Optimizing Management of Hypertension With Combination Therapy
Considerations for the Nurse Practitioner

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Hypertension is an important contributor to the risk of cardiovascular disease and death, yet success in achieving blood pressure (BP) control has been limited. Most patients will require 2 or more medications to control their BP. Nurse practitioners play a vital role in treating patients with hypertension and can help overcome barriers to reaching BP goals. Measures to improve therapeutic adherence include educating the patient and simplifying the medication regimen. Use of single-pill combination therapy, which reduces the pill burden, can contribute to improved medication persistence and compliance. Rational combination therapy combines medications with complementary mechanisms of action, such as a calcium channel blocker (CCB) and a renin-angiotensin-aldosterone system (RAAS) inhibitor; it is often more efficacious than monotherapy and allows the use of lower doses of the individual components, which usually results in improved tolerability. Current guidelines support the first-line use of combination therapy in many patients. Initiating therapy with a RAAS inhibitor–based combination can reduce BP and cardiovascular risk and may be more effective for some patients than traditional combinations such as a β-blocker with a diuretic. Adverse events associated with any medication can compromise its therapeutic usefulness. Peripheral edema is a common and dose-dependent adverse event seen with dihydropyridine CCBs, which can cause marked patient distress, reduce adherence to therapy, and result in dose reduction or even discontinuation of therapy. In most cases, CCB-induced peripheral edema can be managed successfully, and CCB therapy need not be abandoned. Management strategies include nonpharmacologic and pharmacologic measures. Several clinical trials have shown a lower incidence of peripheral edema in patients receiving combination therapy with a CCB and a RAAS blocker compared with CCB monotherapy.

KEY WORDS: antihypertensives, calcium channel blockers, combination therapy, edema, hypertension, renin-angiotensin-aldosterone system

Hypertension is well-established as a major independent risk factor for cardiovascular disease and chronic kidney disease. Based on data from 2003–2004, nearly one-third of US adults have hypertension. In addition to the presence of hypertension, many patients have additional cardiovascular risk factors such as diabetes or dyslipidemia. Hypertension and these additional risk factors can potentiate this risk in an additive or synergistic fashion.

Elevations in blood pressure (BP) are strongly correlated with the risk of major cardiovascular events. Individuals with high-normal BP (130–139/85–89 mm Hg) have significantly greater cardiovascular risk than do those with optimal BP (<120/80 mm Hg). In addition, the risk of death from stroke or ischemic heart disease doubles with each 20–mm Hg increase in systolic BP above 115 mm Hg and with each 10–mm Hg increase in diastolic BP above 75 mm Hg.

Despite providers’ awareness of the known risks associated with hypertension, success in achieving BP control in practice has been suboptimal. Recent data indicate that only 63.9% of patients being treated for hypertension achieve their goal BP. Furthermore, only 33.2% of patients with diabetes who are being treated for hypertension achieve their BP goal of less than 130/80 mm Hg.

Nurse practitioners play a vital role in identifying and treating patients with hypertension, and they have
a critical opportunity to help patients reduce their risk of serious cardiovascular events. In addition to providing essential patient education, nurse practitioners can help identify and overcome barriers to reaching BP goals, as discussed in the next section of this article.

Although the Framingham 10-year risk score for coronary heart disease is widely used as a risk assessment tool, it may be more important to evaluate the patient’s lifetime risk for cardiovascular disease and events. This lifetime risk is often substantially higher than the 10-year risk, particularly in younger individuals, because of the cumulative damage that occurs over time from untreated or inadequately treated hypertension or other risk factors and because of the potential for changes in risk factor status as individuals age; this is particularly true for women. Global risk stratification can aid in the identification of at-risk individuals who would especially benefit from early interventions to reduce their risk. Placing lifetime risk in a clinical context may help motivate patients to engage in therapeutic lifestyle changes and promote better adherence to therapy.

In this article, we review the factors inhibiting successful antihypertensive therapy and practical measures to overcome these factors. We also review the current literature regarding the increasingly prominent role of combination therapy in helping patients reach BP goals, in particular combination therapy with a calcium channel blocker (CCB) and a renin-angiotensin-aldosterone system (RAAS) inhibitor. We discuss practical management of adverse events associated with antihypertensive therapy, particularly edema associated with CCBs, that could otherwise interfere with achievement of BP goals.

