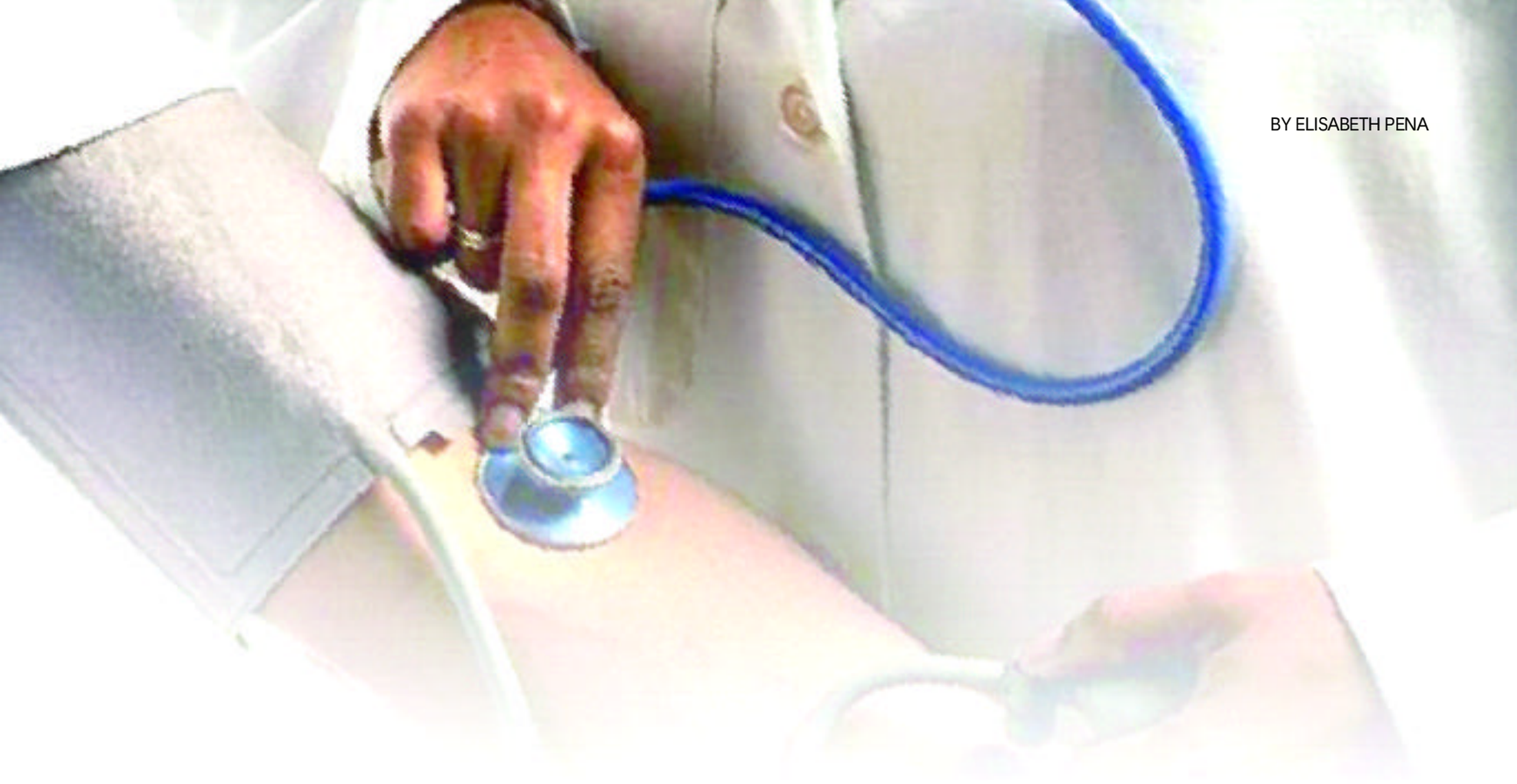

BY ELISABETH PENA

Raising Standards to Reduce PRESSURE

Last year, the landscape for **HYPERTENSION MEDICATIONS** was **SHAKEN** by study results and guideline recommendations. But despite all the noise, has anything **CHANGED IN THIS MARKET?**

In the last quarter century, a number of new medications have been developed for the treatment of hypertension, but it has not been clear which specific class of antihypertensive medication was best for preventing hypertension-related cardiovascular diseases, including coronary heart disease, congestive heart failure, and stroke. Prompted by results from ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), new clinical-practice guidelines for hypertension were issued by health organizations throughout the world. In the United States, The National Heart, Lung, and Blood Institute released JNC VII, for the prevention, detection, and treatment of high blood pressure. The guidelines proposed a number of major changes in the way physicians treat the disease, but opinions differ as to whether these recommendations really change anything for pharmaceutical manufacturers.

