Angiographic Prevalence of High-risk Coronary Artery Disease in Patient Subsets (CASS)

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SUMMARY The prevalence of coronary artery stenoses $\geq 70\%$ or left main stenosis $\geq 50\%$ was evaluated in 20,391 patients who underwent angiography in the Coronary Artery Surgery Study from 1975–1979. After the patients with unstable angina or myocardial infarction were excluded, the disease prevalence in the 8157 patients with definite angina, probable angina, and nonspecific chest pain was 93%, 66% and 14% in men and 72%, 36% and 6% in women (p < 0.001).

The age and sex of the patients and character of chest pain were important determinants of disease prevalence and severity. Left main or three-vessel coronary disease occurred in more than 50% of middle-aged men and older women with definite angina and in more than 50% of men who had probable angina and were older than 60 years of age. In contrast, left main coronary disease occurred in less than 2% of 1282 men and less than 1% of 1397 women with nonspecific chest pain regardless of age. In this latter patient subset, less than 5% of men and less than 1% of women in each decade under 60 years had left main or three-vessel coronary artery disease.

Thus, high-risk coronary disease is common in middle-aged patients with definite angina and older patients with probable angina, but is rare in patients with nonspecific chest pain. Indications and guidelines for diagnostic noninvasive tests and coronary angiography could be based on these results.

THE INDICATIONS for cardiac catheterization in patients with suspected coronary artery disease are changing as new noninvasive diagnostic tests and treatments become available.1-10 The ability of different noninvasive tests, such as stress ECG, myocardial scintigraphy and radionuclide cineventriculography, to detect the presence and extent of coronary artery disease is dependent on the population under study.^{1, 11, 12} The Bayesian theory has been reviewed extensively in recent years using clinical and angiographic data obtained from cardiac catheterization results published in the late 1960s. 18-18 The quality of cineangiography has improved considerably in the last decade and clinical-angiographic correlations are now available not only for disease prevalence, but also for disease severity.

Coronary bypass surgery has been shown to improve survival in certain groups of patients with left main and/or three-vessel coronary artery disease. 19, 20 A high index of suspicion for this type of coronary disease has become in itself an indication for cardiac catheterization even in patients with nonspecific chest pain or asymptomatic patients. Few data are available on the incidence of left main and/or three-vessel disease in subgroups of patients with different types of chest pain. This knowledge is required to quantitate the diagnostic yield of noninvasive tests in terms of

disease severity and cost-effectiveness and to redefine some of the current indications for coronary angiography.

The present study correlates clinical and angiographic findings in 20,391 patients who underwent cardiac catheterization in the Coronary Artery Surgery Study (CASS) from 1975–1979. The prevalence and severity of coronary artery disease were evaluated after patients were subdivided into groups based on age, sex and type of chest pain.

Methods

Patient Population

The CASS registry includes all patients seen at 15 medical centers (appendix 1) in whom the primary reason for cardiac catheterization was suspected or proved coronary artery disease. Criteria used to exclude patients from the registry included significant nonischemic valvular heart disease, nonischemic cardiomyopathy, a significant language barrier or inaccessibility for follow-up, and refusal to give informed consent. Patients with previous aortocoronary bypass surgery were included in the registry but excluded from the present analysis. The number of patients contributed by center is shown in figure 1. The method of data collection in CASS has been described.²¹

The patients were characterized according to type of chest pain reported. The patients with definite angina described a substernal discomfort that was precipitated by exertion and relieved by rest or nitroglycerin in less than 10 minutes. Most patients reported typical radiation to the shoulders, jaw or inner aspect of the arm. The patients with probable angina had most of the features of definite angina, but

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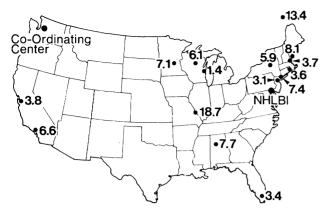


FIGURE 1. Geographic display of the percentage of patients enrolled by site.

were atypical in some aspects, e.g., atypical radiation of pain, nitroglycerin not always effective, the pain was relieved only after 15–20 minutes of rest. The patients that probably did not have angina described an overall pattern of chest pain that did not fit the above descriptions, e.g., chest pain unrelated to activity, unrelieved by nitroglycerin and apparently noncardiac in origin.

