Experts Provide a Glimpse of the New Post-SPRINT Era of Hypertension

Susan L. Worley

New guidelines for the management and treatment of hypertension, one of the leading causes of death and disability throughout the world,1 are scheduled to be released in 2017 by several internationally recognized organizations. In the U.S., these guidelines, jointly prepared for the first time by the American College of Cardiology and the American Heart Association (AHA), will serve as an update to the hypertension management guidelines prepared by the Eighth Joint National Committee (JNC 8) and published in 2014.2 Findings from several recent clinical trials and analyses—most notably from the Systolic Blood Pressure Intervention Trial (SPRINT)3— are expected to form the basis of these new guidelines, which should feature new hypertension treatment targets and new approaches to the treatment of the elderly, among other recommendations.

For the first time in decades, the primary focus in the field has moved from pharmaceuticals to the meticulous analysis and interpretation of cumulative research data and the translation of key findings to best clinical practices and directions for public health policy.4 While antihypertensive drug therapy has evolved to such a degree that a range of relatively inexpensive and well-tolerated medications (Table 1)3 can be used alone or in combination to provide satisfactory control of hypertension in a majority of individuals requiring treatment,5 questions surrounding the intricacies of hypertension management remain. The herculean task of sifting through available data for clinical pearls—including optimal ways to achieve more intensive treatment goals, the best methods for monitoring and assessing hypertensive patients, and the magic keys to ensuring adherence to treatments—will occupy researchers long after the release of new guidelines. Yet just one year after the publication of SPRINT findings, leading experts have already begun to distill information from that landmark trial that is meaningful for clinicians and their patients.

In Search of Treatment Targets

Sufficient evidence to suggest that a reduction in elevated blood pressure can lead to a reduction in the incidence of heart disease, including congestive heart failure and coronary artery disease, as well as stroke and chronic kidney disease (CKD), across a range of patient populations has been available for nearly two decades. However, experts have long had difficulty reaching a consensus with regard to appropriate blood pressure targets during treatment. This uncertainty can be attributed in part to concerns about risks associated with blood pressure–lowering in some individuals and in part to a lack of clear evidence to support intensive treatment. Inconclusive or unexpected clinical trials results have added to the uncertainty. For instance, the landmark Action to Control Cardiovascular Risk (ACCORD) trial, published in 2010, found that intensive blood pressure–lowering (to less than 120 mm Hg versus less than 140 mm Hg) did not reduce overall cardiovascular events among patients with type-2 diabetes, although there was a reduction in strokes in the intensively treated group.6 Still, to those outside the field who have long been accustomed to the standard definition of hypertension (readings of 140/90 mm Hg and higher), it may seem puzzling that a target systolic blood pressure (SBP) of less than 150 mm Hg, rather than below 140 mm Hg, was recommended by JNC 8 for people 60 years of age and older in guidelines published less than three years ago.2 Perhaps more puzzling is that this target represented an increase in SBP compared with the treatment goal of 130 mm Hg that appears in 2003 guidelines7 for individuals with CKD or diabetes. But Raymond R. Townsend, MD, Director of the Hypertension Program and Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania, who served as a member of the JNC 8 panel, says the recommended SBP target of less than 150 mm Hg for people older than 60 years can be explained by the panel’s unyielding commitment to evidence-based medicine.

“When our panel convened in 2008, our directives were to establish guidelines based not on our professional opinions, but rather on evidence from clinical trials,” explains Dr. Townsend, who in 2016 was named Physician of the Year by the AHA. “After extensive research, we found that there simply was no solid evidence to support a systolic blood pressure target of below 140.”

The panel was able to confirm only that positive outcomes in a range of clinical trials were consistently reported for older patients whose SBP was lowered to a target of below 150 mm Hg. Panel members were not able to consider findings from SPRINT, which was launched in 2010, two years after the panel convened.

To more clearly determine the potential benefit of intensive treatment, SPRINT randomly assigned 9,361 individuals (50 years of age or older) with an SBP of 130 mm Hg or higher and an increased risk of cardiovascular disease to intensive treatment (SBP target of less than 120 mm Hg) or standard treatment (SBP target of less than 140 mm Hg).3 In 2015, the trial was stopped early after participants in the intensive group were found to have a 25% lower risk of major cardiovascular events and a 27% lower relative risk of death from any cause compared with those in the standard treatment group. In addition, although noteworthy patient populations were excluded from the trial (including those under the age of 50 years, those with diabetes, and those who had previously

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had a stroke), consistent benefits were seen across six different subgroups when participants were treated to a lower target SBP. Consequently, most experts agree that SPRINT will be practice-changing, although it may take time to extract and refine its most important clinical implications.

