Long-term Changes of Serum Cholesterol with Cholesterol-altering Drugs in Patients with Coronary Heart Disease

Veterans Administration Drug-Lipid Cooperative Study

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SUMMARY

In a controlled secondary prevention trial of estrogen and cholesterol-lowering drugs on 570 veterans, all of whom had had one or more episodes of acute myocardial infarction, changes in serum cholesterol were followed for at least five years. The findings included the following:

1) Estrogen, 1.25 mg daily, had no appreciable effect on cholesterol level.
2) Aluminum nicotinate, 4 g/day, resulted in a 20% reduction in cholesterol level for about 2½ years after which levels slowly rose to a level 12% below the baseline level in good adherers; poor adherers had smaller ultimate changes.
3) Dextrothyroxine, 4 mg/day, had a sustained cholesterol-lowering effect of approximately 7% throughout the study.
   The above values were obtained after adjusting for an underlying upward trend in all cholesterol values during the five-year observation period.
4) Discontinuation of both aluminum nicotinate and dextrothyroxine resulted in a significant rise in cholesterol within three months.
5) The 6% rise in the cholesterol level found in the control group over five years of follow-up could be attributed to aging and laboratory drift.
6) Regression toward the mean rather than pharmacological effect accounted for the greater response to treatment of patients with high initial cholesterol.

Additional Indexing Words:
Secondary prevention trial
Dextrothyroxine
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Aluminum nicotinate
Double-blind design
Myocardial infarction
Age and cholesterol

THE VA Drug-Lipid Study was designed as a clinical trial of secondary prevention of coronary heart disease. In 1962, when the study began, an association between high serum cholesterol and increased risk of coronary heart disease (CHD) had been established, but it was not clear whether treatment of hypercholesterolemia would be prophylactically effective, either for primary (in persons with no manifest CHD) or secondary (in persons with evidence of CHD) prevention. Furthermore, while it was assumed that the lower rate of CHD in middle-aged women was due to their natural estrogens, it was not clear if treatment with these steroids would be therapeutically useful for men recovered from an infarct.

The primary objective of the VA Drug-Lipid Study was to assess the long-term efficacy and safety of the use of estrogen, dextrothyroxine, and aluminum nicotinate, and combinations of each of the latter two drugs with estrogen, in men with proven myocardial infarction. The central hypothesis of this trial was that lowering the serum cholesterol level might result in a reduction of the incidence of events associated with CHD in men with myocardial infarction. Therefore, the study protocol provided for detailed monitoring of serum cholesterol levels throughout the trial. The effects of treatment on cardiovascular mortality and

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See Appendix to this paper for a list of the participating researchers in the VA Drug-Lipid Cooperative Study.

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morbidity is the subject of a separate report.*

This report is restricted, however, to presentation of the findings on long-term effects of these drugs on serum cholesterol, as well as a description of the methodology required in a program monitoring serum cholesterol over several years. Salient features of the study are described below.

Materials and Methods

Between February 1963 and August 1966, 570 male patients entered the study from 26 cooperating VA Hospitals, under a common protocol. The ages of these men ranged between 28 and 75; 95% were between 38 and 70 years. The average age was 51 yr. Ninety-two percent of the men were white. The infarction on the basis of which the patient was entered into the study was the first in 83% of the cases and the second in 15%. Two percent of the patients had had more than two infarcts at entry. Fifty-six percent of the patients entered the study between 1 and 5 months after their most recent infarct; the rest entered between 6 and 12 months postinfarction.

The patients were randomly assigned to six regimens in the following way. Approximately one-quarter of the patients was assigned to each of the following: 1) placebo; 2) estrogen; 3) a cholesterol-lowering agent; or 4) a cholesterol-lowering agent plus estrogen. Groups 3 and 4 were split: half was given aluminum nicotinate and half was given dextrothyroxine as the cholesterol-lowering agent. This design was used to ensure that in the final comparisons there would be comparable numbers of subjects when evaluating the effects of estrogen alone, cholesterol-lowering agent alone, and the combination of each cholesterol-lowering agent with estrogen.

Three types of physically different tablets were used with identical placebo for each. There were estrogen,1 1.25 mg, or placebo, one pill daily; aluminum nicotinate, 0.5 gram, or placebo, 8 pills per day; and dextrothyroxine, 2 mg, or placebo, 2 pills per day. The aggregate daily dose for each agent thus was: estrogen, 1.25 mg; aluminum nicotinate, 4 g; dextrothyroxine, 4 mg. With the double-blind design each patient took the same number of tablets daily. The central statistician held the code of patients on placebo or active medication. Informed consent for participation was obtained from each patient after explanation of the nature of the trial. The protocol provided for modification of dosage by clinic physicians to deal with side effects attributable to the study medication, or to treat concurrent illness. The clinician was free to treat any such illness according to his or her medical judgment.

