American Academy of Nurse Practitioners

REVIEW

Hypertension treatment update: Focus on direct renin inhibition

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Abstract

Purpose: To provide an educational update for the nurse practitioner (NP) on the care of patients with hypertension, particularly in high-risk populations. Barriers to reaching blood pressure goals are reviewed in the context of identifying and addressing the sequelae of uncontrolled hypertension. Available antihypertensive agents are reviewed, including a description of direct renin inhibition with aliskiren, the newest agent and antihypertensive class available. Treatment recommendations are discussed in light of recent clinical trial data demonstrating improved cardiovascular (CV) outcomes, including myocardial infarction, stroke, and death.
Data sources: Clinical studies and state-of-the-art articles indexed on PubMed
Conclusions: Current hypertension guidelines provide detailed management strategies, particularly for patients at high risk for CV events. NPs may help improve CV outcomes through careful diagnosis, risk stratification, and disease management, including improved patient education of the benefits of rational and sustained management of hypertension.
Implications for practice: Early diagnosis, evidence-based treatment, and ongoing disease management of hypertension can be expected to improve CV outcomes. Treatment initiation with combination therapy, preferably with single-pill combinations that incorporate an agent that modulates the renin-angiotensin-aldosterone system, provides an approach that is safe, effective, and well tolerated and which can be tailored to the needs of the individual patient.

Hypertension carries a tremendous public health and cost burden, affecting 1 in 3 adults in the United States with estimated direct and indirect costs of $73.4 billion for 2009 (Lloyd-Jones et al., 2008). The prevalence of hypertension increases with advancing age despite reportedly greater awareness and treatment over recent years (Figure 1; Ong, Cheung, Man, Lau, & Lam, 2007). Extensive evidence suggests that incremental elevations in blood pressure (BP) above goal are strongly correlated with the risk of major cardiovascular events, such as myocardial infarction, stroke, and death. However, in the United States only 66% of patients with hypertension are aware of their diagnosis, and of these only 54% are treated (Ong et al., 2007). In addition, BP control, defined as $< 140/90$ mmHg in patients with uncomplicated hypertension, remains low (33% in the United States; Ong et al., 2007). A more rigorous target of $< 130/80$ mmHg is also appropriate in patients at high risk for coronary artery disease (Rosendorff et al., 2007) and diabetes (Chobanian et al., 2003) and all patients with chronic kidney disease (KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease, 2007).

Barriers to reaching BP goals

There are numerous provider-related and patient-related factors that account for the low overall attainment of BP goals. One of the most stubborn provider-related factors is therapeutic inertia, which occurs when providers do not adequately intensify treatment, when BP remains in poor control and instead rely too heavily on monotherapy (Margolis et al., 2005; Spranger, Ries, Berge, Radford, & Victor, 2004). A majority of patients with hypertension will require pharmacotherapy (often with two or more agents that have different

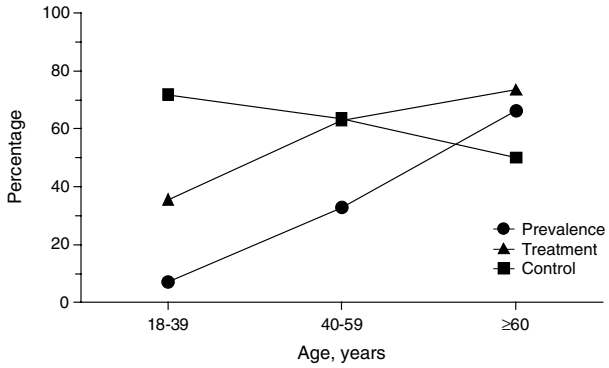

Figure 1 Blood pressure prevalence, treatment, and control rates as a function of age in patients being treated for hypertension. (Data from Ong, K. L., Cheung, B. M., Man, Y. B., Lau, C. P., & Lam, K. S. (2007). Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. *Hypertension, 49*(1), 69–75.)

mechanisms of action) in addition to lifestyle changes to control their BP. Types of patients who have typically required multiple agents include African Americans and patients who are obese or have diabetes (Bramlage et al., 2004; Chobanian et al., 2003). Patient-related factors that contribute to the low overall attainment of goal BP include poor medication adherence stemming from advanced age (which can be associated with increased incidence of changes such as affective disorders or cognitive impairment), attitudes and beliefs about the importance of the medication, or other reasons that result in the patients' failure to follow prescribed medication regimens, including adverse effects associated with drug–drug interactions (Lee, Grace, & Taylor, 2006).