The Impact of SPRINT on Clinical Practice

At first glance it appears that the results of SPRINT have direct implications for people 50 years of age and older with an SBP of at least 130 mm Hg while taking up to three antihypertensive medications (patients with an SBP higher than 160 mm Hg while taking three or more medications were not included in the trial). However, the process of generalizing findings from a selective patient population in a large trial and applying them to patients commonly seen in clinical practice is challenging for a number of reasons, Dr. Townsend notes.

“One of several important factors to consider is that patients enrolled in a clinical trial tend to be more motivated than patients that we typically see in clinical practice,” Dr. Townsend says. “The patients enrolled in SPRINT tended to take their medicines and tended to show up for their visits. They regularly provided their urine samples, and so forth. In clinical practice, about a quarter of the time patients don’t really take their medicines, or take them inconsistently, or they are less careful about reporting their habits.”

The relatively ample time and resources available to investigators and patients in a large trial likewise do not reflect the circumstances under which patients are typically monitored during office visits and therefore can generate results that are out of reach in clinical practice.

“Patients enrolled in SPRINT often would spend an hour or more per visit receiving attention and care, and asking questions,” Dr. Townsend says. “They also received free medication, periodically would undergo free EKGs [electrocardiograms], and always were carefully attended to by a group of nurses and coordinators. In contrast, when a patient visits a busy office for a standard blood pressure check, the patient is usually lucky to spend 15 minutes with the doctor.”

Perhaps most important, patients in a standard clinical practice are unlikely to experience the results achieved in the intensive treatment arm of SPRINT unless they actually meet the trial’s inclusion and exclusion criteria.

“Patients whose systolic blood pressure can be lowered to less than 120 mm Hg with three or fewer medications are not the kind of patients we typically see at a hypertension center. Primary care physicians might encounter these patients, but

### Table 1: Selected Hypertension Medications

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Available Strengths</th>
<th>Dose Range Per Day</th>
<th>Daily Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Chlorthalidone</td>
<td>25 mg</td>
<td>12.5–25 mg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Furosemide</td>
<td>20 mg, 40 mg, 80 mg</td>
<td>20–80 mg</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td>25 mg</td>
<td>25–50 mg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Triamterene/hydrochlorothiazide</td>
<td>75/50 mg</td>
<td>37.5/25 mg–75/50 mg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Amiloride</td>
<td>5 mg</td>
<td>5–10 mg</td>
<td>1–2</td>
</tr>
<tr>
<td>Angiotensin-converting</td>
<td>Lisinopril</td>
<td>5 mg, 10 mg, 20 mg, 40 mg</td>
<td>5–40 mg</td>
<td>1</td>
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<tr>
<td>angiotensin-receptor</td>
<td>Losartan</td>
<td>25 mg, 50 mg, 100 mg</td>
<td>25–100 mg</td>
<td>1–2</td>
</tr>
<tr>
<td>blockers</td>
<td>Azilsartan</td>
<td>40 mg, 80 mg</td>
<td>40–80 mg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Azilsartan/chlorthalidone</td>
<td>40/12.5 mg, 40/25 mg</td>
<td>40/12.5–40/25 mg</td>
<td>1</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>Diltiazem</td>
<td>120 mg, 180 mg, 240 mg, 300 mg</td>
<td>120–540 mg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Amlodipine</td>
<td>2.5 mg, 5 mg, 10 mg</td>
<td>2.5–10 mg</td>
<td>1</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Metoprolol tartrate</td>
<td>25 mg, 50 mg, 100 mg</td>
<td>50–200 mg</td>
<td>1–2</td>
</tr>
<tr>
<td></td>
<td>Atenolol</td>
<td>25 mg, 50 mg, 100 mg</td>
<td>25–100 mg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Atenolol/chlorthalidone</td>
<td>50/25 mg</td>
<td>50/25 mg</td>
<td>1</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Hydralazine</td>
<td>25 mg, 50 mg, 100 mg</td>
<td>50–200 mg</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Minoxidil</td>
<td>2.5 mg, 5 mg, 10 mg</td>
<td>2.5–80 mg</td>
<td>1–2</td>
</tr>
<tr>
<td>Alpha2 agonist</td>
<td>Guanfacine</td>
<td>1 mg, 2 mg</td>
<td>0.5–2 mg</td>
<td>1</td>
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<tr>
<td>Alpha blocker</td>
<td>Doxazosin</td>
<td>1 mg, 2 mg, 4 mg, 8 mg</td>
<td>1–16 mg</td>
<td>1</td>
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<tr>
<td>Potassium supplements</td>
<td>Potassium chloride tablets</td>
<td>20 mEq</td>
<td>20–80 mEq</td>
<td>1–2</td>
</tr>
<tr>
<td></td>
<td>Potassium chloride oral solution</td>
<td>20 mEq/15 mL</td>
<td>20–80 mEq</td>
<td>1–2</td>
</tr>
</tbody>
</table>

