Effects of Aspirin Treatment on Diabetic Retinopathy

ETDRS Report Number 8

EARLY TREATMENT DIABETIC RETINOPATHY STUDY RESEARCH GROUP*

Abstract: Aspirin treatment did not alter the course of diabetic retinopathy in patients enrolled in the Early Treatment Diabetic Retinopathy Study (ETDRS). In this randomized clinical trial supported by the National Eye Institute, 3711 patients with mild-to-severe nonproliferative or early proliferative diabetic retinopathy were assigned randomly to either aspirin (650 mg per day) or placebo. Aspirin did not prevent the development of high-risk proliferative retinopathy and did not reduce the risk of visual loss, nor did it increase the risk of vitreous hemorrhage. This was true both for eyes assigned randomly to deferral of photocoagulation and for eyes assigned randomly to early argon laser photocoagulation. The ETDRS results indicate that for patients with mild-to-severe nonproliferative or early proliferative diabetic retinopathy, it is likely that aspirin has no clinically important beneficial effects on the progression of retinopathy. The data also show that aspirin 650 mg per day had no clinically important harmful effects for diabetic patients with retinopathy. These findings suggest there are no ocular contraindications to aspirin when required for cardiovascular disease or other medical indications. *Ophthalmology 1991; 98:757–765*

The Early Treatment Diabetic Retinopathy Study (ETDRS), a multicenter collaborative clinical trial sponsored by the National Eye Institute, was designed to evaluate combinations of scatter (panretinal) photocoagulation and focal photocoagulation for macular edema, and aspirin treatment in patients with mild-to-severe nonproliferative or early proliferative diabetic retinopathy. This report provides a comparison of results from 1856 patients assigned randomly to 650 mg of aspirin per day and 1855 patients assigned randomly to placebo.

The primary endpoint for comparing aspirin and placebo, defined at the beginning of the study, was to be the development of high-risk proliferative diabetic retinopathy, a severity of retinopathy demonstrated by the Diabetic Retinopathy Study[1] to be associated with a particularly high risk of severe visual loss. The rationale for testing the effect of aspirin in the ETDRS as well as for the dose chosen is presented elsewhere in this issue of *Ophthalmology* along with study design, methods, and baseline characteristics.[2] Various terms used in this report such as high-risk proliferative retinopathy are defined in Table 1.

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* A list of the ETDRS Research Group investigators appears at the end of ETDRS report number 7 in this supplement to *Ophthalmology*.

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METHODS

All ETDRS patients were assigned randomly to 650 mg of aspirin per day (two tablets) or to two placebo tablets per day. Both the placebo and aspirin (Bayer) were supplied to the ETDRS drug distribution center by Glenbrook Laboratories (a division of Sterling Drug Inc, New York, NY). As Figure 1 illustrates, in addition to the random assignment of patients to aspirin or placebo, each patient had one eye assigned randomly to early photocoagulation and the other eye to photocoagulation only if "high-risk proliferative diabetic retinopathy"[1] developed during follow-up. Separate analyses were performed for eyes assigned to early photocoagulation and eyes assigned to deferral.

Table 1. Definitions of Commonly Used Terms

A. Macular edema
   Thickening of retina within 1 disc diameter of the center of the macula; and/or hard exudates ≥ standard photograph 3^{10} in a standard 30° photographic field centered on the macula (field 2), with some hard exudates within 1 disc diameter of the center of the macula
B. Clinically significant macular edema (CSME)
   Retinal thickening at or within 500 μm of the center of the macula; and/or hard exudates at or within 500 μm of the center of the macula, if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening 1 disc area in size at least part of which was within 1 disc diameter of the center
C. Mild nonproliferative retinopathy
   At least one microaneurysm, and definition not met for D, E, F, or G below
D. Moderate nonproliferative retinopathy
   Hemorrhages and/or microaneurysms ≥ standard photograph $2A^{10}$; and/or soft exudates, venous beading, or intraretinal microvascular abnormalities definitely present; and definition not met for E, F, or G below
E. Severe nonproliferative retinopathy
   Soft exudates, venous beading, and intraretinal microvascular abnormalities all definitely present in at least two of fields 4 through 7; or two of the preceding three lesions present in at least two of fields 4 through 7 and hemorrhages and microaneurysms present in these four fields, equaling or exceeding standard photo 2A in at least one of them; or intraretinal microvascular abnormalities present in each of fields 4 through 7 and equaling or exceeding standard photograph 8A in at least two of them; and definition not met for F or G below
F. Early proliferative retinopathy (i.e., proliferative retinopathy without DRS high-risk characteristics)
   New vessels; and definition not met for G below
G. High-risk proliferative retinopathy (proliferative retinopathy with DRS high-risk characteristics)
   New vessels on or within 1 disc diameter of the optic disc (NVD) ≥ standard photograph $10A^{10}$ (about 1/4 to 1/3 disc area), with or without vitreous or preretinal hemorrhage; or vitreous and/or preretinal hemorrhage accompanied by new vessels, either NVD < standard photograph 10A or new vessels elsewhere (NVE) ≥ 1/4 disc area
H. Less severe retinopathy
   Mild or moderate nonproliferative retinopathy
I. More severe retinopathy
   Severe nonproliferative or early proliferative retinopathy
J. Severe visual loss
   Visual acuity < 5/200 at two consecutive follow-up visits (scheduled at 4-month intervals)
K. Moderate visual loss
   Loss of 15 or more letters between baseline and follow-up visit, equivalent to a doubling of the initial visual angle (i.e., 20/20 to 20/40 or 20/50 to 20/100)

