The Treatment of Cerebrovascular Disease With Clofibrate

FINAL REPORT OF THE VETERANS ADMINISTRATION COOPERATIVE STUDY OF ATHEROSCLEROSIS, NEUROLOGY SECTION

BY THE VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP

Abstract: The Treatment of Cerebrovascular Disease With Clofibrate

A cooperative study in 20 Veterans Administration hospitals investigated the effect of clofibrate on morbidity and mortality due to atherosclerotic vascular disease in men with either an established cerebral infarction or transient cerebrovascular ischemic attacks (TIA). Follow-up observations were made for up to 4.5 years in 532 patients assigned on a random basis to placebo medication or to treatment with 2 gm of clofibrate daily. Baseline and follow-up cholesterol and triglyceride levels were measured.

Recurrence of cerebral infarction was increased in patients receiving clofibrate as compared to controls. The incidence of new myocardial infarction and new TIA was similar in both groups. Despite the more frequent strokes in treated patients, they had a decrease in mortality, partially explained by a lower death rate from these recurrences. There was no correlation between pretreatment lipid (cholesterol and triglyceride) values and the result of therapy. Use of clofibrate, however, was associated with a slight reduction of cholesterol and a sustained fall in triglyceride.

These findings do not support recently published reports that clofibrate reduces the occurrence of myocardial ischemia; however, the investigative design and type of data collected in these various studies are different and make it difficult to compare results.

Additional Key Words: atherosclerosis, myocardial infarction, lipids, lipid reduction, collaborative investigation, stroke, stroke mortality

Elevated blood lipids are believed to be important in the pathogenesis of atherosclerosis. Levels of cholesterol, triglyceride and other fat fractions frequently are high in patients with certain forms of occlusive vascular disease. However, information still is inconclusive as to whether the course of such disorders can be influenced favorably by reducing the serum level of these substances. Until recently, the lack of a safe and effective lipid-lowering agent has prevented study of this problem.

Extensive experience since 1962 with ethyl-p-chlorophenoxysobutyrate (clofibrate) indicates that within two to three weeks after starting treatment this drug significantly depresses cholesterol, triglycerides, lipoproteins, phospholipids and postprandial lipemia. Clinical trials on several thousand patients have shown clofibrate to be well tolerated and without significant toxicity; side effects were noted in relatively few patients and included transient SGOT elevations, weight gain, nausea and muscle pain. The mechanism by which this agent acts on lipid metabolism remains unknown. Interruption in the early stages of hepatic cholesterol synthesis has been proposed. The drug alters coagulation through complex and as yet not completely understood methods, among which are reduced platelet adhesiveness, enhanced fibrinolysis and diminished fibrinogen activity. When clofibrate is given simultaneously with anticoagulants, doses of the latter must be reduced.

Most investigations to date have reported the effects of clofibrate on lipid fractions in normal persons or in those with coronary atherosclerosis. Recently, however, several papers have been published which indicate that clofibrate is clinically beneficial in patients with ischemic heart disease.
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In addition, the drug has been claimed to improve cutaneous xanthomata,18 diabetic retinopathy,19 and lipemia retinalis.20 A seven-month clinical trial of clofibrate in patients with cerebrovascular disease suggested that its use reduced the incidence of both transient ischemic attacks (TIA) and recurrent cerebral infarction.21 No other studies using clofibrate in the management of cerebral atherosclerosis have been published.

This paper will report a controlled investigation of clofibrate administration in male veterans with established occlusive disease of the cerebral arteries. The objective was to determine whether this drug reduced subsequent morbidity and mortality. In addition, data were obtained concerning the effect of clofibrate on cholesterol and triglyceride levels.

Methods
A detailed protocol, carefully outlining case selection methods, randomization and treatment, was developed by the participants in cooperation with statisticians from the Veterans Administration Central Office and the National Research Council of the National Academy of Sciences. Only male veterans with one or more cerebral infarctions or TIA were eligible. An interval of less than 12 months was required between the onset of the qualifying event and entrance into the study.