Cardiac Catheterization

Coronary angiography was performed using either the brachial or the femoral approach. Coronary stenoses $\geq 70\%$ of the arterial luminal diameter in any view were considered significant lesions; stenoses of large diagonal or marginal branches were counted as lesions of the left anterior descending and circumflex coronary arteries, respectively. Right coronary disease in a left-dominant circulation was not considered. Left main coronary lesions were counted as two-vessel disease and were considered present when the luminal diameter was reduced by 50%. Left main equivalent coronary disease was considered when a luminal stenosis ≥ 70% was present in the left anterior descending coronary artery before the first septal branch and in the proximal circumflex coronary artery before the first obtuse marginal branch in the absence of left main coronary artery disease.

The differences between groups were analyzed using the chi-square test for categorical variables.²²

Results

Coronary disease prevalence increased with age and was most frequent in men with a history of myocardial infarction; the likelihood of obstructive coronary disease after a myocardial infarction ranged from 85-98% in men and 79-91% in women who were 30 years or older. The effect of age as a determinant of disease prevalence was most striking in patients without an infarct (fig. 2).

The patient population was subdivided according to age, sex and character of chest pain because each of these variables can affect the likelihood of coronary disease. In addition, patients with a previous myocar-

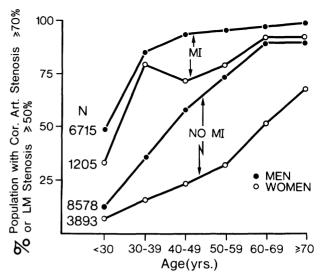


FIGURE 2. The prevalence of obstructive coronary disease is higher in men and relatively constant in patients with a history of myocardial infarction (MI). Cor. Art. = coronary artery; LM = left main coronary artery.

dial infarction or patients who had unstable angina at the time of angiography were excluded to obtain a group of patients with chronic stable chest pain in whom the diagnosis of coronary disease was not known a priori.

Coronary Disease Patterns in Men

The prevalence of obstructive coronary disease in men with definite angina, probable angina and nonspecific chest pain was 93%, 66% and 14%, respectively (p < 0.001) (table 1). Among the 1919 men with definite angina, one- two- and three-vessel disease occurred in 21%, 29% and 43% of the population, respectively. In these patients, the prevalence of three-vessel disease increased markedly with age and ranged from 20% in men 30-39 years old to 70% in men of the oldest age group (fig. 3). Of the men with definite angina who were 50 years or older, 50% had three-vessel or left main coronary artery disease. Left main coronary stenosis \geq 50% occurred in 24% of the men with definite angina who were 70 years or older, and in 8-18% in the younger decades.

Among the 2146 men with probable angina, one-, two- and three-vessel disease occurred in 22%, 22% and 22% of the population, respectively. In all age groups, less than 50% of men with probable angina had three-vessel or left main coronary artery disease. Left main coronary artery stenosis \geq 50% occurred in 15% of men who were 70 years or older and in 10% or fewer of men in the younger decades (fig. 3). The average number of diseased vessels in men with probable angina was less than in men with definite angina in each decade, which indicates that coronary artery disease was more severe in patients with definite angina.

Of the 1282 men with nonspecific chest pain, one-, two- and three-vessel disease occurred in 8%, 4% and

Table 1. Coronary Artery Disease Prevalence in Men with Stable Chest Pain and No History of Myocardial Infarction*

	n		Luminal stenosis < 50%						Prevalence of specific coronary artery disease patterns			
A					Number of vessels with luminal stenosis $\geq 70\%$ or LM stenosis $\geq 50\%$			Mean number of — diseased	LM stenosis		LMEQ ≥ 70%, no LM - stenosis	LM stenosis ≥ 50% or three- vessel stenosis
Age (years)					1	2	3	vessels	≥50%	≥ 70%	≥ 50%	≥ 70%
Definite a	angina	l										
30-39	66	9	5	3	38	25	20	1.78	8	3	5	23
40-49	402	7	4	1	27	29	32	2.05	11	6	4	35
50-59	840	2	1	2	20	31	43	2.24	14	10	10	46
60-69	539	2	2	1	16	28	51	2.38	18	10	12	55
≥ 70	67	2	0	1	9	18	70	2.63	24	16	12	73
$\mathbf{Total}\dagger$	1919	3	2	2	21	29	43	2.24	15	9	9	46
Probable	angin	ıa										
30-39	171	42	8	4	19	19	8	1.79	2	1	2	9
40-49	568	28	10	5	23	16	18	1.92	5	3	2	20
50-59	919	13	10	6	24	25	22	1.97	7	4	4	23
60-69	434	10	7	5	21	25	32	2.15	10	5	6	33
≥ 70	46	2	4	0	22	26	46	2.26	15	11	4	48
Total†	2146	18	10	6	22	22	22	2.00	7	4	4	24
Nonspec	ific ch	est pain										
< 30	51	98	2	0	0	0	0	0.00	0	0	0	0
30-39	249	83	10	4	2	0.4	0.8	1.56	0	0	0	0.8
40-49	391	61	20	7	9	2	1	1.34	0	0	0.3	1
50-59	440	51	19	12	11	5	2	1.51	2	0.7	0	3
60-69	129	39	19	15	12	9	6	1.78	0.8	0.8	0.8	6
≥ 70	22	14	18	5	9	32	22	2.21	0	0	5	23
Total	1282	60	17	9	8	4	2	1.57	0.6	0.3	0.2	3
Total†	5347	23	9	5	18	20	25	2.10	8	5	5	27