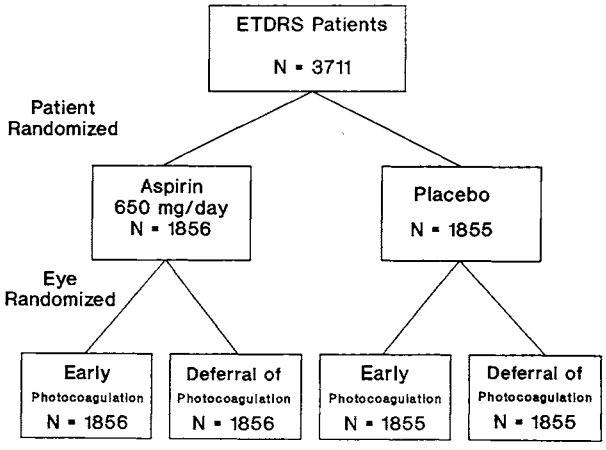


Fig 1. Eligible patients randomized to aspirin or placebo treatment. One eye of each patient was assigned randomly to immediate photocoagulation and the fellow eye was assigned to deferral with photocoagulation treatment initiated during follow-up if high-risk proliferative retinopathy developed.

The primary endpoint for assessing the effect of aspirin in the ETDRS was the development of high-risk proliferative retinopathy. Other endpoints identified during study planning were change in visual acuity, development of macular edema, worsening of retinopathy, and occurrence of vitreous or preretinal hemorrhage in eyes assigned to either early photocoagulation or deferral of photocoagulation.

To determine the earliest development of this high-risk retinopathy, all eyes were assessed ophthalmoscopically at each follow-up visit, scheduled at 4-month intervals. In addition, scheduled photographs (taken at the 4-month follow-up visit and each annual follow-up visit), as well as photographs that were required at any visit when high-risk proliferative retinopathy was detected for the first time, were evaluated centrally at the ETDRS Fundus Photograph Reading Center.

High-risk proliferative retinopathy was identified initially by ophthalmoscopy and confirmed at the Reading Center for 90% of the eyes that developed this severity of retinopathy. In the remaining 10% of eyes, high-risk proliferative retinopathy was identified initially at the Fundus Photograph Reading Center, with subsequent assessment by the Clinical Center ophthalmologist. Overall agreement between clinical and photographic evaluation was approximately 85%. When disagreements occurred, the clinical assessment took precedence.

From the beginning of the study in April 1980 until September 1983, measures used to assess compliance with study medication were serum thromboxane B_2 levels at annual visits, urine salicylate levels at annual visits, and assessment by clinical center staff of adherence based on counts of pills and patient interviews at each follow-up visit. Thromboxane B_2 measurements were discontinued

Table 2. Patient Enrollment and Close-out

		Patients			
			Survival through Close-out		
Enrollment Year	Years Follow-up*	No. Enrolled	No.	Complete Close-out Examinations	Deaths
1980	8	366	251	234 (93%)	115
1981	7	780	579	538 (93%)	201
1982	6	761	621	567 (91%)	140
1983	5	874	719	672 (93%)	155
1984	4	669	590	562 (95%)	79
1985	3	261	245	234 (96%)	16
Total	—	3711	3005	2807 (93%)	706

* Close-out visits occurred between August 1, 1988 and June 30, 1989.

after September 1983; the other measures were continued throughout the study.

