

Recent Landmark Drug Trials in Cardiovascular Disease Prevention

Gagandeep Singh Wander, MD, Manish Bansal, MD, DNB, *Gurgaon, Haryana, India*

Lifestyle management including healthy diet and physical activity is considered an integral part in prevention and management of cardiovascular diseases. The evidence for such treatment strategies is not complete. We discuss here a few trials published in recent past that have provided a new insight in success of various strategies in prevention of cardiovascular diseases.

Look AHEAD Study. Action for Health Diabetes study

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes. *N Engl J Med.* 2013;369:145-54.

Various short term studies show that weight loss improves glycemic control, risk factors for cardiovascular disease, quality of life, and other obesity-related illnesses. This randomized multicenter trial was conducted to see if intensive lifestyle intervention designed to achieve weight loss through caloric restriction and increased physical activity decrease cardiovascular morbidity and mortality among overweight or obese adults with type 2 diabetes. The NIH sponsored trial randomized 5,145 patients at 16 US sites from August 2001 to April 2004. Patients were randomized to intensive lifestyle intervention that promoted weight loss of at least 7% through decreased caloric intake and increased physical activity (intervention group) or to receive diabetes support and education (control group). The inclusion criteria was type 2 diabetes between age group 45 to 75 with a body-mass index of 25.0 or more (27.0 or greater in patients taking insulin); a glycated hemoglobin level

of 11% or less; a systolic blood pressure of less than 160 mmHg; a diastolic blood pressure of less than 100 mm Hg; a triglyceride level of less than 600 mg/dL (6.77 mmol/L); the ability to complete a valid maximal exercise test, suggesting it was safe to exercise; and an established relationship with a primary care provider. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina during a maximum follow-up of 13.5 years. The trial was stopped early on the basis of a futility analysis when the median follow-up was 9.6 years. Weight loss was greater in the intervention group than in the control group throughout the study (8.6% vs. 0.7% at 1 year; 6.0% vs. 3.5% at study end). The primary endpoint occurred in 403 patients in the intervention arm and 418 patients in the control arm. This difference was not statistically significant. In addition, there was no statistically significant difference between the treatment arms with regard to secondary outcomes. The intensive lifestyle intervention, however, produced greater reductions in glycated hemoglobin and greater initial improvements in fitness and all cardiovascular risk factors, except for low-density-lipoprotein cholesterol levels.

Perspective

The trial showed that an intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events in overweight or obese adults with type 2 diabetes.

PREDIMED Study

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. *N Engl J Med.* 2013;368:1279-90.

Earlier secondary prevention trial (Lyon Heart Study) and cohort studies have shown an inverse relationship between adherence to the Mediterranean diet and cardiovascular risk. This trial was designed to see

From: Institute of Cardiology, Medanta - The Medicity, Gurgaon, Haryana, India (G.S.W., M.B.)

Corresponding Author: Manish Bansal, MD, DNB
Institute of Cardiology, Medanta - The Medicity, Sector 38, Gurgaon, Haryana, India

Email: manishaiims@hotmail.com

if this diet pattern works in primary prevention of cardiovascular disease. This multicenter trial in Spain enrolled 7,447 patients in age group 55 to 80 years, who were at high cardiovascular risk but did not have established cardiovascular disease. The patients were randomized to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat). The primary endpoint was the rate of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes). The study was stopped when an interim analysis at 4.8 years revealed a clear benefit among subjects eating the Mediterranean diets. A primary endpoint event occurred in 288 participants. The multivariable-adjusted hazard ratios were 0.70 (95% CI, 0.54 to 0.92) and 0.72 (95% CI, 0.54 to 0.96) for the group assigned to a Mediterranean diet with extra-virgin olive oil (96 events) and the group assigned to a Mediterranean diet with nuts (83 events), respectively, versus the control group (109 events).

Perspective

A Mediterranean diet supplemented with either extra virgin olive oil or mixed nuts may cut the risk of cardiovascular events by as much as 30% in subjects at high risk of developing heart disease, as compared with people advised to eat a reduced-fat diet.

n-3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors

The Risk and Prevention Study Collaborative Group. N Engl J Med. 2013; 368:1800-8.

Trials have shown a beneficial effect of n-3 polyunsaturated fatty acids in patients with a previous myocardial infarction or heart failure. This trial evaluated the potential benefit of such therapy in patients with multiple cardiovascular risk factors or atherosclerotic vascular disease who had not had a myocardial infarction. Total 12,513 patients were enrolled and were randomly assigned to n-3 fatty acids or placebo (olive oil). The initial primary end point was the cumulative rate of death, nonfatal myocardial infarction, and nonfatal stroke. The primary endpoint was revised at 1 year as time to death from cardiovascular causes or admission to the hospital for cardiovascular causes. After 5 years of median follow up, primary endpoint occurred in 11.7% in n-3 fatty acid group and 11.9% in placebo group (adjusted hazard ratio with n-3 fatty acids, 0.97; 95% confidence interval, 0.88 to 1.08; $p=0.58$).

Perspective

In patients with multiple cardiovascular risk factors, daily treatment with n-3 fatty acids did not reduce cardiovascular mortality and morbidity.