Long-Term Effects of Clofibrate (Atromid-S) on Serum Lipids in Man

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SUMMARY
Clofibrate was administered to 45 patients for varying periods of time up to 4 years with no evidence of chronic toxicity. Clofibrate was more effective in lowering serum triglycerides than serum cholesterol, with more than 75% of all patients with elevated triglycerides having at least a 25% reduction in triglycerides, the absolute reduction in triglycerides being directly correlated with pretreatment values. A reduction in serum cholesterol of 15% or more was obtained in 50% of all patients, those individuals with elevations of triglycerides having the greatest reduction in serum cholesterol as well as being most likely to respond.

Additional Indexing Words:
Hyperlipidemia therapy

In 1962, in association with Thorp's experimental observations, Oliver reported that a combination of ethyl-p-chlorophenoxyisobutyrate and androsterone reduced serum cholesterol and triglycerides in men with ischemic heart disease. These findings were subsequently confirmed by others, although later studies have shown that ethyl-p-chlorophenoxyisobutyrate (clofibrate), without androsterone, is equally effective in lowering serum cholesterol and triglycerides in man. With the exception of reports of Berkowitz and Oliver, the duration of therapy in the majority of the reported studies documenting the efficacy of clofibrate in lowering serum cholesterol and triglycerides has been 1 year or less, and the number of patients followed by individual investigators has been small. The purpose of the present communication is to present our experience with clofibrate in 45 patients, some of whom have been on continuous therapy 4 or more years, and to emphasize the type of patient most likely to have a lowering of serum lipids from clofibrate administration.

Methods
After a thorough discussion of the purpose and procedures of this investigation, 28 male and 17 female patient volunteers, ranging in age from 27 to 65 years, with persistent elevations of serum cholesterol (>250 mg/100 ml) or glyceride glycerol* (>15 mg/100 ml), were selected for further study. Patients with secondary causes of hyperlipidemia were excluded except for those with well-controlled diabetes. Patients with gross chylomicronemia are part of a separate investigation and are not included in this study. Those individuals who were not on appropriate dietary therapy were instructed on restriction of calories.

*Since glycerol comprises approximately 10 to 11% of the majority of the naturally occurring triglycerides, multiplying the glyceride glycerol by 10 will convert this value to milligrams of triglyceride.
cholesterol, or carbohydrate and changes in the ratio of unsaturated to saturated fatty acids. Dietary therapy was continued throughout the study, and patients with recent dietary changes were not entered into the control period of observation for this study until their weight was stable and any serum lipid changes stabilized.

The 35 patients in the crossover study were randomly assigned to placebo-clofibrate or clofibrate-placebo sequence, each treatment period with clofibrate and placebo being of 6 weeks’ duration. Following completion of the crossover study, all patients were given clofibrate and an additional 10 patients were entered into the long-term study without participating in the crossover study. Patients were seen at bi-weekly intervals during a control period of at least 6 weeks and during the crossover study and then at intervals of 4 to 6 weeks thereafter. Blood for lipid analyses was obtained at each clinic visit after an overnight fast with serum cholesterol being determined by the ferric chloride method utilizing the auto-analyzer and glyceride glycerol by the method of Azarnoff. Periodic 24-hr collections of urine were obtained from all patients and assayed for clofibrate to assess reliability of clofibrate ingestion. All patients received approximately 25 mg/kg of clofibrate daily in four divided oral doses while placebo medication consisted of identical appearing capsules containing corn oil. The Wilcoxon’s signed rank test for matched pairs was used for statistical analyses with each patient’s values for a specific treatment period compared to the control or placebo values as indicated in the “Results.”

