# Effect of Aspirin Alone and Aspirin Plus Dipyridamole in Early Diabetic Retinopathy

## A Multicenter Randomized Controlled Clinical Trial

THE DAMAD STUDY GROUP

**In a double-blind randomized controlled clinical trial conducted in two French and two United Kingdom centers, the effect of antiplatelet agents, i.e., aspirin alone (330 mg 3 times daily) or in combination with dipyridamole (75 mg 3 times daily), was tested versus placebo in 475 patients with early diabetic retinopathy. The assessment of retinopathy was based on change in the number of microaneurysms (MAs) present in the macular field, as seen on fluorescein angiograms, over 3 yr. Forty-one patients did not complete the study. At least three readable initial and yearly angiograms were available on 420 patients (266 treated with insulin and 154 not treated); the results reported are based on these patients. The mean yearly increase in definite MAs was similar in insulin-treated and non-insulin-treated diabetic patients. There was no significant difference between the aspirin-alone group (0.69 ± 5.1 mean ± SD, $n$ = 145) and the aspirin-plus-dipyridamole group (0.34 ± 3.0, $n$ = 142). In the placebo group the mean yearly increase (1.44 ± 4.5, $n$ = 133) was significantly higher than in the treated group ($P$ = .02, 1-tailed $t$ test). There was a clear relationship between the deterioration in ophthalmological signs and the increase in mean yearly MAs (clinically stable, 0.38 ± 3.96, $n$ = 293; deteriorating, 1.79 ± 4.89, $n$ = 127; $P$ = .002, 2-tailed $t$ test). We conclude that aspirin alone and in conjunction with dipyridamole significantly slows the progression of MA evolution in early diabetic retinopathy. *Diabetes* 38:491–98, 1989**

In diabetic retinopathy the earliest clinically recognizable lesions are small areas of capillary occlusion, visible on fluorescein angiograms. Microaneurysms (MAs), the hallmark of early diabetic retinopathy, occur after capillary nonperfusion. The pathogenesis of the lesions is not known, but because of the platelet abnormalities commonly seen in diabetes, some research suggests that abnormal platelet function results in the vascular occlusion (1–5). To test this hypothesis, a randomized controlled clinical study in early retinopathy was designed in which the effects of aspirin alone or in conjunction with dipyridamole were compared with a placebo-treated group.

Because the evolution of early diabetic retinopathy is often slow, an accurate method capable of detecting small changes is necessary. The many photographic grading systems available are not sufficiently sensitive to show these small changes (6–9). We chose the use of MA counts from fluorescein angiograms as a quantitative assessment. They are an easily recognizable early lesion at the posterior pole, as judged by the Wisconsin system (9), and reflect the severity of early diabetic retinopathy (10). In addition, a valid reproducible method for their quantification has been developed by our group (11). Alternatives such as prolonged studies over 5–10 yr are conceivable but would be expensive. In this article, we report the final results of a study of the changes in early retinopathy, as evaluated by changes in the MA count, in three randomized groups of patients.

### PATIENTS AND METHODS

**Patients.** This trial was carried out in two diabetes clinics in France and in two United Kingdom centers; the general medical and ophthalmological protocols have been reported previously (12–14), and only a brief summary is given in this article.

Patients who had type I (insulin-dependent) or type II (non-insulin-dependent) diabetes mellitus were eligible for the study if they were between the ages of 17 and 67 yr, had no other intercurrent disease, i.e., no coronary artery disease (diagnosed from ECG based on the Minnesota coding sys-

| | | | |
|---|---|---|---|
| Cholesterol | 1 mM = 38.7 mg/dl | Glucose | 1 mM = 18 mg/dl |
| Creatinine | 1 μM = 0.011 | | |

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TABLE 1
Baseline characteristics

