SEMINARS IN
NEPHROLOGY

Hypertension in Special Populations

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Hypertension is a multifaceted disease that may present somewhat differently in various populations. It is clear that hypertensive treatment reduces cardiovascular, renal, and cerebrovascular outcomes for all patients, yet recent clinical trial data suggest that some groups may benefit more than others from specific drug intervention. Furthermore, these data justify specific approaches for some special populations. This article reviews important features of the presentation, rationale for treatment, and treatment recommendations for the treatment of hypertension in special populations. The special populations addressed include diabetic patients, the elderly, and women.
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Hypertension is a multifaceted disorder. Although the description refers to simply an increase in blood pressure, it is much more than a configuration of numbers. Not only is hypertension complicated by many pathophysiologic variations, but it also takes on different presentations in various patient profiles. These differences highlight the importance of focusing on special populations because the best treatment may hinge on the specific group to which a patient belongs.

Hypertension in Diabetes

The Relationship Between Diabetes Mellitus and Hypertension

Diabetes has a particularly potent effect on the risk for cardiovascular disease (CVD) in hypertensive individuals. Approximately 70% of type 2 diabetic patients have clinical hypertension.[1] Over a 12-year follow-up period of men in the Multiple Risk Factors Intervention Trial (MRFIT) study, among normotensive patients diabetes increased the relative risk for CVD by 4.4-fold, whereas in hypertensive patients (systolic blood pressures of >200 mm Hg) diabetes increased the risk by 1.89-fold.[2] Thus, the CV risk from hypertension and diabetes is additive.

In type 1 diabetic patients, hypertension usually is caused by underlying diabetic nephropathy and typically manifests at the onset of microalbuminuria. In type 2 diabetic patients, however, hypertension is present in one third of patients at the time of diagnosis of diabetes. Hypertension in type 2 diabetes may be related to underlying nephropathy, concurrent essential hypertension, or, possibly, secondary hypertension.[3] Increased blood pressure markedly accelerates the progression of diabetic nephropathy and microalbuminuria is a risk factor. Aggressive blood pressure treatment decreases the rate of decrease in glomerular filtration rate and prolongs the progression to renal failure.[4,5]

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Rationale for Treatment

Recent clinical trials of hypertensive diabetic patients showed important benefits of antihypertensive therapy. In the UK Prospective Diabetes Study, a 5-year study that was designed to determine the role of blood pressure control in improving morbidity and mortality in diabetic patients, patients were randomized to tight (<150/85 mm Hg) and less tight (<180/105 mm Hg) blood pressure control. They were assigned randomly to captopril or atenolol for 5 years. Both drugs were equally effective in reducing blood pressure and the macrovascular end points. However, the reduction of end points according to blood pressure treatment level yielded a clear advantage of tight blood pressure control, with a 24% decrease in diabetes-related end points ($P = .0046$), a 32% decrease in death related to diabetes ($P = 019$), a 44% decrease in strokes ($P = .013$), and a 37% decrease in microvascular end points. These results support the concept of aggressive blood pressure management. However, the achieved blood pressures in this trial (144/82 mm Hg in the tight control group and 154/87 mm Hg in the less tight group) are far higher than our current recommendations for blood pressure control in diabetic patients.[6] Furthermore, tight blood pressure control was more effective in reducing CVD outcomes than tight blood glucose level control.

In other cardiovascular studies that included diabetic patients, the diabetic patients seemed to derive even greater

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benefits of antihypertensive treatment than nondiabetic patients. In the Hypertension Optimal Treatment study, the primary objective was to determine whether aggressive blood pressure lowering to a diastolic blood pressure of less than 90, less than 85, or less than 80 mm Hg, by using felodipine-based therapy, was more effective in reducing cardiovascular end points.[7] Of the 18,790 participants, 1,501 were diabetic. There was a 51% reduction in major cardiovascular events comparing the less than 80–mm Hg group with the less than 90–mm Hg group, among the diabetic patients in the study ($P < .005$). The actual difference in blood pressure between the 2 groups was 4–mm Hg systolic and 3.9–mm Hg diastolic pressure. Further, in the Systolic Hypertension in the Elderly Study (SHEP) diabetic participants, a decrease in systolic blood pressure and diastolic blood pressure of 10 mm Hg and 2 mm Hg, respectively, reduced the risk for cardiovascular events by up to 34%. Compared with nondiabetic patients, diabetic patients benefited more from the diuretic-based therapy with a reduction in relative risk for coronary heart disease (0.44 versus 0.81).[8]

