Figure 10.2. EXPERIMENTAL PLANS: An Example from Heart Disease Research

EM8803: Kitchener-Waterloo Record, January 28, 1988, page E3

Aspirin may cut heart attack risk

The Washington Post

WASHINGTON – Healthy men can cut their risk of a heart attack nearly in half by taking an aspirin every other day, according to a major new study.

Previous research has shown that daily aspirin use can vastly reduce second heart attacks, but this is the first time that regular aspirin use has been shown to prevent initial heart attacks.

The conclusion that aspirin can lower the risk of a first heart attack was reached in one of the largest prospective studies of heart disease ever conducted in the Unied States, with more than 22,000 participants. The results were so dramatic that the study was ended three years early so that participants and the public could be told of aspirin's effects.

Because more than 1.5 million Americans have heart attacks each year, the results are expected to encourage millions to begin using aspirin regularly.

"There will be many thousands of people whose heart attacks will be prevented by this," said Dr. Lawrence S. Cohen of Yale Medical School.

Heart attacks are the leading cause of death in the United States, killing more than 500,000 persons each year, according to the American Heart Association.

All 261,248 male physicians ages 40 to 84 living in the United States during 1982 were invited to participate in the aspirin study. More than 59,000 volunteers were screened and 22,000 physicians entered the trial, which began in 1983.

Of the 11,034 who took aspirin every other day, 104 had heart attacks. In the 11,037-person group that took placebos, 189 had heart attacks. Because the test sample was so large, there was only a minute statistical probability that the difference between the groups was caused by chance.

What the numbers mean is that an ordinary aspirin tablet taken every other day reduced the risk of a heart attack for healthy people by 47 per cent.

The study had generated intense interest in the medical community for years, and the tablet taken every other day by the 22,000 physicians came to be known as a Hennekens Pill, after Dr. Charles H. Hennekens, who directed the study at the Harvard Medical School and Brigham and Women's Hospital in Boston.

"It's a big, whopping decrease," Hennekens said of the results. But like other physicians familiar with the research, he urged that Americans use caution before they began to take the pills regularly.

"Do the results now justify the widespread use of aspirin for primary prevention" of heart attacks? wrote Dr. Arnold S. Relman, editor of *The New England Journal of Medicine*, in an editorial accompanying the report to be published today. "Any answer at this time must be tentative and carefully qualified."

The participants were screened heavily. No one who had trouble tolerating aspirin or who had a peptic ulcer, gout, liver, kidney disease or history of heart disease was included.

The use of aspirin as a preventive therapy for heart patients has been debated for more than a decade, but smaller studies have been inconclusive.

In 1985 federal health officials changed the labeling of aspirin to reflect evidence that it could reduce the likelihood of dying from second heart attacks and lower the risk of suffering from "unstable angina" – chest pains that change in severity or character and are associated with heart attacks.

Aspirin is thought to inhibit the action of special cells in the blood that play a role in clotting. That reduces the danger that a clot will form and block the flow of blood to the heart, causing a heart attack.

The study also found that regular use of aspirin seemed to increase the likelihood of one form of stroke. Although there was a major difference in the incidence of heart attacks between the two groups, there was no difference in the death rates from heart and blood vessel diseases. The researchers said the participants were unusually healthy and that the study would have had to continue into the 21st century to prove that aspirin affects death rates.

Dr. Claude Lenfant, director of the National Heart, Lung and Blood Institute, said that people with heart risk factors – such as high blood pressure, elevated cholesterol, smoking, diabetes or a family history of heart disease – should be considered for aspirin therapy.

But he urged patients to first discuss treatment with their physicians.

REFERENCE: A.S. Relman: Aspirin for the Primary Prevention of Myocardial Infarction. *New Engl. J. Med.* **318**(#4): 245-246 (1988); see also the Steering Committee Special Report on pages 262-264 of this journal and the subsequent Final Report: **321**(#3): 129-135 (1989). [DC Library call number: PER R11.B7]

1 Identify the matter(s) mentioned in the article which are components of a proper Plan for such an investigation.

2 Identify matter(s) *not* explicitly mentioned in the article which are components of a proper Plan for such an investigation.
- For each missing component you identify, indicate whether it would be practicable to incorporate it into this investigation; give reason(s) in each case.

3 Explain why it was necessary to carry out this investigation using an *experimental* Plan rather than an *observational* Plan.
- Would there be any *advantages* of an observational Plan in this context? Explain briefly.

4 A later study of *British* doctors, carried out using a Plan similar to that of the American investigation described in the article, found little relationship between aspirin consumption and a reduced risk of heart attack. Suggest reason(s) for the different Answers from the two investigations.
- Why would the British investigation have been undertaken when there was already a clear Answer from U.S. data?