The protocol stated that each patient, before he was assigned to one of the six regimens, should have three cholesterol determinations at weekly intervals. The average of these pretreatment values was to serve as the baseline from which changes could be measured for each individual.

During the treatment period, cholesterol determinations were done monthly for 24 months, and bimonthly for the remaining 36 months. Each determination was performed centrally in a special lipid laboratory established at the VA Hospital in Durham, North Carolina. A modification of the Abell-Kendall method1 was used throughout the study.

Results

Baseline Findings

Figure 1 shows the distribution of the average pretreatment cholesterol values, referred to as baseline from here on. The distribution centered about 241 mg/100 ml, the mean baseline value, and it was skewed to the right, the median being 236 mg/100 ml. For each subject the standard deviation (sd) was calculated for the three pretreatment values. The mean for these standard deviations was 11.5.

In spite of random allocation to the treatments, the baseline cholesterol values of the six groups were not as close as might be desired. The average values and the 95% confidence limits (x ± 1.96 sd) are as follows: placebo (P), 242 ± 7.6; estrogen (E), 233 ± 7.6; aluminum nicotinate (N), 246 ± 10.6; dextrothyroxine (T), 234 ± 9.8; E + N, 245 ± 10.6; E + T 255 ± 15.5. From here on, all effects on cholesterol will be measured as percent change from baseline of the respective group.

The relationship between age and cholesterol at baseline was inverse. In a simple regression analysis of cholesterol on age, it was found that a good fit was obtained to a straight line with a significant negative slope (b = −0.71). The data points in figure 2 represent average baseline cholesterol values for the study population divided by age into six groups which were of comparable size. The elevated cholesterol levels of the younger coronary patients suggest a relation.

![DISTRIBUTION OF BASELINE CHOLESTEROL](image)

Figure 1


1 Conjugated equine estrogen supplied as Premarin by Ayerst.

2 Supplied as Nicalex by Walker.

3 Supplied by Baxter-Travenol, later marketed as Choloxin.

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Distribution of baseline cholesterol by age. Symbol = mean ± one standard deviation. The slope (b) is −0.71.

Effects of the Drug Regimen

The five-year changes in cholesterol level for the six regimens are shown in figure 3, which includes patients who remained in the study for the entire five-year follow-up. The effect of estrogen (E) on levels of total serum cholesterol was similar to that of placebo. Similarly, the addition of estrogen to d-thyroxine (E + T) and to aluminum nicotinate (E + N) had little effect on the total cholesterol-lowering capacity of either drug. For the purposes of further analysis of the cholesterol data, patients treated with placebo and estrogen were grouped together and used as controls for groups resulting from the merging of the two aluminum nicotinate regimens (N and E + N) and the two dextrothyroxine regimens (T and E + T).

Figure 4 shows the cholesterol responses of these three principal groups. Aluminum nicotinate had a greater effect on cholesterol levels than dextrothyroxine with a 17% immediate fall that was maintained for six months. The reduction with dextrothyroxine was only half that achieved with nicotinate for the first six months, after which all cholesterol responses, control and treatment, rose gradually throughout the five years. At the end of the study cholesterol levels had been lowered in the aluminum nicotinate group by 4%, and in the dextrothyroxine group, by 1%, while the control group’s level (P + E) was 6% higher than the levels at entry.

Cohorts — consisting of those subjects who began and finished the 5-year follow-up — were analyzed in order to avoid bias that may be introduced when the numbers of patients who die or who are lost to follow-up are included and are not evenly distributed among the various treatment groups. However, cohorts who remain under observation may not be representative of the entire study population. Concern over this question was resolved by demonstrating that the mean cholesterol values of the 5-year cohorts differed only very slightly from those of all patients, as shown in figure 5, where the solid lines represent the cohorts and the dotted lines are for all patients observed at each time point.

In order to estimate the net long-term effect of the two combined treatment regimens (aluminum nicotinate or d-thyroxine), the rising trend of cholesterol values, as shown by the control group, had to be adjusted for. For each regimen, the percent change (decrease or increase) in the control group was subtracted from the observed result for the drug group, thus yielding a value that represented the net drug effect.
Over the entire five-year period was 6.5% reduction the rising trend had been adjusted for. The average reduction over the entire five-year period was 6.5% for dextrothyroxine and 12.6 for aluminum nicotinate. The reduction in cholesterol level from the use of dextrothyroxine was maintained steadily throughout the study, while the more marked initial effect of aluminum nicotinate decreased slowly after two years.