In the Systolic Hypertension in Europe (Syst-Eur) study of hypertension in the elderly, which compared nitrendipine with placebo, 492 of the study population were diabetic. With similar blood pressure reduction the relative risk for total mortality, cardiovascular mortality, cardiovascular events, and strokes were consistently higher in diabetic than in nondiabetic patients.[9,10] Therefore, in diabetic patients, in whom the leading cause of death is from cardiovascular disease, blood pressure lowering has a potent effect beyond that of blood glucose level reduction and beyond the proven benefits of lowering blood pressure in nondiabetic patients.

In the Micro–Hypertension Outcomes Prevention Evaluation study (a substudy of the Hypertension Outcomes Prevention Evaluation study), compared with placebo, ramipril showed a 25% reduction in the combined outcome of myocardial infarction, stroke, and CVD death in 3,477 diabetic patients that remained significant even after adjustment for blood pressure difference (-2.4/-1.0 mm Hg). Ramipril reduced myocardial infarction by 22%, stroke by 33%, cardiovascular death by 37%, total mortality by 24%, revascularization by 17%, and overt nephropathy by 24%. This study suggested that there may be a benefit of renin-angiotensin blockade beyond blood pressure alone.[11]

The Losartan Intervention For Endpoint reduction in hypertension study further implied a unique effect of renin-angiotensin blockade. In this trial, in which hypertensive patients with left ventricular hypertrophy were treated with losartan or atenolol for 4 years to determine the effects of these treatments on mortality and morbidity, once again diabetic patients showed a greater benefit than nondiabetic patients. Similar to the findings in the entire study population, losartan was superior to atenolol in reducing CVD events, however, the treatment difference in the overall population was 14%, whereas it was 25% in the diabetic subpopulation.[12]

Meta-analysis of cause and clinical studies by Bakris et al[13] showed a clear relationship of systolic blood pressure to the decrease of glomerular filtration rate (GFR); thus, highlighting the importance of lowering blood pressure in reducing progression of renal disease. Recent clinical trials of diabetic renal disease have shown distinct benefits of blocking the renin-angiotensin system. Losartan, irbesartan, and valsartan all have been shown to reduce the progression of renal disease in type 2 diabetic hypertensive patients.[14] In the Irbesartan for MicroAlbuminuria in Type 2 Diabetes study, 590 patients with type 2 diabetes, hypertension, 20 to 200 μg/min albuminuria, and normal serum creatinine levels were randomized to placebo or irbesartan 150 or 300 mg/d for 2 years. After 2 years, blood pressures were similar in the 3 treatment groups (145/84, 143/84, and 142/84 mm Hg). After adjustment for baseline microalbuminuria and the blood pressure achieved during the study, compared with placebo the risk reduction for diabetic nephropathy was 44% in the 150-mg irbesartan group and 68% in the 300-mg irbesartan group. Albuminuria was reduced 2%, 24%, and 38% in the placebo, 150-mg irbesartan, and 300-mg irbesartan groups, respectively. Although not statistically significant, there was a difference in nonfatal cardiovascular disease of 8.7% in the placebo group and 4.5% in the 300-mg irbesartan group.[15]