Factors Contributing to Patients Not Reaching BP Goal

The factors that contribute to patients not reaching BP goal generally fall into 1 of 2 categories: provider-related and patient-related factors. Healthcare provider-related factors are generally due to therapeutic inertia and overreliance on monotherapy. Therapeutic inertia is the failure of healthcare practitioners to intensify therapy by either increasing the dose or adding another agent when the BP remains above goal and can be avoided with practitioner focus on BP goals and guidelines.

Patient-related factors are usually due to poor medication adherence, stemming from patients’ failure to follow prescribed medication regimens. This failure to follow prescribed medication regimens is often associated with the appearance of adverse events and may also be associated with complex or burdensome dosing regimens (eg, more than once daily), increased pill burden, and higher cost burden with multiple copays for multiple medications. Therapeutic adherence is also influenced by individual patient characteristics such as age, depression, cognitive impairment, and existing beliefs about their disease and therapy. Adherence to therapy for asymptomatic conditions such as hypertension and dyslipidemia is notoriously poor, especially when these conditions coexist and patients are prescribed multiple medications.

Awareness concerning all the factors that interfere with patients’ compliance with hypertensive treatment regimens is critical for approaching this issue. The American Heart Association has addressed many of the issues surrounding compliance and provides guidance for healthcare provider actions directed to increase adherence with treatment recommendations. Compliance with therapy can be improved when nurse practitioners provide effective education that is tailored to their patients. In a study of hypertensive outpatients who underwent usual medical care only (n = 76) or usual care plus telephone-mediated nurse care management intervention (n = 74) over a 6-month period, it was demonstrated that patients receiving telephone-mediated nurse care management achieved greater reductions in office BP than did those receiving usual care. Reductions in BP observed in the group without nurse management was 5.7 ± 18.7/ 3.4 ± 7.9 mm Hg compared with 14.2 ± 18.1/6.5 ± 10.0 mm Hg for patients with nurse management; differences were statistically significant between groups for systolic (P < .01) and diastolic (P < .05) BP. At least part of the reason for the improved BP response could be explained by improved adherence to medication. The adherence rate to therapy was significantly greater (P = .03) in the nurse management group (81%) compared with the usual care group (69%).

It is important for a healthcare provider to understand their patient population and the challenges and issues that they face. Socioeconomic, cultural, and ethnic factors can all exert a profound influence on patients and greatly affect their compliance with therapeutic lifestyle changes and with medication regimens. Medication cost can be a major factor in compliance, particularly for lower-income patients, and it may be helpful to direct patients to seek help from organizations that exist to help patients overcome these cost barriers as well as programs, when available, that can provide direct cost reductions.

Additional factors that can influence therapeutic success include patient race and lifestyle. For example, racial disparities in BP control have been documented, and whites and blacks differ in average responses to antihypertensive drugs. However, whites and blacks respond similarly to the major categories of available antihypertensive agents, with large overlaps within each group in their responses. Thus, a decision to use a specific drug is better made based on individual efficacy, compelling indication, or cost rather than on
race. In addition, although many cardiovascular consequences of hypertension in minorities may be attributable to less access to healthcare or to socioeconomic conditions, lifestyle changes such as weight loss and sodium reduction effectively lower BP in minority individuals. Obesity is a significant contributing factor for resistant hypertension. However, even modest weight loss (≥10% of body weight) can significantly decrease BP; regression analysis indicated that for each 10 kg (22 lb) of body weight loss, BP would decrease by 3.3/2.5 mm Hg. In addition, because body weight frequently shows a progressive increase throughout middle age, weight stabilization is also important. These data illustrate the importance of lifestyle changes in the reduction of cardiovascular risk.

There is a critical need for patient education to promote the understanding that hypertension is an asymptomatic but serious condition that is important to control. Patients must also gain an appreciation for the need to take their medication faithfully and, probably, for the rest of their lives. Practitioners can conduct motivational interviews with patients who are believed to be poorly compliant, discussing facts and observations about their personal barriers to compliance while expressing empathy and avoiding argumentative or judgmental statements.