**Effects of Adherence**

To clarify the apparent "escape" phenomenon in the aluminum nicotinate group, the influence of adherence to the prescribed regimen was evaluated. Of the 85 patients in the aluminum nicotinate cohorts, 31 were good adherers, that is, they took at least 75% of the dose for 75% or more of the time. Figure 7 shows that in the good adherers reduction of cholesterol level of nearly 20% was sustained for about 2½ years before an increase occurred, but in those who adhered less faithfully there was less effect for less time. In the dextrothyroxine group, poor adherence did not present a problem. At the completion of the study, 89% of patients on dextrothyroxine were on full dosage. This difference in adherence is most certainly due to side effects of aluminum nicotinate (see footnote on p 999).

**Evaluation of Rising Trend in Mean Cholesterol**

To clarify the reasons for the rising trend in all groups regardless of treatment, we evaluated the apparent increase of 6% in serum cholesterol over the five-year period demonstrated by the control group. It was assumed that a parallel phenomenon also counteracted the drug effects in the treatment groups. First, the possible effect of aging was assessed. For this purpose we used the Framingham data on longitudinal cholesterol changes for different age groups of males, by applying the 5-year differences to our control group age by age. We found that aging could account for a rise of 6 mg (2.5%), which was somewhat less than half the observed rise. (The possibility, of course, exists that aging might affect cholesterol values of coronary patients quite differently from those of normals.)

Next, the possibility of a factitious trend in laboratory determinations was explored. Figure 8 shows the mean cholesterol values for a cohort of the control group that was observed for the same five calendar years, namely, those who entered the study in 1963 and 1964. The cholesterol readings as originally determined from 1964-1968 are represented by the solid line, which suggests an upward trend, or at least a substantial rise in 1968. The

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**Figure 5**

Mean percent change in serum cholesterol from the baseline average for cohorts and for all patients.

Figure 6 shows the effect of each drug alone, after the rising trend had been adjusted for. The average reduction over the entire five-year period was 6.5% for dextrothyroxine and 12.6 for aluminum nicotinate. The reduction in cholesterol level from the use of dextrothyroxine was maintained steadily throughout the study, while the more marked initial effect of aluminum nicotinate decreased slowly after two years.

**Figure 6**

Net effect of aluminum nicotinate (all N) and dextrothyroxine (all T) on serum cholesterol for cohorts followed 60 months.

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**Figure 7**

Net effect of aluminum nicotinate on serum cholesterol by adherence to regimen for the cohort followed for 60 months. The curves show the adjusted values, N - (P + E), for the aluminum nicotinate cohort.
original specimens, which were stored frozen, were retested in one run at the end of the study; the results are shown by the dotted line in figure 8. The comparison of the two lines suggests that a laboratory “drift” did occur. This drift in the original determinations would chiefly affect the findings at years 4 and 5 of follow-up, and result in values that would be roughly 4% too high. The combined effects of aging and laboratory “drift” during the course of the study probably account for the 6% rising trend in cholesterol values.

Effects of Discontinuation of Therapy

An independent estimate of the effect of five years of therapy was obtained by looking at the effect of discontinuation of therapy. Cholesterol readings at three months posttherapy were available on 242 patients. In 117 patients treated with placebo the posttherapy change was −0.1%, but the cholesterol values rose 6.8% for the aluminum nicotinate group and 5.2% for the dextrothyroxine group. The increases in both treated groups after cessation of therapy represent significant changes (P < 0.02) from the last treatment values.

Regression Toward the Mean

It is often said that lipid-lowering agents or diet have a greater effect on patients with high initial values. This appeared to be true in our study. However, adjustment for the effect of regression toward the mean as observed in the control group eliminated most of the apparent differences. Figure 9 shows the response to aluminum nicotinate for the patients in three groups — those with high initial values (greater than or equal to 250 mg/100 ml), those with middle range values (213–249 mg/100 ml), and those with low values (less than or equal to 212 mg/100 ml). In part a of the figure, the response of the high group appears much greater than the response for the low group. Part b of the figure shows the high, medium, and low group trends for the placebo-treated group. Here the high group shows a downward tendency and the low group values tend to rise, reflecting the regression toward the mean effect. Part c is the graph of the drug effects for the high, middle,
and low groups after adjustment for the regression toward the mean. In this part of the figure, there is virtually no difference in the percentage response to nicotinate whether the cholesterol values were initially high or low.

**Discussion**

The VA Drug-Lipid Study was the first of the long-term secondary prevention efforts of CHD with cholesterol-lowering drugs. At the time when the study was planned, aluminum nicotinate and dextrothyroxine were the drugs best known to have a cholesterol-lowering effect. Since clofibrate and cholestyramine became available later, they did not become part of the study. Earlier secondary prevention drug studies dealt exclusively with estrogen but at the time this study was begun the effectiveness of estrogen was still controversial.