In the Reduction in Endpoints in Non–Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan trial of 1,513 participants with type 2 diabetes and nephropathy, the study participants received losartan or placebo in addition to other antihypertensive agents to achieve a goal of blood pressure less than 140/90 mm Hg.[16] This 4.5-year planned study was discontinued 1 year early because of the mounting evidence that angiotensin-converting enzyme (ACE) inhibitors were cardioprotective. Blood pressure was reduced similarly in both treatment groups. The primary end point of doubling of the serum creatinine level, progression to end-stage renal disease (ESRD), or death was reduced by 16% in the intention-to-treat analysis and by 22% in patients who remained on treatment. Losartan treatment reduced doubling of the serum creatinine level by 25%, and ESRD by 28%. Interestingly, 87% to 90% of the patients in this study on losartan also were treated with a calcium-channel blocker, which did not appear to affect the benefits of the angiotensin-receptor blocker (ARB) treatment adversely. Losartan prevented 1 case of ESRD for every 16 patients treated during the 3.5 years of the study.[17] The composite cardiovascular end points of mortality and morbidity were not significantly different, however, losartan treatment reduced first hospitalization for congestive heart failure significantly, as well as the number of myocardial infarctions, although not statistically significant.

The Irbesartan Diabetic Nephropathy Trial included 1,713 type 2 diabetic hypertensive patients with proteinuria level of greater than 900 mg/d, creatinine levels of 1.0 to 3.0 mg/dL for women and 1.2 to 3.0 mg/dL for men, and no recent active CVD.[18,19] The patients were randomized to irbesartan 300 mg, amlodipine 10 mg, or placebo for a mean of 2.6 years. The blood pressure goal was 135/85 mm Hg, however, the achieved mean blood pressure after baseline was 140/77 mm Hg in the placebo group. The relative risk for the primary end point including doubling of the serum creatinine level,

progression to ESRD, or death was reduced by 20% in the irbesartan group relative to the placebo group and 23% lower than the amlodipine group. There was no difference between the amlodipine and placebo groups. The unadjusted relative risk for doubling the serum creatinine level was 33% lower in the irbesartan group compared with placebo and 37% lower in the irbesartan group than in the amlodipine group. The unadjusted relative risk for ESRD was 23% lower in the irbesartan group than in the amlodipine or placebo groups. Doubling of the serum creatinine level and ESRD did not differ between the amlodipine- and placebo-treatment groups. These effects of irbesartan remained significant after adjustment for blood pressure differences in the groups. Based on this study, to prevent 1 patient from having a primary event it is necessary to treat 15 patients with irbesartan 300 mg or treat 10 patients to prevent 1 patient from doubling their serum creatinine level.

There was no difference in all-cause mortality or composite CVD end points among the study groups in the Irbesartan Diabetic Nephropathy Trial, however, there were some differences in individual cardiovascular outcomes. Irbesartan reduced congestive heart failure 35% compared with amlodipine and 27% compared with placebo, whereas amlodipine compared with placebo showed no difference in congestive heart failure. Interestingly, amlodipine significantly reduced nonfatal myocardial infarction compared with placebo, yet irbesartan did not show the same effect. There were no differences in strokes between the treatment groups.[20]

A recent study comparing the ARB telmisartan, with the ACE inhibitor enalapril, was conducted in type 2 diabetic hypertensive patients over a 5-year period. The primary outcome was a decrease in GFR, and the secondary outcome was an annual change in GFR, serum creatinine level, urinary albumin excretion, and blood pressure; and the rates of ESRD, CVD, and death from all causes. The change in GFR for telmisartan and enalapril was not statistically different at the end of 5 years (−17.9 versus −14.9 mL/min/1.73 mo,[2] respectively). Notably, the confidence intervals were wide for these treatments. There were no differences in other end points.[21] Thus, these new clinical trials showed strong evidence of organ protection from renin-angiotensin–system blockade in the kidney as well as in the heart and brain in diabetic patients.

A recent observation in a large clinical trial of hypertension implied a possible role for the renin-angiotensin system in patients with diabetes. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) Study, comparing valsartan-with amlodipine-based regimens, showed that new-onset diabetes was 25% less in the valsartan-treated group.[22] The mechanism of this effect is not yet clear.