The Cox proportional hazards model was used to assess the relative risk (along with the 99% confidence interval)[3] of these endpoints (e.g., development of high-risk proliferative retinopathy or development of vitreous or preretinal hemorrhage) for patients assigned to aspirin compared with patients assigned to placebo. When the relative risk is 1.0, there is no difference between the endpoint for patients assigned to aspirin and for patients assigned to placebo. A confidence interval including 1.0 indicates that the observed data are consistent with no difference between the two treatment groups. A relative risk substantially less than 1.0 indicates a reduced risk of the endpoint for patients assigned to aspirin compared with patients assigned to placebo, while a relative risk substantially more than 1.0 indicates an increased risk for patients assigned to aspirin compared with patients assigned to placebo.

A two-sample Z-test of equality of proportions[4] was used when comparing proportions of eyes with a given endpoint. The Cutler-Ederer life table method[5] was used to estimate cumulative event rates and treatment effects for selected endpoints. In the absence of the specified event, observations were censored at the patient's last visit or death. The Mantel-Cox statistic[3] was used when comparing life table results for the entire period of follow-up.

Because multiple endpoints were compared at frequent intervals during the course of the study, a probability level of 0.01, rather than 0.05, was considered statistically significant for the primary endpoints. For other comparisons, P-values between 0.01 and 0.001 provided some evidence of differences between treatments, and P-values less than 0.001 provided stronger evidence of such differences.

Power calculations during the design phase of the ETDRS were based on a total enrollment of 4000 patients with approximately equal numbers assigned to aspirin and placebo. Recruitment ended with a total of 3711 enrolled. With 1855 patients assigned to placebo and with a 40% 5-year rate of development of high-risk proliferative retinopathy in eyes assigned to deferral of photocoagulation, the power was more than 99% (alpha = 0.01, two-sided test) to detect a 25% treatment effect of aspirin in the primary endpoint (i.e., a reduction in the 5-year rate of the development of high-risk proliferative retinopathy from 40% to 30%).

Decreased compliance will reduce the study power. For example, if the true 5-year rates for persons taking placebo or aspirin were 40% and 30%, respectively, but 85% of the patients assigned to aspirin were taking study drug or known aspirin and 75% of the patients assigned to placebo were not taking aspirin, the expected 5-year rates after adjusting for noncompliance would be 37.5% for patients assigned to placebo and 31.5% for patients assigned to aspirin. The power to demonstrate a difference of this magnitude was 89%.

RESULTS

Results presented in this report include all data processed at the ETDRS Coordinating Center as of November 8, 1990. The distribution of the 3711 patients by each year of study recruitment, the number of deaths, and the number of patients followed from the beginning to the end of the study are shown in Table 2. Only 7% of the surviving patients enrolled did not attend the close-out visit. During the first 3 years of follow-up, between 90 and 95% of expected follow-up visits were completed. This decreased to between 80 and 90% for follow-up beyond 3 years. The proportions of patients missing visits were similar in the aspirin and placebo groups. There was no statistically significant difference in overall mortality; deaths numbered 340 among the patients assigned to aspirin and 366 among the patients assigned to placebo (P = 0.28).

The percentages of patients whose prescription of study medication was discontinued were similar (Table 3), increasing from approximately 8% at 1 year to approximately 30% at 5 years. The major reason for discontinuing study medication was a requirement for aspirin or other platelet-affecting drugs (e.g., for cardiovascular disease or arthritis).

Assessment of compliance using thromboxane B_2 or urine salicylate or using judgments by clinical center staff of adherence based on pill counts and patient interviews showed that more than 80% of the patients were taking

Table 3. Study Medication Not Prescribed

	Aspirin		Placebo	
	No.	Percent	No.	Percent
1-Year Visit				
Patients completing medical review	1696		1707	
No study medication prescribed	139	8.2	127	7.4
Reasons: Pregnancy	3	0.2	5	0.3
Use of platelet-affecting drug(s)	60	3.5	55	3.2
Unmasked treatment assignment	1	0.1	0	0
Nonmandatory reason(s)	63	3.7	53	3.1
3-Year Visit				
Patients completing medical review	1526		1469	
No study medication prescribed	307	20.1	277	18.9
Reasons: Pregnancy	12	0.8	4	0.3
Use of platelet-affecting drug(s)	162	10.6	157	10.7
Unmasked treatment assignment	6	0.4	1	0.1
Nonmandatory reason(s)	136	8.9	122	8.3
5-Year Visit				
Patients completing medical review*	883		880	
No study medication prescribed	268	30.4	252	28.6
Reasons: Pregnancy	3	0.3	1	0.1
Use of platelet-affecting drug(s)	166	18.8	157	17.8
Unmasked treatment assignment	3	0.3	2	0.2
Nonmandatory reason(s)	99	11.2	99	11.2
7-Year Visit				
Patients completing medical review*	231		236	
No study medication prescribed	71	30.7	88	37.3
Reasons: Pregnancy	0	0	0	0
Use of platelet-affecting drug(s)	46	19.9	56	23.7
Unmasked treatment assignment	0	0	0	0
Nonmandatory reason(s)	27	11.7	34	14.4