Results

Crossover Study

The effect of clofibrate on the serum cholesterol and glyceride glycerol of the 35 patients in the crossover study is illustrated in figure 1. For each 6-week period of treatment with either placebo or clofibrate, the serum cholesterol represents the mean of each bi-weekly determination while the control cholesterol represents the mean of three or more bi-weekly determinations obtained just prior to beginning this study. For the 20 patients in the placebo-clofibrate sequence (A), the mean serum cholesterol values of 306 and 297 mg/100 ml for the control and placebo periods, respectively, were not significantly different ($P > 0.1$); the mean serum cholesterol of 265 mg/100 ml during the clofibrate period was significantly lower than the mean during the placebo period ($P < 0.01$). For the 15 patients in the clofibrate-placebo sequence (B), the mean serum cholesterol of 248 mg/100 ml during the clofibrate period was significantly lower than the mean of 317 mg/100 ml for the control period ($P < 0.01$), while the mean serum cholesterol of 279 mg/100 ml during the placebo period was significantly higher than the clofibrate treatment period ($P < 0.02$). The placebo values had not returned to the control level, suggesting that the effect of clofibrate had persisted into the placebo period since no significant difference in cholesterol values was noted between control and placebo period in the placebo-clofibrate sequence. Many patients who

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*The clofibrate used in this study was generously supplied by Dr. Jerome Noble of Ayerst Laboratories.
switched from clofibrate to placebo had little or no change in their serum cholesterol values after 2 weeks, but later demonstrated an increase. After the crossover study was completed, all patients were placed on clofibrate and the mean serum cholesterol of 245 mg/100 ml for the first 3 months of treatment with clofibrate was significantly lower than the mean value of 279 mg/100 ml for the placebo period in the 15 patients in the B sequence (P < 0.01).

In the A sequence the mean serum glyceride glycerol of 32.3 and 29.7 mg/100 ml for the control and placebo periods, respectively, was not significantly different (P > 0.10), but the mean of 17.9 mg/100 ml for the clofibrate period was significantly lower than the placebo period (P < 0.02). In the B sequence, the mean glyceride glycerol value of 24.3 mg/100 ml for the clofibrate period was significantly lower than the mean control period value of 45.3 mg/100 ml (P < 0.01) and the mean value of 33.4 mg/100 ml for the placebo period was significantly higher than the clofibrate period (P < 0.01). The mean glyceride glycerol values for the placebo period in the 15 patients in the B sequence were also compared with the mean of 22.0 mg/100 ml for their subsequent 3 months of clofibrate, and significant lowering with clofibrate was again noted (P < 0.05). No significant weight changes occurred during the crossover study. This type of experimental design also minimizes the influence of weight or dietary changes should they occur, and thus further validates the drug as the factor responsible for the reduction in serum lipids.

**Long-Term Effects**

The long-term effects of clofibrate on the serum cholesterol and triglycerides are summarized in tables 1 and 2. The data are derived from the 35 patients in the crossover study with the zero time for this group being completion of the crossover study and from 10 other patients who were entered into this study after completion of control period only. All values are compared to the control period because of persistence of the effect of clofibrate into the placebo period. The decreasing number of patients in the longer treatment periods is primarily the result of the patients being entered into the study at different times. Also, two patients died and three moved from the vicinity during the early phases of the study.

The effect of clofibrate on the mean serum cholesterol calculated from all absolute values obtained during each 3-month period is illustrated in table 1. A significant reduction in serum cholesterol followed during clofibrate administration for the first 12 months of treatment whether the change was calculated as an absolute value or percentage for each patient. Thereafter, the reduction was not statistically significant, although the percentage of patients with a reduction of 15% or more in concentration of serum cholesterol was reasonably stable throughout the study. The effect of clofibrate on the mean serum triglycerides for each treatment period is illustrated in table 2. A significant and persistent reduction in serum triglycerides was noted throughout the study and 75 to 80% of all patients with elevated triglycerides had at least a 25% reduction following clofibrate administration.

The correlation between the individual mean control serum glyceride glycerol values and the individual mean absolute change in glyceride glycerol for the 38 patients completing 6 months of treatment with clofibrate is plotted in figure 2. The magnitude of reduction following clofibrate is closely correlated with the control glyceride glycerol value (r = 0.870). The one patient with a mean control glyceride glycerol of 98 mg/100 ml having a reduction of only 14 mg/100 ml following clofibrate was an obese male who was 50 pounds over his ideal weight.

