Panel Discussion II: Day 2

Dr. Abrams. In a recent issue of the *Journal of the American College of Cardiology*, there is an interesting article that contradicts what many of the proponents of silent ischemia have been saying. The report is of an 11-year follow-up at Duke University of a large population of patients who had been referred for chest pain. All underwent catheterization and treadmill testing. On the treadmill, some did and some did not have angina. All patients had 75% obstruction of at least one major coronary artery. In contradistinction to the trials with which we are familiar, this study found that patients who had angina on the treadmill had a much worse prognosis than did patients with ST segment depression and no angina; the prognosis of the latter was identical to that of patients with no ST segment depression whatsoever. Thus the rate of coronary events in the so-called silent ischemia group was the same over the long term as in patients who had no ST segment depression. The authors referred to other papers that also discussed the prognostic importance of a gradient of chest pain.

Would Dr. Shell respond? I think the frequency and duration of angina should not be ignored. Although silent ischemia may be important, active angina also is.

Dr. Shell. The Duke data base is a selected group of patients referred from various parts of the Southeast, and the selection alone may explain some of the findings. From our clinical experience, though, we know that when anginal frequency changes, it goes from a relatively stable rate to an increase in angina, not ischemia as measured by Holter monitoring. Since it is likely that the patients at Duke had been referred because of a change in anginal pattern, it is not surprising that that data base showed the importance of chest pain to prognostic events. It is a case of how the question was asked.

Dr. Scheidt. The Duke findings are diametrically opposed to those from another huge data base, the Coronary Artery Surgery Study (CASS), which found the presence or absence of angina irrelevant (Ryan TJ, Weiner DA, McCabe CH, et al. Exercise testing in the Coronary Artery Surgery Study randomized population. Circulation 1985; 72[suppl V]:31-8). Instead, there was a major differential in survival over the next 5 years based on the presence or absence of ST segment depression. The group that had silent ST depression on a treadmill did just as poorly as the group that had angina with ST depression, and both groups did much worse than the group with no change in ST segment.

Dr. Shell. The CASS group was selected by excluding patients who had a recent change in anginal pattern; thus the data base itself is almost diametrically opposed to the Duke data base.

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Dr. Abrams. Perhaps Dr. Morris of Duke University would comment.

Dr. Morris. I was involved with the Duke study and was shocked that our data were totally different from the CASS findings. The reason may be, as Dr. Shell suggested, that we studied patients who were referred because of a changing anginal pattern. I would like to point out, however, that 95% of the information about mortality is found in three factors: (1) number of coronary arteries involved, (2) ventricular function, and (3) a changing clinical pattern. Unfortunately, we used only stress testing; we should have also included 48 hours of Holter monitoring. The data were surprising, but I believe that they reflect the population.

Participant. Do you think that each ischemic event is harmful to the patient, or is each simply an indication that all is not well?

Dr. Shell. Some experimental data support the first contention. The study that I did with Dr. Ganz in 1975 measured enzyme release after each of a series of occlusion-release cycles, 5 minutes at a time. After two or three cycles, there were no changes, but by the sixth, seventh, or later cycles, increasing amounts of enzyme were released. At this point, levels of adenosine triphosphatase (ATP) fall and do not completely recover. The ability to maintain membrane structure is disturbed when the ATP levels fall below approximately 2.5 μmol/gm, and the effect is cumulative. If 30 anginal episodes occur in 2 days, each one is worse than a single episode occurring once a month.

Dr. Scheidt. Some of these changes in intracellular metabolites persist for days.

Dr. Shell. Yes. When ATP is depleted, the adenosine is deaminated, and the heart has no way of reaminating it. If the baseline level is 5.4 μmol/gm and it drops to 4 μmol/gm, it takes 1 or 2 weeks to restore that level. These have been our observations in animal models, which presumably hold for humans.

Dr. Abrams. Is this relevant to stable exertional angina?

Dr. Shell. It must be. If it is, we should be able to demonstrate over time that people who have multiple ischemic events, whether silent or asymptomatic, will experience heart failure. It would be difficult to prove this in a single patient, but in a larger sample, the relevance might be demonstrated.

Dr. Scheidt. The data on prognosis and the various factors related to prognosis usually do not include the number of anginal episodes daily.

Participant. When would you not study anatomically patients with and without symptoms who have significant ST segment depressions during Holter monitoring and on the treadmill?

Dr. Shell. From your question, it sounds as if you define this as unstable angina.