* Patients whose close-out visit was specified visit have been excluded since no study medication was prescribed at this visit.

prescribed study medications and refraining from using nonprotocol platelet-affecting drugs. Compliance with study medication in the ETDRS was similar to that reported for other trials of aspirin.[6–8]

The life table rates for the primary endpoint of first occurrence of high-risk proliferative retinopathy in eyes assigned to deferral of photocoagulation (Table 4) (Fig 2) show little difference between the patients assigned to aspirin and the patients assigned to placebo. The relative risk of developing high-risk proliferative retinopathy for the entire follow-up period in patients assigned to aspirin compared with patients assigned to placebo is 0.97 with a 99% confidence interval of 0.85 to 1.11.

The eyes represented in Figure 2 are divided into two groups in Figure 3. In the group of 609 eyes with the least severe retinopathy enrolled in the ETDRS (level ≤ 35)[9] (Fig 3, second row left) (Table 5), retinal lesions were limited to microaneurysms plus hard exudates, soft exudates, and/or mild-to-moderate retinal hemorrhages, with or without macular edema (one eye had microaneurysms only). The second group included the remaining 3102 eyes with retinopathy severity level 43–71[9] (Fig 3, third row left) (Table 6). There was no statistically significant difference of rates in eyes assigned to deferral between eyes in patients assigned to aspirin and patients assigned to placebo in either retinopathy subgroup. The relative risk (99% confidence interval) for developing high-risk retinopathy in eyes with the least severe retinopathy (level ≤ 35) was 0.77 (0.45–1.31); for the remaining eyes (retinopathy severity level 43–71) it was 0.98 (0.85–1.12).

The life table rates in Table 7 (Fig 4) are for the first occurrence of worsening of retinopathy by two or more levels according to central assessment of fundus photographs,[9] taken at the 4-month and the annual follow-up visits, or the occurrence of high-risk proliferative retinopathy or vitreous or preretinal hemorrhage noted on clinical examination at any other visit, for the 609 eyes with retinopathy severity level of 35 or less shown in Figure 3 (second row left). For most of these eyes, worsening by two or more levels according to photographic grading meant the development of severe retinal hemorrhages, moderately extensive intraretinal microvascular abnormalities, or mild venous beading.[10] Comparison of these life table rates for eyes assigned to deferral of photoco-

Table 4. Development of High-risk Proliferative Retinopathy* in All Eyes Assigned to Deferral

Interval	Aspirin			Placebo		
	No. at Risk	No. of Events	Event Rate (%)	No. at Risk	No. of Events	Event Rate (%)
Baseline	1856		0.0	1855		0.0
1-Year visit	1646	229	12.5	1640	214	11.7
2-Year visit	1453	142	20.5	1453	152	20.3
3-Year visit	1292	116	27.2	1260	144	28.8
4-Year visit	1053	104	33.6	1000	103	35.2
5-Year visit	715	88	40.5	696	73	41.0
6-Year visit	418	42	45.3	426	45	46.0
7-Year visit	205	28	50.6	222	26	51.1
>7 Years		7			11	
Total events		756			768	

* Life table event rates of first occurrence of high-risk proliferative retinopathy using Cutler-Ederer actuarial estimates; Mantel-Cox test statistic = 0.31, $P = 0.58$; relative risk (aspirin to placebo) = 0.97, 99% confidence interval 0.85–1.11.

