Risk Stratification of Older Patients

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Cardiovascular disease is a growing global health threat due in part to demographic shifts, in particular the growing elderly population in which cardiovascular disease is highly likely to develop. Older individuals have numerous coexisting conditions that contribute to increased risk for morbidity and mortality. In the past, physicians primarily used diastolic blood pressure (BP) as the indicator for measuring relative risk. However, since the early 1970s observational studies have found that systolic BP rather than diastolic BP is a better predictor of cardiovascular events, particularly in the older population. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) recommended specific goals for the treatment of hypertensive patients. Specifically, JNC-VI reinforced the notion of more aggressive BP goals for patients at the greatest risk for an event. The approach to patients who are not at goal is different from earlier guidelines.

Therapy is now aimed at building therapeutic regimens. Currently, there are five classes of agents that have been shown to reduce the morbidity and mortality associated with cardiovascular and renal disease: diuretics, β-blockers, angiotensin converting enzyme inhibitors, calcium antagonists, and angiotensin receptor blockers. If a patient is not at goal and there is no response to an agent from one of these classes or troublesome side effects develop, then and only then should that drug be stopped and a different one used. Otherwise, a multidrug regimen is constructed and additional agents added in logical fashion. A majority of patients with higher risk can attain control at the specified BP goal safely and effectively by using a combination of agents. Am J Hypertens 2002;15:77S–81S © 2002 American Journal of Hypertension, Ltd.

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On the basis of estimates from the American Heart Association, the leading cause of death in the United States in both men and women is heart disease. Cancer and then stroke are ranked second and third. Approximately 450,000 men and 550,000 women die each year from heart disease. Cardiovascular disease is a growing health threat, due in large part to demographic shifts, in particular, the growing elderly population. This demographic trend is evident not only in the United States and other developed countries, but is also present worldwide. This review will examine various clinical studies focusing on the relationship between blood pressure (BP) indices (systolic BP, diastolic BP, and pulse pressure) and cardiovascular events, especially in relation to older patients, and currently available therapeutic agents and their implications.

The Third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 to 1994, and the 1990 US census indicated that 73% of the 47 million hypertensive patients in the United States were more than 50 years old. It is expected that by the year 2020, 80% of hypertensive Americans will be aged more than 50 years with increasing numbers in their 70s and 80s. Longitudinal data in the NHANES III survey revealed that as the population ages from 18 years of age to more than 80 years of age, the average systolic BP increases, whereas the average diastolic BP increases until the mid-50s, after which it decreases. This is evident in both men and women of non-Hispanic African American, non-Hispanic white, and Mexican American background. The decrease in diastolic BP represents a physiologic change (increased stiffness and noncompliance) in large arteries rather than a “healthy survivor effect,” resulting from the deaths of individuals with high diastolic BP levels.

Clinical Studies
Pulse Pressure and Cardiovascular Events

In a 1990 analysis by MacMahon et al., the relationship between stroke and coronary heart disease (CHD) and usual diastolic BP showed that as diastolic BP increases, so does the risk of these two major events. The study showed that based on a usual diastolic BP of 91 mm Hg, an individual has a four times greater likelihood of developing a stroke if the diastolic BP is 105 mm Hg and a...
one-third lower likelihood if the diastolic BP is 76 mm Hg. The same trend exists for CHD, although the increase in relative risk is somewhat less steep.

Data from the Framingham Heart Study, however, showed that systolic BP is a better predictor of cardiovascular outcomes than diastolic BP. This finding has been confirmed in many other studies, most convincingly in the observational data from the Multiple Risk Factor Intervention Trial (MRFIT). Neaton and Wentworth examined 316,000 white men, 35 to 57 years of age, from the original sample size in the MRFIT study, to investigate the effect of elevated BP on CHD mortality over a 12-year period. The frequency of events in individuals with stage 1 hypertension based on a systolic BP of 140 to 159 mm Hg was not increased as diastolic BP increased from less than 70 to 100 mm Hg. In contrast, individuals with an allegedly “normal” diastolic BP between 75 and 79 mm Hg had an increased risk of CHD mortality as systolic BP increased. In this group of men, the highest risk of mortality was associated with the individuals who had the widest pulse pressure (the difference between systolic and diastolic BP). Individuals with BP more than 160/70 mm Hg (pulse pressure greater than 90 mm Hg) were most likely to have a fatal CHD event.