Rigid clinical and laboratory criteria were established to eliminate patients with cerebral embolism or hemorrhage and those with brain tumors. Additional reasons for exclusion included major medical disorders, such as accelerated hypertension, severe diabetes, cancer, serious nonvascular neurological conditions, dementia and personality disturbances. Individuals residing beyond a reasonable traveling distance from the participating hospital were not randomized.

The principal investigator in each institution carefully examined every prospective candidate. Therapy was not initiated until one month after discharge, at which time patients were assigned by a prearranged random procedure to treatment and control regimens. Prior to randomization, blood was collected for three baseline lipid determinations. Identical capsules containing either 500 mg of clofibrate or a placebo (lactose) were given four times daily. Follow-up observations were made monthly for three months, then at two-month intervals until one year had elapsed, and thereafter every three months. At each return visit, patients were evaluated, without knowledge of whether they were receiving clofibrate, both for possible episodes of vascular disease and for side effects. A physical examination was performed and uric acid levels, SGOT, hematocrit and white blood count were done. In addition, blood was sent to the Cooperative Lipid Laboratory at the Veterans Administration Hospital, Durham, North Carolina, for cholesterol and triglyceride measurements. Electrocardiograms were obtained once a year. Initial and subsequent findings were recorded on special forms, all of which were reviewed by the Chairman for accuracy and completeness. All fatalities and recurrent vascular events were analyzed by a special committee. Considerable effort was made to determine the cause of death in each patient.

Analysis
Between July 8, 1966, and October 1, 1970, 541 patients were randomized by 20 participating Veterans Administration Hospitals. Nine of these patients were excluded from all follow-up; eight were randomized by a hospital not continuing in the study, and one was ineligible because of a concurrent malignancy. Therefore, the final report is based on 532 patients. Approximately 5,300 individuals were evaluated for possible inclusion in the study, but only 10% were randomized. The majority (more than 70%) were rejected as too old (over 70 years of age), or because of significantly impaired health. Clofibrate was given to 268 patients, and 264 patients were placed on the placebo medication.

During the entire study, 127 patients were lost to follow-up, but their data were included in the analysis to the point of drop-out. Of these, 70 were on clofibrate and 57 received the placebo. Information on a patient was not included if he did not take the assigned drug for two months or longer. The majority of such cases (60) resulted from irregular attendance or failure to return. In 34 instances, information was not compiled because the investigators at three participating hospitals could no longer follow their patients. A small number of individuals were removed from treatment because they had an intercurrent illness, cooperated poorly, or moved from the area (table 1).

The major clinical characteristics of the control and treatment categories are seen in table 2. Some differences are noticeable. The control group had slightly higher percentages of patients who were nonwhite, over 60 years of age, and with strokes in the vertebral-basilar circulation. Hypertension (defined as a blood pressure recording above 160 systolic and/or 95 diastolic either before randomization or within the first month of observation) was found in 69% of control patients and in 60% of those receiving clofibrate. The two groups were almost comparable as to the existence of diabetes.

<table>
<thead>
<tr>
<th>Event</th>
<th>Clofibrate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct</td>
<td>Ischemia</td>
<td>Infarct</td>
</tr>
<tr>
<td>Randomized</td>
<td>244</td>
<td>28</td>
</tr>
<tr>
<td>Excluded</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Dropped</td>
<td>51</td>
<td>10</td>
</tr>
<tr>
<td>Died</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>Alive (3/31/71)</td>
<td>166</td>
<td>15</td>
</tr>
</tbody>
</table>

TABLE 1
Status of All Patients as of March 31, 1971, by Qualifying Event, by Regimen
and the previous occurrence of cerebral infarction and TIA. There were more treated than control patients with abnormal electrocardiograms, previous myocardial infarction and greater degrees of disability. The qualifying cerebral infarction occurred approximately four months prior to the date of randomization in both the treated and control cases.