Recommendations for Treatment

The current recommendation for the treatment of hypertension in diabetic patients is based on the findings from these clinical trials showing the clear benefit of ACE/ARB in the target organ damage in this high-risk group of patients. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends ACE/ARB as an initial component of the antihypertensive treatment. The goal of therapy is blood pressure less than 130/80 mm Hg.[23]

Elderly

The elderly represent another high-risk group for developing hypertension. Based on the Framingham Study and National Health and Nutrition Examination and Survey (NHANES), the prevalence of hypertension is highest in the elderly and the risk for developing hypertension in individuals who are over 55 years old is 90%.[24,25] Most often they suffer from systolic hypertension that is consistent with poor arterial compliance or increased arterial stiffness. Over a lifetime, systolic blood pressure increases progressively, whereas diastolic blood pressure increases until late middle age when it begins to decrease. Thus, the pulse pressure is widened because of the increased systolic blood pressure that has been associated with increased cardiovascular risk.[26,27] Contrary to early assumptions that hypertension in the elderly was not detrimental to health and thus did not warrant treatment, several clinical trials in the elderly confirm that systolic hypertension in the elderly increases cardiovascular risk and treatment clearly improves outcomes.

Rationale for Treatment

There have been 3 major clinical trials of hypertension in the elderly. The SHEP, Syst-Eur, and Syst-China studies have investigated similar elderly patient populations comparing placebo with drug treatments varying from diuretics and β-blockers to dyhydropyridine calcium-channel blockers.[28] First, the SHEP study used chlorthalidone or placebo, with optional add-on therapy including atenolol and reserpine to reach the target blood pressure. The primary outcome of stroke was reduced by 36%, and cardiovascular events were reduced by 32% in the treated group. There was no difference in the development of new diabetes, however, glucose, uric acid, and cholesterol levels were increased more often in the treatment group compared with the placebo group. In this study the achieved blood pressure reduction was −27/−9 mm Hg.[29] Second, in the Syst-Eur study, which was similar to the SHEP study in patient selection, however, patients were randomized to receive nitrendipine or placebo, with possible add-on therapy of enalapril or hydrochlorothiazide. Stroke was reduced by 42%, cardiovascular events were reduced by 30%, and dementia was reduced by 50% in the treatment group. In this study the achieved blood pressure reduction was −23/−7 mm Hg.[30] A third placebo-controlled study in the elderly was the Syst-China study, which used nitrendipine as the active treatment, with possible add-on therapy of captopril or hydrochlorothiazide. Active treatment reduced strokes by 38%, all-cause mortality by 39%, cardiovascular mortality by 39%, stroke mortality by 58%, and all fatal/nonfatal cardiovascular end points by 37%. In this study the achieved blood pressure reduction was −20/−5 mm Hg.[31] The SHEP, Syst-Eur, and Syst-China tri-

als shared similar study populations in age (72, 70, and 66 y, respectively) and mean baseline blood pressure (170/77, 174/85, and 170/86 mm Hg, respectively), however, despite differing treatment regimens the achieved reduction in blood pressure (−27/−9, −23/−7, −20/−5 mm Hg, respectively) as well as the reduction in stroke and cardiovascular end points were similar. These trials clearly showed the benefits of treating systolic hypertension in the elderly regardless of the treatment selected.

Treatment Recommendations

The current recommendations from JNC 7 for the elderly are similar to the goals for younger adults, thus treat to the goal of less than 140/90 mm Hg uncomplicated hypertension, which is supported by clinical trials.[23] However, in complicated hypertension the goal of less than 130/80 mm Hg is less well supported in the elderly.[28] This is clearly an area in which additional clinical trials are needed. However, it is advisable to monitor symptoms as blood pressure is lowered; a more gradual reduction likely will be tolerated better in the elderly. The agents that have been shown to be effective are dihydropyridine calcium-channel blockers, diuretics, and β-blockers in placebo-controlled studies, yet this does not clearly show superiority over other agents in this population.

Women

Historically, women have received less focus in hypertension because in young and middle-aged adults the prevalence is lower in women compared with men. Yet among the elderly, women have a higher prevalence of hypertension than men.[32] The increase in the prevalence of hypertension seems to occur with menopause. The change in hormonal levels is associated with this increase in blood pressure, yet the nature of this association is not defined clearly. Nevertheless, the cardiovascular, renal, and cerebrovascular consequences of hypertension are the same for women as seen in men.