Glynn et al confirmed this finding and further demonstrated that if patients with a diastolic BP of 80 to 89 mm Hg and a systolic BP of <130 mm Hg were assigned a relative risk of 1.00, then the lower the diastolic BP, the higher the relative risk. Similarly, as systolic BP increases at any given diastolic BP, so does relative risk.

The analysis by Franklin et al of the Framingham data showed that at any level of systolic BP, the risk of CHD decreases as diastolic BP increases. This means that the higher systolic and the lower diastolic BP is, the higher the risk. The pathophysiologic foundation for this observation is based on the stiffness of large arteries. The natural progression of rising systolic and falling diastolic BP in later life results in an increase in pulse pressure. The widening pulse pressure has clinical and pathophysiologic correlates such as increasing systolic load on the left ventricle, increasing myocardial oxygen demand, impaired diastolic relaxation, some subendocardial ischemia, increasing wall tension and systolic pressure, and, potentially, reduced coronary perfusion, in addition to back-reflected waves and further left ventricular hypertrophy (LVH). One of the first studies linking cardiovascular risk and pulse pressure was done by Madhavan et al and focused on hypertensives in a work site program. Two thousand two hundred seven individuals were divided into tertiles based on treated pulse pressure. Individuals in the lowest tertile in comparison to those in the highest were younger, more often men than women, and more often African American than white. They appeared be at higher risk due to a greater prevalence of LVH, higher serum cholesterol, and more prior cardiovascular disease.

On the basis of only diastolic BP, those in tertile 3 appeared to be the best-controlled group because these individuals had the lowest diastolic BP. But this group also had the highest systolic BP, both at the beginning and at the end of the observational period. The study showed that the patients in this tertile who had the widest pulse pressure, also had more myocardial infarctions (MI), cardiovascular disease, and cardiovascular deaths. Pulse pressure, male gender, age, smoking, history of cardiovascular disease, and cholesterol were all factors that predicted MI in all three tertiles, whereas race, LVH, weight, and either systolic or diastolic BP, considered independently, did not.

In the East Boston survey investigating hypertension in the elderly, Chae et al reported on BP correlates of heart failure (HF). They observed a progressive increase in HF as systolic BP increased, whereas a U-shaped relationship existed for diastolic BP. Here too, pulse pressure was the single most informative BP parameter. Franklin et al reported a similar correlation in the Framingham data, showing a progressive increase in risk at all levels of systolic BP.

Specific Goals for Hypertensive Patients

The rather disappointing data that shows that only 27% of Americans with hypertension are at goal was highlighted in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI). Worse still is the further observation that 27% is only an average. Rates of controlled hypertension in older people are lower still, perhaps as low as 15% or even less. Patients less than 40 years primarily have diastolic hypertension, whereas at age 50 years, there are equal rates of isolated systolic and combined systolic and diastolic BP elevations. As patients reach 60, 70, and 80 years of age, hypertension is characterized predominantly by systolic BP elevation without elevated diastolic BP as would be expected from the progression of changes with aging already discussed.