The Effects of Treatment on Mortality

Table 3 shows that there were 30 deaths in patients taking the placebo and only 22 deaths among those receiving clofibrate. There were 476 man-years of follow-up in the placebo group and 489 man-years of follow-up in treated cases. The average duration of observation was 21.6 months in the former category and 21.9 months in the latter. Average annual mortality per 1,000, therefore, was 63 and 45 deaths, respectively. When patients who qualified because of TIA were evaluated separately, the average annual mortality was 109 for placebo and 44 for patients given clofibrate, but these figures were based on only 47 cases.

The leading cause of death was proved or presumed heart disease (23 cases); of these, seven were due to myocardial infarction and 16 were labeled as sudden death (table 3). The latter diagnosis was based on a carefully confirmed history of the patient’s abrupt demise. A smaller number (12) died either of cerebral infarction or of its complications, a designation used when death after the event was delayed by 30 or more days. These results showed no significant differences between placebo and treated groups, indicating that the use of clofibrate did not affect the total number of patients who died from myocardial or cerebrovascular occlusive disease. The category of death entitled “all other vascular diseases” included cerebral hemorrhage, heart failure and ruptured abdominal aneurysm; all three clofibrate-treated patients in this group died of heart failure, whereas the three deaths from abdominal aneurysm occurred in those on placebo. Extraneous causes of death were due to nonvascular etiologies and included cancer, suicide, complications of surgery, pneumonia and one that was unexplained; again, the placebo and control groups were similar. In the placebo group 24 of the 30 deaths were secondary to vascular disease, and 19 of the 22 patients on clofibrate who died also were in the same category.

Deaths among patients dropped from observation were not included in table 3; 25 persons died after follow-up had been terminated, and of these, 13 were on placebo and 12 had received clofibrate. Unfortunately, not all causes of these deaths are known, but six in the placebo group and only two of those who had received clofibrate are known to have died from vascular disease.

The Effects of Treatment on Vascular Morbidity

During follow-up, there were 37 recurrent cerebral infarctions in patients receiving clofibrate, whereas only 23 occurred in those on placebo (table 4).
number of TIA, myocardial infarctions or episodes of angina were the same regardless of regimen. Excluding the categories just mentioned, there were 28 events of vascular disease (congestive heart failure, claudication, thrombophlebitis, pulmonary embolism and onset of hypertension) in 26 patients on placebo and 47 such episodes in 44 individuals receiving clofibrate (table 5). The major differences between the placebo and treatment groups were in congestive heart failure (four versus 15, respectively) and in hypertension (eight versus 15); on the other hand, claudication and thrombophlebitis occurred more often in the controls (nine versus five for the former condition and four versus one for the latter). During the first year of follow-up, only two patients on placebo and seven taking clofibrate had new EKG abnormalities. In the 47 patients who qualified originally for randomization because of TIA, seven of the 20 on placebo and 17 of the 27 receiving clofibrate had some type of recurrent event. Cerebral infarction occurred in five of the TIA patients given clofibrate and in none of those on placebo. Two of the patients on drug and one on placebo who qualified for the study with TIA had a subsequent myocardial infarction.

Toxic Effects

There were very few toxic events. The total number of reported side effects was 28 in the placebo group and 23 in the clofibrate group. The major category was gastrointestinal, with 11 such episodes (mainly nausea and/or vomiting) in placebo patients and 14 in drug-treated patients. Among possible "drug reactions" was a small number of miscellaneous complaints, none predominant in either group and therefore not meriting further attention. A white blood count, hematocrit, SGOT and uric acid were obtained at each follow-up visit. No significant changes were found, other than a few persons with increased SGOT; which occurred in random fashion equally among patients on clofibrate and placebo; in some cases the investigator determined that these elevations followed bouts of acute alcohol ingestion. There was a weight gain during observation in both groups, averaging 1 lb in patients on placebo and 2 lb in those receiving clofibrate. The change was consistent throughout the study and was progressive in men on clofibrate through the first 18 months of follow-up. However, there was no correlation between maximum weight changes and the occurrence of vascular events in either group.