"When one looks at the results of ALLHAT and the recent JNC VII recommendations, three very important themes are evident," says Kenneth Borow, M.D., president and CEO of The Covalent Group. "First, diuretics should be part of most patient's treat-

DR. JEAN SIEBENALER

The trials did not show that the medicines are bad; they all control hypertension. But two-thirds of patients will require a second medication, which is very important to keep in mind.

ment program for hypertension. Second, we must be much more aggressive in our approach to treating hypertension. In many cases, a multidrug therapy will be required to attain the JNC VII treatment goals. Finally, while most drug classes are able to achieve similar antihypertensive effects, there are important class differences regarding end-organ protection, for example, renal, left ventricular hypertrophy, and protection against subsequent cardiovascular events that make one class of drug, for example, beta blockers, preferable to another."

High blood pressure is a major risk factor for heart disease and the chief risk factor for stroke and heart failure, and it also can lead to kidney damage. The condition affects about 50 million Americans, or one in four adults. Treatment seeks to lower blood pressure to less than 140 mmHg systolic and less than 90 mmHg diastolic for most persons with hypertension (less than 130 mmHg systolic and less than 80 mmHg diastolic for those with diabetes and chronic kidney disease).

The market for antihypertensives is an attractive target for pharmaceutical companies because of the sheer size of the patient population, which was estimated to be about 171.4 million across the seven major markets (United States, Japan, France, Germany, Italy, Spain, and the United Kingdom) in 2001 and forecast to grow to 196.1 million by 2015.

At first glance, diuretics, a class of hypertension treatments that is primarily marketed by generic manufacturers, appears to have won favor, given that ALLHAT results found them to be superior compared with other

DR. KENNETH BOROW

Companies are becoming interested in the ancillary beneficial effects of antihypertensives, including actions that counter the development of atherosclerosis and improve age-related altercations in vascular stiffness.

hypertensive medicines in preventing one or more major forms of cardiovascular disease. In addition, JNC VII recommended that diuretics should be used in drug treatment for most patients with uncomplicated hypertension.

"From having the experience of 20 years in primary-care medicine, I believe these new guidelines change everything," says Jean Siebenaler, M.D., therapeutic director of cardiovascular services and medical director at Kendle International Inc. "There is no doubt about it; this has turned the treatment of hypertension upside down. When it comes to choosing a first-line medication, the guidelines have very much clarified things for physicians."

Still, none of the antihypertensives in the trial was found to be ineffective at controlling hypertension, and the differences between medications were minor. Manufacturers of competing, patent-protected hypertension treatments view the results from a different perspective.

"For our drug, Norvasc, we've been very pleased to finally have a large trial that confirms what we've been saying — that Norvasc is effective and safe," says Dahlia Garza, M.D., medical director for Norvasc at Pfizer. "This trial suggests that it is certainly possible to control blood pressure but that sometimes you may need more than one medication. All of the drugs that were tested in this trial are safe and effective with some minor qualifications."

Although many patients will require two antihypertensives, these results and the guidelines are expected to increase the use of diuretics, a drug class that had been experiencing a decline in use because of the emergence of newer, and more expensive, drugs.

"We have already seen a re-emergence of diuretics," says Curt Furberg, M.D., Ph.D., chairman of the ALLHAT steering committee and professor of public health sciences at Wake Forest University School of Medicine. "In the 1980s about 60% of all hypertensive patients

were on diuretics. That number is now down to 20%, but it is on the rise. I am sure we are going to increase the market share quite a bit, and I hope we can get up to at least 40% of all hypertensive patients on diuretics."

Another direct result of the recent events in the hypertension landscape is expected to be the marketing efforts of the manufacturers of nondiuretic antihypertensives.

"We will see the companies with marketed, branded antihypertensives focus very much on the need for combination therapy and the need to treat patients holistically," says Christine Hollidge, cardiovascular analyst at Datamonitor Plc. "We have certainly already begun to see an increased emphasis on single pill diuretic combinations in these companies' marketing efforts."

