EPIDEMIOLOGY 168

Fall 1983

Final Examination

December 15, 1983

Instructions:

1. Please WRITE ALL ANSWERS FOR SECTIONS I AND II ON THE ANSWER SHEETS PROVIDED -- You may keep the examination questions. Please write your essay for Section II on 8-1/2 by 11 lined notepaper.

2. PLEASE:

   Write LEGIBLY.
   Indicate clearly if you change your mind about an answer.

3. Please write the last four digits of your social security number in the upper right-hand corner of each page of your answers. (You may do this after the examination.)

4. Pay attention to the wording of each question. Some are true-false, some ask you to choose the best answer, some require that you give support for your answer.

5. Pace yourself so that you have time to attempt every question.

6. This examination is closed book. However, you may use:
   - a calculator
   - an English, foreign language, or medical dictionary (a medical dictionary has been provided for your use).

6. When you have finished the examination, please:

   - make certain your code number appears on all pages;

   - sign your name on the signout sheet, under the pledge:

     "I have neither given nor received help from others in completing this examination."

   - Remove the staple from the printed answer sheets for Sections I and II, and place each answer page on the corresponding pile.

   - Staple your essay for Section III and place in the appropriate pile.

7. Answers will be available by Monday; grades will probably be posted Tuesday.

Good luck and have a Happy Holiday! Thank you for taking EPID 168.

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Section I: Beta-Blocker Heart Attack Trial [39 points]

The following questions relate to the article "A randomized trial of propranolol in patients with acute myocardial infarction" (Beta-Blocker Heart Attack Trial Research Group, JAMA March 26, 1982:247:1707-1714). Pages 1707-1710 from this article are attached at the end of the examination booklet.

(2 pts.) 1. Based on this article, which of the following statements <u>best</u> characterizes the nature of the evidence concerning the effect of beta-blockers on survival after myocardial infarction (MI) at the time the present study was <u>initiated</u>? [Choose <u>one best</u> answer]

____ A. A plausible biologic rationale that had not yet been tested in animal or human studies;

____ B. Support from animal studies and clinical experience, but no experimental studies in humans;

____ C. Support from animal studies and epidemiologic cohort studies, but no human experimental studies;

____ D. Support from animal studies and inconclusive results fom human experimental studies.

(2 pts.) 2. Indicate an <u>advantage</u> of using total mortality (rather than arteriosclerotic heart disease mortality) as the principal outcome variable for this study:

_____

_____

_____

(3 pts.) 3. a. Indicate a <u>drawback</u> of using total mortality (rather then arteriosclerotic heart disease mortality) as the principal outcome variable; and

b. <u>briefly</u> assess whether this drawback was of consequence in this trial (<u>cite data</u> from the trial to support your answer):

a. _____

_____

b. _____

_____

(2 pts.) 4. What is a crucial advantage of randomized assignment of participants to treatment and control groups?

(2 pts.) 5. What is a major reason, <u>in addition to</u> the opportunity to randomize, for using a contemporaneous control group rather than historical controls for studying the effectiveness of beta-blockers and prognosis after MI?

(2 pts.) 6. The importance of knowing the inclusion and exclusion criteria in a study of this type primarily involves: [Choose <u>one best</u> answer]

____ A. external validity (generalizability);

____ B. statistical significance or power;

____ C. effect modification;

____ D. internal validity (selection bias).

(3 pts.) 7. Which exclusion criterion is the most problematic for drawing a conclusion in the form of a treatment recommendation? <u>Support your answer in one sentence</u>.

(3 pts.) 8. The article states that "All enrolled patients, regardless of final eligibility determination or degree of adherence to medication, are . . . counted in the study group to which they were assigned originally." [p. 1709, 3rd col.]

Which of the following statements is(are) TRUE and which is(are) FALSE? [Indicate TRUE or FALSE for <u>each</u> statement.]

TRUE	FALSE		
____	____	a.	This policy preserves the crucial advantage provided by the randomization.
____	____	b.	A high noncompliance rate in the propranolol group could cause a beneficial effect of propranolol to fail to be documented.
____	____	c.	The fact that 13% of control subjects were prescribed beta-blockers outside of the trial mechanism would tend to exaggerate the observed propranolol effect.

(2 pts.) 9. "Because of the issue of multiple significance testing, only the significance level (P value) for the primary response variable (total mortality) is unambiguous. For other outcome variables, the indicated significance values should be interpreted cautiously." [p. 1710, 1st col.]

Which of the following statements concerning the statistics shown in Table 3 is(are) TRUE and which is(are) FALSE? [Indicate TRUE or FALSE for <u>each</u> statement.]

TRUE	FALSE		
____	____	a.	There is less than a 5/1000 probability that the observed difference in <u>total</u> mortality rates was due to chance;
____	____	b.	The P-values for the differences in cardiovascular disease and arteriosclerotic heart disease death rates <u>may overestimate</u> the possible role of chance;

(4 pts.) 10. Draw a flow-chart of the study showing the recruitment and follow-up phases. Include dates for both stages and the number of subjects in each category including loss to follow-up. Do not give a detailed breakdown of the excluded subjects.

(2 pts.) 11. Which of the following statements concerning the results shown in Table 2 is(are) TRUE and which is(are) FALSE? [Indicate TRUE or FALSE for each statement.]

TRUE	FALSE	
____	____	a. The effect of propranolol on prognosis (as measured by the relative risk of death comparing the propranolol group to the placebo group) is stronger at 12 months than at 36 months.
____	____	b. The absolute difference in cumulative mortality risk is greater at 36 months than it is at 24 months.

(2 pts.) 12. Give a major reason for preferring life-table or survivorship analysis of the data for this trial as in Table 2 over comparison of overall cumulative mortality as in Table 3.

_____

_____

_____

(2 pts.) 13. If it were desired to explore the possible impact of loss to follow-up, what would be the most conservative assumption about the fate of the subjects lost to follow-up? [Note: interpret "conservative" to mean "in the direction of a no-effect result".]

_____

_____

_____

_____

(5 pts.) 14. Which of the following statements concerning Table 4 is(are) TRUE and which is(are) FALSE? [Indicate TRUE or FALSE for <u>each</u> statement.]