Since 1963, other secondary prevention trials of cholesterol-lowering drugs have been instituted, the most extensive of which, the Coronary Drug Project (CDP), was launched in 1965. Although the CDP has approximately 12 times the number of patients in the VA Study, the two studies are similar in several ways. Both studies were designed to use: 1) placebo; 2) nicotinic acid (4 g/day in VA Study; 3 g/day in CDP); 3) dextrothyroxine (4 mg/day in VA; 6 mg/day in CDP); and 4) estrogen (1.25 mg/day in VA; 2.5 and 5.0 mg/day in CDP). The CDP had an additional clofibrate regimen (1.8 gm/day), while the VA Study used combinations of estrogen with aluminum nicotinate or dextrothyroxine. Two other controlled secondary prevention trials used clofibrate and placebo regimens only.

The results of the VA Study showed that the cholesterol-lowering effect by both aluminum nicotinate and dextrothyroxine lasted throughout the five years of the study. Aluminum nicotinate was the more effective of the two drugs, resulting in an average serum cholesterol reduction of 13% with greater reduction in the first three years and less in the final two years. This reduction could have been larger if more subjects assigned to the aluminum nicotinate regimen had adhered to full dosage. On the other hand, dextrothyroxine produced only a moderate average cholesterol reduction of 7%, but this was maintained steadily throughout the five years and the regimen was well adhered to by the subjects. It caused no untoward effects, unlike the results reported in the CDP Study. It is noteworthy, however, that the dextrothyroxine dosage was higher for the CDP subjects. In fact, none of the drugs, in the dosages used in the VA Study, produced side effects sufficiently severe to warrant discontinuation of treatment.

The magnitude of cholesterol reduction in the VA Study can be compared to that found in other secondary prevention trials, especially those using clofibrate, such as the Newcastle Study and the Scottish Trial. In order to compare the results reported in these two studies with the results of the VA Study, we attempted to handle their data according to methods used in our study. The reported cholesterol changes were expressed as percent reductions from baseline rather than as changes in the actual mean values of serum cholesterol. In addition, adjustment was made for changes occurring in the control group, thus obtaining the "net drug effect." Looking at their published data in this manner, the average cholesterol response to clofibrate in the Newcastle Study amounted to approximately 8%, over 48 months, and that in the Scottish trial was also less than 9% over three and a half years. No published report on the magnitude of cholesterol reduction by the CDP regimens is available to date.

Another way to achieve serum cholesterol reduction in secondary prevention studies is by use of dietary measures. The Research Committee to the Medical Research Council reported one such controlled study, which was conducted in London between 1960 and 1965. In that study, the average net reduction in cholesterol was 12% over the 5-year period of follow-up. The other large controlled dietary study was conducted in Oslo and began in 1958–60, also for a five-year follow-up period. This study reported an average net reduction of 14% due to diet. Thus the cholesterol reduction obtained in the VA study with dextrothyroxine was about the same as the results found in the clofibrate studies, while the effects of aluminum nicotinate matched what was found in the dietary studies.

From a methodological point of view, it was found to be very important to include a concurrent control group in this type of clinical drug trial. Without taking into account the changes occurring in the control group, interpretation of changes in the treatment groups might be erroneous. This was true in our own study, where, in order to evaluate the true effect of the drugs, the changes occurring without the cholesterol-lowering drug (control group) had to be assessed. The method used was subtraction of the percent change found in the controls from the percent change in each treatment group, thus obtaining a more valid treatment effect. The adjustment procedure is particularly applicable when the treatment groups are subdivided according to initial levels and a larger response to treatment is observed in subgroups with higher initial values. If adjustment according to tendencies noted in the control eliminates the differential response, the phenomenon is due to ordinary regression toward the mean. Although this phenomenon is well known to
many investigators, clinicians and drug companies often fail to acknowledge its effects and interpret improvement in those with higher initial levels as if it were due to a greater treatment effect.

In addition to relating treatment effects to control values, future study designs should use a more uniform method of expressing cholesterol changes as percent of baseline so that the results of future studies of the efficacy of various cholesterol-lowering agents would be comparable.

The benefits of cholesterol-lowering therapies in respect to morbidity are presented in a separate paper. That report will also discuss the incidence of side effects and details of adherence to therapy.

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References

10. CORONARY DRUG PROJECT RESEARCH GROUP: The Coronary Drug Project: Initial findings leading to modification of its research protocol. JAMA 214: 1300, 1970
11. CORONARY DRUG PROJECT RESEARCH GROUP: The Coronary Drug Project: Findings leading to further modifications of its protocol with respect to dextrothyroxine. JAMA 220: 996, 1972


Appendix

The Veterans Administration Drug-Lipid Cooperative Study

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