| | Non-insulin-treated patients ($n$ = 176) | | | Insulin-treated patients ($n$ = 299) | | |
|---|---|---|---|---|---|---|
| | Placebo ($n$ = 58) | Aspirin ($n$ = 59) | Aspirin + dipyridamole ($n$ = 59) | Placebo ($n$ = 99) | Aspirin ($n$ = 98) | Aspirin + dipyridamole ($n$ = 102) |
| Males (%) | 38 (66%) | 42 (71%) | 37 (63%) | 62 (63%) | 61 (62%) | 65 (64%) |
| Nonsmoker | 36 (63%) | 34 (58%) | 35 (59%) | 61 (62%) | 56 (58%) | 45 (44%) |
| Age at entry (yr) | 53 ± 8 | 53 ± 8 | 55 ± 8 | 44 ± 12 | 42 ± 12 | 43 ± 11 |
| Body mass index (kg/m²) | 26 ± 4 | 25 ± 4 | 25 ± 3 | 24 ± 3 | 24 ± 3 | 24 ± 3 |
| Duration of diabetes (yr) | 9 ± 6 | 9 ± 6 | 11 ± 7 | 15 ± 7 | 15 ± 7 | 15 ± 8 |
| Age at diagnosis (yr) | 44 ± 8 | 44 ± 9 | 44 ± 8 | 29 ± 12 | 27 ± 12 | 28 ± 12 |
| Plasma glucose (g/L) | | | | | | |
| Fasting | 1.52 ± 0.50 | 1.70 ± 0.70 | 1.46 ± 0.45 | 1.75 ± 0.97 | 1.84 ± 0.95 | 1.81 ± 0.98 |
| Postprandial | 1.64 ± 0.67 | 1.82 ± 0.86 | 1.70 ± 0.67 | 1.87 ± 1.03 | 2.00 ± 0.96 | 2.11 ± 0.93 |
| $HbA_1$ (%) | 9.8 ± 2.2 (19) | 10.0 ± 2.5 (20) | 8.4 ± 2.2 (20) | 10.6 ± 2.3 (42) | 10.7 ± 2.2 (40) | 10.4 ± 2.4 (45) |
| Glucosuria | | | | | | |
| g/24 h | 17 ± 17 | 13 ± 18 | 15 ± 16 | 24 ± 30 | 36 ± 34 | 27 ± 31 |
| Positive (%) | 32 (12 of 37) | 39 (14 of 36) | 51 (21 of 42) | 67 (36 of 53) | 74 (40 of 54) | 65 (36 of 55) |
| Sulfonylurea (% yes) | 12 (21%) | 19 (32%) | 6 (10%) | | | |
| Biguanide (% yes) | 14 (25%) | 14 (24%) | 19 (32%) | 1 (1%) | 5 (5%) | 3 (3%) |
| Both (% yes) | 15 (26%) | 15 (25%) | 22 (38%) | | | |
| Diabetes treatment | | | | | | |
| Diet only (% yes) | 16 (28%) | 11 (19%) | 12 (20%) | | | |
| Insulin (U/day) | | | | 46 ± 20 | 48 ± 19 | 50 ± 22 |
| Triglyceride (g/L) | 11.2 ± 0.59 | 1.46 ± 1.04 | 1.16 ± 0.69 | 1.05 ± 0.74 | 1.17 ± 1.18 | 1.22 ± 1.11 |
| Cholesterol (g/L) | 2.24 ± 0.49 | 2.30 ± 0.52 | 2.27 ± 0.37 | 2.24 ± 0.45 | 2.19 ± 0.47 | 2.19 ± 0.47 |
| Creatinemia (g/L) | 0.98 ± 0.26 | 1.02 ± 0.18 | 1.03 ± 0.28 | 0.97 ± 0.22 | 0.99 ± 0.25 | 0.97 ± 0.22 |
| 24-h proteinuria | | | | | | |
| g/24 h | 4 ± 5 | 5 ± 3 | 3 ± 3 | 7 ± 6 | 12 ± 23 | 30 ± 52 |
| Positive (%) | 8 (3 of 36) | 7 (2 of 27) | 3 (1 of 32) | 12 (5 of 43) | 11 (5 of 45) | 9 (4 of 45) |
| Blood pressure (mmHg) | | | | | | |
| Systolic | 145 ± 19 | 146 ± 18 | 148 ± 22 | 137 ± 17 | 139 ± 18 | 136 ± 20 |
| Diastolic | 84 ± 11 | 82 ± 11 | 83 ± 12 | 80 ± 11 | 80 ± 10 | 80 ± 9 |
| ECG (%) | | | | | | |
| Normal | 39 (80%) | 47 (88%) | 39 (87%) | 73 (93%) | 73 (89%) | 70 (84%) |
| Possibly abnormal | 8 (16%) | 4 (8%) | 6 (13%) | 5 (6%) | 8 (10%) | 9 (11%) |
| Probably abnormal | 2 (4%) | 2 (4%) | 0 (0%) | 1 (1%) | 1 (1%) | 4 (5%) |

Values are means ± SD; numbers in parentheses indicate number of patients or percentage of total.

tem) or hypertension with diastolic blood pressure >105 mmHg at three successive examinations, and no condition contraindicating the prolonged use of aspirin (e.g., hemorrhagic tendency, history of peptic ulcer). Only patients with established diabetes were recruited into the study, and all had fasting blood glucose >6 mM and 2-h postprandial blood glucose >10 mM before treatment. They were subdivided according to treatment for diabetes into non-insulin-treated (NIT) and insulin-treated (IT) patients. The latter group included patients with type I or type II diabetes; C-peptide assay was not available to us during the first years of the study. Once in the study, patients were analyzed according to their original treatment group, even if treatment changed during the follow-up. The protocol was accepted