A similar plot of the cholesterol values from the same patients is shown in figure 3. The unbroken line represents the correlation for all patients and there is an overall tendency for a greater reduction in serum cholesterol with higher control serum cholesterol values (r = 0.539). If these patients were subdivided into those with glyceride glycerol values above and below 25 mg/100 ml, those patients with serum glyceride glycerol values above 25

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Table 1

Effect of Clofibrate on Serum Cholesterol

<table>
<thead>
<tr>
<th>Duration of treatment (mo)</th>
<th>0-3</th>
<th>3-6</th>
<th>6-12</th>
<th>12-18</th>
<th>18-24</th>
<th>24-30</th>
<th>30-36</th>
<th>36-42</th>
<th>42-48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>45</td>
<td>38</td>
<td>31</td>
<td>22</td>
<td>20</td>
<td>18</td>
<td>13</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Control serum cholesterol of patients in each period</td>
<td>339 ± 16*</td>
<td>346 ± 18</td>
<td>327 ± 17</td>
<td>320 ± 18</td>
<td>322 ± 20</td>
<td>320 ± 22</td>
<td>311 ± 29</td>
<td>333 ± 40</td>
<td>372 ± 62</td>
</tr>
<tr>
<td>Mean serum cholesterol for specific Rx period</td>
<td>288 ± 15*</td>
<td>284 ± 16</td>
<td>289 ± 18</td>
<td>292 ± 22</td>
<td>303 ± 26</td>
<td>300 ± 22</td>
<td>298 ± 34</td>
<td>316 ± 45</td>
<td>357 ± 81</td>
</tr>
<tr>
<td>Mean reduction (%)</td>
<td>15.0</td>
<td>17.9</td>
<td>11.6</td>
<td>8.8</td>
<td>5.9</td>
<td>6.3</td>
<td>4.2</td>
<td>5.1</td>
<td>4.0</td>
</tr>
<tr>
<td>P values</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&gt;0.10</td>
<td>&gt;0.10</td>
<td>&gt;0.10</td>
<td>&gt;0.10</td>
<td>&gt;0.10</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Percentage of patients with reduction in serum cholesterol of at least 15%</td>
<td>53</td>
<td>47</td>
<td>48</td>
<td>45</td>
<td>40</td>
<td>33</td>
<td>46</td>
<td>33</td>
<td>60</td>
</tr>
</tbody>
</table>

* Mean serum cholesterol in mg/100 ml ± standard error (see text for method of calculation).

Table 2

Effect of Clofibrate on Serum Glyceride Glycerol

<table>
<thead>
<tr>
<th>Duration of treatment (mo)</th>
<th>0-3</th>
<th>3-6</th>
<th>6-12</th>
<th>12-18</th>
<th>18-24</th>
<th>24-30</th>
<th>30-36</th>
<th>36-42</th>
<th>42-48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>45</td>
<td>38</td>
<td>31</td>
<td>22</td>
<td>20</td>
<td>18</td>
<td>13</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Control, glyceride glycerol values of patients in each period</td>
<td>36.7 ± 4.9*</td>
<td>34.5 ± 4.6</td>
<td>33.4 ± 4.9</td>
<td>33.5 ± 6.5</td>
<td>30.8 ± 5.9</td>
<td>32.6 ± 5.9</td>
<td>29.7 ± 5.9</td>
<td>28.9 ± 7.3</td>
<td>29.9 ± 12.0</td>
</tr>
<tr>
<td>For specific Rx period</td>
<td>20.0 ± 2.3*</td>
<td>17.5 ± 2.4</td>
<td>16.9 ± 2.2</td>
<td>17.9 ± 3.3</td>
<td>17.5 ± 3.0</td>
<td>15.1 ± 3.7</td>
<td>16.1 ± 3.2</td>
<td>11.2 ± 2.2</td>
<td>14.0 ± 5.5</td>
</tr>
<tr>
<td>Mean reduction (%)</td>
<td>45.5</td>
<td>49.3</td>
<td>49.4</td>
<td>46.6</td>
<td>43.2</td>
<td>53.7</td>
<td>45.8</td>
<td>61.3</td>
<td>46.8</td>
</tr>
<tr>
<td>P values</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Percentage of patients (control glyceride glycerol &gt;15 mg/100 ml) with reduction of at least 25%</td>
<td>74</td>
<td>79</td>
<td>87</td>
<td>77</td>
<td>75</td>
<td>80</td>
<td>73</td>
<td>100</td>
<td>75</td>
</tr>
</tbody>
</table>