Barriers to reaching BP goal can be attributed, at least in part, to factors including nonadherence and patient perception of well-being. For example, sexual dysfunction induced by antihypertensive agents is a poorly recognized side effect that affects patients' adherence to medication. Certain classes of antihypertensive agents are known to contribute to sexual dysfunction or exacerbate existing problems. Although reports are variable, diuretics, β-blockers, and calcium channel blockers (CCBs) have been associated with sexual dysfunction in patients with hypertension (Ferrario & Levy, 2002). On the other hand, the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have not been associated with sexual dysfunction. In fact, ARBs have been associated with favorable effects on sexual function (Ferrario & Levy, 2002). Angiotensin II (ANG II), one of the active components of the renin-angiotensin-aldosterone system (RAAS), may play a role in inhibiting penile erectile function by stimulating contraction of vascular and corporal smooth muscle. Thus, inhibition of the formation or action of ANG II would be expected to increase blood flow into the corpus cavernosum and facilitate erection (Ferrario & Levy, 2002).

An additional factor that affects compliance is pill burden. Patients receiving single-pill combination therapy have a reduced risk of medication noncompliance compared with patients taking multidrug regimens (Bangalore, Kamalakkannan, Parkar, & Messerli, 2007). One of the challenges in treating hypertension is that patients can often feel well despite elevated BP, making compliance even more challenging. Taken together, these factors emphasize that patient education is critical to promoting the understanding that hypertension is a serious condition and that it is important to control BP to avoid the macrovascular and microvascular complications associated with high BP (Bangalore et al., 2007; Tesfaye et al., 2005).

Implications of high BP

Although a patient with hypertension may feel fine, uncontrolled hypertension leads to a cascade of microvascular and macrovascular complications that have substantial clinical impact. In patients with hypertension, the sympathetic nervous system and the RAAS are upregulated, resulting in an increase in total peripheral resistance and increased BP. ANG II induces vasoconstriction, vascular smooth muscle cell migration and hypertrophy, vascular remodeling, and endothelial dysfunction and inflammation (Dzau, 2001). All of these changes are associated with kidney damage and cardiovascular events, including heart failure, stroke, and myocardial infarction. Hypertension-induced microvascular changes contribute to renal complications by damaging glomeruli, thus causing microalbuminuria (Brenner, 2002). Microvascular changes can also result in retinopathy, which can lead to blindness (Bakris et al., 2000; Chobanian et al., 2003; Tesfaye et al., 2005).

Treatment of hypertension: Antihypertensive agents

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7; Chobanian et al., 2003) and European Society of Hypertension/European Society of Cardiology guidelines for treatment of hypertension (Mancia et al., 2007) recommend lifestyle changes followed by pharmacotherapy that encompasses a wide range of agents (Table 1), all of which have been shown to reduce BP to a similar extent (Chobanian et al., 2003).

Table 1 Examples of available oral antihypertensives sorted by class

Thiazide and thiazide-like diuretics	β-blockers[a]	ACE Inhibitors	ARBs	DRI	MRBs	CCBs
Chlorothiazide	"Nonselective"	Benazepril	Candesartan	Aliskiren	Spironolactone	Dihydropyridine
Chlorthalidone	Propranolol	Captopril	Eprosartan		Eplerenone	Amlodipine
Hydrochlorothiazide	Timolol	Enalapril	Irbesartan			Felodipine
Indapamide	"Cardioselective"	Fosinopril	Losartan			Nicardipine
Metolazone	Bisoprolol	Lisinopril	Olmesartan			Nisoldipine
Polythiazide	Metoprolol	Moexipril	Telmisartan			Nifedipine
	Atenolol	Perindopril	Valsartan			Benzodiazepine
	"Vasodilating"	Quinapril				Diltiazem
	Carvedilol[b]	Ramipril				Phenylalkylamine
	Labetalol[b]	Trandolapril				Verapamil
	Nebivolol[c]					

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; DRI = direct renin inhibitor; MRB = mineralocorticoid receptor blocker.

Data adapted from Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., Jr., et al. (2003). Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*, *42*(6), 1206–1252.

[a]Data adapted from Bristow, M. R. (2000). Beta-adrenergic receptor blockade in chronic heart failure. *Circulation*, *101*(5), 558–569.

[b]Vasodilating activity because of α-1 adrenoceptor blocking activity.

[c]Vasodilating activity because of potentiation of nitric oxide.

