114

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).139 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.140 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

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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 intravitreal 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-

<p>| Table 6. Summary of Clinical Recommendations for Primary and Secondary Interventions for Diabetic Retinopathy |
|-------------------------------------------------|--------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Evidence Level(^\text{a})</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic control</td>
<td>A, I</td>
<td>Any lowering of Hba(_1c) level advantageous in reducing development of new or progression of existing DR In patients with DR, Hba(_1c) level &lt;7% is ideal</td>
</tr>
<tr>
<td>BP control</td>
<td>A, I</td>
<td>Any lowering of systolic and/or diastolic BP is advantageous in reducing development and progression of DR In patients with DR, systolic BP &lt;130 mm Hg is ideal</td>
</tr>
<tr>
<td>Lipid-lowering therapy</td>
<td>A, II</td>
<td>Lowering of LDL-C levels reduces macrovascular complications of diabetes and may be advantageous in DME</td>
</tr>
<tr>
<td>PRP</td>
<td>A, I</td>
<td>Prompt PRP is recommended in patients with PDR, especially if high-risk features are present</td>
</tr>
<tr>
<td></td>
<td>A, II</td>
<td>Early PDR with less severe PDR (fist 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</td>
</tr>
<tr>
<td>Focal laser photocoagulation</td>
<td>A, I</td>
<td>Focal laser therapy recommended in eyes with DME involving the macula of center 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 6/9 or better Treatment is ideally guided by a fluorescein angiogram and is unlikely to be beneficial in the presence of significant macular ischemia</td>
</tr>
<tr>
<td>Surgical vitrectomy</td>
<td>B, II</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>B, III</td>
<td>Vitrectomy may be advantageous in selected cases of diffuse severe DME not responsive to other therapies, especially in presence of vitreomacular traction</td>
</tr>
<tr>
<td>Intravitreal steroids</td>
<td>B, II</td>
<td>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</td>
</tr>
<tr>
<td>Intravitreal anti-VEGF agents</td>
<td>B, II/III</td>
<td>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</td>
</tr>
<tr>
<td>Aspirin and other medical treatment</td>
<td>C, I</td>
<td>Aspirin does not reduce risk of developing DR or increase the incidence of retinal or vitreous hemorrhage</td>
</tr>
<tr>
<td></td>
<td>C, II/III</td>
<td>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</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; DME, diabetic macular edema; DR, diabetic retinopathy; GH, growth hormone; Hba\(_1c\), glycosylated 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 HbA1c 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 HbA1c 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 alendro 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 1 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 RCTs89 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 reinsertion. 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.

Author Contributions: Dr Wong had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Mohamed, Gilles, Wong. Acquisition of data: Mohamed, Gilles. Analysis and interpretation of data: Mohamed, Wong. Drafting of the manuscript: Mohamed, Gilles, Wong. Critical revision of the manuscript for important intellectual content: Gilles, Wong. Statistical analysis: Mohamed, Wong. Obtained funding: Gilles. Administrative, technical, or material support: Mohamed, Gilles, Wong. Study supervision: Gilles, Wong.

Financial Disclosures: Dr Gilles reported that he is included as an inventor on patents relating to the formulation of triamcinolone for ocular use and its use for the treatment of retinal neovascularization but not diabetic macular edema. Dr Gilles and Dr Wong reported serving on advisory boards for and as investigators in clinical trials in diabetic retinopathy sponsored by Pfizer, Novartis, and Allergan and receiving grants, honoraria, and traveling fees from these companies. No other disclosures were reported.

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rhage in diabetic retinopathy: four-year results of a