



# Diabetic Retinopathy: A Position Statement by the American Diabetes Association

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Diabetic retinopathy diagnostic assessment and treatment options have improved dramatically since the 2002 American Diabetes Association Position Statement (1). These improvements include the widespread adoption of optical coherence tomography to assess retinal thickness and intraretinal pathology and wide-field fundus photography to reveal clinically silent microvascular lesions. Treatment of diabetic macular edema is now achieved by intravitreal injection of anti-vascular endothelial growth factor agents, and the same drugs are now used for proliferative diabetic retinopathy. Improvements in medications and devices for the systemic therapy of diabetes have also improved the ability of patients to optimize their metabolic control. This Position Statement incorporates these recent developments for the use of physicians and patients.

Diabetic retinopathy is a highly specific neurovascular complication of both type 1 and type 2 diabetes, the prevalence of which strongly correlates to both the duration of diabetes and level of glycemic control. A pooled meta-analysis involving 35 studies conducted worldwide from 1980 to 2008 estimated global prevalence of any diabetic retinopathy and proliferative diabetic retinopathy (PDR) among patients to be 35.4% and 7.5%, respectively (2). Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. Glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in people with diabetes.

In addition to diabetes duration, factors that increase the risk of or are associated with retinopathy include chronic hyperglycemia (3,4), nephropathy (5), hypertension (6), and dyslipidemia (7). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy (8,9).

Lowering blood pressure has been shown to decrease retinopathy progression in people with type 2 diabetes, although tight targets (systolic blood pressure <120 mmHg) do not impart additional benefit over targets of <140 mmHg (9,10). In patients with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy (NPDR) at baseline (7). Several case series and a controlled prospective study suggest that pregnancy in patients with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic control is poor at the time of conception (11,12).

## NATURAL HISTORY

### Recommendations

- Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. **A**

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- Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. **A**

In general, retinopathy advances from mild nonproliferative abnormalities, characterized by increased numbers of microaneurysms that may wax and wane. With increasing severity, there is increased vascular permeability and occlusion and progression from moderate and severe NPDR to PDR, characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous (see Table 1 for definitions of diabetic retinopathy stages). Pregnancy and puberty can accelerate these changes (12,13). Cataract surgery has not been definitely demonstrated by recent studies to accelerate the progression of diabetic retinopathy, especially in the more recent era of treating both diabetic macular edema (DME) and PDR with the use of anti-vascular endothelial growth factor (anti-VEGF) agents (14).

Vision loss due to diabetic retinopathy results from several mechanisms. First, central vision may be impaired by macular edema as the result of increased vascular permeability and/or capillary nonperfusion. Second, the new blood vessels of PDR and contraction of the accompanying fibrous tissue can distort the retina and lead to tractional retinal detachment,

producing severe and often irreversible vision loss. Third, the new blood vessels may bleed, adding the further complication of preretinal or vitreous hemorrhage. These clinically evident vascular changes are accompanied by damage to retinal neurons (15), the final common pathway for vision loss.

Several epidemiological studies have described the progression rates for diabetic retinopathy. The cohort with the longest follow-up is the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), which reported the 25-year progression of diabetic retinopathy in patients with type 1 diabetes (16). However, the WESDR started recruitment in 1979 when options for glycemic, blood pressure, and lipid control were markedly limited compared with the options available today. The risk factors identified in WESDR—longer duration of diabetes, greater hyperglycemia, increased blood pressure, and dyslipidemia—remain relevant while the progression rates in more recent studies may differ markedly. For example, the WESDR progression data predicted a progression rate near 40% over 4 years for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, but the actual progression rate in people with type 2 diabetes at the study’s conclusion was only 10%. Table 2 shows the odds ratios associated with the most consistently associated retinopathy risk factors in

studies performed in the modern era of expanded options for glucose, lipid, and blood pressure control.

The WESDR found a relationship between onset of retinopathy and duration of diabetes. It established that progression of retinopathy was a function of baseline retinopathy. More severe baseline retinopathy led to a greater frequency of progression to vision-threatening retinopathy. Among patients with type 2 diabetes whose baseline photographs showed no retinopathy, there was 54% less progression to PDR over 10 years compared with those with severe NPDR at baseline (17). The WESDR epidemiological data were limited primarily to white Northern European extraction populations and may not be applicable to African American, Hispanic American, or Asian American populations or to others with a high prevalence of diabetes and retinopathy.