A growing body of evidence challenges the use of thiazide diuretics as well as β-blockers as first-line therapy for the treatment of hypertension because of their association with adverse metabolic changes (Cutler & Davis, 2008; Messerli, Bangalore, & Julius, 2008). In patients with newly diagnosed, uncomplicated hypertension, drugs associated with fewer metabolic disturbances may be more appropriate initial choices for hypertension treatment, particularly in older patients or patients at risk for diabetes (Bangalore, Wild, Parkar, Kukin, & Messerli, 2008; Messerli et al., 2008).

Both classes of agents have a similar BP-lowering efficacy compared with other available classes of antihypertensive drugs. However, β-blockers are not as effective in reducing stroke as other classes of antihypertensives, which is another reason their use as first-line agents has been questioned (Lindholm, Carlberg, & Samuelsson, 2005). Thiazide diuretics are generally safe and inexpensive and have been indicated and widely used as first-line monotherapy in uncomplicated hypertension (i.e., hypertension in the absence of comorbidity; Chobanian et al., 2003). Current evidence suggests that thiazide diuretics decrease BP mainly by decreasing extracellular fluid volume and peripheral vascular resistance. However, other mechanisms may be involved in the long-term effects of thiazide diuretics on BP (Ellison & Loffing, 2009).

Thiazide diuretics (e.g., hydrochlorothiazide [HCTZ]) and some β-blockers are associated with various physiologic changes, such as altered lipid metabolism, decreased potassium levels, elevated fasting glucose, and reduced peripheral insulin sensitivity (Luna & Feinglos, 2001). Based on a meta-analysis of 59 clinical trials investigating the effects of antihypertensive agents on potassium and glucose, Zillich et al. reported that the thiazide diuretics induced hypokalemia and suggested that treatment with potassium supplementation to resolve the electrolyte imbalance may also help reverse glucose intolerance and prevent subsequent development of diabetes (Zillich, Garg, Basu, Bakris, & Carter, 2006). However, the need for potassium supplementation, which is most accurately administered in conjunction with periodic checks of electrolyte balance, calls into question the stereotype of diuretics as inexpensive drugs.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which captured metabolic adverse events in patients with hypertension, demonstrated a higher absolute difference in the risk of new-onset diabetes in the first 2 years of the trial in patients receiving chlorthalidone, another thiazide diuretic, compared with those receiving the CCB amlodipine (Barzilay et al., 2006). Indeed, a recent meta-analysis showed that, although HCTZ conferred a 33% reduction in heart failure, it had no additional benefits on all-cause mortality, cardiovascular mortality, myocardial infarction, or stroke (Messerli et al., 2008). However, depending on the clinician's experience and patient's acceptance, there are several classes of drugs that are as effective and better tolerated than diuretics for initial use in hypertension (Table 1).

CCBs cause relaxation of arterial smooth muscle and therefore reduce peripheral vascular resistance. CCBs produce reductions in BP similar to other classes of antihypertensives and provide slightly better protection

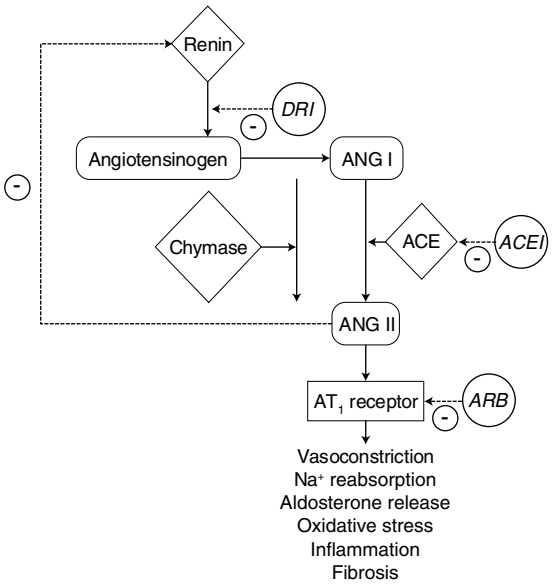

Figure 2 The renin-angiotensin-aldosterone system. ACE = angiotensin converting enzyme; ACEI = ACE inhibitor; ANG = angiotensin; ARB = angiotensin receptor blocker; AT_1 = angiotensin II type 1 receptor; DRI = direct renin inhibitor.

from stroke than ACEIs, ARBs, diuretics, and β-blockers (Turnbull, 2003). However, ACEIs provide better protection against heart failure than CCBs (Turnbull, 2003). Conditions and special populations for which CCBs are indicated for the treatment of hypertension include stroke, pregnancy, isolated systolic hypertension in the elderly, and African Americans (Mancia et al., 2007).

