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Coronary drug project: experience with niacin

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Summary. Niacin was one of the treatments compared in the Coronary Drug Project, a placebo-controlled, multicenter trial of lipid-lowering drugs in the secondary prevention of coronary heart disease. A total of 1119 men, aged 30–64 at entry, were randomized to niacin and 2789 to placebo by the end of recruitment in March 1969. Although side-effects interfered with adherence to the niacin regimen, it was the most effective agent in achieving cholesterol-lowering (10% overall); other agents in the trial were clofibrate, dextrothyroxine, and conjugated equine estrogens. At the scheduled conclusion of the trial in February 1975, the niacin-treated group exhibited a statistically significantly lower incidence of definite, nonfatal myocardial infarction (MI) than the placebo group. There was a trend toward improvement in the life-table mortality curve, but this was not statistically significant. In 1981 an extended follow-up was carried out concerning vital status for the 6008 men who were still alive at the end of treatment and active follow-up in the trial in 1975 (827 in the niacin group and 2008 in placebo groups). Vital status was determined for 99.1% of these men after a mean of 9 years from conclusion of the trial. In the group previously randomized to niacin, there were 69 (11%) fewer deaths than were expected on the basis of mortality in the placebo group. This difference was significant ($z = -3.52$; $P = 0.0004$). The data also suggested that patients with a higher baseline cholesterol experienced greater benefit from niacin therapy, as did those with the best response to the drug. No such efficacy was noted in the other regimens, although the two estrogen groups and dextrothyroxine were discontinued before completion of the trial because of adverse effects. The extended follow-up did not provide data on the use of lipid-lowering agents or other treatment in members of either the niacin or the placebo group subsequent to 1975. It was concluded that the late benefit in the niacin group may have been the result of earlier benefit in reducing nonfatal reinfarction, the result of cholesterol lowering, or both.

Key words: Niacin, coronary heart disease, cholesterol, triglycerides

Niacin (nicotinic acid) was introduced as a lipid-lowering agent in the mid-1950s [1, 2]. The early studies were not sufficiently large or long to establish efficacy in the primary or secondary prevention of clinical atherosclerosis. By the time planning for the Coronary Drug Project (CDP) began in 1962, there was sufficient clinical evidence to warrant the inclusion of niacin as one of the regimens characterized by lipid-lowering efficacy, acceptability, and safety [3]. The CDP was designed to test the efficacy and safety of lipid influencing drugs in the secondary prevention of coronary heart disease in men aged 30–64 years with proven previous myocardial infarction (MI). It was a randomized, multicenter, long-term trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI). Fifty-three clinical centers recruited 8341 patients who were randomly assigned to one of the following six treatment groups: conjugated estrogens (ESG) at two dosage levels (2.5 and 5.0 mg/day), clofibrate (1.8 g/day), dextrothyroxine (D-T_4) (6.0 mg/day), niacin (3.0 g/day), and a lactose placebo (PLBO). The allocation schedule was designed to assure approximately five patients in the placebo group for every two patients in any of the active treatment groups [4].

The first patient was randomly allocated to treatment in March 1966 and the last in October 1969. Patients were seen in follow-up every 4 months in a double-blind fashion. The follow-up period on study drug ranged from 5 to $8\frac{1}{2}$ years, and the mean follow-up was 6.2 years. The primary end-point was all-cause mortality. Patient follow-up and data collection for the active phase of the trial were completed February 1975.