After duration of diabetes, hyperglycemia has been the most consistently associated risk factor for retinopathy. A large and consistent set of observational studies and clinical trials document the association of poor glucose control and retinopathy. The Diabetes Control and Complications Trial (DCCT), a randomized controlled clinical trial of intensive glycemic control versus conventional glycemic control in people with type 1 diabetes, demonstrated that intensive therapy reduced the development or progression of diabetic retinopathy by 34–76% (51). In addition, the DCCT demonstrated a definitive relationship between hyperglycemia and diabetic microvascular complications, including retinopathy (18). Early treatment with intensive therapy was most effective. In addition, intensive therapy had a substantial beneficial effect over the entire range of retinopathy. A 10% reduction in HbA<sub>1c</sub>, for example from 10 to 9% or from 8 to 7.2%, reduces the risk of retinopathy progression by 43% (52).

The UK Prospective Diabetes Study (UKPDS) of patients newly diagnosed with type 2 diabetes conclusively demonstrated that improved blood glucose control in those patients reduced the risk of developing retinopathy and nephropathy and possibly reduced the risk for neuropathy (8). The overall microvascular complication rate was decreased by 25% in patients receiving intensive therapy versus conventional

**Table 1—Diabetic retinopathy stages\***

Diabetic retinopathy stage	Description
Mild NPDR	Small areas of balloon-like swelling in the retina’s tiny blood vessels, called microaneurysms, occur at this earliest stage of the disease. These microaneurysms may leak fluid into the retina.
Moderate NPDR	As the disease progresses, blood vessels that nourish the retina may swell and distort. They may also lose their ability to transport blood. Both conditions cause characteristic changes to the appearance of the retina and may contribute to DME.
Severe NPDR	Many more blood vessels are blocked, depriving blood supply to areas of the retina. These areas secrete growth factors that signal the retina to grow new blood vessels.
PDR	At this advanced stage, growth factors secreted by the retina trigger the proliferation of new blood vessels, which grow along the inside surface of the retina and into the vitreous gel, the fluid that fills the eye. The new blood vessels are fragile, which makes them more likely to leak and bleed. Accompanying scar tissue can contract and cause retinal detachment—the pulling away of the retina from underlying tissue, like wallpaper peeling away from a wall. Retinal detachment can lead to permanent vision loss.

\*Adapted from <https://nei.nih.gov/health/diabetic/retinopathy>.

**Table 2—Recent estimates of the association between major risk factors and diabetic retinopathy**

Risk factor	Reference	Strength of association, odds ratio (95% CI)
Duration of diabetes	Xu et al. (48)	1.16 (1.10–1.22) per year increase
	Kajiwara et al. (49)	1.13 (1.09–1.17) per year increase
HbA <sub>1c</sub>	Xu et al. (48)	1.73 (1.35–2.21) per 1% increase
	Kajiwara et al. (49)	1.21 (1.08–1.36) per 1% increase
	Jin et al. (50)	1.12 (1.01–1.24) per 1% increase
Blood pressure	Kajiwara et al. (49)	1.02 (1.01–1.03) per mmHg increase in systolic blood pressure
	Jin et al. (50)	1.80 (1.14–2.86) if systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg

therapy. Epidemiological analysis of the UKPDS data showed a continuous relationship between the risk of microvascular complications and glycemia, such that every percentage point decrease in HbA<sub>1c</sub> (e.g., 9% to 8%) was associated with a 35% reduction in the risk of microvascular complications.

More recently, the ACCORD trial of medical therapies demonstrated that intensive glycemic control reduced the risk of progression of diabetic retinopathy in people with type 2 diabetes of 10 years duration (9). This study included 2,856 ACCORD participants who were enrolled into the ACCORD Eye Study and followed for 4 years.

The results of the DCCT, UKPDS, and ACCORD Eye Study showed that while intensive therapy does not prevent retinopathy completely, it reduces the risk of the development and progression of diabetic retinopathy. This can be translated clinically to a higher likelihood of preserving sight and to a reduced need for treatment. Furthermore, all three studies demonstrated that years after the initial clinical trial ended, the treatment effect of intensive glycemic control persisted, despite the fact that both treatment groups had similar levels of HbA<sub>1c</sub>. In fact, 25 years after the cessation of the DCCT, ocular surgery rates were reduced in those who had been assigned to intensive glycemic control (19). In the DCCT, at varying intervals, the beneficial effects of intensive glycemic control persisted but declined over time. This persistent beneficial effect beyond the clinical trial was true for people with type 1 and type 2 diabetes.