* Mean serum glyceride glycerol in mg/100 ml ± standard error. (See text for method of calculation.)
† Total number of patients with control glyceride glycerol >15 mg/100 ml.
mg/100 ml have a greater reduction in serum cholesterol following clofibrate as evidenced by the steeper slope of the line and the correlation is also better \((r = 0.748)\). Conversely, the group with glyceride glycerol values below 25 mg/100 ml have a less consistent reduction in serum cholesterol following clofibrate with the slope of the line being slight and the correlation also is poor \((r = 0.170)\).

To emphasize further the different responses to clofibrate in the two subgroups mentioned above, the long-term effects of clofibrate on the serum cholesterol and glyceride glycerol in these subgroups are summarized in tables 3 and 4. The reduction in serum lipids was calculated as the mean of the percentage of mean change of the values for individual patients for each treatment period up to 30 months. After 30 months, the number of patients was too small to make meaningful comparisons. Throughout the study, the reduction of serum cholesterol and glyceride glycerol was always greater in the group whose control glyceride glycerol was greater than 25 mg/100 ml.

### Table 3

**Mean Reduction in Serum Cholesterol in Subgroups**

<table>
<thead>
<tr>
<th>Group</th>
<th>0-3</th>
<th>3-6</th>
<th>6-12</th>
<th>12-18</th>
<th>18-24</th>
<th>24-30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean reduction (%) ± standard error*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients†</td>
<td>13.7 ± 3.1‡</td>
<td>15.3 ± 3.3‡</td>
<td>10.3 ± 4.0‡</td>
<td>8.9 ± 4.3</td>
<td>5.8 ± 5.2</td>
<td>4.5 ± 4.9</td>
</tr>
<tr>
<td></td>
<td>(45)</td>
<td>(38)</td>
<td>(31)</td>
<td>(22)</td>
<td>(20)</td>
<td>(18)</td>
</tr>
<tr>
<td>Patients with glyceride glycerol &gt;25 mg/100 ml</td>
<td>18.1 ± 5.6‡</td>
<td>22.9 ± 5.9‡</td>
<td>17.4 ± 6.0‡</td>
<td>19.3 ± 7.0§</td>
<td>23.1 ± 8.3‡</td>
<td>16.2 ± 10.6</td>
</tr>
<tr>
<td></td>
<td>(21)</td>
<td>(17)</td>
<td>(11)</td>
<td>(7)</td>
<td>(6)</td>
<td>(6)</td>
</tr>
<tr>
<td>Patients with glyceride glycerol &lt;25 mg/100 ml</td>
<td>9.8 ± 3.6‡</td>
<td>9.1 ± 3.3‡</td>
<td>6.7 ± 5.3</td>
<td>4.0 ± 5.1</td>
<td>-1.4 ± 5.5</td>
<td>-1.2 ± 4.9</td>
</tr>
<tr>
<td></td>
<td>(24)</td>
<td>(21)</td>
<td>(20)</td>
<td>(15)</td>
<td>(14)</td>
<td>(12)</td>
</tr>
</tbody>
</table>

* See text for method of calculation.
† Number of patients in group recorded in parenthesis.
‡ \(P < 0.02\).
§ \(P < 0.05\).
Table 4

Mean Reduction in Serum Glyceride Glycerol in Subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>Duration treatment (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-3</td>
</tr>
<tr>
<td>All patients†</td>
<td>Mean reduction (%) ± standard error*</td>
</tr>
<tr>
<td></td>
<td>29.9 ± 5.1†</td>
</tr>
<tr>
<td></td>
<td>(45)</td>
</tr>
<tr>
<td>Patients with glyceride</td>
<td>Mean reduction (%) ± standard error*</td>
</tr>
<tr>
<td>glycerol &gt;25 mg/100 ml</td>
<td>54.2 ± 5.1†</td>
</tr>
<tr>
<td></td>
<td>(21)</td>
</tr>
<tr>
<td>Patients with glyceride</td>
<td>Mean reduction (%) ± standard error*</td>
</tr>
<tr>
<td>glycerol &lt;25 mg/100 ml</td>
<td>8.6 ± 6.0§</td>
</tr>
<tr>
<td></td>
<td>(24)</td>
</tr>
</tbody>
</table>

* See text for method of calculation.
† Number of patients in group recorded in parentheses.
‡ P < 0.01.
§ P < 0.05.