Life Table Analyses

Table 6 provides the life table analyses of all patients entering the study following cerebral infarction, using death from any cause as the end point. The cumulative mortality at 3.5 years (1,081 days or more after randomization) in patients on placebo was 19%, while mortality in the group receiving clofibrate was 13%. This difference is not statistically significant, although it appeared to be widening as the duration of observation increased. To further examine this difference, the patients were subdivided by age, and separate life table analyses were prepared for those under 55 years of age and those 55 years and older. The cumulative mortality curves in figure 1 show that for both age groups mortality generally was less in the drug-treated than in the placebo-treated patients. Surprisingly, the older men appeared to benefit more from clofibrate than did the younger individuals.

Life table analyses using as an end point the first occurrences of either myocardial or cerebral infarction or death from vascular disease are shown in figure 2. In these analyses, the advantage from clofibrate is present only in patients over 55 years of age. This difference is reversed for those under 55 years of age. In older patients, one or more of these events occurred in 49% of the control group, whereas only 32% of treated patients had similar

### Table 5

**Cardiovascular Disease Other Than Myocardial Infarction and Angina During Active Follow-Up, by Regimen**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Clofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive failure</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Claudication</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Total events</td>
<td>28</td>
<td>47</td>
</tr>
<tr>
<td>Total patients</td>
<td>26</td>
<td>44</td>
</tr>
</tbody>
</table>

**TABLE 5**

**Summary of Life Table Analysis for All Patients Whose Qualifying Event Was a Cerebral Infarction (End Point Death From any Cause), by Regimen**

<table>
<thead>
<tr>
<th>Period after randomization (days)</th>
<th>Under observation beginning of period</th>
<th>Proportion alive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Clofibrate</td>
</tr>
<tr>
<td>1 to 180</td>
<td>244</td>
<td>241</td>
</tr>
<tr>
<td>181 to 360</td>
<td>222</td>
<td>216</td>
</tr>
<tr>
<td>361 to 540</td>
<td>154</td>
<td>171</td>
</tr>
<tr>
<td>541 to 720</td>
<td>134</td>
<td>128</td>
</tr>
<tr>
<td>721 to 900</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>901 to 1,080</td>
<td>71</td>
<td>74</td>
</tr>
<tr>
<td>1,081 to 1,260</td>
<td>54</td>
<td>55</td>
</tr>
<tr>
<td>Total end points*</td>
<td>Placebo 24, Clofibrate 20</td>
<td></td>
</tr>
</tbody>
</table>

*These end points are only for patients whose qualifying event was a cerebral infarction and whose death occurred within 1,260 days (three more placebo patients died at 1,393, 1,437 and 1,459 days, respectively). Table 3 shows end points in all patients randomized.
problems. Figure 2 suggests that the benefit from clofibrate on mortality in young men is not due to a reduction in the incidence or recurrence of major vascular events, but results from a lower fatality after they occurred. To clarify this possibility, the fatality after attacks of vascular disease in the two age groups is summarized in table 7. This table shows that only 16% of drug-treated patients under 55 years of age died after a vascular event, while 32% of those on placebo died. No such differences were present in the older subjects.