TRUE	FALSE	
____	____	a. Mortality risk was monotonically related to "Risk group".
____	____	b. The SMR for the propranolol group, using the placebo group as the standard, would be less than 1.0. [see note below]
____	____	c. The direct age-adjusted mortality rate in the propranolol group, using the placebo group as the standard, would be <u>slightly higher than</u> the unadjusted rate (of 7.2%). [see note below]
____	____	d. A comparison of propranolol and placebo group mortality based on age-adjusted rates would be misleading since it would mask the heterogeneity in <u>direction</u> of effect. [see note below]
____	____	e. The fact that the most favorable life-table relative risk was observed in the 30-39 year old subjects is convincing evidence that age modifies the propranolol effect.

Note: This was a convenient location for questions on age adjustment; they are not necessarily relevant to this study.

(3 pts.) 15. Two medical friends of yours are disputing the importance of the beta blocker results. One asserts that a 26% reduction in mortality is very impressive. The other responds that although statistically significant, the 3% difference in cumulative mortality is too small to have any public health impact. What would you say to your friends?

Section II: Myocardial infarction in women under 50 years of age [36 points]

The following questions relate to the article "Myocardial infarction in women under 50 years of age", by Lynn Rosenberg, Donald R. Miller, David W. Kaufman, et al. (JAMA November 25, 1983;250:2801-2806). An excerpt consisting of the introduction, methods, and tables 1-6 is attached at the end of the examination booklet.

(2 pts.) 1. The primary purpose of this study was to: [Choose <u>one best</u> answer]

____ A. Exaluate the effects of various factors on myocardial infarction (MI) in women under 50;

____ B. Test the hypothesis that smoking is the major risk factor for MI women under 50;

____ C. Investigate whether the risk associated with smoking diminishes with advancing age.

____ D. Test whether oral contraceptive use increases risk of MI in women under 50;

(3 pts.) 2. Cases were recruited from among about 585 women admitted to one of 155 hospitals with an acute MI meeting World Health Organization criteria for the diagnosis. This report is concerned with 256 cases. Which of the following accounts for most of the difference in number of cases studied? [Choose one <u>best</u> answer.]

____ A. refusal of the in-hospital interview;

____ B. refusal of the home visit;

____ C. death of the patient prior to interview;

____ D. exclusion due to location of residence relatively inaccessible to the investigators;

____ E. exclusion for use of drugs affecting plasma lipid levels.

(4 pts.) 3. Most of the information for this study was collected several months (median 16 months) after the subject's MI. Give <u>two (2) disadvantages</u> of this study design characteristic:

a. _____

_____

b. _____

_____

(4 pts.) 4. In this study, is age a confounder of the association between being an <u>ex-smoker</u> and nonfatal MI risk? Support your answer by <u>presenting an appropriate calculation</u> based on data from Table 1. Show all work. [The support is worth 3 points.]

(2 pts.) 5. Multiple logistic regression analysis was used to evaluate the potential confounding effects of several factors and to test for trends in risk.

Which of the following statements concerning logistic analysis of these data is(are) TRUE and which is(are) FALSE? [Indicate TRUE or FALSE for <u>each</u> statement.]

TRUE	FALSE	
____	____	a. In order to test for a trend in risk, a dichotomous exposure variable should be used.
____	____	b. A logistic model without interaction terms assumes a multiplicative relationship among the various exposure variables on odds of MI.

(2 pts.) 6. If the relative risk from hypertension [see Table 6] had been estimated using a multiple logistic model, what would be the approximate value of the beta coefficient? [Show formula and/or calculation.]

(3 pts.) 7. What is a principal advantage of multiple logistic regression analysis over stratification analysis for controlling confounding and how essential was it for this study?

(4 pts.) 8. For total cholesterol levels below 250 mg/dL is the joint relationship among:

- HDL (< versus >= 40 mg/dL),
- total cholesterol (< versus >= 200 mg/dL), and
- MI risk

in Table 3 better described as additive or multiplicative? [Support your answer with appropriate data from the table (the support is worth 3 points).]

(4 pts.) 9. Cite two (2) of Bradford Hill's criteria that would support an inference that cigarette smoking is causally related to nonfatal MI in women under 50:

a.

b.

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(6 pts.) 10. The case-control design is particularly susceptible to several types of biases that are absent or greatly reduced in cohort studies. Indicate <u>two</u> such types of bias (be more specific than saying merely "selection bias" and "misclassification bias") and <u>for each type briefly</u> assess how important it <u>might</u> be in causing the results of this study to differ from what would be found in a cohort study of myocardial infarction and cigarette smoking in women under 50.

a. _____

_____

_____

b. _____

_____

_____

(2 pts.) 11. The authors concluded that cigarette smoking is the dominant identified risk factor of MI in young women. Which of the following would be the <u>most</u> appropriate measure for describing the proportion of nonfatal first MI among women under age 50 that could be avoided if cigarette smoking were eliminated? [Choose <u>one best</u> answer]

____ A. etiologic fraction in the exposed (attributable fraction);

____ B. etiologic fraction (population attributable fraction);

____ C. excess risk;

____ D. odds ratio.

Section III: Commentary [25 points]

For any one of the topics listed below, write a succinct commentary in which you:

(1) Summarize the background and major findings on the topic;

(2) Describe the key methodologic issues involved (i.e., study designs, problems of measurement, analytic questions, etc.);

(3) Draw implications for policy and/or make recommendations for furter research, where indicated.

PLEASE:

(1) Write your commentary on 8 1/2 by 11 inch lined note paper.

(2) Write on every other line and use only one side of each sheet.

(3) Limit your commentary to 800 words (about four (4) sides written on every other line).

The clarity of your handwriting will be appreciated as well as that of your exposition.

TOPICS (Choose only one):

a. Low dose ionizing radiation and cancer risk -- is there a threshold?

b. Should home delivery be encouraged?

c. Do oral contraceptives reduce risk of breast cancer?

d. Overweight -- how much is too much?

e. Should the Amer Acad of Pediatrics officially recommend that parents abstain from smoking in the presence of their children?

f. Should mild hypertension be treated with drugs?

g. Nonpercutaneous communication of hepatitus B virus infection -- epidemiologic evidence and implications.