Discussion

Previous studies have demonstrated a 10 to 25% mean reduction in serum cholesterol following clofibrate administration3, 5, 8, 9, 14–18 with generally a greater reduction in serum triglycerides ranging from 20 to 50%.8, 9, 15, 17, 18 Our results are comparable except for the long-term reduction of serum cholesterol, which in our patients is less than that previously described by Berkowitz8 and Oliver.9 An accurate assessment of the reduction in serum lipids produced by clofibrate over prolonged periods of time would require a carefully matched control group which was not feasible in our study because of the limited number of patients. Rifkind and coworkers19 reported a 10% reduction in serum cholesterol by clofibrate compared to placebo over a 12-month period in a double-blind study of patients with peripheral vascular disease. The short-term crossover design of our study, utilizing each patient as his own control, also demonstrated a significant reduction in serum cholesterol and triglycerides following administration of clofibrate.

Some of the factors which may influence the results of previously reported studies with clofibrate include seasonal variation, patient selection, and previous or concomitant dietary therapy. In our study an attempt was made to achieve reduction of the serum cholesterol and triglycerides by caloric restriction as well as the proper control of fat, cholesterol, or carbohydrate intake before patients were entered into the study. Since this study was done with outpatients, compliance to our dietary recommendations was not known, and the results cannot be construed to evaluate the effect of clofibrate over maximal dietary response. No attempt was made to exclude potential nonresponders, that is, patients with marked elevations of cholesterol and tendon xanthomata, many of whom had failed to respond to previous dietary or drug therapy.

Although the percentage of all patients achieving a 15% reduction in serum cholesterol remained relatively constant throughout the study (33 to 50%), a statistically significant reduction in serum cholesterol was not observed after 12 months. This may be partially due to the small number of patients followed for the longer periods, but other factors appear more important. During the early phase, the majority of patients entering this study had familial hypercholesteremia (type 2 hyperlipoproteinemia).20 The data in table 3, as well as that of others, indicate that this group of patients does not respond satisfactorily to clofibrate administration. This lack of response was not due to poor compliance with drug ingestion as judged by the urinary excretion of clofibrate and its glucuronide in these patients, although this test would confirm only the recent ingestion of clofibrate.

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However, the group with initial glyceride glycerol levels of >25 mg/100 ml had a persistent reduction in serum cholesterol throughout the study. Since the longer periods of observation contain more potential nonresponders, our results cannot be simply interpreted to mean that clofibrate is ineffective after 1 year of administration.

The recent classification of patients with hyperlipidemias according to the lipoprotein patterns described by Fredrickson and associates appears to be of value in predicting a patient’s response to clofibrate. Serum lipoprotein patterns were not obtained on a sufficient number of our patients to warrant our using this classification, the patients being arbitrarily divided into those with serum glyceride glycerol levels above and below 25 mg/100 ml to define those patients with hypercholesteremia most likely to respond to clofibrate. Patients with glyceride glycerol values above 25 mg/100 ml (primarily type III and IV hyperlipoproteinemias) had a much greater reduction in serum cholesterol than those patients with glyceride glycerol below 25 mg/100 ml (primarily type II hyperlipoproteinemia).

The majority of the previous studies suggest that clofibrate is more effective in lowering serum triglycerides than serum cholesterol, and this was further substantiated in our study. More than 75% of all patients with elevated glyceride glycerol (>15 mg/100 ml) had at least a 25% reduction in triglyceride values following clofibrate administration. Although both subgroups in our study had a significant reduction in triglycerides, the degree of reduction following clofibrate administration was much greater in the group whose control glyceride glycerol level was >25 mg/100 ml. The only patients without a significant reduction in triglycerides were those with normal or minimal elevation of triglycerides associated with the type II hyperlipoproteinemias, and one markedly obese individual who had only a modest decrease. The reduction which occurred following clofibrate therapy persisted throughout the study for all patients.