Dr. Scheidt. Are you asking whether someone with 1 mm

of horizontal ST depression in the first minute of stage 4 needs to be studied?

Participant. Yes, and I am also asking whether a patient without symptoms who has 2 to 3 cm depression in stage 3 should be studied anatomically. If there are changes in the status of patients with known coronary disease, then they too should be studied.

Dr. Shell. When I have relatively young patients with 3 mm of ST depression during treadmill testing and noticeable events during Holter monitoring, I study them. I also follow patients whose ST segment depression develops in the fourteenth minute of exercise, with negative Holter results. Actual clinical practice may vary by individual physician and according to the region of the country, the West Coast being much more aggressive than the Northeast in moving patients into the catheterization laboratory. The South seems to be somewhat intermediate.

Dr. Scheidt. Yet there is no difference in mortality and morbidity from coronary heart disease in the various regions of the country.

Dr. Shell. Is that true?

Dr. Scheidt. Yes, there is a Medicare-based study showing this.

Dr. Shell. The Heart Association of Los Angeles looked at this issue about 4 years ago and found that the age-adjusted death rates in Los Angeles were lower than elsewhere, perhaps because of the Asian population. The geographic pattern in death rates should be studied much more carefully.

Participant. My question concerns the mechanics of dosing the nitrates. It is important to prevent attenuation but also to limit the length of the drug-free interval. Should the drug-free interval last 8 or 12 hours, or can the sulfhydryl groups be replenished in less time?

Dr. Abrams. In basic animal preparations of vascular smooth muscle, vascular rings, or Packer's study on heart failure, the time needed for the nitrate-free interval is directly related to the length of nitrate exposure, that is, to the time needed to produce tolerance. Thus the longer the exposure, the longer the nitrate-free interval should be. This has been shown by Packer in the heart failure model.

However, in my opinion, there is no absolute answer, because it depends on the dose, the preparation, the degree of exposure, and individual responsiveness. Some studies in patients with angina are looking at short drug-free intervals, but I am not aware of any positive data concerning removal of the patches for only 8 hours or less. There are positive data for keeping the patches on for 14 hours and off for 10. Isosorbide dinitrate, four times daily dosing is clearly not as good as three times daily with respect to attenuation, as Elkayam and Parker have shown.

Dr. Scheidt. Several studies show that responsiveness to a stress test is restored even with a regimen involving 10 hours off medication, so one could be reasonably comfortable with that practice. Only a few small studies examined the effects of leaving a nitroglycerin patch off for 8 hours (Luke R, Sharpe N, Coxon R. Transdermal nitroglycerin in angina pectoris: efficacy of intermittent application. J Am Coll Cardiol 1987;10:642-6). One study showed restoration of drug effect and the other showed continued tolerance, so the 8-hour free interval is still problematic.

I want to comment on the time of day when the patch is removed. Can the patient remove the patch before going to bed, even if that means he will not be wearing it when he assumes the upright position in the morning? If most of our patients led the life that I lead—getting out of bed, showering, shaving, and heading off on my bicycle within 29 minutes—they would probably need some protection for the first hour. However, the patient could take a sublingual nitroglycerin tablet and get nearly immediate protection in the morning. The patch gives a reasonable blood level of nitroglycerin within 30 to 60 minutes and so there would really be cause for concern only during that amount of time.

My suspicion is that most of our patients have time to start their day slowly, and thus immediate protection on first arising is not an enormous clinical problem. Clearly, the time of lowest ischemic risk for angina, myocardial infarction, sudden death, and silent ischemia is during the night. Given the choice, I believe patients would want the patch off at night, unless they plunge into daily activity as soon as they wake up.

Dr. Marsh. Are there any angioscopic data on the time it takes for an unstable plaque to heal? How long do we have to worry about that lesion?

Dr. Shell. Our best data come from angioplasty laboratories. The angioplasty lesion is essentially the same as one that occurs naturally. An angioplasty lesion is generally believed to heal in 6 to 12 weeks.

Participant. Dr. Morris, what types of problems, if any, do we create when we inject contrast media into the coronary artery and manipulate the artery with angioplasty instruments and wires?

Dr. Morris. Several studies have looked at serial ventricular function. Left ventricular function is decreased within seconds after a large bolus of contrast material is injected into a coronary artery. This effect seems to subside over a few minutes.

