Prognosis and Treatment of Asymptomatic Coronary Artery Disease

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Despite the large number of studies dealing with the natural history of angiographically defined coronary artery disease, there is still a paucity of data on the prognosis of totally asymptomatic persons. From the small number of reported studies, it appears that prognosis in selected asymptomatic patients may be better than that of symptomatic patients. However, the annual mortality rate in the subgroup of asymptomatic patients with triple vessel disease was as high as 4 to 5% in some studies that included patients with prior myocardial infarction or mild symptoms, or both. This has reinforced the views of those who advocate a more aggressive medical/surgical approach to asymptomatic patients with left main and triple vessel disease, especially if they have had a prior infarction. Although several small series of surgically treated patients have been reported to have excellent short-term survival rates, the absence of adequate control groups in nearly all of these studies has left the issue of prophylactic revascularization unresolved. Until there is more knowledge of prognosis in patients not operated on, it is likely to remain unresolved.

The foundation for a rational plan of therapy in any disease is a clear understanding of the natural history of that disease. If the natural history of asymptomatic disease is not known and there is little possibility of its being known in the near future, physicians caring for affected persons have to make difficult decisions concerning therapy. They first must decide if treating is worse than not treating, and then if they are to treat, how aggressive that treatment should be. This review will address the unresolved issue of treatment for asymptomatic coronary artery disease after first considering what is known about the prognosis of patients with this syndrome (1–6).

Prognosis in Asymptomatic Coronary Artery Disease (Table 1)

In coronary artery disease, the most reliable natural history studies began with the widespread adoption of coronary arteriography in the late 1960s. The early arteriographic studies noted the different prognosis attached to one, two and three vessel disease, with the more ominous prognosis attached to the latter (7). More recent surveys not only confirm these initial observations (8), but in many instances serve as useful comparisons between surgically and nonsurgically treated patients (9,10). What has not been clearly defined in these studies is the effect of lack of anginal symptoms (chest pain or pressure or its usual equivalent) on prognosis, although some studies have commented on different prognoses attached to more severe types of angina (11).

Limiting factors in defining prognosis. One problem in defining prognosis in totally asymptomatic patients (as opposed to those who are asymptomatic after a myocardial infarction) is the relatively small number of such patients who undergo coronary arteriography. It is not surprising that there is a dearth of such statistics; many physicians are concerned by the thought of referring asymptomatic patients for an invasive procedure with a small, but definite, risk of morbidity or mortality. Their uneasiness is obviously compounded by the lack of natural history studies. Because the latter cannot be obtained at present without angiographic data, a vicious cycle occurs: the lack of prognostic data in asymptomatic subjects leads to questions concerning the need for study in such persons, which in turn ensures that the number of persons available for prognostic surveys is small. In the absence of an adequate data base concerning natural history, decisions about therapy are based on anecdotal experiences or are avoided altogether. (The situation in the postinfarction patient who becomes asymptomatic is somewhat different, and will be commented on subsequently.)

Available surveys on asymptomatic coronary artery disease. Of the few surveys that have provided prognostic data about asymptomatic coronary artery disease, the one from the U.S. Air Force School of Aerospace Medicine has

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Table 1. Prognosis in Asymptomatic Patients With Angiographically Confirmed Coronary Artery Disease

Reporting Institution	No. of Patients	Mean Follow-up (mo)	Total Cardiac Events*	Mortality
U.S. Air Force, School of Aerospace Medicine (1)	78	36	22(29%)	3(1% per yr)
Yale University (2)	12	57	4(33%	0
National Institutes of Health (NIH) (3)	147	25	27(17%)	8(3% per yr)
Duke-Harvard† (4)	44	42	13(30%)	4(2.7% per yr)
University of Washington† (5)	217	66	NA	NA for entire group
Green Lane† (6)	50	54	24(49%)	5(~2% per yr)