Results and Guidelines

ALLHAT was a practice-based clinical trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and initiated in 1994. The trial, which lasted eight years, was designed to test whether physicians should first treat high blood pressure with a calcium channel blocker (amlodipine), an angiotensin converting enzyme (ACE) inhibitor (lisinopril), an alpha blocker (doxazosin), or the standard, long-standing treatment for hypertension, a diuretic (chlorthalidone).

ALLHAT was the largest antihypertensive trial and the second largest lipid-lowering trial ever undertaken. The study included large numbers of patients older than 65, women, African-Americans, and patients with diabetes, treated largely in community practice settings.

"It was decided back in the early 1990s that we needed to have more information about the newer classes of antihypertensive agents that had emerged on the market, the ACE inhibitors and the calcium channel blockers," Dr. Furberg says. "The trial also looked at whether these drugs added value to the generic diuretics. The new drugs are obviously more expensive, so the issue was the added value. The trial was set up to evaluate whether the new drugs were superior."

Two years ago, the question was partially answered when it was determined that doxazosin, the alpha blocker, was less effective than chlorthalidone, a diuretic, in preventing combined cardiovascular disease, including heart failure.

ALLHAT final results, which were released in December 2002, showed that the thiazide-type diuretic remains the drug of choice for first-step antihypertensive therapy because it is more effective than the other drugs tested in preventing one or more manifestations of cardiovascular disease (heart failure, compared with amlodipine, and combined CVD, for lisinopril).

"Physicians find ALLHAT very interesting because the study demonstrates the relevance of well-established antihypertensive therapies — diuretics — particularly with uncomplicated hypertension," says Ruth Brown, Ph.D., an analyst at Decision Resources.

Several elements of the ALLHAT results were met with controversy. One point of contention was the racial make up of the patients; a large portion of the participants were minorities, particularly African Americans, which the trial designers say reflects the real-world situation in the United States, Canada, and the Caribbean. But these groups typically respond differently to antihypertensives.

Another criticism levied against the trial's conclusions was that angiotensive receptive blockers, the newest class of antihypertensives,

The Seven Antihypertensive Classes and the Best-Selling Products in the Seven Major Markets

(United States, Japan, France, Germany, Italy, Spain, and the United Kingdom)

Drug	Product	Company
Alpha blockers	Harnal (tamsulosin)	Yamanouchi
	Cardura (doxazosin)	Pfizer
	Hytrin (terazosin)	Abbott; GSK (UK); Aventis (Germany)
	Xatral (alfuzosin)	Sanofi-Synthelabo
Angiotensin converting enzyme (ACE) inhibitors	Prinivil/Zestril (lisinopril)	AstraZeneca/Merck & Co.
	Vasotec (enalapril)	Merck & Co.
	Altace (ramipril)	Aventis/King Pharmaceuticals/Wyeth
	Accupril (quinapril)	Pfizer
	Lotrel (benazepril/amlodipine)	Novartis
	Monopril (fosinopril)	Bristol-Myers Squibb
	Lotensin (benazepril)	Novartis
Angiotensin receptor blockers	Cozaar (losartan)	Merck & Co.
	Diovan (valsartan)	Novartis
	Aprovel/Avapro (irbesartan)	Sanofi-Synthelabo/BMS
	Blopress/Atacand (candesartan)	Takeda/AstraZeneca
	Micardis (telmisartan)	BI/GSK/Bayer/Abbott
	Teveten (eprosartan)	Solvay/Biovail
	Benicar (olmesartan)	Sankyo/Forest/Menarini
Beta blockers	Seloken (metoprolol)	AstraZeneca
	Tenormin (atenolol)	AstraZeneca
	Coreg/Dilatrend (carvedilol)	GSK/Roche
	Concor/Ziac (bisoprolol)	Merck KGaA/Wyeth-Ayerst
Calcium channel blockers	Norvasc (amlodipine)	Pfizer
	Adalat/Procardia XL (nifedipine)	Bayer
	Plendil (felodipine)	AstraZeneca
	Amlodin (amlodipine)	Sumitomo
	Coniel (benidipine)	Kyowa Hakko Kogyo
	Cardizem (diltiazem)	Aventis
Centrally acting antihypertensives	Catapresan (clonidine)	BI
	Cynt (moxonidine)	Lilly
	Physiotens (moxonidine)	Solvay
	Loftyl (buflomedil)	Abbott
Diuretics	The majority of medications in this class are unbranded generics.	

Source: Datamonitor Plc., Market Dynamics: Anti-hypertensives, July 2003. For more information, visit datamonitor.com.

DR. RUTH BROWN

Therapy has to be tailored to the individual, depending on the complications that they have.