Patients also were subdivided according to their initial baseline cholesterol levels of above and below 250 mg %, and triglyceride values above and below 160 mg %. Life tables were prepared, using as an end point the first recurrent cerebral infarction, myocardial infarction or death. Among those with low cholesterol, there was a 9% difference in such end points favoring the placebo group at 3.5 years. There was no disparity between categories when the baseline cholesterol was 250 mg % or higher. In patients with triglyceride values below 160 mg %, those receiving clofibrate were slightly favored over controls. However, among the various analyses, the most striking difference was observed when the baseline triglycerides were high. A major episode or death during follow-up occurred in 40% of patients with elevated triglyceride baseline levels receiving clofibrate, whereas only 17% of control cases had similar events. The largest number of attacks in this group were cerebral infarctions, with five among placebo patients and eight among those treated with clofibrate. Only two of those on clofibrate and none on placebo died. The significance of these figures is reduced by the fact that relatively few patients were involved.

Using the same compound end point, either death or myocardial or cerebral infarction, life tables were prepared to compare treated and control patients among those who were hypertensive or normotensive, diabetic or nondiabetic, with a previous cerebral or myocardial infarction or not, or

<p>| TABLE 7 |
|-------------------|-------------------|
| Fatality of Major Vascular Events (M.I. or C.I.), by Regimen, by Age |</p>
<table>
<thead>
<tr>
<th>No. of patients with event</th>
<th>Vascular deaths*</th>
<th>Other deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNDER 55</td>
<td>Placebo</td>
<td>15</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>55 AND OVER</td>
<td>Placebo</td>
<td>26</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>17</td>
<td>7</td>
</tr>
</tbody>
</table>

*Deaths included herein are only due to acute vascular disease and not all other causes, such as complications of vascular events.

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End point rates. LEFT SIDE: End point = death from any cause for patients who were under 55 years of age at randomization and whose qualifying event was a cerebral infarction. RIGHT SIDE: End point = death from any cause for patients who were ages 55 or over at randomization and whose qualifying event was a cerebral infarction.
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End point rates. LEFT SIDE: End point = cerebral infarction, myocardial infarction, angina or vascular death for patients who were under 55 years of age at randomization and whose qualifying event was a cerebral infarction. RIGHT SIDE: End point = cerebral infarction, myocardial infarction, angina or vascular death for patients who were age 55 or over at randomization and whose qualifying event was a cerebral infarction.

depending upon the degree of disability at randomization. Small differences were apparent, but there were no significant variations in any of these categories between control and treated patients.

**Lipid Values**
Prior to randomization, three blood specimens were obtained from most patients and used in determining baseline lipid levels (cholesterol and triglyceride). Cholesterol values were measured on three or more specimens in 190 men given placebo and in 194 patients treated with clofibrate. A few individuals in each group had baseline values obtained from either one or two samples. The mean cholesterol level in all sera obtained prior to treatment was 241 mg % in the placebo group and 242 mg % in those receiving clofibrate. The mean triglyceride level in 210 men on placebo was 162 mg %, and it was 174 mg % in 221 receiving clofibrate. Table 8 gives the number of cholesterol determinations made during follow-up, their average value, and the ratios of follow-up to baseline levels. In the placebo group, average cholesterol results were stable during follow-up. However, in the clofibrate-treated patients, there was a large initial average drop, but thereafter the values gradually increased to those present before treatment.

Table 9 shows comparable triglyceride data, demonstrating that once again placebo group

![Graph showing end point rates](image)

**TABLE 8**

<table>
<thead>
<tr>
<th>Period after randomization (months)</th>
<th>Number of observations</th>
<th>Average value</th>
<th>Average ratio of current to base determination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Clofibrate</td>
<td>Placebo</td>
</tr>
<tr>
<td>1 – 6</td>
<td>894</td>
<td>875</td>
<td>239.6</td>
</tr>
<tr>
<td>7 – 12</td>
<td>475</td>
<td>485</td>
<td>238.8</td>
</tr>
<tr>
<td>13 – 18</td>
<td>283</td>
<td>327</td>
<td>243.5</td>
</tr>
<tr>
<td>19 – 24</td>
<td>233</td>
<td>235</td>
<td>241.2</td>
</tr>
<tr>
<td>25 – 30</td>
<td>160</td>
<td>158</td>
<td>239.3</td>
</tr>
<tr>
<td>31 – 36</td>
<td>111</td>
<td>121</td>
<td>234.4</td>
</tr>
</tbody>
</table>
averages were stable during observation. However, in patients on clofibrate there was a large fall in triglyceride within the first month after initiating treatment, and these average levels did not return to prerandomization figures during the entire follow-up period. The effect of clofibrate on triglycerides was consistently more pronounced and enduring than on cholesterol.