Regarding the effects of the angioplasty catheter, we can look at the difference between Folts dogs—those dogs that have the constrictor on and go through intermittent periods of obstruction—and humans. At 6 to 8 weeks, most of those dogs have huge endothelial lesions, and they eventually have a myocardial infarction. Since the Folts dogs are a perfect replication of the angioplasty laboratory, it amazes me that all of the patients undergoing angioplasty do not develop clots. It seems that even though you may rupture a plaque and denude the area locally, the artery will function fairly well if there is healthy endothelium on either side of it. The reocclusion rate is 30%, but 70% of the arteries stay open. It is possible that angioplasty destroys endothelium that has grown over a plaque and restores normal endothelium. In addition, angioplasty destroys a plaque and denudes it, but it also markedly increases flow. Spontaneous implosion of a plaque does the same thing, but, more important, it reduces flow.

Participant. I find it somewhat distressing that we spend so much time and effort in treating angina when there is no clinical evidence, only laboratory experiments, showing that any of the therapies reduce coronary events or prolong

life. Is it necessary to treat the average patient in the United States who has one to three episodes of angina a week with anything other than sublingual nitroglycerin? Are we not just covering up occasional episodes of angina with all this antianginal medication, when what we really need to look for is a change in anginal patterns? Why is it important to treat angina? To reduce the total ischemic burden to zero? What is our goal?

Dr. Shell. First, there is evidence that screening for occult coronary disease does prolong life. If this screening uncovers lesions in the left main coronary artery, for example, those proponents of the anatomic school of thought would argue that life is prolonged.

Participant. I do not disagree with screening for coronary disease. However, if there is angina during the treadmill test and you treat the angina, does that prolong life?

Dr. Shell. Don't forget, you are not treating the angina, you are treating the anatomic lesion. The reason to screen for occult coronary disease is to find the triple-vessel lesions and main left lesions that lead to hemodynamic instability.

The problem of suppressing angina or changing the anginal pattern has a fairly long history and goes back to the early 1920s. Were we to begin to look at that as a disease today, we would be forced to demonstrate that we could prolong life before the traditional treatments were implemented.

It will be difficult to alter that tradition, because society is probably not prepared to spend between $20 million and $100 million to prove that hypothesis and to indemnify every cardiologist who does not try to suppress angina. As a physician, you may want to defy tradition and not treat the patient with angina, but just give sublingual nitroglycerin. The probability is that the relatives of such an untreated patient who dies would sue for malpractice, and you would be asked whether you had followed the pattern of treatment in your community. You are absolutely correct that there are no indisputable data from double-blind studies, so we are forced to look for indirect indexes that we are altering prognosis.

Dr. Scheidt. We do have some indirect indexes. In the Framingham study, the mortality rate for angina was 4% per year. In the Veterans Administration study, it was more than 4% in the medically treated group (Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. Eleven-year survival in the Veterans Administration Randomized Trial of Coronary Artery Bypass Surgery for Stable Angina. N Engl J Med 1984;311:1333-9). This study was done before calcium blockers and long-acting nitrates were available. In the European Cooperative study in the late 1960s and early 1970s, the mortality rate was 3.3% per year (European Coronary Surgery Study Group. Long-term results of prospective randomized study of coronary artery bypass surgery in stable angina pectoris. Lancet 1982;2:1173-80), and in CASS, which was conducted from 1975 to 1977, the death rate for the medically treated group was 1.6% (CASS Principal Investigators and their associates. Coronary Artery Surgery Study[CASS]: a randomized trial of coronary artery bypass surgery. Survival data. Circulation 1983;68:939-50). There has been an enormous decline in mortality due to angina, perhaps because of β-blockers, calcium channel blockers, nitrates, aspirin, or antilipid agents.

Participant. Let me make it a clinical question. Let us say you have a 55-year-old patient who has a positive treadmill test during his executive physical. Perhaps he has symptoms. Maybe 1 in every 5 days he walks to his mailbox and develops a little angina. Catheterization results show two-vessel coronary disease with normal left ventricular function. During Holter monitoring, he has 40 minutes of ischemia a day. On the one hand, I could give that patient a bottle of nitroglycerin tablets, and if he had to take one nitroglycerin pill for 1 day a week, that would be 50 pills per year. On the other hand, I could give him a nitroglycerin patch or β-blockers, or for $300 a month, thousands of diltiazem pills per year. With any of these treatments, will he live longer, have fewer infarcts, or have a better quality of life than with a bottle of nitroglycerin in his pocket?