Blood pressure control has also been studied in several observational and clinical trials, including the UKPDS. The

UKPDS showed a 37% reduction in microvascular abnormalities, including diabetic retinopathy and specifically DME, with lowering of systolic blood pressure from a mean of 154 mmHg to 144 mmHg (20). However, the more recent ACCORD Eye Study did not show either a harmful or a beneficial effect when comparing systolic pressure of 120 mmHg vs. 140 mmHg in a similar cohort of patients (9).

Several observational studies have suggested that dyslipidemia may play a role in the progression of diabetic retinopathy. Dyslipidemia is associated with retinal hard exudate and visual loss. Two trials of fenofibrate have been conducted to reduce the levels of serum triglycerides in an effort to reduce cardiovascular risk (9,21). Although fenofibrate does not have an effect on cardiovascular risk, both studies showed an effect on the progression of diabetic retinopathy. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study demonstrated the beneficial effects of fenofibrate (200 mg daily) versus placebo in reducing the need for laser photocoagulation (hazard ratio 0.69, 95% CI 0.56–0.84,  $P = 0.00002$ ) (21). A substudy of the FIELD participants with fundus photographs showed the beneficial effect on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, especially in those with retinopathy at baseline and also on the development of macular edema (hazard ratio 0.66, 95% CI 0.47–0.94,  $P = 0.02$ ). The ACCORD Study also compared fenofibrate 160 mg daily with simvastatin versus placebo with simvastatin and found that the risk of progression of diabetic retinopathy was reduced by one-third. The effect was particularly demonstrated in those with preexisting diabetic retinopathy. The effect of

fenofibrate was not evident after the drug was stopped in the clinical trial of ACCORD. This suggests that the treatment with fenofibrate therapy may indeed be real.

The results of these two large randomized trials, ACCORD Eye Study and FIELD, suggest that fenofibrate may be a potential therapy for people with diabetic retinopathy. These results were not subgroup analyses, and these beneficial effects were supported by two large randomized controlled clinical trials. Because of the lack of beneficial effects on cardiovascular disease, medical physicians have been reluctant to prescribe fenofibrate for people with diabetic retinopathy. There are sufficient data to suggest developing collaboration between the ophthalmologists (eye care providers) and the medical physician to consider this treatment for people affected with diabetic retinopathy.

## SCREENING

### Recommendations

- Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**
- If there is no evidence of retinopathy for one or more annual eye exams, then exams every 2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations for patients with type 1 or type 2 diabetes should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**
- Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. **B**
- Eye examinations should occur before pregnancy or in the first trimester in patients with preexisting type 1 or type 2 diabetes, and then

these patients should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

- While retinal photography may serve as a screening tool for retinopathy, it is not a substitute for a comprehensive eye exam, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. **E**

Screening strategies depend on the rates of appearance and progression of diabetic retinopathy and on risk factors that alter these rates. While population-based studies often are the best source for evaluating the rates of progression, data from other studies, including observational studies and clinical trials, have provided important information as well. A summary of screening recommendations is in Table 3.

With regard to retinopathy onset, vision-threatening retinopathy rarely appears in type 1 diabetes patients in the first 3–5 years of diabetes or before puberty (22,23). Because retinopathy takes at least 5 years to develop after the onset of hyperglycemia, adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the diagnosis of diabetes.

Up to one-fifth of patients with type 2 diabetes have retinopathy at the time of first diagnosis of diabetes (24,25). Patients with type 2 diabetes who may have had years of undiagnosed diabetes and have a significant risk of diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of diagnosis.

Subsequent examinations for patients with type 1 or type 2 diabetes are generally repeated annually for patients with

minimal to no retinopathy. Exams every 2 years may be cost-effective after one or more normal eye exams and, in a population with well-controlled type 2 diabetes, there was essentially no risk of development of significant retinopathy with a 3-year interval after a normal examination (26). Examinations will be required more frequently by the ophthalmologist if retinopathy is progressing.

Pregnancy can be associated with rapid progression of diabetic retinopathy in the setting of type 1 and type 2 diabetes (27). Women who develop gestational diabetes mellitus do not require an eye examination during pregnancy and do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (28). Women with preexisting type 1 or type 2 diabetes who plan to become pregnant should have an ophthalmic examination prior to pregnancy and receive counseling about the risk of development and progression of diabetic retinopathy. When pregnant, an eye examination should be performed during the first trimester with follow-up visits scheduled depending on retinopathy severity (12,29). Rapid implementation of tight glycemic control in the setting of retinopathy can be associated with worsening of retinopathy (12).