TABLE 2
Characteristics at 3 yr

| | Non-insulin-treated patients ($n$ = 159) | | | Insulin-treated patients ($n$ = 275) | | |
|---|---|---|---|---|---|---|
| | Placebo ($n$ = 52) | Aspirin ($n$ = 55) | Aspirin + dipyridamole ($n$ = 52) | Placebo ($n$ = 87) | Aspirin ($n$ = 95) | Aspirin + dipyridamole ($n$ = 93) |
| Body mass index (kg/m²) | 26 ± 4 | 26 ± 3 | 26 ± 3 | 24 ± 3 | 24 ± 3 | 24 ± 3 |
| Plasma glucose (g/L) | | | | | | |
| Fasting | 1.66 ± 0.67 | 1.56 ± 0.55 | 1.55 ± 0.68 | 1.71 ± 1.00 | 1.80 ± 1.00 | 1.85 ± 1.00 |
| Postprandial | 1.72 ± 0.67 | 1.83 ± 0.83 | 1.86 ± 0.82 | 2.02 ± 1.03 | 1.81 ± 1.00 | 2.00 ± 0.88 |
| $HbA_1$ (%) | 8.9 ± 2.7 | 8.5 ± 2.8 | 8.1 ± 2.6 | 9.5 ± 2.1 | 9.2 ± 2.4 | 9.6 ± 2.3 |
| Blood pressure (mmHg) | | | | | | |
| Systolic | 143 ± 23 | 146 ± 22 | 148 ± 23 | 139 ± 19 | 144 ± 25 | 141 ± 23 |
| Diastolic | 82 ± 14 | 85 ± 11 | 83 ± 12 | 81 ± 10 | 82 ± 13 | 80 ± 12 |
| Insulin dose (U/day) | | | | 45 ± 19 | 49 ± 19 | 51 ± 22 |

Values are means ± SD.

TABLE 3
Patients who did not complete study

| | Placebo | Aspirin | Aspirin + dipyridamole |
|---|---|---|---|
| Non-insulin treated | 6 | 4 | 7 |
| Insulin treated | 12 | 3 | 9 |
| Total | 18 (11%) | 7 (4%) | 16 (10%) |

Comparisons are significant at $P = .07$.

by the ethics committees of the four participating hospitals, and all patients gave informed consent to participate in the trial.

Ophthalmic criteria included the presence of early diabetic retinopathy with at least five MAs visualized by fluorescein angiograms of the field centered on the fovea; fewer MAs were considered if there was a definite area or areas of nonperfusion. Patients were excluded if they had macular edema, proliferative lesions, or previous photocoagulation. To be included in the study, there had to be no other eye disease present (e.g., early cataract, glaucoma), and good-quality fluorescein angiograms had to be obtained.

For the recruitment, a record of screening was kept in France only. Out of 11,135 case notes, 10,357 were excluded because of age (24%), diabetes (37% newly diagnosed, 5% with diabetic complications), intercurrent illness, treatment (side effects), or refusal to participate (27%). This left 778 patients sent for eye assessment. Of these, 58% were excluded on ophthalmological examination and/or fluorescein angiography, leaving 326 patients in the study, i.e., 2.9% of the case notes reviewed.

## METHODS

After a preliminary period of 1 mo, during which all patients received the placebo 3 times daily, patients in each center were randomized and stratified by treatment of diabetes (IT or NIT) into three treatment groups. Each patient received 3 capsules/day containing aspirin (330 mg/capsule) or aspirin and dipyridamole (330 mg aspirin and 75 mg dipyridamole/capsule) or the placebo, depending on the assigned treatment group. All capsules were identical in appearance. Compliance was checked by the number of clinic visits per subgroup of patients, by measurement of the inhibition of arachidonic acid–induced platelet aggregation (15), and in one center, by tablet count.

**Follow-up.** Patients were seen every 4 mo throughout the 3-yr study period. On each visit, side effects of the drugs, glycemic control, and blood pressure were noted. Blood was taken for measurement of $HbA_1$ (with affinity chromatography in UK and a low-pressure liquid chromatography technique derived from the Trivelli method in France) and fasting and 2-h postprandial plasma glucose (Beckman analyzer). Annual full clinical examination was supplemented by ECG, 24-h proteinuria estimation, measurement of serum creatinine, fasting plasma triglycerides, and cholesterol measured in the laboratories of each center, as described previously (12,13).

**Ophthalmological examinations.** Ophthalmological examinations were carried out initially and at yearly intervals. The best corrected visual acuity was obtained, intraocular pressure was measured, and both the anterior segment and the retina were examined with direct and indirect ophthalmoscopy and biomicroscopy. The patients then had color photographs of two standard fields, one centered on the disk and one on the macula, as described in the ophthalmological protocol (14). One eye in each patient was studied by fluorescein angiography (always the right eye, unless it had intercurrent eye disease or was not photographable). For the fluorescein angiography, 5 ml of 10% (France) or 20% (UK) fluorescein sodium was injected rapidly into an antecubital vein. Photographs were taken of a field centered on the fovea before the appearance of the dye and at ~1-s intervals from the first appearance of the dye until completion of the capillary phase. Late photographs were taken of the disk, macula, and each retinal quadrant; late photographs were also taken of the second eye in the same fields.