**Patients with Transient Cerebrovascular Ischemic Attacks (TIA)**

There were 21 patients with TIA who were randomized to the placebo group and 28 to clofibrate. Although small, these numbers require special attention. Five patients died while under observation; three deaths occurred on placebo, of which two were due to myocardial infarction while one was of unknown etiology. The cause of death in the two clofibrate-treated TIA patients was a new stroke. There were four placebo-treated patients with recurrent TIA and one reported a new anginal episode during follow-up. Among treated patients, two had myocardial infarction and four experienced recurrent TIA. Thus, the difference between the treated and control groups in mortality (109 deaths per 1,000 man-years of observation in those on placebo as compared to 44 deaths per 1,000 man-years of observation in the treated men) cannot be attributed to prevention of vascular disease, but may be due to the possibility that clofibrate ameliorates the severity of such episodes.

**Discussion**

There has been an expectation that mortality and morbidity due to atherosclerotic vascular disease can be reduced by decreasing serum lipid values. The advent of clofibrate, a relatively effective and safe lipid-lowering agent, has allowed this hypothesis to be tested without dietary manipulations. Recently, several studies have reported the use of this agent in ischemic heart disease.14-17 The combined data from two British trials14-16 showed that death from myocardial infarction during periods of from five to six years occurred in 79 (13%) of 620 patients receiving placebo and in 59 (10%) of 594 cases on clofibrate. Although these results were not striking, there were some interesting findings in the analyses of certain subgroups. A significant reduction in mortality, especially from sudden deaths and total vascular events, occurred when clofibrate was given to patients who entered the study because of angina; individuals randomized following a myocardial infarction without associated angina received less protection from medication. There also was a reduction in the incidence of nonfatal myocardial infarctions, which was more pronounced in subjects with previous angina. The authors postulated that clofibrate was most beneficial in patients with continuous myocardial ischemia because the drug possibly prevented dysrhythmic sudden deaths. In addition, protection by clofibrate was greater in smokers than nonsmokers, perhaps due to the increased frequency of disturbed heart rhythms in the former group. The results in the treated cases were not related to changes in serum lipids and occurred regardless of whether the initial serum cholesterol was high or low. These findings could not be explained by the investigators,16 although they thought that the effect was mediated through some mechanism other than the lipid-reducing properties of the drug.

Another recently published clinical trial of clofibrate in ischemic heart disease also reported definite benefit from treatment.17 The previous investigations14-16 resembled ours in that subjects had to have experienced some type of vascular disease (angina and/or myocardial infarction). The latter study, however, involved mostly individuals without any evidence of ischemic heart disease. In addition, the study design differed radically from this or the British investigations, since neither selection by randomization nor double-blind evaluation was employed, and the patients were younger. The incidence of nonfatal myocardial infarction was reduced significantly by clofibrate, but the medication had no effect on mortality during periods of observation varying from 32 to 39 months. Of
interest in this prospective study was the virtual absence of coronary artery disease in patients who had initially normal lipid levels, whereas this condition appeared frequently in those with elevated lipids if they were not given clofibrate. However, as in the previously described series, treatment significantly reduced morbidity from myocardial ischemia, even in patients with persisting hyperlipidemia.