Table 5. Development of High-risk Proliferative Retinopathy* in Eyes with the Least Severe Retinopathy (Level ≤ 35)† Assigned to Deferral

Interval	Aspirin			Placebo		
	No. at Risk	No. of Events	Event Rate (%)	No. at Risk	No. of Events	Event Rate (%)
Baseline	288		0.0	321		0.0
1-Year visit	282	2	0.7	311	3	0.9
2-Year visit	274	4	2.1	297	7	3.2
3-Year visit	262	9	5.4	277	14	7.9
4-Year visit	224	5	7.3	225	13	12.8
5-Year visit	161	11	12.7	146	11	18.2
6-Year visit	95	4	15.6	85	3	20.5
7-Year visit	43	6	23.5	45	2	23.4
>7 Years		0			1	
Total events		41			54	

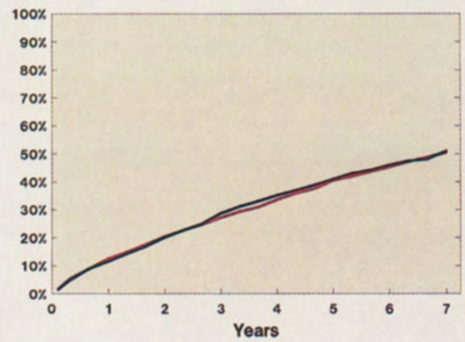
* Life table event rates of first occurrence of high-risk proliferative retinopathy using Cutler-Ederer actuarial estimates; Mantel-Cox test statistic = 1.68, $P = 0.20$; relative risk (aspirin to placebo) = 0.77, 99% confidence interval 0.45–1.31.

† In this group, retinal lesions were limited to microaneurysms plus hard exudates, soft exudates, and/or mild to moderate retinal hemorrhages, with or without macular edema (one eye had microaneurysms only).

Table 6. Development of High-risk Proliferative Retinopathy* in Eyes with Retinopathy Severity Level 43–71[9] Assigned to Deferral

Interval	Aspirin			Placebo		
	No. at Risk	No. of Events	Event Rate (%)	No. at Risk	No. of Events	Event Rate (%)
Baseline	1568		0.0	1534		0.0
1-Year visit	1364	227	14.7	1329	211	14.0
2-Year visit	1179	138	23.9	1155	145	23.9
3-Year visit	1030	107	31.3	982	130	33.2
4-Year visit	829	99	38.5	776	90	40.0
5-Year visit	554	77	45.7	550	62	45.8
6-Year visit	323	38	50.8	341	42	51.1
7-Year visit	163	22	55.7	177	24	56.4
>7 Years		7			10	
Total events		715			714	