**Evaluation of ophthalmoscopy.** To evaluate the deterioration of retinopathy during the 3 yr of follow-up, we classified each patient as *stable* or *deteriorating*. This evaluation was based on the ophthalmoscopy of the posterior pole, as noted in a questionnaire by the ophthalmologist during the annual consultation. Six clinical signs were evaluated: hard exudates (round or scattered), cotton-wool spots (soft exudates), macular edema, other macular lesions, neovascularization (new vessles on disk or elsewhere), and other complications (fibrosis, detachment of the retina, vitreous hemorrhage). Each sign was classified as *present* or *absent*, but no account was taken of the type of worsening or of its severity. A clinical status was established before treatment, for each sign and each patient. If at least one sign, initially absent, appeared during the 3 yr of follow-up, at any time, the patient was classified as deteriorating; if no new signs were noted, stable.

**Photographic analysis.** MAs were counted from the frame of the fluorescein angiogram that showed the best capillary detail (as chosen by the individual reader) by the method described by Baudoin et al. (11). Briefly, the angiogram was projected on a Zeiss Jena documentor DL 2 microfilm reader

TABLE 4
Deaths during study

| Treatment group | Cause | Months into study | Age (yr) | Sex | Type of diabetes |
|---|---|---|---|---|---|
| Placebo | Unknown | 8 | 61 | F | NIT |
| | Myocardial infarction | 32 | 58 | M | NIT |
| | Suicide | 8 | 63 | M | IT |
| Aspirin | Jaw cancer | 20 | 38 | M | IT |
| | Myocardial infarction | 36 | 66 | M | NIT |
| Aspirin + dipyridamole | Myocardial infarction | 24 | 55 | M | NIT |

NIT, non-insulin treated; IT, insulin treated.

TABLE 5
Photocoagulations performed during study

| | Placebo ($n$ = 157) | Aspirin ($n$ = 157) | Aspirin + dipyridamole ($n$ = 161) |
|---|---|---|---|
| Focal at posterior pole | 1 | 0 | 3 |
| Panretinal (outside macular field) | 4 | 3 | 2 |
| Focal and panretinal | 5 | 2 | 4 |

$n$ = number of patients.

TABLE 6
Causes of discontinuation of treatment

| | Placebo ($n$ = 157) | Aspirin ($n$ = 157) | Aspirin + dipyridamole ($n$ = 161) |
|---|---|---|---|
| Gastric pain | 2 | 6 | 7 |
| Ulcer | 1 | 5 | 4 |
| Gastrointestinal bleeding | 1 | | 0 |
| Myocardial infarction | 1 | | 2 |
| Other causes* | 5 | 11 | 4 |
| Total | 10 (6%) | 22 (14%) | 17 (11%) |

Comparisons are significant at $P$ = .09. Treatment was discontinued in 20 (or 11%) of the non-insulin-treated patients and 29 (or 10%) of the insulin-treated patients. $n$ = number of patients.
*Vomiting, hiatal hernia, esophageal stricture, gastritis, anal fissure, erythema, capillary fragility, dialysis, pregnancy, refusal of treatment, unknown.

onto a sheet, which indicated the center of the fovea and a 5° and 20° field outside it, which was divided into 37 areas. For accurate superimposition of serial photographs, marker vessels were drawn in all four quadrants. For reading, a mask covered all but one area at a time, and the reading was always done from left to right and from top to bottom. MAs were defined by comparison with standard dots. MAs >33 μm in diameter in the retina were noted as *definite*, with those >25 but <33 μm termed *possible*. Smaller MAs were disregarded.

**Masking of angiograms.** All the angiograms of the trial were prepared for reading in batches of 30 masked angiograms with two computerized randomization steps. In the first step, 30 patients were chosen, and in the second step, 1 angiogram from each of the patients was selected. From each selected angiogram, the 4–10 photographs of the capillary phase were pulled, and a number between 1 and 30 was given for identification in the batch. Individual readers were given the batches, with care taken to ensure that readers would not analyze more than 1 angiogram from any patient in a fortnight. The readers were trained and tested before participation in the study to ensure reproducibility of the results. Eighty percent of angiograms were read several times (2–6 times) by six trained readers. During the study, reproducibility of the method was tested by the rereading of 2059 angiograms. There were several reasons for rereading the angiograms. There was a change of readers during the 5 yr, and between-observer reproducibility had to be ensured. Furthermore, rereading ensured avoidance of temporal drift and stimulated the self-discipline of the readers. Finally, from a statistical point of view, data based on the mean of several measurements are more reproducible than data from just one. The intraclass correlation coefficient (16) between at least two readings was 0.871 for definite and 0.864 for total MAs (definite and possible). To evaluate the final number of MAs on an angiogram with replicate reading, averages of definite and total MAs were computed.