^{*}All numbers in the table are expressed as a percentage of n in each age category except the mean number of diseased vessels. Percentages > 1% are rounded to the nearest whole number.

Abbreviations: LM = left main coronary artery; LMEQ = left main equivalent lesion.

2% of patients, respectively. Obstructive coronary disease did not occur in the 51 men younger than 30 years of age. Left main coronary disease did not occur in the 691 patients younger than 50 years of age, nor did it exceed 2% per decade in the older patients. Threevessel or left main coronary artery disease was uncommon in patients younger than 70 years of age and occurred in 23% of the 22 older men older than 70 years of age (fig. 3).

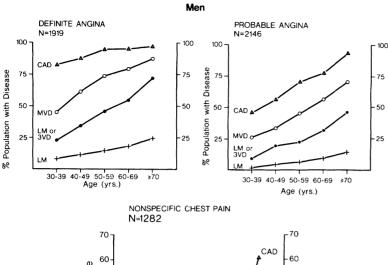
Coronary Disease Patterns in Women

The prevalence of obstructive coronary disease in women with definite angina, probable angina and non-specific chest pain was significantly different: 72%,

36% and 6%, respectively (p < 0.001) (table 2). The likelihood of obstructive coronary disease in women with definite angina was less than in men, although the difference was less evident in patients older than 70 years. As in men, the prevalence of three-vessel disease in the 401 women with definite angina increased sharply by decade. Three-vessel or left main coronary artery disease occurred in over 40% of women older than 60 years of age (fig. 4). The prevalence of left main coronary disease, however, was less common than in men.

Among the 1012 women with probable angina, one, two- and three-vessel disease occurred in 17%, 11% and 8% of the population, respectively. The prevalence of left main coronary disease did not exceed 5%

[†]Data of five and eight men less than 30 years of age with definite and probable angina, respectively, are excluded from the table; n is too small to subdivide into disease category.



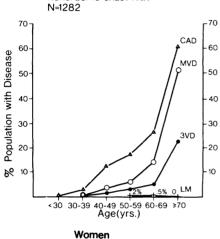
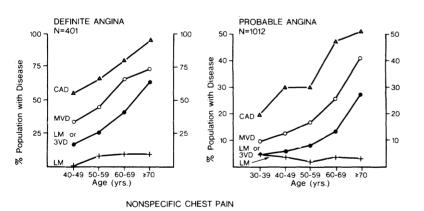


FIGURE 3. The percentage of men with obstructive coronary artery disease (CAD), multivessel disease (MVD), left main artery or three-vessel disease (LM or 3VD) and left main coronary artery disease (LM) are illustrated for men with definite angina, probable angina and nonspecific chest pain. High-risk coronary pathology (LM or 3VD) is common in middle-aged or older men with definite angina and rare in men younger than 70 years of age with nonspecific chest pain. For illustration purposes, the y-axis scale in men with definite and probable angina is from 0-100%. In men with nonspecific chest pain, the y-axis scale is 0-70%.



8

2

FIGURE 4. For illustrative purposes, the y-axis scale in women with definite angina is 0-100%, with probable angina 0-50%, and with nonspecific chest pain 0-10%. The prevalence of left main or three-vessel disease (LM or 3VD) in women is less than that in men for each chest pain category and is almost nonexistent in women with non-specific chest pain. CAD = coronary artery disease; MVD = multivessel disease.

regardless of age. Three-vessel or left main coronary artery disease was uncommon in women younger than 70 years of age.