### Combination Therapy Can Help Achieve BP Goals

A majority of patients with hypertension will require pharmacotherapy in addition to lifestyle changes to control their BP. Indeed, most patients will require combination therapy with 2 or more agents to achieve BP control as shown in the Hypertension Optimal Treatment (HOT), Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) studies. Initial treatment with combination therapy can lead to better BP control. The Simplified Treatment Intervention to Control Hypertension (STITCH) trial compared a simplified 4-step combination therapy protocol (step 1, initiate therapy with angiotensin-converting enzyme [ACE] inhibitor/diuretic or angiotensin receptor blocker/diuretic combination; step 2, up-titrate combination therapy to the highest doses; step 3, add a CCB and up-titrate; and step 4, add 1 of the non–first-line antihypertensive agents) with a guidelines-based protocol using the Canadian Hypertensive Educational Program, which lists 12 possible initial treatment options. Patients in the STITCH (simplified combination therapy) arm of the study had a 20% greater chance of reaching the optimal target BP than did those in the guidelines-based care group.

Combination therapy uses medications with complementary mechanisms of action, for example, RAAS inhibitor–based combinations with diuretics or CCBs. The RAAS plays a central role in the regulation of BP, fluids, and electrolytes; in vascular disease, it is involved in vascular remodeling and inflammation. In RAAS blockade, vessel wall elasticity improves and arterial stiffness decreases, as shown by a reduction in the central aortic augmentation index. Examples of RAAS inhibitors include ACE inhibitors, angiotensin II receptor blockers (ARBs), and the newest class of agents, direct renin inhibitors; these all act via distinct pathways to interfere with the RAAS. Among combination therapies, the combination of a RAAS inhibitor and a CCB may be more effective in reducing central aortic pressure. In an Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) substudy, the Conduit Artery Function Evaluation (CAFÉ) study, patients were treated with either ACE inhibitor/CCB or β-blocker/diuretic combination therapy, and the effects on brachial systolic BP and central aortic systolic BP and pulse pressures were measured. Both the ACE inhibitor/CCB and β-blocker/diuretic groups had similar reductions in brachial systolic BP, but central aortic systolic BP and central aortic pulse pressure were decreased more with ACE inhibitor/CCB therapy than with the β-blocker/diuretic regimen.

Studies also have shown that RAAS inhibitor–based combination therapies effectively lower BP in diverse patient populations (eg, elderly persons, people with diabetes, obese persons, or those at high risk for cardiovascular events) and can do so more effectively than some other combination therapies or monotherapies. The Irbesartan/HCTZ Blood Pressure Reductions in Diverse Patient Populations (INCLUSIVE) study examined the effects of irbesartan/hydrochlorothiazide (HCTZ) in patients with hypertension (baseline BP, 154/91 mm Hg) with uncontrolled systolic BP on monotherapy. The INCLUSIVE patient population was diverse: 52% women, 37% black or Hispanic, 30% with diabetes, and 46% with metabolic syndrome. Treatment with irbesartan/HCTZ resulted in 69% of patients achieving both systolic and diastolic BP goals of less than 140/90 mm Hg (<130/80 mm Hg in patients with type 2 diabetes). Patients with left ventricular hypertrophy (LVH) were treated with perindopril/indapamide combination therapy as first-line treatment compared with enalapril monotherapy in the Preterax in a Double-Blind Controlled Study Versus Enalapril in LVH (PIXCEL) trial. Decreases in systolic BP, diastolic BP, pulse pressure, and LVH were greater with the combination therapy regimen than with monotherapy. In ASCOT-BPLA (ASCOT-Blood Pressure Lowering Arm), most patients were elderly, obese, and hypertensive with preexisting cardiovascular disease, yet treatment with a regimen of amlodipine adding perindopril lowered BP more than did treatment with a regimen of atenolol plus bendroflumethiazide.
The International Verapamil-Trandolapril Study (INVEST) study compared clinical outcomes after using a CCB-based regimen or a non–CCB-based regimen to treat hypertension in patients with documented coronary artery disease. The INVEST study population included women (52%), elderly patients (>70 years; 33%), blacks or Hispanics (49%), and patients with diabetes (28%). Of the patients treated with a verapamil/trandolapril combination regimen, 65% and 88.5% achieved their systolic and diastolic BP goals, respectively. In those receiving the atenolol/trandolapril combination regimen, 64% and 81% achieved their systolic and diastolic BP goals, respectively. More than half of the patients in the study required 3 or more drugs to achieve BP control. Although no differences between groups were observed in the outcome of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke, significant differences were seen favoring the CCB versus non-CCB strategy for decreased angina frequency and new diagnosis of diabetes. On the other hand, outcomes in the non-CCB strategy group were better than those in the CCB strategy group in those with prior heart failure.34