The two estrogen regimens [5, 6] and the dextrothyroxine [7] regimen were discontinued prior to the sche-

* For a list of the key bodies and senior staff members of the Coronary Drug Project, see p. 380 of [8]

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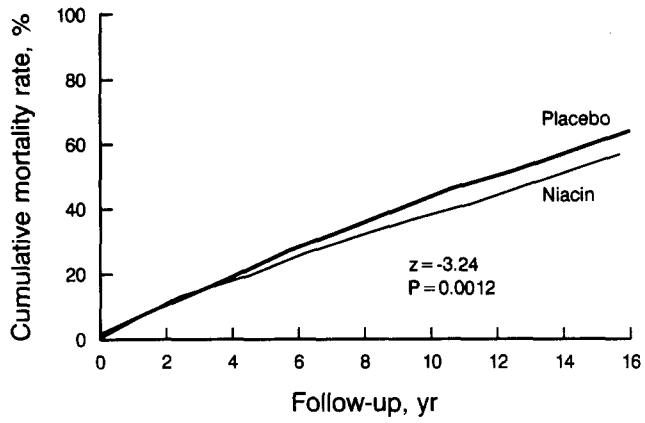

Fig. 1. Coronary Drug Project extended follow-up: life-table cumulative total mortality

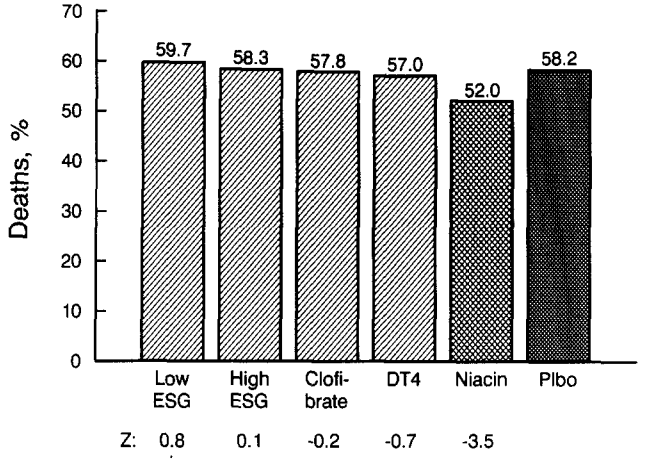

Fig. 2. Coronary Drug Project: total mortality (%) 9 years after the conclusion of active treatment and follow-up

duled end of the trial because of adverse effects of these drugs.

Three groups – clofibrate, niacin, and placebo – were continued to the scheduled end of the trial [8]. Side-effects of niacin, such as flushing and gastrointestinal irritation, resulted in compliance problems, so that nearly 30% of patients treated according to that regimen took less than 60% of the protocol-specified amount. Even so, niacin was the most effective lipid-lowering agent in that trial. The mean decrease from the pretreatment serum cholesterol was 10.1% at the end of the 1st year, and this decrease was well maintained during subsequent follow-up. It also proved to be the most effective agent in lowering triglyceride levels (−26.9%). The clofibrate group showed no benefit with respect to mortality or nonfatal cardiovascular events. Niacin had no effect on total mortality, except for a slight suggestion of divergence of the life-table mortality curve from that for the placebo group at the very end of the follow-up period. However, patients in the niacin group had a statistically significant lower incidence of definite nonfatal MI those who received placebo.

In June 1981, the CDP Coordinating Center was awarded a contract to carry out a mortality follow-up program for patients who were still alive at the end of the CDP in early 1975. For all patients reported as having died since the conclusion of the CDP an attempt was made to determine the dates and causes of death. A multistage approach was followed to determine vital status of the CDP patients:

1. Information was requested from CDP clinic investigators.
2. Letters and questionnaires were mailed to patients.
3. Telephone calls were made to patients.
4. The National Death Index file was searched.
5. The Social Security Administration files were searched.
6. Certified letters were sent to patients.
7. Telephone calls were made to patients' relatives, friends, employers, and personal physicians.
8. For the deaths ascertained in this program, attempts were made to obtain the death certificates from the various state offices of vital records.