### EVALUATION OF QUALITY

Because the quality of the angiogram may influence under- or overreading of the MA count, the quality of the angiograms was evaluated after the study by an experienced technician. This technician did not know the patient-treatment group or the MA count. All angiograms were evaluated together in two steps. They were first arranged in order of decreasing quality, then graded on a continuous visual scale ranging from unreadable (0 mm) to excellent (160 mm). Angiograms with zero quality were eliminated. Weighting was introduced, based on the dispersion of the quality for the angiograms of each patient according to the formula $1/(|Q - M| + 1)$, where Q is quality of a given angiogram and M is mean of quality of all the angiograms of that patient. The values of this coefficient of weighting varied between 0 and 1. When the quality of a given angiogram equaled the mean of all the angiograms of that patient, the weight was equal to 1. As long as the quality remained similar throughout the study, the filtered quality of information would not change, and thus the slope that measures the evolution would not change.

### STATISTICAL ANALYSIS

Retinal changes were determined by the mean yearly increase in the number of MAs, calculated for each individual as the slope of the regression of the number of MAs versus time (17), as stated in the protocol and based on a method published by our group (18). Sample size was based on this criterion; in patients with early retinopathy, the mean yearly increase in MAs was between 5 and 10, and a reduction of 2.5 ± 5.5 MAs/yr was postulated in the treated group. The calculations used a one-tailed $t$ test with $\alpha = 0.05$ and $\beta =$

TABLE 7
Inhibition of platelet aggregation

| | Non-insulin-treated patients | | | Insulin-treated patients | | |
|---|---|---|---|---|---|---|
| | Total ($n$) | Inhibited ($n$) | Percentage of total | Total ($n$) | Inhibited ($n$) | Percentage of total |
| Placebo | 30 | 4 | 13 | 45 | 4 | 9 |
| Aspirin | 39 | 27 | 69 | 53 | 40 | 75 |
| Aspirin + dipyridamole | 28 | 18 | 64 | 44 | 35 | 80 |

Inhibition was defined by an optical density <30%, with 1 mM arachidonic acid.

TABLE 8
Ophthalmic characteristics at baseline

| | Non-insulin-treated patients ($n$ = 176) | | | Insulin-treated patients ($n$ = 299) | | |
|---|---|---|---|---|---|---|
| | Placebo ($n$ = 58) | Aspirin ($n$ = 59) | Aspirin + dipyridamole ($n$ = 59) | Placebo ($n$ = 99) | Aspirin ($n$ = 98) | Aspirin + dipyridamole ($n$ = 102) |
| Visual acuity (6 of 6 or better) | 48 (83) | 48 (81) | 46 (78) | 85 (86) | 81 (83) | 92 (90) |
| Ophthalmoscopy of posterior pole | | | | | | |
| Hard exudates (punctuate, round) | 17 (29) | 14 (24) | 18 (31) | 22 (23) | 18 (18) | 23 (23) |
| Soft exudates (cotton-wool spots) | 4 | 5 | 2 | 4 | 7 | 5 |
| Macular edema | 2 | 3 | 2 | 5 | 0 | 4 |
| Other macular lesions | 2 | 1 | 3 | 3 | 1 | 4 |
| Neovascularization (on disk or elsewhere) | 1 | 0 | 1 | 0 | 2 | 1 |
| Other complications* | 0 | 0 | 0 | 0 | 0 | 0 |

Numbers in parentheses are percentages.
*Fibrosis, detachment of the retina, vitreous hemorrhage.

0.05. With an anticipated dropout rate of 20%, a total sample size of 450 patients was required. The computation of the slopes was weighted by the coefficient for quality described above. In agreement with the protocol, the survey was limited to a 3-yr follow-up, and a patient had to have at least three readable angiograms for inclusion in this analysis. The study was designed to test two independent hypotheses, *1*) that aspirin and dipyridamole together are more effective than aspirin alone (2-tailed test = $2P$) and *2*) that the effect of treatment (aspirin alone or aspirin + dipyridamole) is different from that of placebo (1-tailed test = $P$). Statistical analyses were performed with two-way analysis of variance (3 × 2 factorial design with fixed levels, one factor for treatment, the other for type of diabetes), which permitted the testing of the two hypotheses relative to the effect of treatment, the effect of the type of diabetes, and the interaction between treatment and type of diabetes therapy (16). The level of significance was fixed at $P$ = .05.