The targeting of multiple pathways with combination therapy can allow the use of lower doses of individual component therapies, translating into improved tolerability.35,36 Recently updated hypertension guidelines recognize that the use of 2 drugs with complementary mechanisms of action can minimize the appearance of adverse events, and fewer adverse events are generally seen with a combination of low doses of 2 agents than with high doses of a single agent.35–37

Single-pill combination therapy can help provide effective BP control and promote improved persistence and compliance with therapy by reducing the pill burden, simplifying medication regimens, and decreasing medication copays.18,38 Therapeutic regimens with fewer daily doses and fewer changes in medications are associated with better adherence.39,40

Among several studies illustrating the vital role of combination therapy (Table 1) was the ASCOT-BPLA.27 Involving 19,257 patients aged 40 to 79 years with 3 or more risk factors for cardiovascular disease in addition to hypertension, this study compared an amlodipine-based antihypertensive regimen (adding

| TABLE 1 | Studies Illustrating the Vital Role of Combination Therapy |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| **ASCOT-BPLA27** | **ADVANCE61** | **ACCOMPLISH28,42** | **INVEST34** |
| **Total patients, no.** | 19,257 | 11,140 | 10,704 | 22,576 |
| **Patient characteristics** | | | | |
| Age | 40–79 y; Hypertension ≥3 CV risk factors | Age ≥55 y; type 2 diabetes; ≥1 other CV risk factor | Age >60 y; hypertension, obese; CV disease, renal disease, or hypertensive damage in ≥2 target organs | Age ≥50 y; documented coronary artery disease; hypertension |
| **CCB dose, mg/d** | Amlodipine 5–10 | None | Amlodipine 5–10 | Verapamil 120–480 |
| | ± Perindopril 4–8 | Perindopril 2–8 | | |\pm| Trandolapril 1–8 |
| **RAAS blocker dose, mg/d** | | | Benazepril 20–40 | Hydrochlorothiazide 12.5–50 |
| **Other agents, mg/d** | | | As needed β-blockers, α-blockers, clonidine, loop diuretics | Atenolol 25–200 |
| | ± Doxazosin 4–8 | | + Hydrochlorothiazide 12.5–25 | | | ± As needed, β-blockers, α-blockers, clonidine, loop diuretics |
| **Comparator treatments, mg/d** | Atenolol 50–100 | Placebo | Benazepril 20–40 | | | | ± | As needed, β-blockers, α-blockers, clonidine, loop diuretics |
| | ± Bendroflumethiazide 1.25–2.5 | | + | | | | ± | Hydrochlorothiazide 12.5–25 |
| | ± Doxazosin 4–8 | | | | | | | ± Doxazosin 4–8 |
| **Treatment strategy** | Stepped care | Initiation with combination therapy | Initiation with combination therapy | Initiation with combination therapy |
| **Study conclusions** | Amlodipine-based regimen was associated with fewer major CV events and a lower incidence of new-onset diabetes than amlodipine-based regimen was. | Fixed-dose combination perindopril/indapamide reduced the risk of major CV events and death and was well tolerated. | Initial therapy with single-pill combination benazepril/amlopidine reduced CV morbidity and mortality by 20% compared with benazepril-hydrochlorothiazide combination. | Initial therapy with Verapamil-based therapy was as effective as atenolol-based therapy in achieving BP goals and in the prevention of major CV events and death. |

Abbreviations: ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm; BP, blood pressure; CCB, calcium channel blocker; CV, cardiovascular; INVEST, International Verapamil-Trandolapril Study; RAAS, renin-angiotensin-aldosterone system.