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Original Contributions

A Randomized Trial of Propranolol in Patients With Acute Myocardial Infarction

I. Mortality Results

β-Blocker Heart Attack Trial Research Group

• **The β-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung, and Blood Institute–sponsored, multicenter, randomized, double-blind, and placebo-controlled trial designed to test whether the regular administration of propranolol hydrochloride to men and women who had experienced at least one myocardial infarction would result in a significant reduction in total mortality during a two- to four-year period. During a 27-month interval, 3,837 persons between the ages of 30 and 69 years were randomized to either propranolol (1,916 persons) or placebo (1,921 persons), five to 21 days after the infarction. Depending on serum drug levels, the prescribed maintenance dose of propranolol hydrochloride was either 180 or 240 mg/day. The trial was stopped nine months ahead of schedule. Total mortality during the average 25-month follow-up period was 7.2% in the propranolol group and 9.8% in the placebo group. Arteriosclerotic heart disease (ASHD) mortality was 6.2% in the propranolol group and 8.5% in the placebo group. Sudden cardiac death, a subset of ASHD mortality, was 3.3% among the propranolol patients and 4.6% among the placebo patients. Serious side effects were uncommon. Hypotension, gastrointestinal problems, tiredness, bronchospasm, and cold hands and feet occurred more frequently in the propranolol group. Based on the BHAT results, the use of propranolol in patients with no contraindications to β-blockade who have had a recent myocardial infarction is recommended for at least three years.**

(*JAMA* 1982;247:1707-1714)

BY THE mid-1970s, β-blocking agents were used commonly in the treatment of coronary heart disease, primarily for the symptomatic relief of angina pectoris. It had also been demonstrated in experimental animal models that these agents decreased myocardial ischemia and limited infarct size.[1,2] Because of indications that β-blockers would be beneficial, a number of clinical trials had been carried out using these agents in the long-term treatment of survivors of myocardial infarction (MI).[3-10] Several of these studies showed trends favoring the use of β-blockers; however, because of small sample size or other limitations in design and analysis, the results were inconclusive. Based on these studies, the National Heart, Lung, and Blood Institute (NHLBI) decided that a study of sufficient size would be needed to address the question of benefit of β-blockade in patients after myocardial infarction. To this end, the NHLBI initiated the β-Blocker Heart Attack Trial (BHAT) in 1977.

The primary objective of the BHAT was to test in a multicenter randomized, double-blind, placebo-controlled trial, whether the daily administration of propranolol hydrochloride to patients who had had at least one documented MI would result in a significant reduction in mortality from all causes during a two- to four-year follow-up period. Secondary objectives of the trial were to study the effect of chronic administration of propranolol on coronary heart disease (CHD) mortality; sudden cardiac death (death from arteriosclerotic heart disease, occurring within one hour of the onset of symptoms); and

From the National Heart, Lung, and Blood Institute, Bethesda, Md.

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CHD mortality plus definite nonfatal MI.

Since 1977, the results of other studies of β-blockers in patients after MI have been reported.[1-4] With regard to mortality, one of these, which evaluated alprenolol hydrochloride, showed benefit in a subset of younger patients,[1] and one, which used propranolol, showed no difference.[2] Two recent trials, one of which studied timolol maleate and the other, metoprolol tartrate, demonstrated benefit from β-blockers.[3,4]

The preliminary findings of the BHAT have been released in a special advance report.[5] This article discusses in more detail the final results of the trial with regard to the effect of treatment on mortality.

METHODS

A detailed description of the BHAT design, sample-size calculation, eligibility criteria, response-variable definitions, randomization, and follow-up procedures[6] is published elsewhere[6,7] and will be only summarized here. Participating centers and investigators are listed at the end of this report.

The screening for study participants began on June 19, 1978, and ended on Oct 2, 1980. Men and women from age 30 through 69 years who were hospitalized with an acute MI documented by appropriate symptoms, and ECG and enzymatic changes were candidates for enrollment in the trial. Patients were excluded from the study if they had medical contraindications to propranolol, such as marked bradycardia; a history of severe congestive heart failure or asthma as an adult; a life-threatening illness other than CHD; had or were likely to undergo cardiac surgery; or were already taking or were likely to have β-blockers prescribed to them. Before enrollment, each patient was informed as to the nature of the study and its possible benefits and hazards, and informed consent was obtained. The coordinating center randomly assigned either propranolol or placebo to eligible patients in a double-blind manner, five to 21 days after hospital admission and while the patient was still hospitalized.

Patients were recruited at 31 centers with 134 participating hospitals. During the approximately two-year recruitment phase, a diagnosis of MI using BHAT criteria was made in about 16,400 patients who survived at least five days after admission and who were age eligible. Of these, 77% were not enrolled—18% because of contraindications to propranolol, 18% because they were already receiving or were likely to have propranolol prescribed to them, 26% because of study design considerations (such as living far from the clinic, having a cardiac pacemaker, having had cardiac surgery, or having other life-threatening diseases), and 15% because they or their private physicians did not consent to participate. About 23%, or 3,837 patients of the target population, were randomized (1,916 to propranolol and 1,921 to placebo).

A regimen of assigned study medication was begun (20 mg of propranolol hydrochloride or matching placebo) immediately after randomization. If no adverse reactions were noted, the dose was increased to 40 mg of propranolol hydrochloride or placebo every eight hours. Blood samples were drawn after a minimum of six consecutive doses on the 40-mg schedule, and eight hours after the last dose. For patients in the propranolol group, if the serum propranolol level,* as determined by a central laboratory, was below 20 ng/mL, the patient was prescribed 80 mg three times a day (240 mg/day) on his

Table 1.—Baseline Comparison

Variable	Group: Propranolol (n=1,916)	Group: Placebo (n=1,921)	z
Male, %	83.8	85.1	−1.15
White, %	89.3	88.4	0.89
Mean age, yr	54.7	54.9	−0.81
Mean systolic BP, mm Hg	112.3	111.7	1.65
Mean diastolic BP, mm Hg	72.5	72.3	0.95
Mean heart rate, beats per minute	76.2	75.7	1.38
Mean cholesterol, mg/dL	212.7	213.6	−0.65
Mean weight, kg			
Men	80.2	79.8	0.83
Women	67.4	66.5	0.89
Current smoker, %	57.4	56.9	0.26
Medical history, %			
Prior MI*	13.9	13.2	0.64
Hypertension	41.4	40.1	0.82
Angina pectoris	35.8	36.5	−0.48
Congestive heart failure	9.0	9.4	−0.42
Diabetes	11.7	11.3	0.38
Taking propranolol or other β-blocker	7.2	6.8	0.46
In-hospital events occurring before randomization, %			
Atrial fibrillation	6.8	5.7	1.49
Congestive heart failure	14.3	14.9	−0.56
Ventricular tachycardia	23.0	23.2	−0.15
Use of antiarrhythmic drug	45.8	46.0	−0.12
Medications being used at time of randomization, %			
Antiarrhythmic	16.6	17.9	−1.03
Anticoagulant	13.9	15.1	−1.02
Antiplatelet	7.1	6.8	0.40
Diuretic	16.1	18.0	−1.59
Vasodilator	36.0	36.3	−0.21
Digitalis	12.5	13.0	−0.50
Oral hypoglycemic	2.2	1.8	0.93
Location of BHAT MI,* %			
Anterior	27.8	25.7	1.47
Anterior and inferior†	9.2	10.0	...
Inferior	31.6	32.4	...
Nontransmural	22.9	22.6	...
Non-BHAT MI	8.6	9.2	...
ECG abnormalities, %			
Q-QS waves	67.3	67.4	−0.04
ST depression	25.8	26.7	−0.58
ST elevation	12.2	14.5	−1.98
T-wave abnormalities	64.8	65.9	−0.66
Ventricular conduction defects	10.3	7.5	2.99
Atrioventricular conduction defects	3.5	3.7	−0.20
Cardiomegaly,‡ %	37.0	34.7	1.34