For patients with diabetes, regular follow-up with early detection and treatment of vision-threatening retinopathy enables the prevention of up to 98% of visual loss due to diabetic retinopathy (30). The preventive effects of therapy and the fact that patients with PDR or macular edema may be asymptomatic provide strong support for screening to detect diabetic retinopathy.

An ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing diabetic retinopathy should perform the examinations. If diabetic retinopathy is present, prompt referral to an ophthalmologist is recommended. Comprehensive evaluation by an ophthalmologist will include dilated slit-lamp examination including biomicroscopy with a hand-held lens (90 or

78 diopter), indirect ophthalmoscopy, and testing as appropriate that may include optical coherence tomography and fluorescein angiography.

Retinal photography, with remote reading by experts, has great potential to provide screening services in areas where qualified eye care professionals are not readily available (31). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care provider. Retinal photography can also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (32). In-person exams are still necessary when the retinal photos are unacceptable and for follow-up if abnormalities are detected. Retinal photos are not a substitute for a comprehensive eye exam, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. Results of eye examinations should be documented and transmitted to the referring health care professional.

**TREATMENT**

**Recommendations**

- Promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy), or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. **A**
- Laser photocoagulation therapy reduces the risk of vision loss in patients with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy. **A**
- Intravitreal injections of anti-vascular endothelial growth factor are indicated for central-involved diabetic macular edema, which occurs beneath the foveal center and may threaten reading vision. **A**
- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

**Table 3—Screening recommendations for patients with diabetes**

Classification	Examination by ophthalmologist or optometrist
Type 1 diabetes	Within 5 years after onset of diabetes
Type 2 diabetes	At time of diabetes diagnosis
Women with preexisting diabetes planning pregnancy or who have become pregnant	Before pregnancy or in first trimester



While optimization of blood glucose, blood pressure, and serum lipid levels in conjunction with appropriately scheduled dilated eye examinations can substantially decrease the risk of vision loss from complications of diabetic retinopathy, a significant proportion of those affected with diabetes develop DME or proliferative changes that require intervention (Table 4).

### CENTRAL-INVOLVED DME

Historically, focal laser photocoagulation has been the standard treatment for eyes with clinically significant macular edema (CSME), defined as either retinal edema located at or within 500  $\mu\text{m}$  of the center of the macula or edema of a disc area or more within a disc diameter of the foveal center. The ETDRS (33) showed that treated eyes with CSME had a significantly reduced risk of further visual loss.

Current treatment thresholds are based on the presence of central-involved DME (CIDME), or edema affecting the 1 mm in diameter retinal central subfield, rather than the presence of CSME. Intravitreal therapy with agents that neutralize VEGF is currently the standard of care in the management of eyes with CIDME, following numerous well-designed randomized phase 3 clinical trials that have shown benefit compared with monotherapy or even combination therapy with laser (34–37). There are currently three anti-VEGF agents commonly used to treat eyes with CIDME—bevacizumab, ranibizumab, and aflibercept. Of these anti-VEGF agents, recent

data from the Diabetic Retinopathy Clinical Research Network (DRCRN) suggest that for eyes with CIDME and good levels of acuity, 20/40 or better, each agent effectively and similarly improves visual acuity. However, in eyes with CIDME and lower levels of acuity, 20/50 or worse, aflibercept appears to be most effective at improving visual acuity (38). Most patients require near-monthly administration of intravitreal therapy with anti-VEGF agents during the first 12 months of treatment, with fewer injections needed in subsequent years to maintain remission from CIDME.

Multiple emerging therapies for retinopathy that target alternative pathways, provide sustained intravitreal delivery of pharmacological agents, or allow oral or topical noninvasive delivery systems are currently under investigation for the treatment of CIDME. Intravitreal steroid therapy for CIDME has been evaluated in multiple phase 3 studies, and the steroid agents dexamethasone and fluocinolone acetonide are approved by the U.S. Food and Drug Administration for the indication of CIDME. Nonetheless, given the inferior visual acuity outcomes to anti-VEGF seen with intravitreal steroid therapy in a large DRCRN trial, as well as the increased adverse events of cataract and glaucoma associated with steroid use, these agents are rarely used as first-line therapy in eyes with CIDME.