Arrow (→) indicates forced titration.

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After a median follow-up of 5.5 years, there were fewer major cardiovascular events and a lower incidence of new-onset diabetes with the amlodipine-based regimen than with the atenolol-based regimen. At the end of the trial, 78% of the patients were taking 2 or more antihypertensive medications.

In the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial, 11,140 patients 55 years or older with type 2 diabetes and at least 1 other documented cardiovascular risk factor (not necessarily hypertension; mean baseline BP was 145/81 mm Hg) were randomized to a fixed-dose combination of perindopril plus indapamide or placebo. After a mean follow-up of 4.3 years, treatment with the ACE inhibitor/thiazide diuretic combination significantly reduced the risk of the primary outcome, a composite of major macrovascular and microvascular events, in this patient population by 9% (P = .041) compared with placebo. These results of the largest BP control study in patients with type 2 diabetes illustrate the value of long-term combination therapy for reducing cardiovascular risk.

The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial was conducted in 10,704 obese patients with severe hypertension, most of whom were 65 years or older, diabetic, and at high risk for cardiovascular events (eg, history of coronary events, myocardial infarction, revascularization, or stroke; impaired renal function; peripheral arterial disease; LVH; or diabetes mellitus). This study compared initial single-pill combination therapy with benazepril/amlodipine to benazepril/HCTZ. Combination therapy for 36 months reduced BP from 145/80 mm Hg to 131.6/73.3 mm Hg in the benazepril/amlodipine group and 132.5/74.4 mm Hg in the benazepril/HCTZ group and increased BP control rates from 37.3% at baseline to 75.4% in the benazepril/amlodipine group and 72.4% in the benazepril/HCTZ group. Despite similar BP reductions with the 2 treatment regimens, the benazepril/amlodipine combination significantly reduced the relative risk of cardiovascular morbidity and mortality by 20% after 3 years, compared with the benazepril/HCTZ combination.

The findings from these studies illustrate the important role of combination therapy, particularly in patients at moderate to high cardiovascular risk. Combination therapy is generally well tolerated and has been shown to effectively lower BP and reduce the risk of cardiovascular disease and mortality, even in older patients with comorbid conditions placing them at high risk for cardiovascular events as described above for ASCOT-BPLA and ACCOMPLISH. In elderly diabetic patients with severe hypertension and a previous history of cardiovascular disease, stroke, or diabetes, RAAS/CCB combination therapy showed improved outcomes compared with ACE/diuretic therapy. The value of ACE inhibitor/diuretic combination therapy should not be diminished; however, this combination was recently shown to significantly reduce BP and improve outcomes in very old persons when compared with placebo treatment.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) indicates that most patients will require a combination of 2 or more drugs from different antihypertensive classes. The seventh JNC report guidelines recommend that patients who have systolic BP greater than 20 mm Hg or diastolic BP greater than 10 mm Hg above the goal should begin therapy with first-line use of a combination of 2 drugs to reach the goal more rapidly and at lower doses with fewer adverse effects. Guidelines from the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) group state that combination therapy should be a first-choice treatment particularly in patients with grade 2 or 3 hypertension (BP ≥160/100 mm Hg) and in patients with grade 1 hypertension with compelling indications such as diabetes, cardiovascular disease, renal disease, or other organ damage.

In recent years, the US Food and Drug Administration has approved several ARB/diuretic and ARB/CCB combination therapies (irbesartan/HCTZ, losartan/HCTZ, valsartan/HCTZ, amlodipine/valsartan, and amlodipine/olmesartan) for patients who do not achieve BP goal after treatment with monotherapy. Among these agents, valsartan/HCTZ, irbesartan/HCTZ, and amlodipine/valsartan have received first-line indications as initial therapy in patients who are likely to need multiple drugs to achieve their BP goals.

**Adverse Events With Antihypertensive Agents and How to Manage Them**

Adverse events are not completely avoidable, and great effort must be placed in limiting adverse events and improving quality of life. Drugs and drug classes differ in the type of adverse events they may induce, and different individuals or groups of patients may be differently prone to develop a given adverse event. Some of these events are well known, and many can be mitigated with dosage adjustments and conservative management strategies. Adverse events associated with diuretics and CCBs are dose related; however, adverse events associated with ACE inhibitors or ARB are not.
However, in some cases, adverse events are troublesome enough to necessitate medication discontinuation.