A total of 8341 patients were originally enrolled in the CDP. Of these, 6008 were still alive at the end of the trial in February 1975. Information on vital status was obtained on 5953 (99.1%) of these 6008 patients [9]. However, for an additional 66 patients, the only information available was „assumed alive" according to Social Security Administration (SSA) records. These were persons who were still making Social Security payments or who were receiving benefit payments. For about 2500 patients we obtained *both* a designation of "assumed alive" from SSA *and* information from independent sources (e.g., letter, telephone calls to patients, etc.) regarding vital status. Thus, it was expected that about 5 of the 66 patients officially assumed alive were actually deceased.

With an average follow-up period of 15 years (6 years receiving the study drug and 9 years after conclusion of the study), cumulative mortality from all causes was 52.0% in the niacin group, compared to 58.2% in the placebo group. There were 69 (11%) fewer deaths in the niacin group than the number expected based on placebo group mortality. The z-value for the niacin-placebo difference in total mortality was −3.52, corresponding to a two-sided P-value of 0.0004. None of the other treatment groups were significantly different from placebo in total mortality. The mortality benefit in the niacin group was present in each major category of cause of death – coronary, other cardiovascular, cancer, and other.

Life-table curves for total mortality are shown in Fig. 1. It can be seen from the horizontal distance between the mortality curves for niacin and placebo that persons previously treated with niacin lived about 1.6 years longer than those in the placebo group. The beneficial effect of niacin on mortality was present in all subgroups of entry characteristics that have been analyzed, including mortality in two age groups and mortality by baseline level of serum cholesterol. The data suggest that patients with higher baseline levels of cholesterol benefit more from niacin treatment, although this was not of statistical significance.

The niacin-treated group was the only one to show a decrease in mortality at the conclusion of the CDP, the incidence of definite, nonfatal MI during the trial was about

10% for niacin and about 14% for placebo patients. It might be asked whether a difference of this size in nonfatal MI could be responsible for a subsequent 52% versus 58% difference in total mortality. The observed reduction in incidence of definite, nonfatal MI during the study by niacin accounted for a savings of about 11 lives over this subsequent 9 years. As there was a total savings of 69 lives in the niacin group compared to placebo, this early reduction in nonfatal MI could account for only a small portion of these.

Another possible explanation of the beneficial effect of niacin on total mortality related to its effectiveness in lowering serum cholesterol and triglycerides. The performance of niacin as a lipid-lowering agent was the best among the five CDP treatment regimens; dextrothyroxine was close behind in lowering cholesterol and clofibrate close behind in lowering triglycerides.

In the placebo group, mortality was higher in patients with a decrease of at least 24 mg/dl between baseline and the end of year 1 than in those with a lesser decrease or with an increase. This may reflect in part patients in failing health who were not eating well and were thus losing weight and had lowered serum cholesterol levels. In the niacin group on the other hand, patients with the larger decrease in serum cholesterol during that period experienced lower mortality (44.5% compared to 59.1% in the placebo group). While analyses of this type, i.e., relating mortality to variables that are themselves affected by the treatment, are fraught with methodologic hazards, the data do suggest that the hypocholesterolemic effect of niacin may be responsible for the reduced mortality. In the Lipid Research Clinics Coronary Primary Prevention Trial [10], reduction in cardiovascular risk was also greater in those with greatest lowering of total cholesterol levels. There was no significant correlation between change in serum triglyceride level and niacin-placebo difference in mortality.

Another possible, but quite improbable, explanation of the beneficial effect of niacin is that patients in the niacin group may have received better medical treatment after the conclusion of the trial than did patients in the placebo and all other CDP treatment groups. There is no information available to assess this unlikely possibility. We also have no information as to what cholesterol-lowering medication, if any, the patients received following the conclusion of the CDP.

The time lag between the lowering of serum cholesterol by niacin and the appearance of a beneficial trend in lowering mortality was 6 years or longer; whereas, a trend indicating benefit in reducing the incidence of nonfatal MI was evident in 2–3 years. Among patients who did survive an infarct, however, those in the niacin group sustained a higher subsequent mortality than was noted in similar circumstances in patient in the placebo group. These observations suggest that niacin treatment may have prevented only milder myocardial infarcts.

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