### PDR

The Diabetic Retinopathy Study (DRS) showed that panretinal laser photocoagulation (PRP) reduced the risk of

severe vision loss in eyes affected with PDR (39). The benefit was greatest among patients whose baseline evaluation revealed high-risk characteristics (HRCs) consisting of disc neovascularization greater than or equal to one-quarter of a disc area in size, any disc neovascularization with vitreous hemorrhage, or vitreous hemorrhage with retinal neovascularization greater than or equal to one-half of a disc area in size. Although some eyes, especially those of patients with type 2 diabetes, benefit from early PRP prior to the development of HRCs, given the risk of a modest loss of visual acuity and of contraction of visual field from PRP, laser therapy has been primarily recommended for eyes approaching or reaching HRCs.

PRP is still commonly used to manage eyes with PDR. However, widespread observations that rapid regression of retinal neovascularization occurs in eyes receiving intravitreal anti-VEGF therapy for CIDME has made these agents a potentially viable alternative treatment for PDR. In a randomized trial by the DRCRN comparing intravitreal ranibizumab to PRP for visual acuity outcomes in patients with PDR, there was no statistically significant visual acuity difference between the ranibizumab and PRP groups at 2 years (40). However, average visual acuity outcomes over the course of 2 years favored the ranibizumab-treated group. Furthermore, significantly more eyes in the PRP group experienced peripheral visual field loss and underwent vitrectomy for

**Table 4—Recommended follow-up**

Indication	Referral to ophthalmologist	Follow-up	Recommended intraocular treatment*
No diabetic retinopathy	Within 1 year	Every 1–2 years	None
Mild NPDR	Within 1 year	Every year	None
Moderate NPDR	Within 3–6 months	Every 6–9 months	None
Severe NPDR	Immediate	Every 3–6 months	Can consider early PRP for patients with type 2 diabetes
PDR	Immediate	Every 3 months	PRP or intravitreal anti-VEGF therapy, especially if HRCs are present
No DME	Within 1 year	Every 1–2 years	None
Non-CIDME	Within 3–6 months	Every 6 months	None, but observe carefully for progression to CIDME
CIDME	Immediate	Every 1–4 months	Anti-VEGF as first-line therapy for most eyes. Consider macular laser as an adjunctive therapy in eyes with persistent CIDME despite anti-VEGF therapy. Intravitreal steroid treatment can be used as an alternative in selected cases.

\*In addition to optimizing systemic control of blood glucose, cholesterol, and hypertension, as well as educating the patient about importance of routine follow-up regardless of whether visual symptoms are present or absent.

secondary complications of PDR than in the ranibizumab group. In addition, whereas 28% of eyes receiving PRP developed DME over the course of 2 years, only 9% of ranibizumab-treated eyes did so. Only 6% of eyes in the ranibizumab group received PRP during the course of the study. Systemic safety outcomes appeared equivalent between the groups, and injection-related endophthalmitis occurred in only one eye (0.5%) in the ranibizumab group.

These results suggest that intravitreal anti-VEGF may be a viable alternative or adjunct to PRP for treatment of eyes with PDR through at least 2 years. However, in applying these findings to clinical practice, factors such as frequency of follow-up, treatment cost, and patient preference must be considered in addition to these safety and efficacy outcomes. Complete application of PRP can sometimes be accomplished in as little as one visit, whereas intravitreal ranibizumab may be required chronically, over numerous visits, to adequately maintain regression of PDR. PRP costs less than a ranibizumab injection and carries no risk of endophthalmitis. However, if CIDME is present in an eye for which intravitreal anti-VEGF therapy is planned, concomitant treatment with PRP may not be necessary, as the anti-VEGF agent will likely effectively manage both the CIDME and the PDR.

### COST-EFFECTIVENESS OF SCREENING AND TREATMENT FOR DIABETIC RETINOPATHY

The cost-effectiveness of both screening and traditional laser treatment for diabetic retinopathy has been established long ago and is no longer in dispute. More recent literature on cost-effectiveness has now focused on the impact of telemedicine on the detection and eventual management of diabetic retinopathy (41). Multiple studies have argued both in support of and against whether telemedicine represents an improvement over eye care provider-based screening (42,43). Although a consensus has yet to be reached, telemedicine appears to be most effective when the ratio of providers to patients is low, the distance to reach a provider is prohibitive, or the alternative is no patient screening (44). In terms of treatment, cost-effectiveness literature has begun

looking at the latest advancement in retinopathy treatment, anti-VEGF therapy. These eye injections have been shown in numerous studies to be more cost-effective than laser monotherapy for DME (45–47). Future studies will be needed to determine the cost-effectiveness of the anti-VEGF medications as a first-line treatment for PDR.

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