RECRUITMENT OF AFRICAN-AMERICAN PATIENTS FOR CLINICAL TRIALS—THE ALLHAT CHALLENGES

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Time is running too short for me to be able to show the slides. So I will make some comments about the importance of recruiting African-American patients into trials. What I want to emphasize are the shortfalls of the studies in which conclusions are extrapolated to African-American individuals. First, in epidemiological studies such as the Framingham study, from which we have learned a great deal about what happens to people with risk factors for cardiovascular diseases, I think most people would agree that not enough African Americans were included to draw meaningful conclusions to this population, although some inferences were there.

There have been several good studies, such as the Evans County study in rural Georgia and the Charleston Heart study, a more urban study in the South, that did help to reinforce some of our information that minorities, specifically blacks, have a disproportionate amount of hypertension and mortality from various complications.

One problem with retrospective epidemiological studies is that the various confounders that are affecting observations are often not reflected in the results. The low socioeconomic status of minorities, various psychosocial problems, and access to care issues are often not considered in these types of studies.

Now what about the treatment trials? A number of trials have been done throughout the world on treatment of hypertension in an effort to learn about whether we can treat individuals effectively over a long period of time and, very important, whether we can affect morbidity and mortality.

The European studies had many shortfalls as far as minorities were concerned. There were frankly no minorities, such as African descendents, in the European studies. So we cannot go to the Medical Research Council Trial of Treatment for Mild Hypertension (MRC) or many of the studies done in Europe to learn about what happens to hypertensive blacks and other ethnic minorities, although the studies were very good for studying the majority population.

Studies done on the continent of Africa and in the Caribbean are helpful, but those populations are not African American. Although some genetics may be shared by African Americans, African Caribbeans, and other people of the African diaspora, there are other factors that are different (eg, environmental) that may have a marked effect of disease behavior and outcome.

Some of the US studies have shortfalls as well. Retrospective studies, in which we try to look at something that has happened and then do subset analyses to draw conclusions, often suffer from the low numbers of blacks in these studies. Most of them were not designed with minorities in mind, and the number and types of minorities may not reflect the distribution of minorities in the country. Also, the various confounders are often not appreciated or are difficult to ascertain.

The pharmaceutical industry has been helpful in doing postmarketing studies, and you saw earlier data, the COLA study, done by the Squibb Pharmaceutical Company, that looked at a large number of hypertensives and then broke out into subsets the blacks, the whites, the old and the young, and so forth. These studies can be very useful. They have large numbers,

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which make them very powerful. How else could you get thousands of patients involved in a study, except through a population-based postmarketing survey? These studies have given results that often lead to more specifically designed prospective studies. So the COLA study, which suggests that captopril may work almost as well in blacks as in whites, should lead to properly designed prospective studies. And, indeed, one of the slides I was going to show was on a study on the comparative efficacy of atenolol, with captopril, and verapamil in African Americans in the treatment of hypertension that was conceived after looking at the results of postmarketing surveillance studies such as the COLA study. So we did show that the response rate, although down in the angiotensin converting enzyme (ACE) inhibitor category, could be improved if the dose was increased.

Another postmarketing study that has been very useful was done by the Parke-Davis Pharmaceutical Company and is called the ADOPT study. Again, a study with thousands of patients being treated in doctors' offices suggested that, unlike what was suspected earlier, when the ACE inhibitor quinapril (Accupril) was used, although the blacks did slightly less well than the whites, they did a lot better than previously thought. About 57% of the blacks responded by reaching the goal of diastolic blood pressure 90 mm Hg when treated with quinapril compared with 67% response by whites. Again, this type of study teaches us that more, but more definitive, placebo-controlled blinded studies are needed.

I think the only good prospective study that has been done on hypertension detection and treatment so far in which we can say that African Americans were enrolled in sufficient numbers would be the Hypertension Detection and Follow-up Program, which was a very large study in which I was involved and in which more than 11 000 patients were studied and a very high number were black. The study showed that, given equal access to care and the aggressive recruitment and treatment of patients for hypertension, the blacks did as well as the whites and the old as well as the young. So we learned something in a study that was well balanced and designed to answer certain questions in a hypertensive population that included a large number of minorities.

In the Treatment of Mild Hypertension Study, which had a significant number of minorities, there was not as much difference, at least for mild hypertension, in the racial response to various antihypertensive agents as we thought.

Now finally, let me get to the ALLHAT study, because this is the kind of study that I think is long overdue. Some of us were speaking to Dr Lenfant as recently as an hour ago, saying that we do not want to stop the study, although recruitment has been slow. The study needs to be done. The ALLHAT study is the antihypertensive and lipid-lowering trial to prevent heart attack. I will just tell you briefly about it. I tried to get a number of the handouts, but we could not get them here in time.

The study involves a total of 40 000 patients nationwide recruited from doctors' offices, clinics, health maintenance organizations, etc, representing a broad segment of the population. In this study, 55% of the patients must be African Americans because of the disproportionate problem of hypertension in blacks. If you want to know whether a particular drug therapy will reduce mortality or morbidity from coronary disease, you have to overrecruit high-risk patients.