The authors of the above reports concluded that the favorable results of clofibrate on morbidity and mortality from coronary artery disease probably are not due to its action on lipid metabolism, but instead are either the consequence of altered coagulation or as yet unknown mechanisms. Clofibrate presumably affects blood clotting by diminishing platelet adhesiveness. The drug also increases fibrinolysin, diminishes fibrinogen and changes the permeability of endothelial intimal cells. The action of clofibrate on blood platelets is difficult to measure, and no attempt to evaluate this or other hematological parameters was made in our study. In addition, the benefits of clofibrate from whatever means may occur only in cardiac and not cerebrovascular disease, although the present study does not provide data supporting such a concept.

This paper reports the use of clofibrate in male veterans with demonstrated cerebral infarction. Particular attention has been given to the effects of this medication on morbidity from vascular disease during follow-up, on mortality, and on cholesterol and triglyceride levels. Our results paralleled those noted in patients with ischemic heart disease as regards the sustained reduction in triglycerides, but differed insofar as there was a less persistent lowering of cholesterol. There was a reduced overall rate of death from all causes. The cumulative mortality at 3.5 years was 13% in patients receiving clofibrate, and 19% in those on placebo, and the difference, although not significant, appeared to be widening with the duration of follow-up. The only specific cause of death for which treated patients were at a disadvantage was congestive heart failure, a result possibly of fluid retention caused by clofibrate. In support of this hypothesis is the fact that our patients on the drug had a consistently higher weight gain than did controls.

Clofibrate did not reduce the number of myocardial infarctions during the period of observation. Since blood lipid alterations seem related more closely to coronary artery disease than to stroke, it was hoped that medication would reduce morbidity from the former cause, an expectation which was not realized in our cases. In regard to the reported favorable results from clofibrate in patients with previous angina, there were so few persons in our study who had this condition prior to randomization that a meaningful comparison is not possible. Our data relating to the outcome in men who had angina and/or myocardial infarction before entering the study appear in tables 10 and 11, but no real trends are evident. There was no reduction in the occurrence of sudden deaths as the British had found. Information on tobacco use in our patients was insufficient so we cannot comment on the possible benefits of clofibrate in smokers. As already mentioned, the study in which clofibrate reduced subsequent morbidity cannot be compared with this and other trials. Even though a significant decrease in serum triglycerides was obtained in our treatment group, the number of new myocardial infarctions was not reduced in these patients. This finding is not surprising in view of reports that no significant relation existed between changes in serum lipids and the results of clofibrate therapy.

Not only did clofibrate fail in preventing myocardial infarction, patients receiving the drug had a substantially greater number of recurrent occlusive strokes than did those on placebo. No effort was made in this or the other studies to treat

### Table 10

<table>
<thead>
<tr>
<th>Recurrent Vascular Events in Men Randomized With Prior Angina and/or Myocardial Infarction</th>
<th>All patients</th>
<th>Patients with prior angina</th>
<th>Patients with prior myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Clofibrate</td>
<td>Placebo</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>23</td>
<td>37*</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9</td>
<td>8</td>
<td>2 (2)</td>
</tr>
<tr>
<td>TIA only</td>
<td>19</td>
<td>20</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Angina only</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>No events</td>
<td>209</td>
<td>200</td>
<td>11 (1)</td>
</tr>
<tr>
<td>Total patients</td>
<td>264</td>
<td>268</td>
<td>17 (4)</td>
</tr>
<tr>
<td>% with cerebral infarction</td>
<td>12.12</td>
<td>16.80</td>
<td>11.77</td>
</tr>
<tr>
<td>or myocardial infarction</td>
<td>20.83</td>
<td>25.37</td>
<td>35.30</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate patients who had both prior angina and myocardial infarction.

*One man also had a myocardial infarction.
only men with elevated serum lipids, although initially one might have expected that benefits from a lipid-lowering agent would be most apparent in such a group. Therefore, it was interesting to note, in agreement with the previous investigations, \(^{14-17}\) that when our results were analyzed according to whether the baseline cholesterol or triglyceride was high or low, clofibrate did not improve the outcome in patients who had initially increased values of either substance. In fact, those with high triglyceride levels who were on clofibrate had a greater number of end points (death or recurrent vascular events) than did the placebo-treated group.