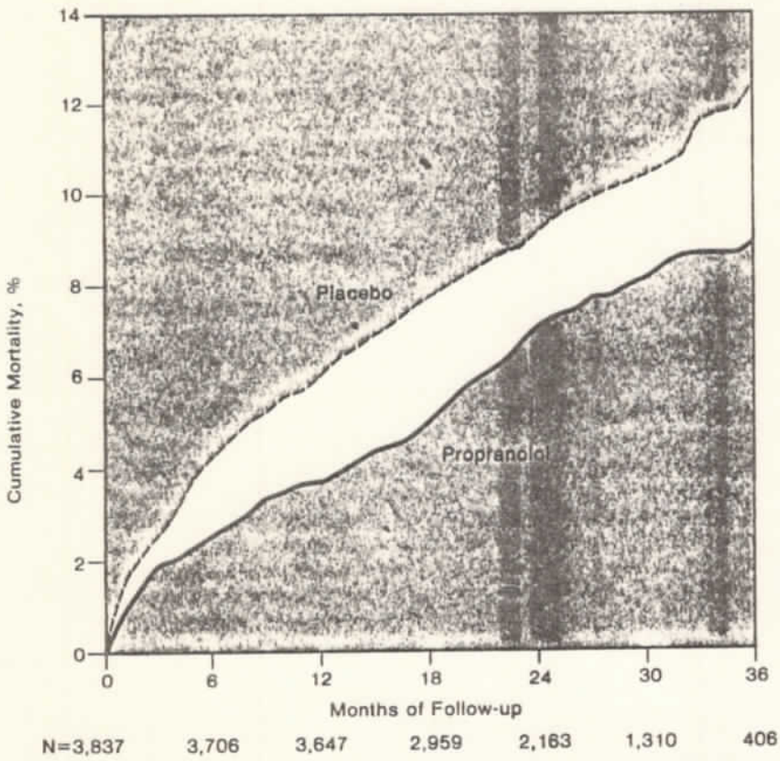
*MI indicates myocardial infarction; BHAT, β-Blocker Heart Attack Trial.

†Evidence of both anterior and inferior MI was present, but it was not determined which was the location of the acute BHAT event.

‡Cardiomegaly is defined as a cardiothoracic ratio of greater than 50% by standard six-foot posteroanterior chest roentgenograms. Data are missing for 15% of BHAT patient population.

Table 2.—Life Tables for Propranolol and Placebo Groups

	Propranolol				Placebo			
Period, mo	No. Alive at Beginning of Intervals	Deaths	Lost to Follow-up	Cumulative Mortality, %	No. Alive at Beginning of Interval	Deaths	Lost to Follow-up	Cumulative Mortality, %
1-3	1,916	37	1	1.93	1,921	50	2	2.60
4-6	1,878	10	0	2.45	1,869	31	0	4.22
7-12	1,868	23	1	3.66	1,838	34	1	5.99
13-18	1,844	24	2	5.03	1,803	30	1	7.69
19-24	1,501	29	0	7.13	1,458	20	1	9.15
25-36	1,087	14	0	9.00	107	22	2	12.52
36+	202	1	0	10.26	204	1	1	13.29
Total	...	138	4	...	...	188	8	...



Life-table cumulative mortality curves for groups receiving propranolol hydrochloride and placebo. N indicates total number of patients followed up through each time point.

return to the clinic at four weeks. If the blood level was at or above 20 ng/mL, the patient was assigned to a schedule of 60-mg tablets of propranolol hydrochloride three times a day (180 mg/day). To maintain the "blind," patients taking placebo were also assigned to either 180- or 240-mg daily dosage schedules. Dosage assignments were made through the coordinating center and remained in effect for the duration of the trial. Of the 3,837 enrolled patients, 82% were assigned the 180-mg/day regimen and 18% were assigned the 240-mg/day regimen.

Patients were asked to report to their clinical center at three-month intervals, with the exception of the first and second visits, which were scheduled for one month and six weeks after entry, respectively. At each visit, adherence to study drug, side effects, health status, the use of non-study medication, and occurrence of morbid events were monitored and additional study medication was dispensed. The clinic physician, on assessment of the patient, could reduce the prescribed dose of medication. Study medication was withdrawn from patients who were prescribed non-study β-blockers, with neither the patients nor the physicians being "unblinded."

All deaths were classified by the mortality classification subcommittee without knowledge of the treatment assignment. Information on cause and circumstances of death was obtained from relatives, witnesses, death certificates, attending physicians, hospital records, and autopsy reports.

Percentages of events in the propranolol and placebo groups, as well as results of life-table analyses, are reported. All enrolled patients, regardless of final eligibility determination or degree of adherence to medication, are included in these analyses and are counted in the study group to which they were assigned originally. Allowances were made in the original sample-size estimate to accommodate the anticipated noncompliance rates.[19,20] Mortality results were analyzed using standard survival analysis methods.[21,22]

Study data were reviewed periodically by a policy and data monitoring board, the members of which were not investigators in the BHAT. Because mortality data were to be analyzed at seven scheduled board meetings during the study, the probability of detecting a significant treatment effect by chance alone was greater than it would have been had the data been analyzed only at the end of the study. A number of statistical methods were proposed to correct for repeated significance testing.[23-26] The policy and data monitoring board was guided primarily by a monitoring technique[26,27] that requires extreme differences between groups early in the trial and smaller differences as the trial proceeds. Thus, the critical z value (observed difference divided by the standard error) at the first meeting of the board, for α=.05 and a two-sided test of significance was 5.46, while at the scheduled end of the trial the critical z value was 2.04. The conventional critical z value for a single test of the data is 1.96.