* This list of medications—the primary formulary for the SPRINT trial—includes all major classes of antihypertensive agents. Other medications are available for this disease.
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I am more likely to have patients referred to me when their blood pressure cannot be adequately controlled on four or more medications. Very recently a patient was referred to me with a blood pressure of 180/110 while taking seven medications. That patient, of course, would not have qualified for SPRINT,” Dr. Townsend says.

The method by which blood pressure was measured in the trial also may have led to results that would be difficult to duplicate in clinical practice. To eliminate confounding circumstances associated with office-based blood pressure measurement—particularly elevated readings that can occur in the presence of an observer (known as white coat hypertension)—an automated approach called automated office blood pressure (AOBP) was used in SPRINT.

“SPRINT investigators were able to obtain much more accurate blood pressure readings, which on average were likely 7 to 10 mm Hg lower than they would have been had those readings been obtained in an office with a standard sphygmomanometer,” Dr. Townsend says. “That limits the generalizability of the trial’s findings as things stand right now—that is, until we have a cultural paradigm shift in terms of how we measure blood pressure in U.S. clinical practices.”

Meanwhile, Dr. Townsend and other hypertension experts anticipate that 2017 guidelines will account for the difference between the automated readings obtained in SPRINT and standard readings, most likely by recommending an SBP treatment target of below 120 mm Hg. If more patients can be encouraged to obtain semiautomated readings at home, which may lead to more accurate and consistent readings than those traditionally obtained with a sphygmomanometer, future guidelines may eventually recommend SBP targets closer to 120 mm Hg. However, patients currently face an important barrier to regular home monitoring.

“Home blood pressure monitors, as valuable as they are, are currently not covered by many health insurance policies,” Dr. Townsend says. “Yet insurance will cover the cost of a glucose monitor for patients who need one—even though when it comes to outcomes, there are far more data supporting the value of lowering blood pressure compared with the value of lowering blood sugar.”

Ideally, home blood pressure monitoring should be used to confirm high readings obtained during in-office screening and to track a patient’s response to treatment. It also may be used to confirm the presence of a white coat effect, when home readings are lower, although whether minor differences due to this effect can be considered an important risk factor for sustained hypertension and related target organ damage is still a matter of debate.

“However,” Dr. Townsend says, “when a patient has a reading of 160/110 in the office and readings of 110/70 at home, that patient’s likelihood of developing real hypertension, both at home and in the office, will be greater—in part because of his or her tendency to significantly overshoot normal regulatory mechanisms while in a medical environment. That tendency will eventually lead to an accumulation of microfractures and other types of damage to blood vessels that will increase the probability of eventual target organ damage.”

Like many hypertension experts in the U.S., Dr. Townsend does not rank the development of new antihypertensive medications among the most important unmet needs in his field. Instead, he would prefer to see the development of a foolproof method for ensuring that patients take their medications.

“We know that the drugs we are currently using work. They provide benefit to the people who take them. So it’s essential that we develop new methods or strategies, perhaps using mobile technologies, for encouraging adherence. Finding ways to foster greater persistence—that is, strategies for ensuring that people continue to take their medications after they already have responded to treatment—also is critical.”

Shaping Public Policy

Findings from SPRINT already have begun to influence not only clinical practice but also research and health care policy throughout the U.S. and around the world. Not long before the trial’s findings were published, the World Health Organization (WHO) formally recognized hypertension as the first noncommunicable disease to rank among primary global causes of major illness and premature mortality. At roughly the same time, the World Hypertension League (WHL) formally designated the U.S. Journal of Clinical Hypertension as the primary forum for its policy statements and position papers regarding the management of hypertension—a partnership that should help coordinate global efforts to optimize the care of hypertensive individuals and accelerate the standardization of information reporting.