## RESULTS

Between 1 October 1976 and 30 September 1981, 475 patients entered the study. Clinical characteristics at entry, treatment of diabetes, and randomization treatment group are shown in Table 1; the groups were comparable for medical parameters tested. They remained similar at 3 yr (Table 2). Forty-one of the 475 patients did not complete the study (Table 3), with the smallest loss in the aspirin group. Eight died, 4 in the treatment groups and 4 in the placebo group (Table 4). Five of the 8 deaths were due to myocardial infarction. Of the 33 who left the study, 12 moved, 14 refused to continue attending, and 7 could not be located for follow-up. Photocoagulation in the eye chosen for study was performed in only 24 patients during the 3 yr (Table 5). Treatment was discontinued in 49 patients (Table 6)—in 26 because of side effects, primarily gastrointestinal, which were 7 times more frequent in the treatment than in the placebo group. In the 49 patients, follow-up was maintained, and they were analyzed in their original treatment groups. Fifty-five patients were not included in the analysis of MAs because they did not have at least three readable angiograms (placebo, 15.3%; aspirin, 7.6%; aspirin + dipyridamole, 11.8%); there was no statistical difference between these percentages.

Adherence to the treatment, when assessed by attendance, was satisfactory; 75% of the patients missed none of the visits scheduled at 4-mo intervals, and >15% missed no annual visits. In France, in a subgroup of 239 patients at the 3-yr assessment, arachidonic acid–induced platelet aggregation was inhibited in 13% of the NIT and 9% of the IT patients in the placebo group and in 64–80% of all patients in the treated groups (Table 7). In one center (Hammersmith Hospital, London), adherence was assessed by tablet count. The mean proportion of examinations with a count for

TABLE 9
Ophthalmic characteristics at 3 yr

| | Non-insulin-treated patients ($n$ = 159) | | | Insulin-treated patients ($n$ = 275) | | |
|---|---|---|---|---|---|---|
| | Placebo ($n$ = 52) | Aspirin $n$ = 55) | Aspirin + dipyridamole ($n$ = 52) | Placebo ($n$ = 87) | Aspirin ($n$ = 95) | Aspirin + dipyridamole ($n$ = 93) |
| Visual acuity (6 of 6 or better) | 34 (65) | 41 (75) | 32 (62) | 67 (77) | 70 (74) | 75 (81) |
| Ophthalmoscopy of posterior pole | | | | | | |
| Hard exudates (punctuate, round) | 14 (27) | 15 (27) | 17 (33) | 26 (30) | 21 (22) | 25 (27) |
| Soft exudates (cotton-wool spots) | 4 | 6 | 1 | 7 | 13 | 7 |
| Macular edema | 3 | 5 | 4 | 1 | 4 | 2 |
| Other macular lesions | 2 | 1 | 3 | 2 | 0 | 3 |
| Neovascularization (on disk or elsewhere) | 3 | 0 | 3 | 2 | 3 | 2 |
| Other complications* | 0 | 1 | 0 | 0 | 1 | 0 |

Numbers in parentheses are percentages.
*Fibrosis, detachment of the retina, vitreous hemorrhage.

TABLE 10
Number of definite microaneurysms at entry

| Treatment | Type of diabetes | | |
|---|---|---|---|
| | NIT | IT | Total |
| Placebo | 3.7 ± 5.2 (52) | 8.7 ± 10.8 (94) | 6.9 ± 9.5 (146) |
| Aspirin | 6.5 ± 12.7 (54) | 7.8 ± 12.8 (91) | 7.3 ± 12.7 (145) |
| Aspirin + dipyridamole | 6.7 ± 7.2 (54) | 9.4 ± 11.7 (95) | 8.4 ± 10.3 (149) |
| Total | 5.6 ± 9.0 (160) | 8.6 ± 11.7 (280) | 7.5 ± 10.9 (440) |

Values are means ± SD; number of patients is indicated in parentheses. NIT, non-insulin treated; IT, insulin treated. Results of statistical comparisons are as follows. Treatment versus type of diabetes, $F^2_{434} = 1.00$, NS; NIT versus IT, $F^2_{436} = 7.73$, $2P < .001$; comparability of treatment groups, $F^1_{436} = 0.75$, NS.

each patient per visit was 78 ± 25%, and the mean rate of consumption assessed for each patient was 81 ± 18% (placebo, 76 ± 24%; aspirin, 82 ± 12%; aspirin + dipyridamole, 84 ± 18%; NS).

At entry, the retinopathy status was comparable among the three treatment groups (Table 8). This status varied widely among the groups by the end of the study (Table 9). The number of MAs at entry was not significantly different among the treatment groups, although the number of MAs was significantly higher in the IT group compared with the NIT group (Table 10).