Agents that modify the RAAS, such as ACEIs, ARBs, or direct renin inhibitors (DRIs), all serve to prevent the synthesis or block the actions of the vasoconstrictor ANG II (Figure 2), the effects of which can be systemic but can also be localized in organs such as the kidney (Dzau, 2001). In addition to their BP-lowering effects, blockade of the ANG II–induced proinflammatory response also appears to provide vascular and renal protection in patients with hypertension (Schmieder, Hilgers, Schlaich, & Schmidt, 2007). ACEIs, ARBs, and DRIs are not associated with an increase in blood glucose levels and can improve insulin resistance (Bosch et al., 2006; Dahlof et al., 2002; Pollare, Lithell, & Berne, 1989; Top et al., 2002; Vitale et al., 2005). Studies comparing these agents to thiazide diuretics have shown more favorable metabolic effects when compared with thiazide therapy alone (Grassi et al., 2003; Hunter et al., 1998). In addition, adding an ACEI, an ARB, or a DRI to HCTZ therapy has been shown to mitigate some of the negative metabolic effects associated with HCTZ monotherapy. The lower incidence of new-onset diabetes among patients at high risk of developing diabetes and who are taking a RAAS inhibitor has been attributed to decreased insulin resistance resulting from hemodynamic and nonhemodynamic effects (Figures 3A and B; Abuissa, Jones, Marso, & O'Keefe, 2005; Jandeleit-Dahm, Tikellis, Reid, Johnston, & Cooper, 2005).

Treatment of hypertension: The importance of initiating combination therapy in high-risk patients or patients with resistant hypertension

Although current guidelines vary in their recommendations of specific agents for first-line therapy, there is a clear consensus that combining agents with complementary mechanisms of action results in improved BP reduction compared with monotherapy (Chobanian et al., 2003; Mancia et al., 2007). Addition of a second drug from a different class is recommended when BP fails to meet goal with a single agent or when BP is more than 20 mmHg above systolic or 10 mmHg above diastolic goals (Chobanian et al., 2003). Further, achieving BP goal quickly and with well-tolerated agents is especially important in high-risk patients, including the elderly and those patients with concomitant diabetes or metabolic syndrome, cardiovascular disease, or renal impairment. Despite earlier diagnosis and improved awareness that elevations in BP are associated with increased age, BP control continues to decline with advancing age.

Current guidelines acknowledge that more than two thirds of hypertensive patients require more than one medication to control their BP and recommend initiating combination therapy in high-risk patients to improve the likelihood of early attainment of BP goal (Chobanian et al., 2003). Combination therapy with lower doses of individual drugs that have complementary mechanisms of action, especially when given as a single pill, which patients are more likely to take, has been shown to more effectively and rapidly reduce BP than higher doses of the component drugs (Burnier, Brown, Ong, Keskinaslan, & Khan, 2009; Law, Wald, Morris, & Jordan, 2003; Mancia et al., 2007; Sica, 2002). Combination therapy with single-pill formulations also addresses issues related to simplifying treatment to improve adherence, including decreased pill burden and the consequent perception of wellness (McKinnon, Mellors, & Swindells, 2009). A traditional clinical paradigm in the treatment of hypertension has been to push to the maximum dosage of a given drug before adding an adjunctive treatment. This approach will not likely add significant antihypertensive effect but can add to adverse events. Combination therapy with lower doses of antihypertensives is associated with a reduced incidence and severity of