In a field that attaches such importance to even minor changes in millimeters of mercury, the standardization of blood pressure measurement is particularly important—an issue that was underscored by findings from SPRINT. Yet for many decades, says Michael A. Weber, MD, Professor of Medicine at SUNY Downstate College of Medicine in New York and Editor-in-Chief of the Journal of Clinical Hypertension, there were few if any discussions about the best method for measuring blood pressure.

“Until about 10 years ago,” Dr. Weber says, “everyone knew, or thought they knew, that using the standard sphygmomanometer with a mercury column and listening with a stethoscope to the sounds over the brachial artery in the upper arm represented the gold standard of blood pressure measurement. Now that method has come under question for several important reasons.”

The high degree of inter- and intraobserver variability in readings that rely so strongly on human performance, particularly hearing, is a primary concern shared by experts in the field, says Dr. Weber, who also serves on the executive committee for the International Society of Hypertension (ISH) and the board of directors for the Center for Medicine in the Public Interest. The potential for inaccuracies caused by simple carelessness or bias also have been a concern. A growing uneasiness with this standard method of measurement has inspired experts to take a closer look at relatively inexpensive automated devices, which have been available in drug stores and department stores for more than a decade. Testing in recent years has shown that compared with traditional measurement by sphygmomanometer these devices are more reliable and consistent.

“A few years ago,” Dr. Weber says, “my office switched to using only automated devices, which we have found to be more...
accurate and free from bias. Another benefit of this method is that our patients can use the same devices at home that we are using in the office.”

The process of validating semiautomated and automated methods of measuring blood pressure involves a comparison of readings from these devices with direct measurements of arterial pressure obtained from patients undergoing cardiac catheterization. The latter procedure, which measures blood pressure in the aorta (central blood pressure) rather than in the arm, represents what many experts believe is the true gold standard of blood pressure measurement. However, because the invasive use of a catheter is not practical for regular use, noninvasive methods for obtaining central blood pressure are under investigation. Pulse-wave velocity, a noninvasive measure of arterial stiffness that has been shown to be predictive of coronary disease and its severity,14 is being used increasingly in clinical trials and may eventually find a place in clinical practice.

Ambulatory blood pressure measurement (ABPM) by noninvasive methods—a technique that Dr. Weber and his colleagues, among others, helped pioneer in the late 1970s—has long been used for home monitoring and still is recommended by the U.S. Preventive Services Task Force as a routine method for confirming the diagnosis of hypertension.15 ABPM also remains an important method of identifying individuals at greater risk for adverse outcomes due to a lack of normal drop in blood pressure during the night. In normal healthy people, blood pressures should fall at night by at least 10%, says Dr. Weber, but approximately 20% to 30% of people do not have that fall in values and may even have values that are higher at night. Although there is broad agreement that such nighttime patterns are strongly predictive of stroke and cardiovascular events, the best approach to preventing events in this population has yet to be determined.

A growing trend toward nighttime dosing of blood pressure medications, however, may provide at least a partial solution.

“We worry most about the early morning hours after people wake up,” Dr. Weber says. “Those first few hours are the most dangerous times of the day, when a disproportionate number of strokes and heart attacks occur. To offer patients greater protection during those hours, I prefer to prescribe blood pressure medications at night, and a few major clinical trials have reported very strong results and good protection for patients with nighttime dosing of medications. When this approach is used regularly with all patients, it may be less important to identify patients who don’t have the appropriate fall in blood pressure at night.”

Nighttime dosing, adds Dr. Weber, also may help to limit the faintness and dizziness that some patients experience during the first few hours after taking their medications.

Salt and Treatment-Resistant Hypertension
Important current research that will continue to influence public health policy in the coming years includes studies focused on salt intake and on approaches to treatment-resistant hypertension.

A consensus among public health scholars that a reduction in salt intake would lead to a population-wide reduction in blood pressure and in turn a reduction in cardiovascular events has led the WHO to recommend a 30% reduction in dietary salt by 2025. However, leading international entities, including the WHO, the WHL, and the ISH, have expressed concern over conflicting and controversial findings regarding salt intake and have uniformly urged greater rigor in salt studies.4 Future studies will be expected to demonstrate, among other things, more accurate methods for quantifying salt intake in individuals, better statistical methodology, improved techniques for 24-hour urine collection, and better assessment of clinical endpoints.