Dr. Shell. As a scientist, I would have to say that there are no data comparing the efficacy of these different regimens. As a clinician, I would give the opinion that the patient will be better at the end of 5 years if he receives the polypharmacy treatment. It is my impression that the number of patients with myocardial infarctions who are admitted to coronary care units has dramatically decreased in recent years. For instance, at Cedars-Sinai, there are 83 beds in the cardiac care unit. Until a year ago, there was never an empty bed, but now the intensive part of that unit is half empty, and the cardiac observation section is one-third empty. The population of Los Angeles is increasing at the same time hospitals are closing, so something is happening.

Dr. Morris. We looked at information in the Duke data bank, which comprises observations dating back more than 20 years, and grouped them in 5-year periods. We corrected for anatomic severity and left ventricular function in our analysis. There is no question that our surgical results are much better and that there has been a dramatic improvement in survival with medical treatment. The impact of coronary artery disease as a cause of death has been reduced.

My bias is to think that the antihypertensive programs, fitness programs, and antismoking programs have been as effective as the pharmacologic programs. Pharmaceutical companies and the prescribing physicians would also like to take credit for the change, as would the aggressive physicians who punch open lesions and perform many angioplasties. I think all of them should take some credit for the change.

Dr. Marsh. Would the panel comment on the use of agents such as ergonovine and acetylcholine that cause spasm in the laboratory?

Dr. Morris. Cleveland Clinic data demonstrate the sensitivity and specificity of ergonovine testing in identifying people with proven vasospasm. A few small studies have found acetylcholine to be as sensitive and even slightly more specific and faster acting. We probably should consider using acetylcholine more than we do now, since it does not require titration. However, one problem with it is that it causes constriction in many people who have 50% or 60% lesions, and it provokes angina in patients with fixed stenoses. Most angiographic laboratories put away

the ergonovine as soon as patients with vasospastic disease come in. Currently, our catheterization laboratory is reconsidering how to screen for patients with Prinzmetal's angina, the ones that cannot be identified by treadmill testing or Holter monitoring.

Dr. Marsh. It seems to me that more and more we have to admit we do not know the answers to certain questions. I often ask my patients their preference for treatment. It takes time to have this discussion, but I have found that many reasonably intelligent patients are deeply gratified that you respect them enough to tell them that you do not know the answer, that they have a choice, and that you will help them make the best choice.

Dr. Scheidt. That is a very good point. Every one of us knows that unless the patient has involvement of the left main coronary artery or proximal triple-vessel disease with decreased left ventricular function, we honestly do not know what the best course of treatment is. If patients are given the nearly identical statistics on annual mortality in angina with surgical versus medical treatment, the pessimistic ones would say, "My God, if the doctors don't know what to do, how am I supposed to decide?" However, optimistic patients could look at the same data and see that there probably is not much difference if no one has yet been able to prove conclusively that either medical or surgical therapy is superior. Patients are always worried about not having the bypass surgery that a friend or relative has had or not having other specific treatments they have heard about. However, if you take the time to tell them the statistics, and the number that I give out these days for chronic stable angina is 2% mortality per year, the patients will understand that statistically they have a rather low-risk disease.

You can literally lay out in three or four pages what the high-risk and low-risk situations are. Most executives who come in after a stress test have no angina and lead a normal life. If there is ST segment depression in stage 3 or 4, they are still at low risk. I think full disclosure of what we know and what the risks are is usually reasonable.

Dr. Morris. Every time we give a patient a drug, it is an individual biologic experiment. We should use good common sense and not make arbitrary yes-and-no decisions. If a therapy does not work, change it, and if the patient improves, stick with it.

I ask my patients to use nitroglycerin continuously. No study has convinced me that I should not do this in treating angina or transient ischemia. In the past 2 years, I asked more than 100 of my patients to use nitroglycerin intermittently for 2 weeks and to tell me which they preferred, continuous or intermittent treatment. Of the 100, two preferred intermittent therapy. Patients should help make decisions about their therapy.

Dr. Abrams. I will not provide a summation of this morning's session, but I would like to comment that many clinicians believe that medical therapy of patients with angina does more than simply relieve chest pain, that it is cardioprotective or beneficial in reducing morbidity and mortality. There are much data in the literature that maintain that treatment of ischemia is important. We may never have the controlled trials that would answer the question definitively, but an abundance of indirect evidence suggests that suppression of painful as well as painless ischemic episodes is probably beneficial.