In JNC-VI, a grid was devised to assist physicians in determining how aggressively to treat and when to start treatment (Table 1). Hypertensives were divided into three risk groups: A, B, and C, with group A having the lowest risk and group C the highest. Group A included only those with no risk factors and no target organ damage or clinical disease; risk group B included people with one or more risk factors, including age more than 60 years, male gender, postmenopausal women, smoking, dyslipidemia, diabetes mellitus, and family history of cardiovascular disease but without target organ or clinical disease; and risk group C included people with target organ damage, clinical cardiovascular disease, or diabetes, whether or not they had other risk factors. This classification is simply a way to semiquantitate absolute risk. Within each stage, relative risk is estimated by BP level: high–normal ranging from 130 to 139/85 to 89 mm Hg; stage 1 from 140 to 159/90 to 99 mm Hg; and stages 2 and 3 are ≥160/≥100 mm Hg. In all cases, the higher stage is
Study (4S) was a secondary prevention study. A patient in the same stage would be a greater risk and have higher event rates than assigned should the systolic or diastolic BP not classify the patient in the same stage.

Lifestyle modification is recommended for any stage of hypertension in all three patient risk groups, but drug therapy is additionally recommended at the outset if the patient is in stage 2 or 3 based on BP. Patients with high–normal BP are candidates for immediate drug therapy if they have HF, renal insufficiency, or diabetes mellitus (ie, group C). The more aggressive BP control recommended by JNC-VI in the presence of diabetes mellitus is a result of the dramatic increase in risk that accompanies the disease. As illustrated in Fig. 1, risk of a cardiovascular event increases significantly with age, male gender, high BP, and increased ratio of total cholesterol to high-density lipoprotein cholesterol. In the presence of diabetes mellitus, the likelihood of suffering a cardiovascular event is so high in either the presence or absence of these factors that it independently represents a risk of greater magnitude, and becomes a reason for special consideration.

Because risk factors play such a significant role in the development of CHD, it is important to distinguish between absolute risk reduction and relative risk reduction in assessing the utility of a given therapeutic approach. The distinction between absolute risk reduction and relative risk reduction can be demonstrated by comparing two lipid-lowering trials. The West of Scotland Coronary Prevention Study (WOSCOPS) was a primary prevention study, whereas the Scandinavian Simvastatin Survival Study (4S) was a secondary prevention study. Individuals in WOSCOPS had high serum cholesterol but had not yet experienced a CHD event. In 4S, subjects already had experienced a CHD event and also had a high cholesterol level. It would be expected that the 4S cohort would be a greater risk and have higher event rates than would those in WOSSCOPS. Although the relative risk reduction was the same in both studies, the absolute risk reduction (placebo event rate minus active drug event rate) was considerably lower in the WOSSCOPS than in 4S. The reciprocal of the absolute risk reduction is the number of individuals who need to be treated to prevent an event. This number is greater for the WOSSCOPS than in 4S. When this same type of analysis is performed using BP as the risk factor, comparing the low-risk individuals between the ages of 45 and 54 years in the Medical Research Council (MRC) trial to those in the WOSSCOPS cohort, the same outcomes become apparent: with treatment, the lower risk group yields similar relative risk reduction, but with lower event rates. In this case there is a small absolute risk reduction requiring many more individuals to be treated to prevent a stroke.

The results derived from the above-named studies have positive implications for the treatment of high-risk elderly patients with CHD. A 40% reduction in stroke can be anticipated with effective antihypertensive treatment. Because those who are relatively free of other risk factors or clinical disease are at comparatively low risk, fewer strokes will be prevented in this more or less healthy cohort like that in the MRC mild hypertension study than would be prevented in an older and higher risk group. Identifying the proper treatments for different classes of patients and, most important, establishing and attaining BP goals are the keys to deriving desired clinical benefits.

For most hypertensive patients, the goal BP is less than 140/90 mm Hg. For individuals with diabetes mellitus, HF, or chronic renal failure, the goal is lower and treatment must be more aggressive. Trial data reflecting this approach was demonstrated in the UK Prospective Diabetes Study (UKPDS).