This whole thing is about added value. Other marketers are saying their drugs are as good as diuretics, but that doesn't mean anything if the product is 20 times more expensive.

DR. CURT FURBERG

were not included in the trial. But this was because the first of these agents was launched as the trial began. Additional issues included the difference in blood-pressure control between the treatment arms and a concern that the primary endpoint did not consider renal protective effects.

"There are a lot of criticisms against the trial and even if physicians do accept ALLHAT's conclusions I don't think it is going to change the market that much," Ms. Hollidge says. "So many patients require combination therapy just to control their blood pressure and so many patients have comorbid conditions for which the antihypertensives are indicated. If the patients have heart failure, they are going to be given beta blockers and ace inhibitors. If they have had a myocardial infarction they will be taking those drugs anyway. The fact that the diuretic is being used first in those situations is of little consequence."

Within six months of the release of the ALLHAT results, NHLBI released JNC VII, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC VII guidelines were prepared by a special committee of the NHLBI's National High Blood Pressure Education Program (NHBPEP). The committee issues new guidelines when warranted by scientific advances; the last guidelines were issued in November 1997.

The guidelines' main points include lowering the blood-pressure measurements for hypertension, the support of diuretics as a first-line treatment for uncomplicated hypertension, and the creation of a prehypertension category.

The new guidelines also streamline the steps by which doctors diagnose and treat patients, concurring with ALLHAT in recommending the use of diuretics as part of the drug treatment plan for high blood pressure in most patients.

In addition, other organizations revised or released hypertension guidelines in 2003. The International Society on Hypertension in Blacks (ISHIB) issued the first-ever guidelines for treating high blood pressure in African Americans. Almost 40% of African Americans suffer from heart disease, and 13% have diabetes.

The European Society of Hypertension issued European Society of Cardiology guidelines for the management of arterial hypertension and the National Heart Foundation of Australia published its Hypertension Management Guide for Doctors 2004. Also, a proposed Pan American standard method for measurement in blood pressure should allow future comparisons between national surveys of blood pressure in North, Central, and South America.

The Cost of Hypertension

Industry experts believe that the cost of the drugs in the ALLHAT trial will play an important role in a physician's choice.

"If one looks at a very practical socioeconomic factor, such as cost, then it makes sense, as ALLHAT and JNC VII have suggested, that one would use a diuretic as first-line therapy," Dr. Borow says. "In patients with uncomplicated mild-to-moderate hypertension, diuretics alone or in combination appear to be appropriate initial therapy, assuming that the diuretic is well-tolerated by the patient."

Dr. Garza doesn't believe that cost should play a primary role in the treatment decision because about two-thirds of the patients required two or more medications to get to the goals of the ALLHAT trial.

"The responsible thing is to use less costly medications when possible, but the data suggest that hypertension isn't a problem that can be treated with one medication," Dr. Garza says. "One needs to use the least expensive alternative first, but beyond that there will continue to be a need for the other medications that are available. Some patients need the less costly diuretic as well as other drugs to effec-

JNC VII Key Points

IN PERSONS OLDER THAN 50 YEARS, systolic blood pressure greater than 140 mmHg is a much more important cardiovascular disease (CVD) risk factor than diastolic blood pressure.

THE RISK OF CVD BEGINNING AT 115/75 MMHG DOUBLES WITH EACH INCREMENT OF 20/10 MMHG; individuals who are normotensive at age 55 have a 90% lifetime risk for developing hypertension.

INDIVIDUALS WITH A SYSTOLIC BLOOD PRESSURE OF 120–139 MMHG OR A DIASTOLIC BLOOD PRESSURE OF 80–89 MMHG should be considered as prehypertensive and require health-promoting lifestyle modifications to prevent CVD.

THIAZIDE-TYPE DIURETICS SHOULD BE USED IN DRUG TREATMENT FOR MOST PATIENTS WITH UNCOMPLICATED HYPERTENSION, either alone or combined with drugs from other classes. Certain high-risk conditions are compelling indications for the initial use of other antihypertensive drug classes (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers).

MOST PATIENTS WITH HYPERTENSION WILL REQUIRE TWO OR MORE ANTIHYPERTENSIVE MEDICATIONS to achieve goal blood pressure (<140/90 mmHg, or <130/80 mmHg for patients with diabetes or chronic kidney disease).

IF BLOOD PRESSURE IS >20/10 MMHG ABOVE GOAL BLOOD PRESSURE, consideration should be given to initiating therapy with two agents, one of which usually should be a thiazide-type diuretic.