*Angina, myocardial infarction, death †Includes patients with prior myocardial infarction (NIH and University of Washington studies also included mildly asymptomatic patients)
NA = not available

provided the largest series of patients. This study of airmen with abnormal rest electrocardiograms was begun by Froelicher et al. (12) in the mid 1970s. Cardiac catheterization was performed on 138 asymptomatic airmen with an abnormal treadmill stress test; 30 had significant coronary artery disease. Subsequent treadmill or radionuclide studies, or both, performed at this center by Froelicher's group and then by Hickman and his colleagues (1) resulted in a total of 78 asymptomatic airmen with asymptomatic coronary artery disease being detected and followed up for prognostic purposes. The most recent follow-up data, reported in preliminary form by Hickman et al. (1) showed that 22 of 78 airmen aged 45 to 54 years who had at least 50% luminal stenosis of one major coronary artery developed overt signs of coronary artery disease within a 4 to 90 month follow-up period (mean 57 months). Sixteen of the 22 developed angina at a mean of 31.5 months, 4 sustained a myocardial infarction and 2 died suddenly. These events occurred at similar rates in patients with one, two and three vessel disease. Six other men developed symptoms at a later time (mean 46 months); five of the six developed angina and one died suddenly. On the basis of their data showing that 45% of the men with subsequent cardiac events had three or more of the standard risk factors for coronary artery disease (cigarette smoking, hyperlipidemia, diabetes or hypertension), the authors concluded that the presence of multiple risk factors strongly influenced the development of such events.

Another series of totally asymptomatic patients with angiographically confirmed coronary artery disease, reported from Yale University by Langou et al. (2), consisted of 12 industrial workers culled from a cohort of 129 subjects by a combination of positive exercise tests and coronary artery calcification on fluoroscopy. Four of the 12 men developed either angina or a myocardial infarction over a 3 year follow-up period.

Surveys on asymptomatic or mildly asymptomatic patients. Three other studies have pertinent data but do not deal exclusively with totally asymptomatic populations. The larger of the three is from the National Institutes of Health. In that study (3), 147 asymptomatic or mildly asymptomatic patients with coronary artery disease were followed up for 6 to 67 months (mean 25). However, only 25 of the 147 patients were asymptomatic and only 5 of the 25 had not had a prior infarction. These numbers are too small to permit accurate appraisal by the authors. However, by considering the entire cohort together, they did find a lower than expected mortality rate of 3% per year. Mortality in three vessel disease was 4% per year. The best clue to the patients remaining asymptomatic was their exercise capacity, presumably reflecting left ventricular function. Only 14% of those who had good exercise capacity died or had progressive symptoms over the course of the 7 year follow-up period.

The importance of left ventricular function is further suggested by studies from the University of Washington's Seattle Heart Watch. In a study of 619 patients with minimal or no symptoms, Hammermeister et al. (5), noted only a 2% annual mortality rate in patients with three vessel disease and ejection fraction greater than 50%. In contrast, the mortality rate was nearly 5% per year in patients with an ejection fraction of 31 to 50%. Most patients in the study had a prior myocardial infarction, but few had congestive heart failure.

The mortality figures from the two preceding studies are similar to those reported from the Duke-Harvard Collaborative Coronary Artery Disease Data Bank (4). Here again, a majority (32) of the 44 asymptomatic patients had a prior infarction. Of the remaining 12 totally asymptomatic patients, nearly all were referred for coronary angiography because of a positive exercise test. The mean age of the group was 47.6 years; 93% were men, 40% had three vessel disease, 30% two vessel disease and none had a left main coronary lesion. Over 70% had an abnormal left ventricular contraction pattern. Only 3 of the 44 patients were taking cardiac medications (propranolol by 2 and propranolol and nitrates by 1). These three patients were asymptomatic after a myocardial infarction but were given medication for prophylactic reasons by their physicians. When analysis of prognosis in these 44 patients was performed, it was not

possible to evaluate the totally asymptomatic patients alone because of the small numbers involved. Nevertheless, mortality for the overall group was 2.7% per year, a figure almost identical to that reported by the National Institutes of Health investigators (3). Again, the subgroup with three vessel disease had the highest yearly mortality rate, nearly 5% per year as compared with 4% in the National Institutes of Health study. It should be stressed that unlike patients in the U.S. Air Force and Yale studies, not all of the patients in the Seattle, National Institutes of Health and Duke-Harvard studies had evidence of ongoing myocardial ischemia, that is, a positive exercise test. A positive exercise test without symptoms is generally regarded as a sign of silent myocardial ischemia (13). Therefore, the prognostic data obtained from these three studies may not be strictly comparable with those of the other two studies cited in which ongoing ischemia was demonstrated and the patients had not sustained a prior myocardial infarction.