The board also considered at each review the probability that a statistically significant treatment effect would be identified if the study continued to its scheduled termination.[28,29] This approach to early stopping is also conservative, since the probability of detecting a significant difference is computed under the hypothesis

Table 3.—Cause-Specific Mortality by Treatment Group

Cause of Death	Propranolol No. of Deaths	Propranolol Mortality, %	Placebo No. of Deaths	Placebo Mortality, %	P* (Two-Sided)
Total mortality	138	7.2	188	9.8	<.005
Cardiovascular disease	127	6.6	171	8.9	<.01
Arteriosclerotic heart disease	119	6.2	164	8.5	<.01
Sudden†	64‡	3.3	89	4.6	<.05
Nonsudden	55	2.9	75	3.9	NS
Other cardiovascular disease	8	0.4	7	0.4	NS
Noncardiovascular disease	11	0.6	17	0.9	NS

*Because of the numerous statistical tests performed, the *P* values for cause-specific mortality should be interpreted cautiously.

†Deaths occurring less than one hour from onset of symptoms.

‡One death coded as sudden occurred approximately one week after cardiac surgery.

Table 4.—Mortality by Selected Baseline Variables, by Treatment Group

Variable	Propranolol, No. (%) Mortality	Placebo, No. (%) Mortality	Life-Table Relative Risk
Infarct location			
Anterior	533 (7.5)	494 (10.9)	0.67
Anterior and inferior	176 (11.4)	192 (15.1)	0.75
Inferior	605 (5.1)	623 (8.2)	0.61
Nontransmural	438 (8.2)	435 (7.8)	1.07
Non-BHAT MI*	164 (6.7	177 (11.3)	0.58
Risk group			
1	267 (13.5)	254 (17.3)	0.74
2	527 (8.2)	501 (11.8)	0.68
3	1,122 (5.3)	1,166 (7.3)	0.71
Age yr.			
30-39	100 (2.0)	95 (6.3)	0.31
40-49	417 (5.8)	405 (6.4)	0.90
50-59	783 (8.6)	788 (8.0)	0.82
60-69	616 (9.7)	633 (14.7)	0.64
Sex			
M	1,605 (7.2)	1,635 (9.5)	0.75
F	311 (7.1)	286 (11.5)	0.62
Diastolic BP, mm Hg			
<70	667 (5.8)	673 (8.3)	0.70
70-76	679 (7.8)	696 (10.5)	0.72
>76	570 (8.1)	552 (10.7)	0.74
Heart rate, beats per minute			
<73	683 (4.5)	708 (7.3)	0.59
73-80	637 (8.2)	648 (9.9)	0.84
>80	596 (9.2)	565 (12.7)	0.70

*BHAT indicates β-Blocker Heart Attack Trial; MI, myocardial infarction.

of no difference in mortality between the treatment groups for the remainder of the study.

On Oct 2, 1981, the policy and data monitoring board of the BHAT concluded that the propranolol therapy was effective and recommended that the trial be ended earlier than planned and that the results be reported promptly. Based on this recommendation, official patient follow-up was stopped on Oct 2, 1981, rather than in June 1982 as scheduled.

Because of the issue of multiple significance testing, only the significance level (*P* value) for the primary response variable (total mortality) is unambiguous. For other outcome variables, the indicated significance values should be interpreted cautiously.

RESULTS

Table 1 shows the distribution of selected baseline characteristics. Overall, there was excellent comparability between the two groups. The mean number of days in the hospital before randomization was 13.9 in the propranolol group and 13.7 in the placebo group. The median number of days was nine in each group. A more extensive discussion of the distribution of baseline characteristics in BHAT is available elsewhere.[16]

After an average follow-up period of 25.1 months, 138 patients in the propranolol group (7.2%) and 188 in the placebo group (9.8%) had died. (Since the earlier report of the findings, eight additional patients were found to have died on or before Oct 2, 1981, the official end of the trial—five in the placebo group and three in the propranolol group.) The life-table is shown in Table 2, and the survival curve is presented in Fig 1. At the end of the trial, vital status was unknown for 12 patients (four in the propranolol group and eight in the placebo group). Based on all randomized patients, the life-table *z* value for all-cause mortality is −2.90 (nominal $P<.005$; if repeated testing is taken into account by means of the indicated technique, two-sided $P<.01$). Adjusting for selected baseline variables by means of the Cox model[17] yielded a *z* value of −3.05 (the adjusting variables were treatment group, age, sex, race, smoking status, leisure time activity, prior MI, diabetes mellitus, angina pectoris, history of hypertension, vasodilator use, complications during the qualifying MI [cardiogenic shock, hypotension, congestive heart failure, use of digitalis, pulmonary edema, ventricular fibrillation, atrial fibrillation, atrioventricular block], diminished right dorsalis pedis pulse, heart rate, hematocrit reading, WBC count, serum cholesterol level, ST-segment elevation on ECG, ventricular conduction defect on ECG, diastolic BP, location of MI, intermittent claudication, serum creatinine level, and antiplatelet therapy).

Cause-specific mortality results are presented in Table 3. Cardiovascular mortality was reduced in the propranolol group (6.6% *v* 8.9%, $P<.01$). A subset of this category, arteriosclerotic heart disease (ASHD) mortality, was also reduced (6.2% *v* 8.5%, $P<.01$). Sudden death, a subset of the ASHD category, was less frequent in the propranolol group (3.3% *v* 4.6%, $P<.05$).

Table 4 shows mortality results analyzed by selected baseline variables. A relative risk of less than 1 indicates lower observed mortality in the propranolol group. Most of the subgroups studied exhibit a trend that is consistent with the overall finding of the study. A possible exception was the subset of patients with a nontransmural infarct. Propranolol was as effective in patients with inferior MIs as in those with anterior

Myocardial Infarction in Women Under 50 Years of Age

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THE CAUSES of myocardial infarction (MI) have been studied extensively in older people, and the important roles played by cigarette smoking, lipoprotein levels, and hypertension are established.[1] The disease has not been well studied in young people, particularly women, among whom MI is very uncommon. It is known that the effects of certain factors depend on age. It has been shown, for example, that cigarette smoking has a powerful effect on the risk of MI at young ages and that the relative increase in risk associated with a given level of smoking diminishes with advancing age.[1-4]

In the present study, the effects of various factors on the risk of nonfatal first MI in women under 50 years of age were evaluated. These include smoking, plasma lipid levels, hypertension, preeclamptic toxemia, angina pectoris, diabetes mellitus, obesity, ABO blood group, family history of MI, personality type, and reproductive factors. Oral contraceptives,[5,6] noncontraceptive estrogens,[7] aspirin,[8] coffee,[9] and alcoholic beverages[10] have been reported on elsewhere.