Effective approaches to treatment-resistant hypertension are among the greatest unmet needs in the field, although both the prevalence and cause of this phenomenon have been difficult to discern. With the use of just three classes of currently available antihypertensive medications, most leading hypertension experts agree that it is possible to control hypertension in at least 80% of all individuals who require treatment, with relatively few side effects.

“Right now most of us work primarily with three types of drugs—those that block the renin-angiotensin system, which include the ACE [angiotensin-converting enzyme] inhibitors and ARBs [angiotensin-receptor blockers]; the calcium-channel blockers; and the thiazide-like diuretics. Those are the big three, the holy trinity of hypertension medications, and using these it is possible to develop effective, well-tolerated regimens for most patients. When we do encounter individuals with so-called treatment-resistant hypertension, most of the time it turns out that these patients are not taking their medications reliably,” Dr. Weber says.

For some patients who are truly resistant to these three classes of medications, Dr. Weber adds, spironolactone17 has proven to be effective. Further research investigating treatment combinations18 and pharmacogenomics19 may result in effective tools for addressing true treatment-resistant hypertension, as well as strategies for eliminating some of the trial and error involved in selecting medications for all patients. Early research focused on renal denervation, a procedure involving the ablation of renal nerves, also has shown promise.20

“If it may turn out that this procedure is helpful in individuals who are not responding to drugs,” Dr. Weber says, “or perhaps more importantly for patients who are unable or unwilling to take their medications reliably.”

The Elderly, Women, and Groups Excluded From SPRINT
As the U.S. population continues to age, there will likely be a growing focus on the treatment of hypertension in the elderly. Results of the SPRINT trial have for the first time shown that targeting a systolic blood pressure of less than 120 mm Hg, a “normal” blood pressure level, is safe and effective for preventing deaths and major cardiovascular events like heart failure and myocardial infarctions in individuals 75 years of age and older with hypertension.21 Earlier notable studies, such as Hypertension in the Very Elderly (HYVET) and the Systolic Hypertension in the Elderly Program (SHEP), which were not designed to address questions regarding appropriate targets, examined only the general effectiveness and tolerability of
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hypertension treatment in the elderly, for whom treatment poses some special risks.

“Blood vessels in the elderly tend to be stiff, so that systolic blood pressure tends to be elevated, while diastolic blood pressure actually tends to be lower than in younger people,” says Suzanne Oparil, MD, Professor of Medicine and Director of the Vascular Biology and Hypertension Program at the University of Alabama at Birmingham, who in 2016 received the Excellence Award for Hypertension Research from the AHA Council on Hypertension. “Electrolyte abnormalities, or low sodium and low potassium, also are a particular concern in the elderly. Postural hypotension, which can lead to falls and serious fractures, is another major concern in individuals who are already frail and unsteady.”

With targeted supplementary funding, SPRINT investigators were able to address some of these concerns by recruiting additional elderly participants, so that close to 30% of the resulting trial population—a subgroup called SPRINT senior—were older than 75 years of age.

“The very frail elderly, such as those in assisted living or in nursing homes, were excluded from the trial,” Dr. Oparil says, “as were individuals with signs of cognitive dysfunction or dementia. So we still lack information about treatment in those individuals. But SPRINT very clearly demonstrated that for the reasonably high-functioning elderly, aggressive treatment to targets as low as 120 mm Hg is safe and effective, and that adverse events in this population were comparable to those seen in younger groups, which was quite surprising.”

Consequently, many experts anticipate less age stratification with regard to recommended treatment targets in future hypertension guidelines. These experts agree that follow-up research examining further stratification of this population by functional status, rather than by age, would likely be of value. Currently, Dr. Oparil says, it makes sense to avoid aggressive treatment of hypertension in frail elderly patients who are already experiencing frequent dizziness and falls.

Meanwhile, a component of the SPRINT trial called SPRINT-MIND is addressing yet another important question regarding elderly patients: the effects of intensive treatment of systolic blood pressure on cognitive function. SPRINT-MIND investigators will aim to discover whether intensive blood pressure-lowering to the 120 mm Hg target reduces cognitive decline and the incidence of all-cause dementia.

