

The Coronary Drug Project: Clofibrate and Niacin in Coronary Heart Disease¹ (1966-1975)

Purpose

- Primary research questions (secondary prevention)
 - Do lipid-modifying drugs that reduce serum cholesterol levels lengthen the lifespan of men with heart disease?
 - Do these drugs prevent further heart attacks in men who have survived an MI?
 - Can they be used safely?
- Primary outcome
 - 5-year total mortality
- Secondary outcomes
 - Cause-specific mortality, especially coronary and sudden death.
 - Non-fatal recurrent MI, coronary insufficiency, angina pectoris, and other cardiovascular events.
- Perceived clinical importance
 - Improved life expectancy and prevention of recurrence of major cardiovascular event, one of the main causes of death in men in that age group.

Background and Context

- Epidemiologic studies had demonstrated the relationship between elevated serum cholesterol levels and mortality from CHD.
- Other studies had shown that clofibrate, niacin, and other drugs affecting lipid metabolism reduced cholesterol. Recent prior use of triparanol had caused serious adverse events in patients.
- It was not known whether these drugs would prevent heart disease, especially the recurrence of acute events in those who already had CHD, or whether they would do so safely.

Date and Place Conducted

- Location: United States
 - 53 clinical centers in mainland US and Puerto Rico

- Recruitment Dates: 1966 to 1969.
 - The initial trial was conducted between 1966 and 1975.
6,008 survivors were followed another ~8.8 years

Principal Investigators

- The Coronary Drug Project Research Group
- Coordinating Center at the Institute of International Medicine, University of Maryland School of Medicine.

Sponsored by/Source of Funding

- National Heart and Lung Institute/NIH

Size and Design

- Number of participants: 8,341
- Participant characteristics: All men
 - 30 to 64 years old at entry
 - had had one or more myocardial infarctions prior to enrollment, as verified by EKG
 - ~7% nonwhite
- Design: Double-blind random assignment to one of six treatment groups, with trimester follow-up:
 - conjugated estrogen, 2.5mg
 - conjugated estrogen, 5.0mg
 - clofibrate (Atromid-S)
 - dextrothyroxine sodium (Choloxin)
 - niacin (several)
 - lactose placebo

Issues Encountered During the Trial

- Poor regimen adherence with both estrogen dosages, due to testicular atrophy, gynecomastia, other such "troublesome side effects"
- Three of the regimens caused severe adverse effects and were discontinued:
 - 5.0mg estrogen (excess nonfatal MIs, pulmonary embolisms, thrombophlebitis), halted in 1970.
 - A subset of the survivors were then enrolled in the CDP Aspirin Study
 - dextrothyroxine sodium (excess deaths), halted in 1971

- 2.5mg estrogen (higher mortality, pulmonary embolism, thrombophlebitis, cancer), halted in 1973

Findings

- Conjugated estrogens, both the 2.5mg and 5mg dose regimen, and dextrothyroxine sodium had caused serious adverse effects and were discontinued.
- Neither clofibrate nor niacin caused severe adverse effects and were allowed to continue until termination of the trial. Neither clofibrate nor niacin showed any benefit in the primary outcome (total mortality) or cause-specific mortality over the 6-year mean follow-up compared to the placebo.
- In the clofibrate group, there was an increase in thromboembolism, angina, intermittent claudication, cardiac arrhythmia and gallstones, and an increase in nonfatal cardiovascular events
- Niacin users experienced a modest reduction in nonfatal MI recurrences compared to those on placebo. However, they had higher rates of atrial fibrillation and other arrhythmias, and also had more gastrointestinal events, as well as elevated plasma glucose, serum enzymes and uric acid levels.
- After an average of 15 years of follow-up, participants who had been in the niacin group experienced an 11% reduced overall mortality compared to the other groups.

Impact

- Based on their data, the investigators recommended against the use of clofibrate to treat persons with coronary heart disease.
- They recommended caution in using niacin, despite its protective effect against nonfatal recurrences of MI because of the abnormal chemistries and other adverse findings.
- This trial raised serious questions about the use of the drugs tested and cholesterol-lowering drugs in general. During several decades after the results were published, researchers debated the injurious effects they believed to be the result of lowering serum cholesterol levels, no matter what drug was used. The primary concerns were increased risk of cancer and violence against self and others.
- The trial's findings prompted a rash of research on variations in mode of action of different cholesterol-lowering drugs, their effects on mood, and the relative benefits in preventing primary

and secondary coronary events.

Unresolved issues

- Concern about the possible long-term mortality effects of having participated in treatment groups that were discontinued were addressed by the researchers, who continued follow-up for roughly a decade after treatment was terminated. They found “no evidence of adverse effects” in any of the discontinued groups or in the clofibrate arm.
- Since those in the niacin group had stopped taking it by the time the beneficial effects were observed 15 years later, their explanation of the presumed mechanism was speculative.
- The adherence to full dosage in the niacin group was poor in 30% of participants. The researchers stated in 1986 “therapeutic benefit may have been derived from less than optimal doses of the drug.” They did not discuss the possibility of misclassification of adherence due to self-reporting during patient interviews.
- The authors reported cholesterol and triglyceride levels, but not HDL vs. LDL.
- No women and few minorities were included, so it is not clear whether the findings would have changed given the treatments.

Summary

The CDP trial was the largest that had ever been conducted on anti-lipid drugs and was done with transparency regarding clinical findings and methodological issues encountered along the way.

It is today hard to conceive that a trial could proceed, single-mindedly determined to focus on the primary outcome despite the “side effects” observed, as this one did. The fact that they appear to have administered dextrothyroxine without first assessing circulating thyroid status, thereby potentially inducing coronary complications in euthyroid or hyperthyroid patients, also is questionable if such testing was feasible at the time. And their conclusions regarding the effectiveness of niacin in preventing recurrent coronary events 15 years after enrollment may be suspect.

These ethical issues and debatable analyses notwithstanding, the trial did make a significant contribution to the field by simultaneously comparing several of the lipid-lowering treatments most commonly employed at the time. Also, they extended follow-up and care to participants and assiduously tracked the vital status of survivors (they succeeded in 99.7% of individuals)

to determine whether there was excess mortality due to cancer and other causes.

Perhaps the trial's greatest contribution is the serious questions—verging on alarm—it raised. Almost fifty years later, investigators still have not answered definitively whether medications employed to lower cholesterol increase the risk of cancer and other non-coronary mortality in the long term.

References

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