SUBJECTS AND METHODS

The data were obtained from a case-control study of first nonfatal MI in relation to oral contraceptive (OC) use in women under 50 years of age.[5,6] The study was conducted in two phases. In the first phase, women who were admitted to a hospital with an acute MI that met World Health Organization criteria for the diagnosis[11] (cases) and women admitted for other disorders (controls) were interviewed in the hospital.[5,6] Subsequently, in the second phase, selected participants were visited in their homes, where further information was collected and a blood sample was drawn. This report is concerned exclusively with those who participated in both phases.

Phase 1

Between June 1976 and June 1979, interviews of cases and controls were carried out in 155 hospitals located in three geographic regions[5,6]—greater Boston, Long Island and the coastal area north of New York City, and the Delaware Valley; the refusal rate in both the cases and controls was about 5%. Information on personal characteristics, habits, and medical and reproductive histories was elicited by standard questionnaires. Lifetime medication histories were elicited by questions on 42 indications for drug use.

There were 556 cases and 3,841 controls. They were 25 to 49 years of age, and none had a history of previous MI. The controls were admitted for diagnoses judged to be unrelated to OC use, mainly fractures and sprains, orthopedic disorders, and acute infections.[6]

Phase 2

In this phase, conducted between June 1978 and June 1981, cases and controls from each of the three geographic regions were selected for a home visit. Only subjects who lived in areas chosen for accessibility were eligible. About half of the cases interviewed in the first phase were included; an attempt was made to also include, for each case, about three controls of similar ages from the same areas. The refusal rate was 14% among eligible cases and 27% among eligible controls.

The home visit was made at least three months after discharge from the hospital, with a median interval of 16 months. A blood sample was drawn for determinations of ABO blood group, total plasma cholesterol level, and plasma high-density lipoprotein (HDL) cholesterol level; 93% of both cases and controls gave nonfasting blood samples. The cholesterol measurements were made on edetic acid-treated plasma by the Framingham Heart Study laboratory with the methods of the Lipid Research Clinics.[12] At the same visit, the subject's weight was recorded, information on history of MI or stroke in the subject's parents and siblings was obtained, and a ten-question personality questionnaire based on the Jenkins Activity Scale[13] was administered. The questionnaire was designed to measure time urgency and competitiveness; possible scores ranged from 0 to 10, with high scores indicating a greater tendency to "type A" personality.

There were 256 cases and 804 controls. The median age was 44 years among the cases and 42 years among the controls. One case and two controls who had used OCs or clofibrate within the month before the home visit were excluded because these drugs can affect plasma lipid levels. Thus, the present report is based on 255 cases and 802 controls.

Analysis

We computed 95% confidence intervals about point estimates of relative risk using Miettinen's method.[14] Unless otherwise noted, estimates given in this report are aggregated over strata of age (<40, 40 to 44, and 45 to 49 years) and cigarette smoking (none, one to 24 cigarettes per day, and ≥25 cigarettes per day) by the Mantel-Haenszel method.[15]

Multiple logistic regression analysis was used to evaluate the potential confounding effects of several factors and to test for trends in risk.[16] The logistic regression equations included terms for each factor considered in this report and for age, geographic region of the admitting hospital, and OC use. The logistic regression estimates were generally similar to those obtained after stratification on age and smoking and are not presented.

The tables show slight variations in the totals because of the exclusion of subjects with unknown values for particular factors.

Table 1.—Cigarette Smoking Among Cases of Myocardial Infarction and Controls

Cigarettes/Day	No. (%) Cases	No. (%) Controls	Relative Risk Estimate*	95% Confidence Interval
Never smoked	24(9)	250(31)	(1.0)†	. . .
Ex-smoker‡	18(7)	126(16)	1.4	0.7-2.8
1-14	8(3)	89(11)	0.9	0.4-2.2
15-24	66(26)	172(22)	4.3	2.6-7.0
25-34	54(21)	73(9)	8.3	5.0-14
≥35	85(33)	86(11)	10	6.5-16

*Allowance made for age.
†Reference category.
‡Last smoked at least one year before admission.

Table 2.—Total Plasma Cholesterol Levels Among Cases of Myocardial Infarction and Controls

Total Plasma Cholesterol, mg/dL	No. (%) Cases	No. (%) Controls	Relative Risk Estimate*	95% Confidence Interval
<200	72(28)	407(51)	0.6	0.4-0.9
200-249	105(41)	296(37)	(1.0)†	. . .
250-299	51(20)	74(9)	1.9	1.2-3.1
≥300	26(10)	21(3)	3.2	1.8-5.9

*Allowance made for age and cigarette smoking.
†Reference category.

Table 3.—Total Plasma Cholesterol Levels Among Cases of Myocardial Infarction and Controls, by High-Density Lipoprotein (HDL) Levels

Plasma HDL, mg/dL	Total Plasma Cholesterol, mg/dL	No. (%) Cases	No. (%) Controls	Relative Risk Estimate*	95% Confidence Interval
<40	<200	45(30)	141(53)	1.5	0.9-2.4
	200-249	59(40)	90(34)	3.1	1.9-5.0
	250-299	31(21)	25(9)	5.2	2.8-10
	≥300	14(9)	8(3)	5.2	2.3-12
≥40	<200	27(26)	264(50)	0.5	0.3-1.0
	200-249	45(43)	203(38)	(1.0)†	. . .
	250-299	20(19)	49(9)	2.0	1.0-4.1
	≥300	12(12)	13(2)	5.5	2.3-14

*Allowance made for age and cigarette smoking.
†Reference category.

Table 4.—Plasma High-Density Lipoprotein (HDL) Levels Among Myocardial Infarction Cases and Controls

Plasma HDL, mg/dL	No. (%) Cases	No. (%) Controls	Relative Risk Estimate*	95% Confidence Interval
<30	47(19)	65(8)	3.1	1.8-5.4
30-39	103(41)	199(25)	2.4	1.5-3.7
40-49	56(22)	232(29)	1.2	0.7-2.0
50-59	32(13)	167(21)	(1.0)†	. . .
≥60	16(6)	130(16)	0.6	0.3-1.3

*Allowance made for age and cigarette smoking.
†Reference category.