To date, hypertension guidelines have not offered specific guidelines for women, even though women have several kinds of high blood pressure—including oral contraceptive- and pregnancy-related hypertension—not found in men. Likewise SPRINT, which had a somewhat larger male population, was not specifically designed to detect gender-related differences in response to hypertension treatment. However, recent meta-analyses have shown that some antihypertensive medications might be more beneficial for women.

“We know that thiazide diuretics more than other drug classes are better for bone health in women,” says Dr. Oparil, coauthor of a recent analysis of ALLHAT, which indicated that women randomized to receive chlorthalidone, a thiazide-type diuretic, had significantly fewer fractures than those randomized to an ACE inhibitor or calcium-channel blocker. “That is important because significant fractures, such as hip and pelvic fractures, require hospitalization and sometimes surgery and can lead to life-ending complications.”

Dr. Oparil adds that, compared with men, research also has indicated that women tend to have a larger number of adverse events while taking ACE inhibitors, such as cough and angioedema. Future research is needed to detect other gender-related differences and identify treatment strategies that will offer greater protection to women. Basic science research is also called for to further investigate the effect that sex hormones, particularly estrogen, have on blood vessels in women as they age.

“I’m particularly interested in examining why the beneficial effects of estrogen disappear as women age,” she adds. “It may be that there is a reduction in the number of estrogen receptors, or it may be that with age receptor proteins are modified in such a way that they don’t signal properly. Perhaps estrogen is metabolized differently with age—we don’t yet know the answers to these questions.”

Questions also remain for a fairly wide range of patients who were excluded from SPRINT, including patients with diabetes, those with previous stroke, and those younger than 50 years of age. Patients with diabetes were excluded from SPRINT largely because of the ACCORD trial; however, experts continue to be uncertain about appropriate blood pressure targets in these patients because of a number of factors that served to confound ACCORD data. SPRINT excluded patients with prior stroke largely because of the Secondary Prevention of Small Subcortical Strokes (SPS) trial, which examined whether an SBP target of less than 130 mm Hg would reduce recurrent stroke in patients who had experienced recent lacunar stroke. Consequently, the impact of intensive blood pressure-lowering on patients with recent stroke was left unanswered by SPRINT.

“The literature clearly indicates that stroke is the outcome that is generally most sensitive to blood pressure—lowering—more so than heart attack and heart failure. And yet, largely because of its inclusion and exclusion criteria, we didn't find that in SPRINT. We found that heart failure was reduced more than any other single outcome,” Dr. Oparil says.

In patients at high risk for stroke and in those with previous stroke, further research is needed to identify best treatment approaches and the extent to which other variables, including the lowering of cholesterol, play a relevant role in the risk for future stroke.

A need also exists for smaller studies that more closely examine the effects of hypertension treatment on other high-risk patient populations, including individuals with a wide range of chronic diseases who were excluded from SPRINT.

“Research has shown, for example, that individuals with HIV [human immunodeficiency virus infection] tend to have accelerated vascular disease and also tend to have increased nocturnal hypertension. We don’t yet know why such
differences exist in these patients. Are they related to cholesterol? Or perhaps to inflammation? We also don’t yet know whether these individuals will respond as well to aggressive blood pressure–lowering.”

Two other important groups excluded from SPRINT, which many hypertension experts feel have been unduly neglected in hypertension literature, are children and young adults at high risk for hypertension, as well as low-risk individuals of all ages. Although the incidence of hypertension in children is increasing, Dr. Oparil says that research designed to determine the best treatment for these patients has yet to be conducted. A closer examination of low-risk individuals also will be increasingly important, in part to gain a better understanding of the mechanisms of hypertension. Answers to all of these questions will almost certainly require the development of new research methods.

“It’s unlikely that we will be able to answer these questions with other large-scale trials such as SPRINT because such trials are prohibitively expensive,” Dr. Oparil says. “As we move into the future, questions will more likely be addressed using big databases, such as those drawn from electronic medical records. The American Heart Association, for example, is using large databases in a study designed to answer some larger questions about cardiovascular disease—a study that will likely provide some valuable information about hypertension.”

Observational trials, and studies that rely on telemonitoring—perhaps making use of the growing trend toward home blood pressure monitoring—will likely play a role in study designs that may replace traditional randomized clinical trials in the guidance of antihypertensive treatment in the future, Dr. Oparil adds.

REFERENCES