The vanguard phase of the study was completed in 1994, and we are now into the main part of the trial, which is going to last 7 years; we will not be finished until 2001. It is important to know that there are two components in this study. The antihypertensive component is to determine whether some of the newer antihypertensive agents, such as ACE inhibitors, calcium channel blockers, and alpha-1 blockers, will reduce the incidence of coronary heart disease in high-risk hypertensives when compared with treatment with diuretics. This is a very important question.

There has been a tremendous growth in the utilization of these newer agents because they do lower blood pressure, have low side effect profiles, and do not produce some of the adverse metabolic effects that some of the older drugs produce. So theoretically, they should reduce mortality and the incidence of coronary disease and stroke; however, we have to prove that this is the case.

A second part of this study is to look at the lipid-lowering component to determine whether reduction of serum cholesterol with provastatin, an HMG co-A reductase inhibitor, reduces total mortality in older, moderately hypercholesterolemic hypertensives. So eligible people, once they get in the blood pressure phase, will be moved to the cholesterol-lowering phase.

The drugs that are being used are amlodipine for the calcium channel blocker, chlorthalidone for the diuretic, doxazosin for the alpha-1 blocker, and lisinopril as the ACE inhibitor.

My final comments on the ALLHAT study relate to the recent news regarding the calcium channel blockers

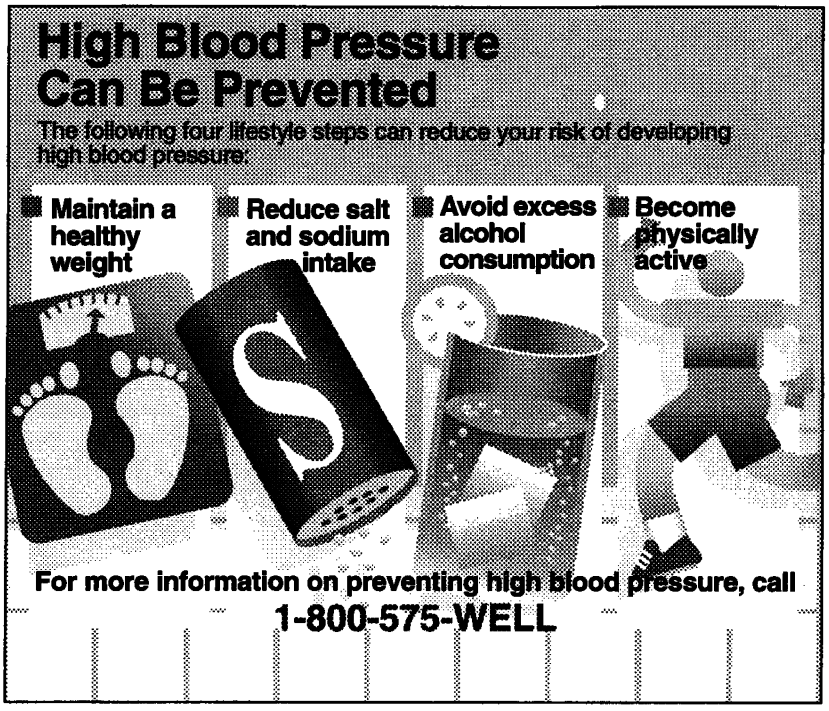
and the incidence of myocardial infarction. I and many of you in the audience got many phone calls from our patients, the public, and newspapers inquiring about what is going on. "You physicians told us that calcium channel blockers work well in African Americans, that it is the best drug to use, and now people are dying like flies from heart attacks," to quote one of my patients.

The NIH, the pharmaceutical companies, and physicians were very responsive. Many of us who were involved in hypertensive programs wrote editorials and press releases explaining the situation. In a retrospective population-based type of study of the kind that was done in that particular "study," conclusions are drawn that should not be used to affect the way doctors treat patients. This is what I said to the newspapers. I took that opportunity to say to the public that that is why we are doing the ALLHAT study. That is why we are doing a study to determine if the ACE inhibitors, the calcium blockers, and alpha-1 blockers will lower the coronary heart disease incidence, as has been shown by diuretics and beta blockers used to treat hypertension.

The recruitment for this study has been slow. So, many of us are going to Houston with the coordinating council this weekend to do all that we can to keep the recruitment effort going. I think that it is a study that we cannot afford not to do.

The problem with recruiting minorities are two. One is education. You have to educate minorities in a more specific way as to what we do not know and why we need to know it. This type of education is very important and should be done through any number of ways, using all kinds of lay people, church and social groups, and people who can communicate at their level.

The second thing relates to access problems, cost of therapy, and convenience of therapy for a study. If a study is located some place in the city or in the county that minorities cannot get to, they are not going to come. You have to educate them to the importance of the study, that it is safe, and that there are questions we must answer, and then you must make it affordable and convenient for them.



Source: National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program.