Regarding patients who entered this study with TIA, there were too few cases for satisfactory analysis. However, the trends in this group paralleled those of the entire patient population with a failure to reduce recurrent vascular events but with an unexplained lowering in mortality. If TIAs are due to acute small embolic episodes (perhaps from an ulcerated plaque), as postulated by some, then reduced platelet adhesiveness might have been expected to decrease the number of episodes. This effect was not apparent in our patients.

The recently reported clinical trials of clofibrate showed reductions in both morbidity and mortality from ischemic heart disease in patients with pre-existing angina \(^{14-16}\) and a lowered occurrence of this disease in asymptomatic men with initial hyperlipidemia; \(^{17}\) in all of these studies the results were independent of the effects on blood lipid levels. In contrast, our investigation revealed no effects from the drug on morbidity due to coronary or cerebral vascular disease and, although use of clofibrate consistently but not significantly decreased mortality, again without regard for alterations in lipid, the latter result was not clearly explained. Possibly, as suggested by the heart disease studies, clofibrate is most effective under special circumstances such as in the presence of angina, in asymptomatic young men with elevated blood lipids or only after long periods of administration. Our patients under 50 did not have results regarding ischemic heart disease substantially different from the older group, but the duration of treatment in either category may not have been sufficiently long. The previously published studies on myocardial ischemia made no mention of cerebrovascular disease and presumably no such episodes occurred; hopefully, further clinical investigations with clofibrate may yield additional data on TIA and cerebral infarction.

The problem of cerebrovascular disease is extremely complex. The etiology is not understood and it is difficult to evaluate the role of various factors in this process. The importance of treating hypertension in reducing the subsequent occurrence of cerebral infarction has been established already, \(^{23}\) but the method by which elevated blood pressures accelerate the occurrence of stroke is not understood. More effective answers as to the possible benefits of lipid and blood pressure reduction as well as the effects of changes in coagulation mechanisms on the morbidity and mortality of cerebrovascular disorders may be achieved by long-term prospective studies in patients without overt manifestations of atherosclerotic disease in the cerebral circulation.

**Participants**

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**TABLE 11**

<table>
<thead>
<tr>
<th>Causes of Death (not including death after drop)</th>
<th>All patients</th>
<th>Patients with prior angina</th>
<th>Patients with prior myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral infarction</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Complications of stroke</td>
<td>4*</td>
<td>3</td>
<td>1†</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8</td>
<td>3</td>
<td>1†</td>
</tr>
<tr>
<td>Sudden death (vascular)</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other death (vascular)</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Extraneous</td>
<td>6</td>
<td>3</td>
<td>2†</td>
</tr>
<tr>
<td>Total deaths</td>
<td>30</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Total patients</td>
<td>264</td>
<td>268</td>
<td>41</td>
</tr>
<tr>
<td>% of deaths</td>
<td>11.36</td>
<td>8.21</td>
<td>19.51</td>
</tr>
</tbody>
</table>

*Includes one death from cerebral hemorrhage.
†Duplication—patient had both prior angina and myocardial infarction.
TREATMENT OF CVD WITH CLOFIBRATE


Participating Veterans Administration Hospitals: Albany, New York; Albuquerque, New Mexico; Allen Park, Michigan; Ann Arbor, Michigan; Atlanta, Georgia; Boston, Massachusetts; Bronx, New York; Brooklyn, New York; Durham, North Carolina; East Orange, New Jersey; Houston, Texas; Long Beach, California; Los Angeles, California; Louisville, Kentucky; Miami, Florida; Minneapolis, Minnesota; San Francisco, California; Wadsworth, Kansas; and Wood, Wisconsin.

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THE VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP

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