LM or 3VD

<30 30-39 40-49 50-59 60-69 Age (yrs.)

N=1397

Population with Disease

8

8

4

2

Only 2% of the 1397 women with nonspecific chest pain had multivessel disease. The prevalence of left

main coronary artery disease was less than 1%, regardless of the age group studied. Three-vessel or left main coronary artery disease occurred in less than 1% of the patients except for women 60-69 years of age, in whom the prevalence was 2%.

Table 2. Coronary Artery Disease Prevalence in Women with Stable Chest Pain and No History of Myocardial Infarction*

Age (years)	n		Luminal stenosis < 50%						Prevalence of specific coronary artery disease patterns			
					Number of vessels with luminal stenosis $\geq 70\%$ or LM stenosis $\geq 50\%$			Mean number of	LM stenosis		LMEQ ≥ 70%, no LM – stenosis	${ m LM}$ ${ m stenosis}$ ${ m \geq 50\%~or}$ ${ m three-}$ ${ m vessel}$ ${ m stenosis}$
					1	2	3	– diseased vessels	≥ 50%	≥ 70%	≥ 50%	≥ 70%
Definite :	angina	ı										
30-39	10	30	0	0	10	30	30	2.29	10	10	0	30
40-49	70	36	4	4	22	17	17	1.92	0	0	3	17
50-59	161	14	10	8	22	22	24	2.02	8	4	4	27
60-69	137	12	4	3	14	27	40	2.32	10	6	7	42
≥ 70	23	4	0	0	22	9	65	2.46	9	4	17	65
Total	401	17	6	5	19	22	31	2.16	7	4	5	33
Probable	angin	ıa										
30-39	39	59	13	8	10	5	5	1.75	5	0	0	5
40-49	257	52	13	4	18	9	4	1.55	4	3	1	6
50-59	414	47	17	6	13	10	7	1.81	2	0.5	1	8
60-69	264	28	17	7	22	14	12	1.79	4	3	3	13
≥ 70	34	26	12	6	15	18	23	2.16	3	0	0	26
Total†	1012	43	16	5	17	11	8	1.76	3	2	2	9
Nonspec	ific che	est pain										
< 30	14	86	7	7	0	0	0	0.00	0	0	0	0
30-39	135	86	10	0	2	2	0	1.40	0.7	0.7	0	0.7
40-49	425	81	13	2	3	0.7	0.2	1.31	0	0	0	0.2
50-59	585	76	14	4	4	2	0	1.28	0.3	0.2	0	0.1
60-69	215	60	19	11	7	1	2	1.48	0.9	0.9	0.5	2
≥ 70	23	61	26	13	0	0	0	0.00	0	0	0	0
Total	1397	76	14	4	4	1	1	1.35	0.4	0.3	0.1	0.6
Total†	2810	55	14	5	11	8	7	1.88	2	1	1	8

^{*}All numbers in the table are expressed as a percentage of n in each age category except the mean number of diseased vessels. All percentages > 1% rounded to nearest whole number.

Abbreviations: LM = left main coronary artery; LMEQ = left main equivalent lesion.

Discussion

In the last decade, the recognition and treatment of coronary artery disease has changed considerably. Numerous studies have shown subgroups of patients with a wide spectrum of disease severity and prognosis. 18-18, 23-25 The detection of the high-risk patient, some of whom may have improved survival after coronary bypass surgery, is an important goal of the noninvasive diagnostic techniques used to assess patients with various chest pain syndromes.

Diagnostic test performance is highly dependent on the population selected for study.^{1, 11, 12} The sensitivity of most current diagnostic techniques is considerably higher in patient subsets with a high prevalence of multivessel disease. 1, 2, 6, 12, 26-28 The predictive accuracy is decreased in patient subgroups with a low prevalence of multivessel disease. Several older studies have correlated the character of chest pain syndromes with angiographic findings but have not stratified groups of patients according to high-risk coronary disease. 13-18 If patients with chest pain could be categorized into high- and low-risk coronary pathology, more precise indications for noninvasive diagnostic techniques and coronary angiography could be established. The CASS registry provides new insight into the prevalence of severe coronary disease in patients with stable chest pain and no history of myocardial infarction.

[†]Data of four women less than 30 years of age with probable angina are excluded from the table; n is too small to subdivide into disease category.