Table 5.—Plasma High-Density Lipoprotein (HDL) Levels Among Myocardial Infarction Cases and Controls by Total Plasma Cholesterol Levels

Total Plasma Cholesterol, mg/dL	Plasma HDL, mg/dL	No. (%) Cases	No. (%) Controls	Relative Risk Estimate*	95% Confidence Interval
<250	<30	33(20)	56(8)	3.5	1.8-6.7
	30-39	71(40)	175(25)	2.3	1.3-3.8
	40-49	40(23)	209(30)	1.2	0.6-2.2
	50-59	23(13)	144(21)	(1.0)†	. . .
	≥60	9(5)	114(16)	0.5	0.2-1.2
≥250	<30	13(17)	9(9)	5.5	2.2-14
	30-39	32(42)	24(25)	6.3	3.9-18
	40-49	16(21)	23(24)	3.8	1.7-8.6
	50-59	9(12)	23(24)	2.9	1.1-7.9
	≥60	7(9)	16(17)	3.5	1.1-12

*Allowance made for age and cigarette smoking.
†Reference category.

Table 6.—Hypertension and Other Conditions Among Cases of Myocardial Infarction and Controls

Condition	No. (%) Cases	No. (%) Controls	Relative Risk Estimate*	95% Confidence Interval
Hypertension	61(24)	99(12)	2.0	1.4-2.9
Preeclamptic toxemia	26(10)	60(8)	1.3	0.8-2.3
Diabetes mellitis	19(7)	14(2)	6.4	3.3-12
Angina pectoris	12(5)	10(1)	3.8	1.5-9.5

*For each factor, the reference category is absence of the factor, allowance made for age and cigarette smoking, with the following exceptions: for hypertension, allowance made for age, cigarette smoking, and preeclamptic toxemia; for preeclamptic toxemia, allowance made for age, cigarette smoking, and hypertension.

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Answers to Final Examination

Section I: Beta-Blocker Heart Attack Trial [39 points]

(2 pts) 1. D

(2 pts) 2. No concern about ambiguities of classification of cause of death; avoids concern that saving of lives from CVD might be offset by increased deaths from some other effect of the drug.

(3 pts) 3. Drawback is dilution of effect (or reduced statistical power) because of inclusion of unrelated causes of death along with relevant ones. Not a serious problem here since over 85% of deaths were from arteriosclerotic heart disease.

(2 pts) 4. Randomization tends to balance the two groups with respect to unknown and/or unmeasurable potential confounders.

(2 pts) 5. Case fatality of MI patients may have changed due to improvements in other aspects of medical care and patient behavior; patients may differ in characteristics that cannot be controlled in the analysis because were not measured in controls.

(2 pts) 6. A

(3 pts) 7. Patients already receiving or likely to have propranolol prescribed - these are exactly the target population to whom the results are to be applied, nor it is not possible clearly to distinguish them from those in the trial. Several other answers were given full credit. Contraindication to propranolol is not very problematic, since such patients are by definition not appropriate for receiving the drug.

(3 pts) 8. TTF

(2 pts) 9. FF

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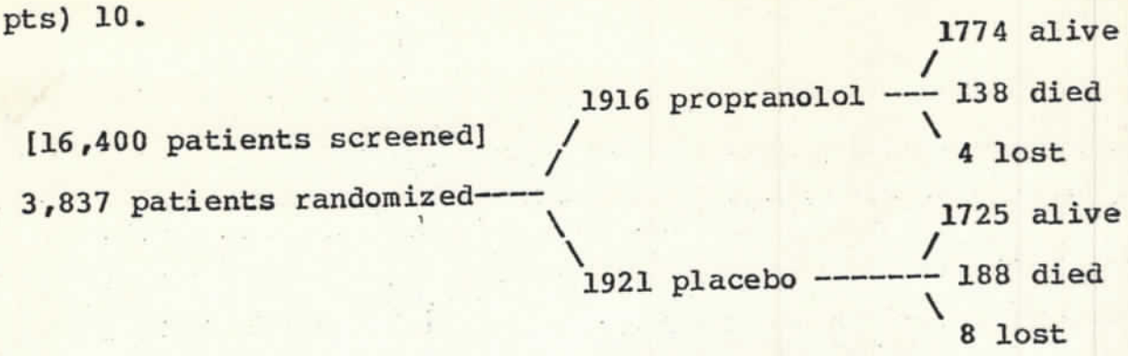
(4 pts) 10.



(2 pts) 11. TT

(2 pts) 12. Different lengths of follow-up, because subjects were recruited over a two-year period (the different lengths of follow-up for subjects are reflected in the 2nd and 6th columns of Table 2);
survivorship analysis takes into account the time to death as well as the fact of death;
better control of loss to follow-up (only gets part credit, since so few subjects were lost).

(2 pts) 13. The subjects lost from the propranolol group all died at time they were lost to follow-up, whereas those lost from the placebo group remained alive at the end of the trial. [1 point if said that those lost from propranolol group died and those lost from placebo group survived.]

(5 pts) 14. TTTFF

(3 pts) 15. Tell them (1) that the observed difference underestimates the real impact, due particularly to analysis of subjects according to their originally assigned group regardless of ultimate beta blocker status; (2) that 3% in cumulative mortality risk applied to such a major cause of death could result in thousands of lives prolonged.

Section II: Myocardial infarction in women under 50 years of age [36 points]

(2 pts) 1. A

(3 pts) 2. D

(4 pts) 3. change in risk factor levels, selective survival, degradation of memory, more time to learn family history

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(4 pts) 4. Age is not an important confounder: crude OR for being an ex-smoker is:

$$\frac{(18)(250)}{(24)(126)} = 1.49 \text{ (vs 1.4 controlled)}$$

(2 pts) 5. FT

(2 pts) 6. Beta coefficients for dichotomous variables in logistic model are natural log of OR [ln(OR)], so beta coefficient for hypertension = ln(2.0) = .7 (it is most logical to use this adjusted relative risk rather than to compute OR from the percent of cases and controls with hypertension, since the logistic model would have adjusted for age, smoking, and preeclamptic toxemia).

(3 pts) 7. Ability to control for many variables simultaneously (important because many MI risk factors but in the end it was necessary to control only age and smoking for most analyses); ability to model dose-response relationships (important because many risk factors examined in this study are ordinal or continuous)

(4 pts) 8. Multiplicative: within each HDL category, total cholesterol between 200-249 mg/dL is associated with a tripling of risk over <200 mg/dL; within each total cholesterol category (<200 and 200-249 mg/dL) HDL < 40 mg/dL is associated with a doubling of risk over HDL >= 40 mg/dL:

Relative risk estimates from Table 3

	HDL<40	HDL>=40
Total cholesterol <200	1.5	0.5
Total cholesterol 200-249	3.1	1.0 [reference category]

(4 pts) 9. Strength (RR estimate of over 8 for heavy smoker), dose-response (Table 1), biological plausability (nicotine and carbon monoxide affect heart and blood vessels), consistency (other studies have shown), antecedent-consequent is not an issue.