* Life table event rates of first occurrence of high-risk proliferative retinopathy using Cutler-Ederer actuarial estimates; Mantel-Cox test statistic = 0.21, $P = 0.65$; relative risk (aspirin to placebo) = 0.98, 99% confidence interval 0.85–1.12.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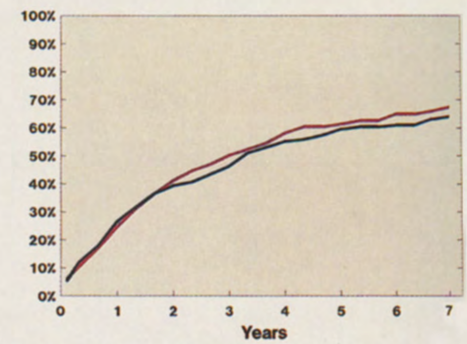
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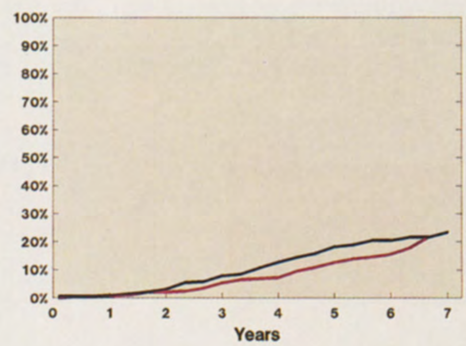
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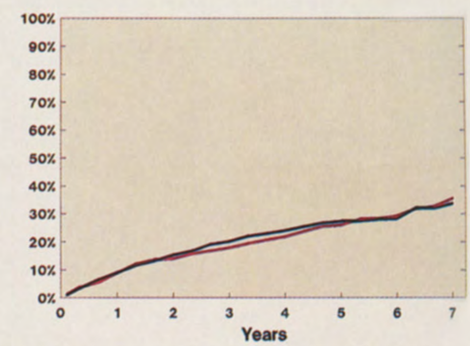
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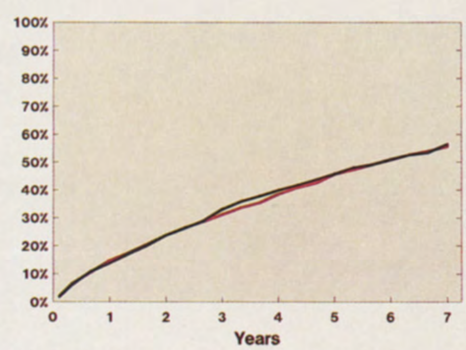
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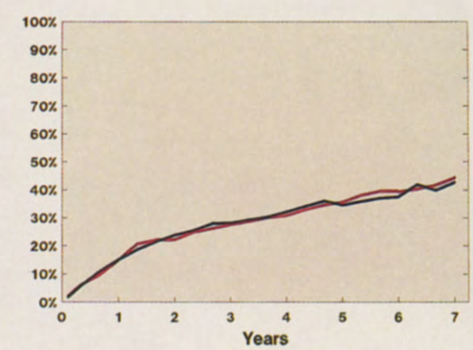
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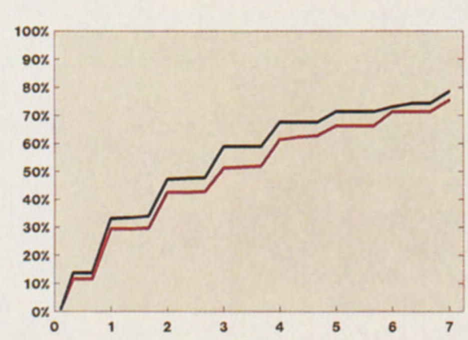
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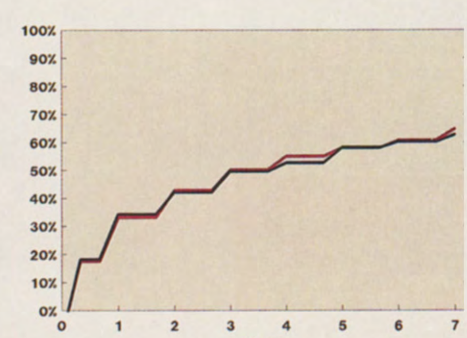
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Fig 2. *Top left,* cumulative life table event rates of first occurrence of high-risk proliferative retinopathy in all eyes assigned to deferral of photocoagulation: patients assigned to aspirin treatment (red) compared with patients assigned to placebo treatment (black). **Fig 3.** *Second row left,* cumulative life table event rates of first occurrence of high-risk proliferative retinopathy in eyes with least severe retinopathy (level ≤ 35) assigned to deferral of photocoagulation: patients assigned to aspirin treatment (red) compared with patients assigned to placebo treatment (black). *Third row left,* cumulative life table event rates of first occurrence of high-risk proliferative retinopathy in eyes with retinopathy severity level 43 to 71 assigned to deferral of photocoagulation: patients assigned to aspirin treatment (red) compared with patients assigned to placebo treatment (black). **Fig 4.** *Bottom left,* cumulative life table event rates of first occurrence of two or more level worsening of retinopathy, high-risk proliferative retinopathy, or vitreous or preretinal hemorrhage in eyes with least severe retinopathy (level ≤ 35) assigned to deferral of photocoagulation: patients assigned to aspirin treatment (red) compared with patients assigned to placebo treatment (black). **Fig 5.** *Top right,* cumulative life table event rates of first occurrence of vitreous or preretinal hemorrhage in eyes with retinopathy severity level 61 to 71 assigned to deferral of photocoagulation: patients assigned to aspirin treatment (red) compared with patients assigned to placebo treatment (black). **Fig 6.** *Second row right,* comparison of percentages of eyes that experienced visual loss of 15 or more letters (equivalent to at least doubling of initial visual angle) in all eyes assigned to deferral of photocoagulation: patients assigned to aspirin treatment (red) compared with patients assigned to placebo treatment (black). **Fig 7.** *Third row right,* comparison of percentages of eyes that experienced visual loss of 15 or more letters (equivalent to at least doubling of initial visual angle) in eyes with clinically significant macular edema assigned to deferral of photocoagulation: patients assigned to aspirin treatment (red) compared with patients assigned to placebo treatment (black). **Fig 8.** *Bottom right,* cumulative life table event rates of first occurrence of clinically significant macular edema (CSME) in eyes without CSME at baseline assigned to deferral of photocoagulation: patients assigned to aspirin treatment (red) compared with patients assigned to placebo treatment (black).

agulation indicated no difference in first occurrence of worsening retinopathy level between patients assigned to aspirin and those assigned to placebo ($P = 0.17$ by Mantel-Cox).

Analyses of the effects of aspirin and placebo on the occurrence of high-risk proliferative retinopathy or worsening of retinopathy in eyes assigned to early photocoagulation gave results similar to those shown in Tables 4 to 7 and Figures 2 to 4. However, the rates of worsening of retinopathy were lower for eyes assigned to early photocoagulation whether the patients were assigned to aspirin or placebo (data not shown).