Angiotensin-converting enzyme inhibitors are associated with the rare but serious adverse event angioedema, seen in 0.1% to 0.5% of patients shortly after they begin ACE inhibitor therapy. More commonly, ACE inhibitors are associated with the development of persistent dry cough, which occurs in up to 39% of patients in some studies. This troublesome adverse event may necessitate discontinuation. Patients who develop angioedema or a cough with an ACE inhibitor will have to discontinue that medication and should not be switched to another ACE inhibitor. Instead, another type of RAAS inhibitor that does not cause angioedema or cough, such as an ARB or a direct renin inhibitor, can be prescribed.

Thiazide diuretics and β-blockers are associated with the development of metabolic disturbances such as hypokalemia and increased plasma glucose levels. Management strategies for these metabolic disturbances include combination therapy with a diuretic and a RAAS inhibitor, which can mitigate the metabolic effects of the diuretic and allow reduction of the diuretic dose. In patients with metabolic syndrome, use of a CCB/RAAS inhibitor combination may be a better alternative. Indeed, the results from the Study of Trandolapril/Verapamil SR and Insulin Resistance Long-Term Extension Trial (STAR-LET) showed that impairment in glycemic control can be reversed by switching from a thiazide diuretic/RAAS inhibitor combination to a combination that does not include a diuretic. Although β-blockers have been a part of the antihypertensive repertoire for some time, recently presented evidence that β-blockers confer no incremental benefit over other antihypertensive medications in the prevention of heart failure and that their use presents an increased risk of stroke in elderly patients has raised questions about their safety in treating hypertension.

Peripheral edema is a common and dose-dependent adverse event seen with dihydropyridine CCBs, such as amlodipine. The peripheral edema induced by dihydropyridine CCBs occurs because of the vasodilatory effects of this class of drugs on the precapillary sphincter, reducing arteriolar resistance with no change in venous resistance and leading to a fluid shift from the vasculature to the interstitial compartment. Peripheral edema induced by CCB is medically benign but can cause marked patient distress, which can reduce adherence to therapy, whereby patients reduce their dose or even discontinue therapy. Edema induced by CCB is characterized by diffuse and bilateral symmetrical swelling in the feet, ankles, and lower legs. In addition to CCBs, there are other potential causes of peripheral edema that should be ruled out, such as other medications, deep venous thrombosis, chronic venous insufficiency, heart failure, renal failure, and liver failure. Furthermore, there are several factors that can predispose an individual to the development of CCB-related edema, including female sex, older age, being overweight or obese, and the presence of diabetes.

It is important to understand and communicate to patients that CCB-induced peripheral edema can be managed successfully in most cases, and CCB therapy should not be abandoned prematurely. Nonpharmacologic management measures include restricting dietary sodium intake, incorporating lifestyle changes (such as regular exercise and weight loss if overweight), elevating the legs as often as possible, and avoiding restrictive clothing and long periods of standing. The use of compression stockings can be helpful, but these are often not well tolerated.

Pharmacologic measures may also be needed to manage CCB-related peripheral edema. Because the edema associated with CCBs is not the result of volume overload, diuretics are not generally recommended to treat CCB-induced edema. Although CCBs cause a reduction in the arteriolar resistance without a corresponding change in the venous resistance, RAAS inhibitors cause balanced arterial and venous dilation leading to a reduction in intracapillary hydrostatic pressure. Notably, several clinical trials have shown a lower incidence of peripheral edema in patients receiving combination therapy with a CCB and a RAAS blocker than in patients receiving CCB monotherapy (Table 2). However, a few studies have reported similar or higher rates of edema with CCB/RAAS blocker combination therapy than with CCB monotherapy. It is worth noting that the edema rates reported in most studies are based on subjective assessment by healthcare professionals or self-reporting by patients; thus, the findings in clinical studies are variable and may not be highly reproducible.