### Table 1. Risk stratification and treatment*

<table>
<thead>
<tr>
<th>Blood Pressure Stages (mm Hg)</th>
<th>Risk Group A (no risk factors; no TOD/CCD)</th>
<th>Risk Group B (at least 1 risk factor, not including diabetes; no TOD/CCD)</th>
<th>Risk Group C (TOD/CCD or diabetes, with or without other risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High–normal (130–139/85–89)</td>
<td>Lifestyle modification</td>
<td>Lifestyle modification†</td>
<td>Drug therapy†</td>
</tr>
<tr>
<td>Stage 1 (140–159/90–99)</td>
<td>Lifestyle modification (up to 12 mo)</td>
<td>Drug therapy</td>
<td>Drug therapy</td>
</tr>
<tr>
<td>Stages 2 and 3 (≥160/≥100)</td>
<td>Drug therapy</td>
<td>Drug therapy</td>
<td>Drug therapy</td>
</tr>
</tbody>
</table>

**Note:** For example, a patient with diabetes and a blood pressure of 142/94 mm Hg plus left ventricular hypertrophy should be classified as having stage 1 hypertension with target organ disease (left ventricular hypertrophy) and with another major risk factor (diabetes). This patient would be categorized as “Stage 1, Risk Group C,” and recommended for immediate initiation of pharmacologic treatment. Lifestyle modification should be adjunctive therapy for all patients recommended for pharmacologic therapy.

† For patients with multiple risk factors, clinicians should consider drugs as initial therapy plus lifestyle modifications.
‡ For patients with heart failure, renal insufficiency, or diabetes clinicians should consider drugs as primary therapy.

Therapeutic Options for Coronary Heart Disease

Currently, there are five classes of agents that have met clinical standards for initial treatment, that is, they have shown a reduction in morbidity and mortality. They are diuretics, β-blockers, angiotensin converting enzyme (ACE) inhibitors, calcium antagonists, and angiotensin receptor (AT-I) blockers. For a compelling indication such as HF, ACE inhibitors and diuretics have been well established as appropriate therapy. Now, β-blockers and AT-I blockers should be considered as well. For post-MI patients, little has changed; β-blockers without sympathomimetic activity and diuretics are still standard therapy. For patients with type 1 diabetes with proteinuria, recommendations are unchanged; but in type 2 diabetes, two new trials, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial and the Irbesartan Diabetic Nephropathy Trial (IDNT), have shown that angiotensin receptor blockers prevent morbidity and mortality. For older patients with isolated systolic hypertension, the value of long-acting dihydropyridines was clearly established in the Systolic Hypertension in Europe (Syst-Eur) trial. The Perindopril PROtection Against REcurrent Stroke Study (PROGRESS) and the Heart Outcomes Prevention Evaluation (HOPE) study established ACE inhibitors and ACE inhibitor–diuretic combinations as agents for poststroke and high-risk hypertensives.

FIG. 1. The percent chance of cardiovascular events in 5 years for men and women (A) without diabetes and (B) with diabetes. HDL = high-density lipoprotein; Chol. = cholesterol. Adapted with permission from the Dyslipidaemia Advisory Group on behalf of the scientific committee of the National Heart Foundation of New Zealand. 1996 National Heart Foundation clinical guidelines for the assessment and management of dyslipidaemia. N Z Med J 1996;109:224–231.
In JNC-VI, the approach to patients who are not at goal is different from earlier guidelines. Therapy is now aimed at building therapeutic regimens. If a patient is not at goal and there is no response to an agent or troublesome side effects develop, then and only then should that drug be stopped and a different one used. Otherwise, a multidrug regimen is constructed and second or third agents are added in logical fashion.

Conclusions

Although in the past, physicians have used diastolic BP as the primary way to assess the risk and plan treatment in hypertension, it is now accepted that systolic BP or, perhaps even, pulse pressure, should be used for risk stratification. This is especially true for specific high-risk individuals such as older individuals and diabetic patients, as it is critical for them to receive appropriate, aggressive BP lowering therapy. New therapeutic approaches featuring combination therapy, either as fixed-dose formulations or as individually titrated components, are often required. The implicit concept is that for the majority of patients, attainment of the BP goal can be safely and effectively reached but most of the time a combination of agents is necessary.

References

1. American Heart Association: Available at: www.americanheart.org.