Treatment effect (based on 1664 angiograms and 3436 readings) was similar in IT and NIT patients. The mean yearly progression of definite MAs was less in the treated group (aspirin alone or aspirin + dipyridamole) than in the placebo group (Table 11 $P = .02$). Aspirin appeared to be slightly less effective alone than in combination with dipyridamole in reducing the yearly increase in definite MAs, but the difference did not reach statistical significance (although the increase was reduced by 30–50%). The slope differed significantly from 0 only in the placebo group (placebo, $P = .002$; aspirin, $P = .05$; aspirin + dipyridamole, $P = .09$). The mean number of definite MAs per year and the annual evolution computed succinctly on the means was placebo, 1.11; aspirin, 0.87; aspirin + dipyridamole, 0.15 (Table 12). During the study, the quality of angiograms was similar among the various treatment groups and also in the IT and NIT patients (the results not weighted by quality for definite MAs were placebo, 1.14 ± 3.79; aspirin, 0.71 ± 5.12; aspirin + dipyridamole, 0.18 ± 3.28; $P = .055$, treated vs. placebo). Total MA count (definite and possible MAs) showed a trend similar to that for definite MAs, with a progression of 3.48 ± 10.50 in the placebo group, 2.53 ± 11.83 in the aspirin-treated group, and 1.54 ± 8.49 in the aspirin + dipyridamole group, but the results were not statistically significant.

Table 13 relates the progression of definite MAs and the clinical evaluation of ophthalmoscopy according to treatment. When the condition of patients deteriorated clinically, the annual progression of MAs was 4 times that of patients clinically stable [clinically stable, 0.38 ± 3.96 ($n = 293$); deteriorating, 1.79 ± 4.89 ($n = 127$); $P = .002$]. Treatment effect was the same in the stable and deteriorating patients. The statistical results of treatment were the same as those in Table 11. Even in patients with no clinical deterioration, there is a clear trend in treatment groups. On the basis of clinical signs alone, there was no treatment effect (Tables 8 and 13; $\chi^2 = .05$, NS).

## DISCUSSION

The study results indicate that in a group of 420 patients with early diabetic retinopathy, aspirin alone or in combination with dipyridamole slows the progression of MA formation. The loss of patients from the study was small, only 41 (or 8.6%), and ~2% died. Assessment of adherence to treatment suggests that at least some of the placebo patients were taking aspirin-containing drugs days before assessment, whereas up to 26% of the active treatment group did not take their drugs regularly. Eleven percent of patients taking aspirin-containing drugs in the placebo group is comparable with results reported in other studies (19); noncompliance in the active treatment group, however, is higher. This could indicate that patients with a serious condition, such as myocardial infarction, will tolerate drugs more than asymptomatic patients. Although these results are disappointing in regard to compliance with therapy, they reinforce the hypothesis of the effectiveness of active treatment.

We decided to use only evolution of the number of MAs

TABLE 11
Progression of microaneurysms

| Treatment | Type of diabetes | | |
|---|---|---|---|
| | NIT | IT | Total |
| Placebo | 1.41 ± 3.74 (48) | 1.46 ± 4.88 (85) | 1.44 ± 4.49 (133) |
| Aspirin | 0.75 ± 5.85 (54) | 0.65 ± 4.63 (91) | 0.69 ± 5.09 (145) |
| Aspirin + dipyridamole | 0.37 ± 1.90 (52) | 0.33 ± 3.52 (90) | 0.34 ± 3.01 (142) |
| Total | 0.83 ± 4.19 (154) | 0.80 ± 4.38 (266) | 0.81 ± 4.30 (420) |

Values are means ± SD; number of patients is indicated in parentheses. NIT, non-insulin treated; IT, insulin treated. Results of statistical comparisons are as follows. Treatment versus type of diabetes, $F^2_{414} = 0.01$, NS; NIT versus IT, $F^1_{416} = 0.004$, NS; aspirin versus aspirin + dipyridamole, $F^1_{416} = 0.46$, NS; aspirin and aspirin + dipyridamole versus placebo, $F^1_{416} = 4.21$, $P = .02$.

TABLE 12
Mean annual number of definite microaneurysms

| Examination | Follow-up (mo) | Treatment group | | |
|---|---|---|---|---|
| | | Placebo | Aspirin | Aspirin + dipyridamole |
| 0 | 0–6 | 6.9 ± 9.4 (149) | 8.0 ± 14.4 (148) | 8.4 ± 10.3 (149) |
| 1 | 6–18 | 7.3 ± 9.6 (140) | 8.4 ± 12.8 (147) | 7.7 ± 10.7 (140) |
| 2 | 18–40 | 9.1 ± 13.4 (131) | 7.8 ± 12.6 (138) | 8.9 ± 11.6 (140) |
| 3 | 40–52 | 10.0 ± 15.8 (132) | 11.1 ± 18.7 (135) | 8.5 ± 11.3 (136) |

Values are means ± SD; number of patients is indicated in parentheses.