The choice of initial antihypertensive combination therapy is dependent not only on patient characteristics and therapeutic efficacy but also on the adverse event profile of individual drugs. The European (ESH/ESC) hypertension guidelines caution against the use of β-blockers, especially in combination with a thiazide diuretic, among patients at risk for diabetes. According to the ESH/ESC guidelines, both β-blockers and thiazide diuretics can cause weight gain, adversely affect lipid metabolism, and increase the incidence of new-onset diabetes compared with other drugs. β-Blockers and thiazide diuretic combination therapy should not be the first-line therapy in patients with diabetes because they can increase insulin resistance and the need for larger doses of antidiabetic medication. Patients with hypertension with microalbuminuria or diabetes should be treated with a drug that affects the RAAS.
of Endocrinology consensus statement on prediabetes also cautions against the use of β-blockers and thiazide diuretics in patients with prediabetes because of their metabolic effects. The consensus statement on prediabetes recommends first-line therapy with an ARB or an ACE inhibitor and second-line therapy with a CCB, suggesting a target BP of less than 130/80 mm Hg.

### Conclusions

Hypertension is a significant contributor to cardiovascular risk. The number of people with hypertension is increasing, and yet the control rate, even among treated patients, is suboptimal. By increasing communication with and education of patients, nurse practitioners play a vital role in helping patients control their BP and reduce their cardiovascular risk.

One of the main patient-related factors contributing to patients with hypertension not reaching BP goals is poor adherence to therapy. Nurse practitioners have a unique opportunity to positively influence outcomes with patient education aimed at overcoming barriers to therapeutic compliance. Clinical trials and guidelines support the first-line use of combination therapy in many patients. Single-pill combination therapy can also

### TABLE 2  Clinical Trials Comparing the Incidence of Peripheral Edema With CCB/RAAS Blocker Combination Therapy Versus CCB Monotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>CCB Dose, mg/d</th>
<th>RAAS Blocker Dose, mg/d</th>
<th>Edema Rate With CCB Monotherapy, n/N (%)</th>
<th>Edema Rate With Combination, n/N (%)</th>
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</thead>
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<td>Chrysant et al</td>
<td>Amlodipine</td>
<td>Benazepril</td>
<td>25/271 (9.2)</td>
<td>15/273 (5.5)</td>
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<td>10</td>
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<td>10</td>
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<td>Olmesartan</td>
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<td>7/37 (18.9)</td>
<td>0/33 (0)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>20</td>
<td></td>
<td>7/37 (18.9)</td>
</tr>
<tr>
<td>SELECT</td>
<td>Amlodipine</td>
<td>Benazepril</td>
<td>23/169 (13.6)</td>
<td>13/166 (7.8)</td>
</tr>
<tr>
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<td>20</td>
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<td>13/166 (7.8)</td>
</tr>
<tr>
<td>Schrader et al</td>
<td>Amlodipine</td>
<td>Valsartan</td>
<td>184/591 (31.1)</td>
<td>39/592 (6.6)</td>
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<td></td>
<td>5</td>
<td>160</td>
<td></td>
<td>39/592 (6.6)</td>
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</tbody>
</table>

Abbreviations: CCB, calcium channel blocker; COACH, Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure; EX-EffCTS, Exforge Efficacy and Control in Treatment of Stage 2 Hypertension; EX-STAND, Exforge Evaluation in Stage 2 Hypertensives of African Descent; EXPLORE, Exploring Lotrel in Hypertensive Patients With Endothelial Dysfunction; RAAS, renin-angiotensin-aldosterone system; SELECT, Systolic Evaluation of Lotrel Efficacy and Comparative Therapies.

Arrow (→) indicates forced titration.

*aQuantitative measurement of ankle-foot volume and pretibial subcutaneous tissue pressure showed significantly less severe ankle edema in the combination treatment group than in the amlodipine monotherapy group.*
improve therapeutic adherence and help patients reach BP goals. Combination therapy can offer improved efficacy at lower doses and reduce the likelihood of adverse events. When they do occur, adverse events can often be successfully managed. Peripheral edema is a common adverse event with CCBs and can often be managed with nonpharmacologic measures. Clinical trials have shown a lower incidence of peripheral edema with CCBs when they are used in combination with an ACE inhibitor or an ARB.

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REFERENCES