THE MOST EFFECTIVE THERAPY prescribed by the most careful clinician will control hypertension only if patients are motivated. Motivation improves when patients have positive experiences with, and trust in, the clinician. Empathy builds trust and is a potent motivator.

IN PRESENTING THESE GUIDELINES, the committee recognizes that the responsible physician's judgment remains paramount.

Source: National Heart, Lung, and Blood Institute, JNC 7 Express: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, May 2003. For more information, visit nhlbi.nih.gov.

tively control hypertension. I am not sure that the debate of one drug versus another drug or the discussion of cost alone is an appropriate way to look at this issue."

Dr. Furberg believes that JNC VII had good points, but has reservations about the guidelines as they relate to cost.

"For many people, particularly older people, cost is an important consideration," he says. "Guidelines in the past haven't addressed cost and the time has come. We need to address this issue because this is what society is facing."

A New Category: Prehypertension

JNC VII's creation of a category called prehypertension targets individuals with a systolic blood pressure of 120 mmHg to 139 mmHg or a diastolic blood pressure of 80 mmHg to 89 mmHg, which covers about 22% of American adults, or about 45 million people. Opinions conflict as to whether the formation of this new category will lead to an increase in physicians prescribing hypertension medications or lead to a decrease in people requiring medicines because the early identification will lead to more patients making lifestyle changes.

"The publication of JNC VII is interesting because the working group has created this prehypertensive set; this, however, isn't going to increase prescriptions of antihypertensive drugs," Dr. Brown says. "By introducing this prehypertensive category and these guidelines, this is a flag to physicians to notice if people have blood pressures in this new category and to then recommend lifestyle modifications first and move on to drug therapy at a later stage."

Ms. Hollidge agrees, saying with the introduction of the prehypertensive category, there isn't any suggestion that these patients should be treated with drug therapy.

"I don't think that will happen," she says. "There was a focus on identifying the patients that would be at risk for hypertension."

But some expect that physicians will begin prescribing medications earlier.

"Use of more than one antihypertensive medication in patients may be driven by the creation of the new prehypertension category," Dr. Garza says. "As physicians realize that there is an increased risk of cardiovascular disease for those in that prehypertension category perhaps they will be a little more aggressive than they have been in terms of getting patients to their recommended goals of a systolic blood pressure of less than 140 mmHg or less than 130 mmHg, depending on whether people have comorbidities such as diabetes."

Some analysts believe that the creation of a

ALLHAT Results

ANTIHYPERTENSIVE TRIAL — 42,418 PARTICIPANTS

BECAUSE OF THE SUPERIORITY OF THIAZIDE-TYPE DIURETICS in preventing one or more major forms of cardiovascular disease and their lower cost, they should be the drugs of choice for first-step antihypertensive therapy.

FOR THE PATIENT WHO CANNOT TAKE A DIURETIC (which should be an unusual circumstance), calcium channel blockers and ACE inhibitors may be considered.

MOST HYPERTENSIVE PATIENTS REQUIRE MORE THAN ONE DRUG. Diuretics should generally be part of the antihypertensive regimen. Lifestyle advice should also be provided.

LIPID TRIAL — 10,355 PARTICIPANTS

ALLHAT PRAVASTATIN AND USUAL CARE GROUPS both attained substantial cholesterol reductions, resulting in a relatively modest cholesterol difference between them.

ACCORDINGLY, ALLHAT FOUND ONLY A SMALL DECREASE in cardiovascular disease event rates (nonsignificant) for pravastatin compared with usual care and no difference in mortality.

THE STUDY RESULTS DO NOT ALTER CURRENT CHOLESTEROL TREATMENT GUIDELINES, which are based on a series of clinical trials with larger cholesterol reductions than that observed in ALLHAT. Thus, cholesterol lowering by lifestyle changes and drug treatment is recommended to reduce cardiovascular disease morbidity and mortality.

Source: Coordinating Center for Clinical Trials, Houston, Texas. For more information, visit allhat.org.

new catagory may lead to increased prescriptions.

"Introducing the prehypertension category really emphasizes that those patients who have blood pressure even marginally over 140/90 should be receiving drug therapy," Ms. Hollidge says. "That is where we will see the major difference, leading to a move away from the idea that some physicians have that patients older than 60 with blood pressure of more than 160 mmHg are fine. The guidelines, hopefully, will reinforce that they are not."

The R&D Impact

Experts also believe the recent events will affect researchers' hypertension drug-development efforts.