The serum cholesterol may not adequately reflect changes in the total body pool; indeed, Ahrens (Personal communication to the authors) has reported that patients may show a negative sterol balance without a change in serum cholesterol following clofibrate administration. Those patients in our study who did have a regression in size of their xanthomas also had significant reductions in their serum cholesterol and triglycerides, and conversely, no gross change in size of xanthomas was noted in patients without a reduction in serum cholesterol and triglycerides.

Hellman and associates observed that clofibrate produced a greater reduction in serum lipids in women. In our study, the response to clofibrate appeared to be better correlated with the pattern of lipid disturbance rather than with sex. The reduction in serum cholesterol and triglycerides was actually greater in the males in the latter treatment periods, but the majority of the females in our study had type II hyperlipoproteinemias. To determine sex differences correctly, the drug will need to be evaluated in pairs matched for type of hyperlipoproteinemia. Although no gross differences between age groups were observed, similar matched patients would be necessary to accurately assess the effect of age on the response to clofibrate.

The mechanism of action of clofibrate in man has not been clearly delineated. Nestel and co-workers have demonstrated that fractional turnover rates of cholesterol-14C are decreased following clofibrate administration, suggesting inhibition of cholesterol or lipoprotein synthesis or a change in pool size. Decreased cholesterol biosynthesis has also been demonstrated in in vitro and in vivo studies in rats. Inhibition occurs at an early step in cholesterol biosynthesis and no evidence of accumulation of cholesterol precursors such as desmosterol has been noted. Decreased release of triglycerides into the plasma following clofibrate has been shown by Azarnoff and associates in the isolated perfused rat liver and in vivo in rats by Gould and associates, although the rate of triglyceride synthesis was increased in the latter study. Clofibrate also

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lowers fasting levels of FFA\textsuperscript{24, 25} and inhibits epinephrine-induced rises of FFA in man,\textsuperscript{24} but the relationship of these findings to the hypotriglyceridemic effect in man has not been established. Thorp has proposed that clofibrate competes with thyroxine for binding sites on plasma proteins with a redistribution of thyroxine into the liver producing a state of local hyperthyroidism.\textsuperscript{26} Studies of plasma-liver relationships of thyroxine following clofibrate administration to humans do not support this concept.\textsuperscript{27}

Clofibrate was not discontinued in any patient because of intolerance to the drug. Several patients complained of increased appetite and weight gain, but the latter was not quantitatively substantiated. While other studies have documented a weight gain in some patients following clofibrate administration, the initial concept that the weight change was due to an increase in total body water was shown to be incorrect.\textsuperscript{28} Urinalyses, blood urea nitrogen, blood glucose, hepatic function studies, and complete blood counts obtained intermittently throughout the study, revealed no evidence of chronic toxicity. The recently described phenomena of muscle cramps and myositis following clofibrate administration\textsuperscript{29} was not noted in any of our patients, but approximately 15\% of our patients do have elevated creatine phosphokinase levels.

Conclusive evidence that a reduction in serum lipids decreases the morbidity and mortality from coronary artery disease is still lacking, although preliminary studies utilizing dietary manipulations to lower plasma lipids suggest that this is a valid approach.\textsuperscript{30, 31} A multi-clinic cooperative study sponsored by the National Heart Institute to evaluate the effectiveness of several hypcholesterolemic agents including clofibrate to control coronary artery disease is currently in progress. The preliminary results of the uncontrolled multi-center trial of clofibrate in the United Kingdom\textsuperscript{32} suggest that the mortality and reinfarction rates for patients with coronary artery disease treated with clofibrate may be decreased, but it is difficult to draw conclusions in the absence of an appropriate control group.

Acknowledgment

The competent technical assistance of Beverly Walker and Wonja Hahn is gratefully acknowledged.

References

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