(4 pts) 10. Selective survival: could well be a problem, since fatalities occur before hospital admission; selective recall/interviewer suspicion bias - could well be a problem because interviewers were probably not blinded to case-control status; antecedent-consequent - probably not serious in this study, since smoking onset occurs in young adulthood and doubtfully following onset of arteriosclerosis

(2 pts) 11. B

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Supplemental Practice Questions based on 1983 Final Examination

The following questions relate to the article "A randomized trial of propranolol in patients with acute myocardial infarction" (Beta-Blocker Heart Attack Trial Research Group, JAMA March 26, 1982:247:1707-1714).

(2 pt) A.1. The BHAT was a "double-blind, placebo-controlled trial." Which of the following statements best describes the double-blind aspect of this trial? [Choose one best answer]

____ A. all subjects were kept in ignorance of both treatment assignment and outcome;

____ B. neither the subject nor the investigators knew the subject's actual treatment assignment;

____ C. neither the subject nor the investigators knew the subject's actual outcome;

____ D. neither the subject nor the investigators knew the subject's treatment assignment or outcome.

(2 pt) A.2. Which of the following statements best describes the meaning of "placebo-controlled" in this study? [Choose one best answer]

____ A. all subjects received, in addition to their pharmacologic treatment, specific verbal reinforcement from the physician in order to control for expectancy effects;

____ B. empirically-verifiable outcomes were used to minimize the impact of expectancy effects on the part of both subject or investigators;

____ C. randomization reduced the likelihood that self-fulfilling expectations could influence the subject outcomes;

____ D. control subjects received an inert pill or capsule with an appearance identical to that of the experimental subjects.

(4 pt) A.3. What are <u>two (2) advantages</u> of having a double-blind, placebo-controlled trial for evaluating the effectiveness of propranolol on the prognosis of MI patients?

a. _____

_____

b. _____

_____

(3 pt) A.4. Table 1 shows z-statistics for differences between propranolol and placebo groups with regard to several prognostic factors. Which of the following statements concerning these z-statistics is(are) TRUE and which is(are) FALSE? [Indicate TRUE or FALSE for <u>each</u> statement.]

TRUE	FALSE	
____	____	a. The randomization was successful in producing two similar groups;
____	____	b. Prognostic factors for which the z-statistic exceeds 1.96 (the critical value for a two-sided alpha of .025) are confounders of the relationship between treatment and mortality;
____	____	c. Prognostic factors for which the z-statistic is less than 1.96 are unlikely to be confounders of the relationship between treatment and mortality.

(3 pt) A.5. Of the exclusion conditions listed, cite <u>one</u> which would probably have little impact on the author's conclusion <u>and support your answer</u> in one sentence.

_____

_____

_____

_____

(2 pt) A.6. Table 2 shows 10.26% cumulative mortality for the propranolol group, whereas Table 3 shows 7.2%. Which of the following gives the <u>best</u> explanation of this difference? [Choose <u>one best</u> answer]

____ A. The computation of cumulative mortality in Table 2 takes into account the smaller contribution to follow-up of subjects who died during the trial;

____ B. The computation of cumulative mortality in Table 2 takes into account the different lengths of follow-up for subjects who did not die during the trial;

____ C. The computation in Table 2 excludes subjects who were nonadherent or where lost to follow-up;

____ D. The computation in Table 2 is more precise than that in Table 3.

The following questions relate to the article "Myocardial infarction in women under 50 years of age", by Lynn Rosenberg, Donald R. Miller, David W. Kaufman, et al. (JAMA November 25, 1983;250:2801-2806).

(3 pt) B.1. 84% of the cases and 53% of the controls smoked cigarettes. Compute the crude relative risk estimate of nonfatal MI for smokers [for full credit, <u>your answer should show</u> the correct formula and the correct substitution in the formula]:

(2 pt) B.2. Tables 2 and 4 present data suggesting that total plasma cholesterol is positively related and HDL cholesterol is inversely related to MI risk. Which of the following statements best characterizes their relationship to MI risk when the influence of the other variable is taken into account. [Choose <u>one best</u> answer]

____ A. The association between total cholesterol and MI risk is due to the influence of HDL;

____ B. The association between HDL and MI risk is due to the influence of total cholesterol;

____ C. Each of the two cholesterol variables contributes to prediction of MI risk;

____ D. There is an interactive effect of the two cholesterol variables, so that the association of total cholesterol with MI risk is <u>present only</u> at lower levels of HDL.

(2 pt) B.3. Support your answer to the preceding question by citing data from Table 3.

_____

_____

_____

_____

Answers to Supplemental Questions

A. Beta-Blocker Heart Attack Trial

(2 pt) A.1. B

(2 pt) A.2. D

(4 pt) A.3. avoid or reduce differential information bias from unequal diagnostic surveillance in experimental and control groups; equalize expectancy effects among trial participants.

(3 pt) A.4. a. T - only two z-statistics exceed the critical value for .05
b. F - a statistical test does not indicate whether confounding has occurred - given the size of the study groups, a difference may be "significant" but not be large enough to affect the survival comparison.
c. T - given the size of the study groups, a difference large enough to affect the comparison is bound to be significant (?)

(3 pt) A.5. Contraindictions to propranolol - such persons would not be eligible to receive the drug even regardless of the trial results; patients living too far from the clinic - could be a problem, but would not expect geographical location to interact with propranolol effect; cardiac pacemaker and cardiac surgery, other life-threatening diseases - not clear what impact of exclusion, but at least easy to identify.

(2 pt) A.6. B

B. Myocardial infarction in women under 50 years of age

(3 pt) B.1. OR=Odds of smoking in cases/Odds of smoking in controls
= (.84/.16)/(.53/.47) = 4.66, or,
OR=ad/bc with some other reasonable numbers.

(2 pt) B.2. C

(2 pt) B.3. for patients with plasma HDL >= 40 mg/dL, total plasma cholesterol is associated with relative risk estimates of 2.0 (for 250-299 mg/dL) and 5.5 (for >= 300 mg/dL) compared to 200-249 mg/dL; a similar association is seen among patients with Plasma HDL < 40 mg/dL; subjects with plasma cholesterol of 200-249 mg/dL have a 3.1 relative risk if their HDL is <=40 mg/dL.

12/27/83