Definite Angina

The prevalence of coronary disease in men with definite angina was lower in the younger age groups, confirming previous reports. The prevalence of multivessel disease increased progressively by decade and ranged from 45–88%. Left main or three-vessel coronary artery disease occurred in 50% of the middleaged men. The prevalence of left main coronary artery disease in older men with chronic stable angina is higher than previously reported and was unexpected because patients with previous infarction and unstable angina were excluded. 29

The prevalence of coronary artery stenosis $\geq 70\%$ in women with definite angina ranged from 56–96%, which is more than has been reported.^{13, 30} Left main or three-vessel coronary artery disease was common in women older than 60 years of age. In contrast to findings in men, the prevalence of left main coronary artery disease in women remained stable (8–9%) over a wide range of ages.

Probable Angina

The prevalence of coronary disease in men with probable angina was considerably less than in men with definite angina. Welch et al. 16 reported that 31% of men who had atypical angina and were younger than 40 years of age had coronary stenosis \geq 50%. The prevalence of coronary stenosis \geq 70% in CASS was 47% in the 171 men younger than 40 years of age, but was 94% in the 46 men who had probable angina and were 70 years of age or older. Multivessel disease was common in middle-aged men and the prevalence of left main coronary artery disease \geq 50% exceeded 10% in the older age groups (\geq 60 years).

The prevalence of coronary artery disease in 300 young women with probable angina was 29%, similar to the 26% reported by Welch et al. ¹⁸ Multivessel disease was uncommon in young women. Left main or three-vessel disease was also uncommon and occurred in 5-13% of women younger than 70 years of age.

Nonspecific Chest Pain

The prevalence of coronary artery disease in patients with nonspecific chest pain was 10%, and is in agreement with the 4-20% range reported by others. 18-18 None of the 51 men and 14 women younger than 30 years of age had obstructive coronary artery disease. Left main or three-vessel disease occurred in less than 1% of patients younger than 50 years of age. In the older age groups, three-vessel or left main coronary artery disease was rare except in older men. None of the women in the eldest group studied had obstructive coronary artery disease. This unusual finding may be explained in part by a relatively small sample size (n = 23). Thus, obstructive coronary disease is infrequent in patients with nonspecific chest pain, and the likelihood of extensive coronary disease is very small.

Indications and Guidelines for Diagnostic Tests Based on CASS Results

The noninvasive diagnostic tests in current use are not 100% sensitive or specific.1-6, 12, 26-28 Thus, the predictive accuracy of each test is dependent on the prevalence of disease in the subgroup of patients studied. The CASS results show that men and women with definite angina and the men with probable angina are three subgroups with a high prevalence of coronary and multivessel disease. The reported sensitivity of current noninvasive tests range from 83-100% for left main or three-vessel coronary artery disease. 1-6, 12, 26-28, 31-33 The likelihood of finding left main or three-vessel coronary artery disease at angiography in these three subsets would be high if $(1) \ge 2$ mm of horizontal or downsloping ST-segment depression occurred in the initial 3 minutes of exercise; 1, 26, 27, 38 (2) marked ischemic changes persisted late into the recovery period;27 (3) systemic hypotension occurred during exercise;34 (4) marked hypoperfusion in three or more myocardial segments occurred during stress scintigraphy;³¹ and (5) a marked drop in ejection fraction or the appearance of a large segmental wall motion abnormality occurred during stress cineventriculography. 3, 35 The false-negative rate of the above tests range from 0-17%. In older patients with a high prevalence of left main or three-vessel coronary disease, the large number of undetected patients may warrant angiography regardless of the test results. Whether combinations of the above tests will reduce the number of false-negative tests to an acceptable level in patients with high-risk coronary pathology is not yet known but is an area of active research.

Men and women with nonspecific chest pain are two subgroups with a low prevalence of severe coronary disease. The women with probable angina are intermediate. In patients who have nonspecific chest pain and no history of myocardial infarction, the very low prevalence of left main or three-vessel coronary disease in all but the most elderly would suggest that diagnostic tests may not be indicated in this patient subgroup. The 1-year prognosis would be excellent even if one-vessel coronary disease were present.28-25 The cost-effectiveness of performing noninvasive diagnostic tests in patients with nonspecific chest pain would be poor because false-positive results would be frequent and false-negative tests are known to occur. Perhaps coronary angiography should not be performed in young or middle-aged patients with nonspecific chest pain if the only reason is to exclude highrisk coronary anatomy.