Epidemiologic studies. In addition to studies in patients with angiographically confirmed coronary artery disease, epidemiologic studies that utilize exercise tests in asymptomatic subjects can provide some idea of the natural history of asymptomatic coronary artery disease. For example, in another aspect of the Seattle Heart Watch Study, Bruce et al. (14) reported that maximal exercise testing identified a small subgroup of patients who had a sevenfold risk of having an overt coronary artery disease event, with a yearly mortality rate of about 0.3%. Obviously, not all of the patients with a positive exercise test have coronary artery disease (as discussed by Uhl and Froelicher [15] earlier in this seminar).

Asymptomatic versus symptomatic patients. If one assumes that the annual mortality rate for asymptomatic patients is about 2 to 3%, how does this compare with the rate for patients with symptomatic disease? Most studies report figures approximately twice as high. For example, the Cleveland Clinic study (8) reported an annual mortality rate in its latest 10 year follow-up series of 4% in patients with one vessel, 7% in patients with two vessel and 12.5% in patients with three vessel disease. In more recent reports such as that from the Coronary Artery Surgery Study (CASS) (10), the one, two and three vessel disease annual mortality rates were 2, 4 and 8%, respectively. The multihospital Veterans Administration study (9) had figures intermediate to those reported from the Cleveland Clinic and CASS groups. In all subgroups in all three studies, prognosis was affected adversely by impaired left ventricular function. The Duke-Harvard Data Bank study is unique in its attempt to evaluate prognosis in a "comparable" group of symptomatic patients. This was done by using a computerized program to "match" the 44 asymptomatic patients in the Duke-Harvard Data Bank with 127 symptomatic patients with similar coronary anatomy, left ventricular dysfunction and number of prior myocardial infarctions. The yearly mortality rate for the symptomatic group was 5.7%, a figure approximately twice that of the asymptomatic patients and consistent with the earlier angiographic studies cited (8–10), considering the mix of high risk and low risk patients in this group.

Thus, from these limited studies it would appear that asymptomatic patients have a better prognosis than symptomatic patients. The selected nature of these patient populations, however, makes these conclusions tentative. They do not fully address the larger question of prognosis that is suggested by the phenomenon of asymptomatic coronary artery disease: because the first overt cardiac event in patients with coronary artery disease is as likely to be sudden death or a nonfatal myocardial infarction as angina, is it possible that asymptomatic coronary artery disease is present in many of these persons for some time before the event? In other words, does the population with asymptomatic coronary artery disease form the pool from which a certain number of persons will surface each year as victims of sudden death or nonfatal myocardial infarctions? Preliminary evidence from the University of Minnesota suggests that this may be so. Sharma et al. (16) studied 19 patients who were successfully resuscitated from ventricular fibrillation that occurred out of the hospital. All had angiographically confirmed multivessel coronary artery disease; 11 of the 19 had no prior history of angina or myocardial infarction. Nearly all the patients developed painless electrocardiographic and angiographic wall motion changes with bicycle exercise. The degree of left ventricular dysfunction was similar in asymptomatic and previously symptomatic patients. The authors concluded that painless ischemia may have a role in the genesis of out of hospital ventricular fibrillation.

Asymptomatic postinfarction patients. In addition to data in populations of totally asymptomatic persons alone or mixed with asymptomatic postinfarction patients, there are also some data focusing exclusively on the latter patients. Because of the widespread use of low level exercise testing 2 to 3 weeks after an uncomplicated myocardial infarction, an increasing number of patients with silent myocardial ischemia are being detected. Short-term survival statistics based on these postinfarction exercise tests indicate that exercise-induced ST segment depression increases considerably the 1 to 2 year mortality rate (17–19). For example, in the study of Theroux et al. (17) 210 patients who had no overt heart failure and had been free of chest pain for at least 4 days were exercised 1 day before discharge from the hospital. The 1 year mortality rate was 2.1% (3 of 146) in patients without ischemic ST changes during exercise and 27% (17 of 64) in those with such changes (probability [p] < 0.001). The authors noted that "angina in the presence of depression of the ST segment did not increase the prognostic importance of depression of the segment." Thus, 10 of 37 patients with ST depression but without angina died compared with 7 of 27 with angina and ST depression.