to assess the efficacy of treatment, because MAs are always associated with occlusion of one or more capillaries (20) and are easily recognized, even on angiograms of moderate quality. In contrast, small areas of capillary occlusion (which should be affected by the drugs used) would only be seen in the immediate perifoveal area and even then, only in the best angiograms. The use of MA counts only is also open to criticism. Although an increase in the number of MAs suggests deterioration of early retinopathy (10), a reduction in number could indicate either improvement when there is capillary remodeling or reperfusion or deterioration when MAs disappear, because the capillaries from which they arise become occluded. We showed the relationship between the deterioration in ophthalmological signs and the progression of MAs. These two evaluations were independent because both the source of information and the evaluator differed; i.e., the ophthalmologist used ophthalmosopy for clinical evaluation, and the technician used the angiogram for MA count. Because of our simple clinical method of assessment, treatment effect was not shown, although MA progression still shows a clear trend between treatments in both the stable and the deteriorating groups. We defined *clinical deterioration* as the development of lesion from absent before treatment to present during treatment. The definition of *stable* included two kinds of patients: those with lesion(s) absent throughout the study and those with the same lesion(s) present throughout the study. But in this subgroup, we did not take account of the increase in severity of sign(s) already present, so deterioration is a more specific criterion than stability, because the stable group included some patients in whom the severity of the lesion increased; thus, it is possible that the progression of MA is inflated. More detailed clinical examination or evaluation of color photographs developed since this study was started (9) could show results comparable with MA count, but we have not collected such data. The method of assessment was thought to be valid because MA count, at least in early diabetic retinopathy, is a good indicator of the overall severity of diabetic retinopathy, and the correlation between replicate readings, as used in this study, shows that it is reproducible. MAs were dichotomized by size into definite and possible. The lower limit in size of ~25 μm still excluded many MAs but ensured the specificity of the method. A similar trend in treatment effect was found in total and definite MAs. Because the total count increases the variability of measurements, the results did not reach statistical significance between the placebo and treated groups.

In a previous study of MA counts, the mean of the MA numbers was used (21). In our study, the slope of evolution (linear regression) was calculated for each patient, a method similar to that used by Job et al. (18). This is a preferred method because it quantifies the evolution separately for each patient (17), and it is the simplest statistical method among those proposed in "The Job Study Revisited" (22). In early retinopathy, the evolution during 3 yr is slow and probably approaches linearity. The slope is at least an indication of the tendency of the MA count to increase, decrease, or remain the same. The change in MA numbers in this study, even in the placebo group, was well below that reported in the Job study (18). Possible reasons for this discrepancy are that the field of reading was smaller (×1.5) in our study (5 disk diameters in the Job study vs. 4 disk diameters in this study), and the reading technique was not stated in the Job study. Despite the slower MA progression, the treatment effect was a reduction of the MA number by 50%. This result was obtained by using a dosage of 1 g of aspirin daily. It is not known, as has been suggested (23–25), whether a smaller dosage would have been more effective. In 1976, when the study was designed, this information was not available. A smaller dosage of aspirin would undoubtedly have resulted in fewer side effects, therefore better compliance, and thus a more marked treatment effect

TABLE 13
Progression of definite microaneurysms relative to ophthalmoscopic observation

| Treatment | Ophthalmoscopic results | | |
|---|---|---|---|
| | Stable | Deteriorating | Total |
| Placebo | 0.73 ± 4.38 (92) | 3.05 ± 4.37 (41) | 1.44 ± 4.49 (133) |
| Aspirin | 0.39 ± 4.64 (101) | 1.36 ± 6.03 (44) | 0.69 ± 5.09 (145) |
| Aspirin + dipyridamole | 0.06 ± 2.59 (100) | 1.03 ± 3.80 (42) | 0.34 ± 3.01 (142) |
| Total | 0.38 ± 3.96 (293) | 1.79 ± 4.89 (127) | 0.81 ± 4.31 (420) |

Values are means ± SD; number of microaneurysms is indicated in parentheses. Results of statistical comparisons are as follows. Treatment versus ophthalmoscopic evaluation, $F^2_{414} = 0.98$, NS; stable versus deteriorating, $F^1_{416} = 9.60$, $2P = .002$; aspirin versus aspirin + dipyridamole, $F^1_{416} = 0.47$, NS; aspirin and aspirin + dipyridamole versus placebo, $F^1_{416} = 4.31$, $P = .019$.

could be expected. We showed that it is possible to see the treatment effect, even when there is no clear clinical evidence of deterioration. Although our results, issued from highly selected patients, are statistically significant, it is difficult to give firm advice concerning aspirin or dipyridamole treatment for retinopathy because of the small clinical difference between placebo and treated groups. However, with other evidence of a beneficial effect of antiplatelet agents in diabetic patients with macrovascular disease (26), these results are an additional argument for the use of such drugs.

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