"The trial showed that combination therapy is an important part of hypertension treatment, and these trials should encourage drug companies to think about single pill combination therapies that would increase compliance," Dr. Brown says. "Perhaps triple therapies within a single pill, where there is an unmet need, would help increase compliance."

In addition, the types of endpoint goals for hypertension clinical trials are expected to change because of these recent events.

"Companies are becoming more and more interested in the ancillary beneficial effects of antihypertensive agents," Dr. Borow says. "These include actions that counter the development and/or progression of atherosclerosis, improve age-related alterations in vascular stiffness, and impact favorably on endothelial function. There is going to be more and more interest from a mechanistic and clinical outcomes perspective on factors besides the surrogate endpoint for hypertension, which is blood pressure."

JNC VII and ALLHAT's support of diuretics also is expected to impact the design of clinical trials for hypertension medicines.

"When a new medication is being developed, there is no doubt that it will have to be compared with a diuretic; diuretics now are the standard,"Dr. Siebenaler says. "The race now will be for adjunctive therapy as a second-line agent."

Although diuretics emerged from the recent studies as an effective and economical choice, the market is still wide open for improved treatments. New approaches to hypertension treatment have shown progress in research into vaccines, renin inhibitors, kinases, and tests that will predict response to antihypertensive medications.

"People always are looking for more effective drugs, and the issue that has been raised is that one drug may not control blood pressure in everyone," Dr. Furberg says. "There is clearly room for more effective agents that would lower blood pressure better and do it in a larger proportion of patients. I hope there will be a positive impact on R&D."

Developers of antihypertensives also will have to consider the many comorbidities and patient populations within the hypertension group when testing new medicines.

"The ideal agent would be a drug that controlled everyone's hypertension 100% of the time with no side effects and at little cost, but there isn't anything like that out there," Dr. Garza says. "The lack of this type of an agent will motivate development to some degree. The difficulty with a disease such as hypertension, however, is that there likely will not be a silver bullet. There is a need to have alternatives because patients are different and have different tolerance to medications. The pathophysiology of their hypertension may make one type of medication more effective than another."

Remaining Issues

Ms. Hollidge believes that angiotensin receptor blockers, which were not included in the ALLHAT trial and are the only class that is completely patent protected, will be the key driver of market growth in the future

"Although ALLHAT was a big landmark study and has been widely publicized, I don't think it is going to impact actual market size and market growth that much," she says. "A far bigger impact on the market has been the introduction of generics for leading brands."

Datamonitor analysts also believe that the niche hypertensive populations contain commercial opportunities for marketers in the future. These populations include groups such as diabetic hypertensives, which represent 25 million patients in the seven major markets who have unmet needs. Analysts believe that for novel therapies, initial adoption in resistant populations will provide a gateway to the larger market.

Dr. Furberg agrees that other population segments of hypertensive patients should be taken into account as well.

"It is a mistake to push for guidelines for hypertension when there should be guidelines for preventing heart attacks and strokes," he says. ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

KENNETH M. BOROW, M.D. President and CEO, Covalent Group Inc., Wayne, Pa.; Covalent is a clinical research organization that designs and manages complex clinical trials for the pharmaceutical, biotechnology, and medical-device industries. For more information, visit covalentgroup.com.

RUTH BROWN, PH.D. Analyst, Decision Resources, London; Decision Resources, with U.S. headquarters in Waltham, Mass., provides in-depth research on the trends, emerging developments, and market potential of the drug industry. For more information, visit dresources.com.

CURT FURBERG, M.D., PH.D. Chairman of the ALLHAT Steering Committee and Professor of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, N.C.; Wake Forest University School of Medicine and North Carolina Baptist Hospital together form one of the major academic medical centers. For more information, visit wfubmc.edu/school.

DAHLIA GARZA, M.D. Medical Director of Norvasc, Pfizer Inc., New York; Pfizer discovers, develops, manufactures, and markets leading prescription medicines for humans and animals. For more information, visit pfizer.com.

CHRISTINE HOLLIDGE. Cardiovascular Analyst, Datamonitor Plc., New York; Datamonitor is an international strategic market analysis company, focusing on the pharmaceutical and biotechnology markets. For more information, visit datamonitor.com.

JEAN SIEBENALER, M.D. Therapeutic Director of Cardiovascular Services and Medical Director, Kendle International Inc., Cincinnati; Kendle is a global provider of quality clinical research and development services. For more information, visit kendle.com.