During the design phase of the ETDRS, there had been concern that use of aspirin might increase the risk of vitreous hemorrhage, especially in eyes with new vessels. Life table rates for the first occurrence of vitreous or preretinal hemorrhage during follow-up in eyes assigned to deferral of photocoagulation that had new vessels "definitely present" (retinopathy severity level, 61–71[9]) based on the central assessment of baseline fundus photographs are shown in Table 8 (Fig 5). The relative risk of vitreous or preretinal hemorrhage for patients assigned to aspirin compared with patients assigned to placebo is 1.05 (99% confidence interval, 0.81 to 1.36). Analyses for eyes assigned to early photocoagulation yielded similar results for the risk of developing vitreous or preretinal hemorrhage (data not shown).

The percentages of eyes assigned to deferral of photocoagulation that had moderate visual loss (a decrease of visual acuity of 15 or more letters; a decrease equivalent to a doubling of the initial visual angle) between baseline and specified follow-up visits are given in Table 9 and Figure 6. No effect of aspirin was seen in either this analysis or a similar analysis limited to eyes with clinically significant macular edema (CSME) at baseline (Table 10) (Fig 7).

For eyes without CSME at baseline, aspirin did not reduce the risk of developing CSME during follow-up, as judged by central assessment of fundus photographs in eyes assigned to deferral of photocoagulation (Table 11) (Fig 8). When the analyses shown in Tables 9 to 11 and Figures 6 to 8 were repeated for eyes assigned to early photocoagulation, they also showed no difference between the patients assigned to aspirin and the patients assigned to placebo (data not shown).

DISCUSSION

The ETDRS data demonstrate no statistically significant beneficial or harmful effects of aspirin (650 mg per day) on the course of diabetic retinopathy in its mild nonproliferative through early proliferative stages, with or without macular edema. Furthermore, aspirin did not significantly increase the incidence of vitreous hemorrhage.

For eyes with the least severe retinopathy in ETDRS (retinopathy severity ≤ 35) at baseline, there was a slight, statistically nonsignificant trend toward a reduction in the rate of development of high-risk proliferative retinopathy in patients assigned to aspirin, as shown in Figure 3. The 99% confidence interval for the relative risk included 1.0 and ranged from a 55% decreased risk to a 31% increased risk in eyes assigned to deferral of patients assigned to aspirin compared with eyes assigned to deferral of patients assigned to placebo. The proportion of eyes in this retinopathy group that had a worsening of two or more levels in retinopathy also was not statistically different between patients assigned to aspirin and those assigned to placebo (Fig 4).

The Dipyridamole Aspirin Micro Angiopathie Diabetique (DAMAD) Study Group reported results of their randomized placebo-controlled clinical trial of aspirin (330 mg three times daily) in persons with mild-to-moderate diabetic retinopathy. Over a 3-year period, the increase in the count of microaneurysms in patients assigned randomly to placebo was significantly greater than in those assigned to aspirin.[11] The importance of this finding is unclear because no effect of aspirin on the rate of progression of the overall level of diabetic retinopathy was observed in either the DAMAD study or the ETDRS. The ETDRS provided no information on the effect of aspirin

Table 7. Worsening of Retinopathy in Eyes with Least Severe Retinopathy (Level ≤ 35[9]) Assigned to Deferral

	Aspirin			Placebo		
Interval	No. at Risk	No. of Events	Event Rate (%)	No. at Risk	No. of Events	Event Rate (%)
Baseline	288		0.0	321		0.0
1-Year visit	249	83	29.4	268	104	33.2
2-Year visit	192	36	42.5	201	43	47.3
3-Year visit	151	23	51.3	151	34	59.0
4-Year visit	112	24	61.5	104	22	67.7
5-Year visit	66	9	66.3	59	7	71.5
6-Year visit	34	5	71.3	32	2	73.2
7-Year visit	14	2	75.4	18	4	78.6
>7 Years		1			0	
Total events		183			216	

* Life table summary of first occurrence of worsening of retinopathy (increase by two or more levels in retinopathy, occurrence of high-risk proliferative retinopathy, or occurrence of vitreous or preretinal hemorrhage) using Cutler-Ederer actuarial estimates; Mantel-Cox test statistic = 1.86, $P = 0.17$; relative risk (aspirin to placebo) = 0.88, 99% confidence interval 0.68–1.14.