Strengths and Limitations of the Present Study

The prevalence rates of coronary disease in CASS reflect the patients selected for angiography, who may not represent the general population. For example, it is difficult to assess how many patients with non-specific chest pain underwent coronary angiography compared with the much larger pool of patients that

did not. However, assuming that only patients with a high probability of disease were selected (e.g., positive stress tests or thallium scintigram), the prevalence of high-risk coronary disease was still extremely small. The CASS clinical and angiographic results can be used to evaluate new noninvasive diagnostic tests. The appropriate percentages of patients with one-, two-and three-vessel and left main coronary artery disease can now be determined for a wide range of patient subsets stratified by age. Once the likelihood ratios of the new tests have been determined in clinical populations with a representative number and location of diseased vessels, the predictive accuracies can be measured according to pretest risk.^{1, 11, 12}

The CASS results represent pooled data from 15 medical centers in different geographic regions. Thus, the CASS results are less likely to be biased than results obtained from a single hospital. We have arbitrarily chosen a 70% luminal narrowing of a major vessel or a 50% narrowing of the left main coronary artery as "significant disease." These angiographic criteria are commonly used to evaluate diagnostic noninvasive tests. 1, 2, 5, 6, 24, 31 The stratification of angiographic data into subsets of patients with one-, two- and three-vessel coronary artery disease provides useful prognostic information and has been used in many studies.20, 24, 25 However, this classification may be somewhat restrictive for individual patients, especially those with stenosis of proximal segments of the left coronary artery. New angiographic definitions of patient subsets as proposed by Hutter³⁶ are being studied and may provide a more accurate estimate of

In a recent review, Diamond and Forrester³⁷ pooled results from 17 studies and stratified 4952 patients according to age, sex and character of chest pain. The data included patients with previous infarction and unstable angina. The severity of coronary disease could not be evaluated in the patient subsets because the data were unavailable in the earlier studies. The CASS results, which were obtained prospectively in 20,391 patients, extend earlier observations and allow us for the first time to determine disease incidence and severity in patient populations with chronic stable chest pain.

In conclusion, current indications for coronary angiography include the preoperative assessment of potential candidates for aortocoronary bypass grafting who have incapacitating angina and the diagnosis of presence and extent of coronary artery disease. The CASS results in this study address the latter indication. The current indications for coronary angiography will probably change as the results of large cooperative studies comparing medical and surgical treatment are reported and as new treatment modalities (e.g., percutaneous transluminal angioplasty)^{9, 10} are evaluated.

The CASS data provide a framework within which the use of noninvasive studies for the detection of high-risk coronary artery disease can be optimized based on symptoms, gender and age. Diagnostic test populations from individual studies can now be measured against the CASS data for disease prevalence and severity, and study conclusions may be evaluated in terms of population fit.

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Appendix

Operating Clinical Sites

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Miami Heart Institute: Arthur J. Gosselin, M.D.*, Larry B. Larsen, M.D., Paul Swaye, M.D.; Montreal Heart Institute: Martial G. Bourassa, M.D.*, Jacques Lespérance, M.D., Bernard R. Chaitman, M.D., Claude Goulet, M.D., Claude M. Grondin, M.D.; New York University: Ephraim Glassman, M.D.*, Michael Schloss, M.D., O. Wayne Isom, M.D.; St. Louis University: George C. Kaiser, M.D.*, J. Gerard Mudd, M.D.*, Hendrick B. Barner, M.D., John E. Codd, M.D., Hillel M. Laks, M.D., Denis H. Tyras, M.D., Robert D. Weins, M.D., Vallee L. Willman, M.D.; St. Luke's Hospital Center, New York: Harvey G. Kemp, Jr., M.D.*, Airlie Cameron, M.D.; Stanford University: Edwin L. Alderman, M.D.*, James F. Silverman, M.D.*, Edward B. Stinson, M.D.: Medical College of Wisconsin: Felix Tristani, M.D.*, Robert J. Flemma, M.D., Harold Brooks, M.D.; Yale University: Lawrence S. Cohen, M.D.*, Alexander Geha, M.D., Graeme L. Hammond, M.D., René Langou, M.D., Richard K. Shaw, M.D.

Coordinating Center

University of Washington: Lloyd D. Fisher, Ph.D., Mary Jo Gillespie, M.S., Kathryn Davis, Ph.D., J. Ward Kennedy, M.D., Richard Kronmal, Ph.D.

Central Electrocardiographic Laboratory

University of Alabama at Birmingham: Thomas Sheffield, M.D.*

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