(*continued overleaf*)

EM8910: Toronto Star, July 20, 1989, page A3

Aspirin cuts heart attack risk by half in healthy men over 50, study shows

BOSTON (AP-Reuter) – Healthy men over age 50 appear to cut their risk of heart attacks in half if they take an Aspirin every other day, although there is no clear evidence that younger men are helped, a study concludes.

A preliminary version of the research was widely publicized a year and a half ago when it found a dramatic reduction in heart attacks among regular Aspirin users.

Now, a more detailed analysis of that voluminous research data suggests that the benefits of Aspirin are most noticeable in older men, who are also at highest risk of heart trouble.

The research, called the Physicians' Health Study, was directed by Dr. Charles Hennekens of Brigham and Women's Hospital in Boston and published in the current issue of *The New England Journal of Medicine*.

Over-all, the study found that men who took a single Aspirin every other day had a 44 per cent reduction in their risk of heart attacks. However, the benefits were limited to those over age 50, who cut their risk about in half.

"We have a clear-cut, conclusive benefit on reducing a first heart attack", said Hennekens.

He said people should not start taking regular Aspirin unless they consult first with a doctor or other health professional. In helping make a decision, doctors should consider a patient's other risk factors, such as blood pressure, cholesterol level and family history of heart disease.

Aspirin – the common name for acetylsalicylic acid or ASA – works by making the blood less likely to clot. Heart attacks usually occur when clots form in the coronary arteries, choking off the heart's blood supply.

In Canada, Aspirin is a trademark of Sterling Drugs Ltd.

Heart disease

In an accompanying editorial, Dr. Valentin Fuster and others from Mount Sinai Medical Center in New York wrote that "Aspirin appears to be beneficial in the prevention of a first myocardial infarction (heart attack), at least in men over the age of 50, and it has its largest effect in those with uncontrolled risk factors.

"Given the available data, it now seems reasonable to advocate the use of Aspirin in a dose of 160 to 325 milligrams a day" in patients with clinical symptoms of heart disease, the three doctors said in the editorial.

Among other findings:

□ Aspirin users were slightly more likely to have strokes, but the number was too small to be statistically meaningful;

□ There was no over-all decrease in cardiovascular deaths among those taking Aspirin, but the study would have had to continue to the year 2000 or beyond to show any impact on mortality;

□ The benefits of Aspirin appeared to be greatest among those with low cholesterol levels – below 160.

The study, sponsored by the U.S. National Institutes of Health, involved 22,071 male doctors who took 325 milligrams of Bufferin ASA, supplied by Bristol-Myers Co., or a placebo, every other day.

The doctors were given packs of pills and randomly assigned to take Aspirin, beta carotene or the placebo, a neutral substance.

The final results include a detailed analysis of all physicians until Jan. 25, 1988, when doctors were informed whether they had been assigned to the Aspirin or placebo group.

After an average follow-up time of five years, the study said that heart attacks among physicians taking aspirin was 44 per cent lower than those taking the placebo, slightly lower than the 47 per cent reduction in risk reported last year in the preliminary report.

The two groups had virtually identical rates of gastrointestinal upsets and ulcers, both of which are frequently associated with higher rates of Aspirin use.

5 At the bottom of the middle column of the article above, it is stated that .... *the number (of strokes) was too small to be statistically meaningful.* Explain briefly what is meant by this statement.

6 Near the top of the right-hand column of the article above, it is stated that .... *the study would have had to continue to the year 2000 or beyond to show any impact (of Aspirin use) on mortality.* Explain briefly what is meant by this statement.

7 Explain briefly how to reconcile the two statements in the article: *(Aspirin use) has its largest effect in those with uncontrolled risk factors* (at the end of the fourth paragraph of the middle column) and: *The benefits of Aspirin appeared to be greatest among those with low cholesterol levels* (in the second paragraph of the right-hand column).

8 The third, fifth and sixth paragraphs of the right-hand column of the article refer to the usual *two* groups [*viz.*, treatment (Aspirin) and control (placebo)] of an experimental Plan but, in the intervening fourth paragraph, there appears to be a *third* ('beta carotene') group. Explain briefly how this discrepancy might be accounted for.

9 From the perspective of an experimental Plan, explain the importance of *random* assigning of subjects to the treatment and control groups, mentioned in the fourth paragraph of the right-hand column of the article.

10 The second-last paragraph of the article refers to a follow-up time of *five years*. Outline the difficulties that are likely to arise from such a *long* duration for the investigation.

11 Answer Questions 1 and 2 overleaf on page 10.3 with reference to the *Toronto Star* article reprinted above.

- Which of the two articles in this Figure do you consider the *better* account of the investigation? Give your assessment in *point* form.