The pathophysiology of hypertension in women is similar to that of men with a few unique caveats. There are some differences in the presentation of hypertension in women, with higher prevalences of labile blood pressure, white-coat hypertension, salt sensitivity, and low-renin, high-volume hypertension compared with men.[33,34] Two distinctly sex-related mechanisms of blood pressure increase are pregnancy and oral-contraceptive use. Hypertension in pregnancy is a particular dilemma because it may present as pre-eclampsia, eclampsia, gestational hypertension, or chronic hypertension. Pre-eclampsia is defined as a pregnancy-specific syndrome observed after the 20th week of pregnancy with a systolic blood pressure of 140 mm Hg or greater or a diastolic blood pressure of 90 mm Hg or greater, accompanied by significant proteinuria. Eclampsia may present in pre-eclamptic women, with seizures that usually occur after mid-pregnancy and may occur postpartum. Gestational hypertension is defined as a blood pressure increase detected for the first time after midpregnancy, in the absence of proteinuria. Chronic hypertension refers to an increased blood pressure before pregnancy. In retrospect, the diagnosis may be made when increased blood pressure in pregnancy fails to normalize after delivery. Currently, there are few therapeutic alternatives for treating pregnant women with pre-existing hypertension. Women with chronic hypertension are at increased risk for superimposed pre-eclampsia (25% risk), preterm delivery, fetal growth restriction or demise, abruptio placentae, congestive heart failure, and renal failure. The outcome for mother and infant is worse than for de novo pre-eclampsia. The effect of treatment of chronic hypertension on the risk for pre-eclampsia and its complications is not known. Because pre-eclampsia is a clear risk for the fetus and the mother, it must be treated. The definitive treatment is delivery of the fetus. The preferred approach in the obstetric community is to substitute α-methyldopa, an agent known to be safe in pregnancy, for the antihypertensive therapy prescribed before the pregnancy. This is because α-methyldopa is the only hypertensive agent with follow-up safety data in infants. On the other hand, ACE inhibitors and ARBs are contraindicated in pregnancy because of the adverse effects on fetal kidney development.[35] The use of oral contraceptives may increase blood pressure yet only a small number of women who take oral contraceptives develop hypertension. In the Nurses Health Study, the relative risk for hypertension in oral contraceptive users is 1.8 compared with never users, yet the absolute risk is small at 41.5/10,000 person-years.[32] Presumably the current risk for oral-contraceptive use is lower because the doses of estrogen and progestin in oral contraceptives has decreased significantly in recent years. Discontinuation of oral contraceptives results in a decrease in blood pressure generally within 3 months. Therefore, the treatment approach in the setting of oral-contraceptive use begins with monitoring blood pressure at 6-month intervals. Factors to consider in the decision to recommend discontinuation of oral contraceptives depends on blood pressure level, the potential risks associated with pregnancy, and the overall cardiovascular risk for the individual.

Treatment Considerations

Early clinical trials of hypertension included very few women, however, more recent trials have included reasonable sample sizes of women. The Individual Data Analysis of Antihypertensive Intervention trial meta-analysis assessed the effect of sex on treatment responses in hypertension clinical trials. The trials in this meta-analysis included 20,802 women and 19,975 men recruited between 1972 and 1990 who were treated with β-blockers and diuretics. There were no statistically significant differences observed between men and women in the benefits of treatment on total mortality, cardiovascular-related death, fatal strokes, all strokes, fatal coronary events, all major coronary events, and main cardiovascular events.[32] There are no specific recommendations for treating hypertension in women with the exception of avoiding ACE and ARBs in women intending to become pregnant.

Summary

The broad presentation of hypertensive disease requires closer assessment of the specific facets of hypertension pathophysiology and treatment in special populations. The NHANES surveys have shown that treatment and control rates have leveled off. Perhaps more specific approaches to hypertension in special populations may help to improve control rates further.

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