Table 8. Development of Hemorrhage* in Eyes with Retinopathy Severity Level 61-71[9] Assigned to Deferral

	Aspirin			Placebo		
Interval	No. at Risk	No. of Events	Event Rate (%)	No. at Risk	No. of Events	Event Rate (%)
Baseline	324		0.0	342		0.0
1-Year visit	257	78	24.7	275	90	26.7
2-Year visit	187	50	41.3	204	42	39.5
3-Year visit	151	26	50.3	178	22	46.4
4-Year visit	114	21	58.2	134	27	55.2
5-Year visit	77	7	61.4	103	11	59.6
6-Year visit	49	5	64.9	72	3	61.0
7-Year visit	24	2	67.4	41	4	64.0
>7 Years		1			4	
Total events		190			203	

* Life table summary of first occurrence of hemorrhage (either vitreous or preretinal) using Cutler-Ederer actuarial estimates; Mantel-Cox test statistic = 0.23, $P = 0.63$; relative risk (aspirin to placebo) = 1.05, 99% confidence interval 0.81–1.36.

Table 9. Moderate Visual Loss* in All Eyes Assigned to Deferral

	Aspirin		Placebo		*Z*-value†
Interval	No. of Eyes	Percentage	No. of Eyes	Percentage	(Aspirin − Placebo)
Baseline	1856		1855		
1-Year visit	1813	8.9	1808	9.1	−0.20
2-Year visit	1768	14.1	1757	15.5	−1.17
3-Year visit	1720	18.0	1684	20.3	−1.74
4-Year visit	1611	22.0	1572	24.1	−1.43
5-Year visit	1287	26.0	1229	27.4	−0.79
6-Year visit	869	29.3	870	28.4	0.44
7-Year visit	527	35.5	513	33.7	0.60

* Moderate visual loss is loss of 15 or more letters (equivalent to at least doubling of initial visual angle) at specified visit.

† *Z*-value is test statistic for difference between observed rate in eyes assigned to deferral in patients assigned to aspirin and in eyes assigned to deferral in patients assigned to placebo.

Table 10. Moderate Visual Loss* in All Eyes with Clinically Significant Macular Edema Assigned to Deferral

	Aspirin		Placebo		Z-value†
Interval	No. of Eyes	Percentage	No. of Eyes	Percentage	(Aspirin − Placebo)
Baseline	890		874		
1-Year visit	863	14.9	843	15.2	−0.14
2-Year visit	838	22.3	806	23.9	−0.78
3-Year visit	806	27.7	761	28.3	−0.26
4-Year visit	746	31.0	704	32.2	−0.52
5-Year visit	604	35.8	551	34.7	0.39
6-Year visit	405	39.5	385	37.7	0.53
7-Year visit	241	44.4	215	42.8	0.35

* Moderate visual loss is loss of 15 or more letters equivalent to at least doubling of initial visual angle.
† Z-value is test statistic for difference between observed rate in eyes assigned to deferral in patients assigned to aspirin and in eyes assigned to deferral in patients assigned to placebo.

Table 11. Clinically Significant Macular Edema* in Eyes without Clinically Significant Macular Edema Assigned to Deferral

	Aspirin			Placebo		
Interval	No. at Risk	No. of Events	Event Rate (%)	No. at Risk	No. of Events	Event Rate (%)
Baseline	925		0.0	933		0.0
4-Month visit	915	161	17.6	917	167	18.2
1-Year visit	742	140	33.2	737	144	34.2
2-Year visit	587	84	42.7	580	70	42.1
3-Year visit	493	64	50.2	497	65	49.7
4-Year visit	378	37	55.0	382	23	52.7
5-Year visit	256	17	58.0	270	31	58.2
6-Year visit	159	10	60.7	159	8	60.3
7-Year visit	76	8	64.8	80	5	62.7
>7 Years		2			3	
Total events		523			516	

* Life table summary of first occurrence of clinically significant macular edema from fundus photographs using Cutler-Ederer actuarial estimates; Mantel-Cox test statistic = 0.08, $P = 0.77$; relative risk (aspirin to placebo) = 1.02, 99% confidence interval 0.87–1.19.

in patients with very mild diabetic retinopathy because such patients were not enrolled.

The ETDRS results indicate that for patients with mild-to-severe nonproliferative or early proliferative diabetic retinopathy, aspirin is likely to have no clinically important beneficial effects on the progression of retinopathy. The data also show that 650 mg per day had no clinically important harmful effects for diabetic patients with retinopathy. These findings suggest there are no ocular contraindications to aspirin when required for cardiovascular disease or other medical indications.

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