Because this study was not specifically designed to assess prognosis in asymptomatic patients, more follow-up is needed for that particular type of patient. The CASS experience (4) should be helpful because one of the subsets in that very large study consists of asymptomatic postmyocardial infarction patients randomized to either medical or surgical therapy. One smaller study has already been performed at Green Lane Hospital in New Zealand (6). One hundred patients who were still pain-free 2 months after a myocardial infarction were randomized to either medical or surgical therapy. Of the 50 nonsurgically treated patients, 9 developed disabling angina and required surgery, 10 had a nonfatal reinfarction and 5 patients died. This yields about a 2% yearly mortality rate for the 4½ year mean follow-up period. Prognosis was worse in patients with an ejection fraction of less than 50%.

Treatment of Asymptomatic Coronary Artery Disease

Because the prognosis in totally asymptomatic coronary artery disease is unclear, decisions concerning therapy remain controversial, expecially when surgery is considered. Even though there is still no totally accepted consensus as to the role of surgery in symptomatic coronary artery disease, there are generally accepted guidelines based on a variety of randomized and nonrandomized studies. No such surgical (or even nonsurgical) guidelines exist for asymptomatic coronary artery disease.

Medical approach. Certainly, the simplest approach is to 1) modify risk factors when they are present, and 2) reduce physical activities so that myocardial ischemia does not develop. Theoretically, patients with silent myocardial ischemia and a defective anginal warning system may be at increased risk during strenuous exertion. Many physicians would not be content with just these measures if coronary arteriography documented a left main coronary lesion, multivessel disease or a very proximal stenosis of the left anterior descending coronary artery. Possible therapy in such patients includes "prophylactic" administration of nitrates, beta-adrenergic blocking agents or calcium antagonists, alone or in combination. The goal would be to improve exercise tolerance by prolonging the time in which a patient could exercise before the silent ST segment depression developed. There is no evidence at present that such therapy can improve prognosis in these patients, but one can argue that it is unlikely that it can do any harm.

Indications for surgery. Conti (20) has outlined an approach for asymptomatic patients with coronary artery disease that appears reasonable. If there is evidence during catheterization of abnormal hemodynamics (such as elevated left ventricular end-diastolic pressure), abnormal lactate metabolism or abnormal left ventricular regional wall motion, or both, in addition to the abnormal exercise electrocardiogram, Conti would begin therapy as just described. After a suitable interval, he would repeat the exercise test with an adjunctive radioisotopic procedure such as thallium-201 imaging. If the test continues to be markedly abnormal, the patient is then considered for surgery. Thus, an aggressive approach might entail surgery or (now) percutaneous transluminal coronary angioplasty if the coronary anatomy is deemed appropriate. As we have noted, surgery for symptomatic disease still has controversial aspects; this is even more true when asymptomatic disease is considered. Some investigators (21) are adamantly against it. Others are in favor of it in limited circumstances, as in selected patients with triple vessel disease or disease of the left main coronary artery (3).

Results of surgery. Coronary artery bypass surgery in small numbers of asymptomatic patients (usually reported in mixed series with mildly symptomatic patients) has been performed at several hospitals (Table 2). For example, Grondin et al. (22) at the Montreal Heart Institute reported on the course of 55 surgically treated patients, 19 of whom were totally asymptomatic. Most of the 55 patients had multivessel disease. Perioperative mortality was zero, but there were four late deaths and seven late infarctions in the 69 month follow-up period, and the authors questioned the value of prophylactic revascularization. Pre- and postoperative exercise test comparisons were not available. At the Peter Bent Brigham Hospital, 20 patients were studied (23). Fourteen of the 20 were totally asymptomatic and 6 were mildly symptomatic. Six patients had sustained a myocardial infarction. All but one patient had multivessel disease; four had left main artery stenosis. Fourteen of 16 preoperative exercise tests demonstrated silent myocardial ischemia. There was no postoperative mortality; one late death occurred 5 years after surgery. Among the 12 patients with both pre- and postoperative exercise tests, in 8 the test result reverted to normal and in 4 showed a less ischemic response to exercise. At the Cleveland Clinic, Thurer et al.(24) reported on 17 patients who were asymptomatic after a myocardial infarction; 11 had multivessel disease. Sixteen of the 17 remained asymptomatic after surgery. There is no mention of pre- and postoperative exercise tests in these patients. The authors were cautious in their conclusions, realizing that "for proper evaluation, surgical results. . .should be compared with the results of nonsurgical therapy in a similar patient group."

As we noted earlier, a randomized trial of surgical versus nonsurgical management was carried out in New Zealand in 100 patients who were asymptomatic after a myocardial infarction (6). With a mean follow-up period of 4½ years, the annual mortality rate was the same (about 2%) in both groups. Patients were not classified according to the number of vessels with disease, though most patients had severe disease. Another related study (5) was performed at the University of Washington as part of the previously cited

Table 2. Surgical Therapy in Asymptomatic Patients With Coronary Artery Disease*

Reporting Institution	No. of Patients	Perioperative Mortality	Mean Follow-up (mo)	Late Mortality
Cleveland Clinic (24)	17	0	75	0
University of Washington (5)	392	15(3.8%)	65	NA
Peter Bent Brigham (23)	20	0	34	1(5%)
Montreal Heart Institute (22)	55	0	69	4(7.3%)
Green Lane (6)	50	2(4%)	54	4(8%)

*All studies include patients with prior myocardial infarction University of Washington, Peter Bent Brigham and Montreal Heart Institute studies also include patients with mild symptoms
NA = not available

Seattle Heart Watch. This was a nonrandomized study in which prognosis was determined for medically and surgically treated patients who were found to have generally similar baseline variables. In this series, 114 patients were asymptomatic and 505 were mildly symptomatic. Both groups were combined for life-table analyses. The surgically treated patients had a significantly lower mortality than their medical counterparts, with the largest difference in survival seen in patients with three vessel disease and moderately impaired left ventricular function (ejection fraction 31 to 50%). This is the only comparative study, although nonrandomized, that suggests a beneficial effect of surgery on mortality in asymptomatic patients. Because prognosis in patients with normal left ventricular function appears excellent, the authors noted that "an enormous sample size in a randomized therapeutic trial would be required to test the hypothesis that surgical therapy improves survival in this subgroup," that is, those with normal left ventricular function. The authors concluded that "prophylactic surgery may be indicated in the asymptomatic or mildy symptomatic patients with three-vessel disease, moderate impairment of left ventricular function, good distal vessels and no other major medical illness." (There were too few patients with left main lesions for the investigators to make any definite statements about that lesion.)

The forthcoming reports from the CASS registry may shed further light on prognosis in other subgroups. Until then physicians must weigh the asymptomatic patient's coronary anatomy and left ventricular function against his or her age and lifestyle in trying to decide whether an aggressive approach is indicated. No "firm" guidelines can be offered beyond those cited here. Whether prophylactic revascularization offers protection against silent myocardial ischemia is still an unresolved issue.

Conclusion

The few natural history studies that relate to totally asymptomatic coronary artery disease show a low annual mortality rate but a higher incidence of other cardiac events (development of angina or myocardial infarction). This suggests that the asymptomatic state may be the forerunner of the clinical state in many patients. However, in other patients, such as those with left main or triple vessel disease, the first manifestation of the clinical state may be sudden death or a massive myocardial infarction, which even if nonfatal could be incapacitating; hence, the need for an open mind toward a more aggressive approach, at least for some persons. We know that silent myocardial ischemia is occurring in some of these persons at relatively low levels of exertion; to protect the myocardium by medical or surgical therapy in such instances certainly seems worthwhile.

In patients who are asymptomatic after a myocardial infarction and who still demonstrate myocardial ischemia, prognosis does seem to be worse than in those without such ischemia. Here an aggressive approach is even more justifiable, though again, the necessary controlled studies are not yet available. In the absence of such studies, the physician must use his own judgment and whatever data seminars like the present one can provide.

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