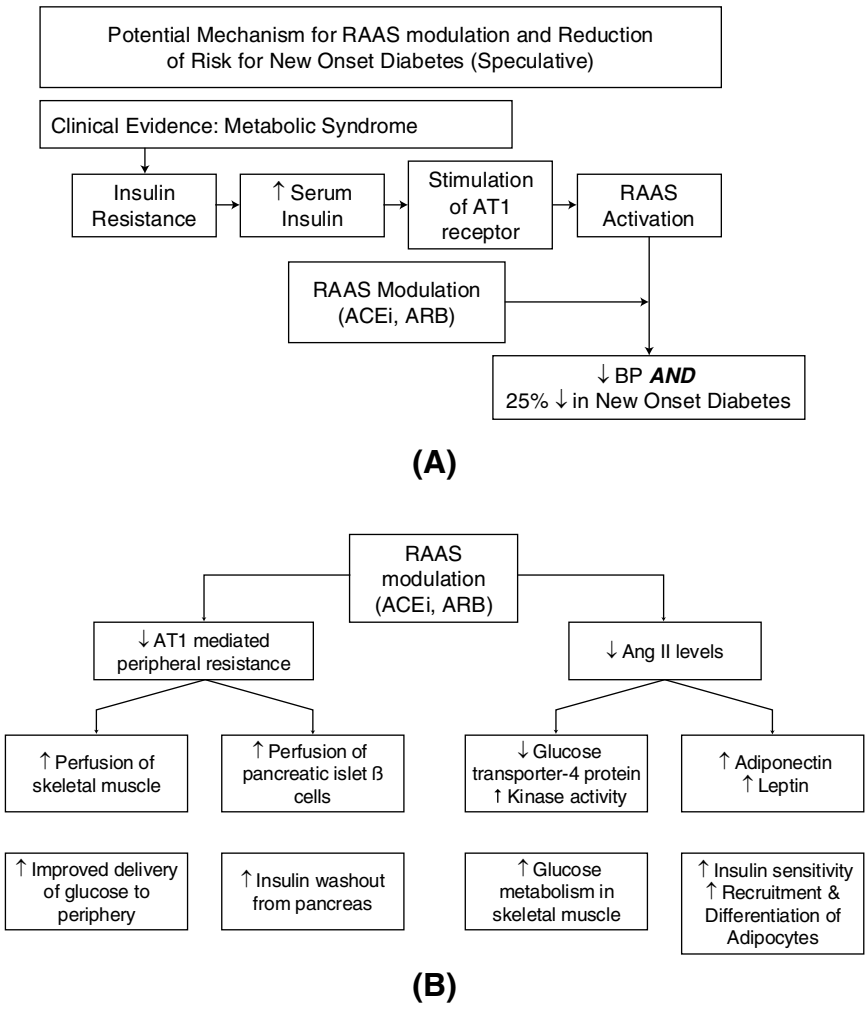

Figure 3 Evidence that RAAS modulation reduces risk for new-onset diabetes (A) and RAAS modulation and risk reduction for new-onset diabetes (B). ACEI = angiotensin-converting enzyme inhibitor; ANG = angiotensin; ARB = angiotensin receptor blocker; AT_1 = angiotensin II type 1 receptor; BP = blood pressure; RAAS = renin-angiotensin-aldosterone system. (Data from Abuissa, H., Jones, P. G., Marso, S. P., & O'Keefe, J. H., Jr. (2005). Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *Journal of the American College of Cardiology*, *46*(5), 821–826; and Jandeleit-Dahm, K. A., Tikellis, C., Reid, C. M., Johnston, C. I., & Cooper, M. E. (2005). Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. *Journal of Hypertension*, *23*(3), 463–473.)

adverse events (Mancia et al., 2007), thereby improving patient adherence and persistence (Chobanian et al., 2003; Neutel et al., 2005; Pool, 2003; Taylor, 2004), leading to improved outcomes. Most importantly, combination therapy is associated with faster attainment of BP goal rates than monotherapy, which is also associated with improved outcomes (Jamerson & Basile, 2008).

Beyond the benefits achieved with BP reduction, combination antihypertension treatment has the potential to provide patients with additional benefits, particularly end-organ protection, which can hold the promise of decreased risk for major clinical events, such as stroke or congestive heart failure (Liu et al., 2005; Patel et al., 2007; Pitt et al., 2003). However, reductions as small as 3 mmHg in BP can result in significant reductions in cardiovascular risk (Yusuf et al., 2000); therefore, definitive protective effects of specific antihypertensive agents (particularly in combination) on clinical outcomes independent of BP reduction is likely to take some time to fully identify. To that end, numerous combinations of drugs from different antihypertensive classes have been investigated for their effect on outcomes, particularly in high-risk patients, such as those with diabetes.

A fundamental strategy in current recommendations (Chobanian et al., 2003) for treatment of most patients with mild to moderate hypertension is to begin with a thiazide diuretic. In patients for whom a thiazide diuretic is contraindicated, monotherapy with an ACEI, ARB, or CCB should be considered. If BP control is not attained with a diuretic, addition of a RAAS-inhibiting agent, such as an ACEI or ARB, is recommended. Inhibitors of the RAAS in combination with other antihypertensive agents effectively lower BP and are generally well tolerated. In particular, the first-line use of these agents has recently gained support from the reported results of the Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) clinical trial (Jamerson et al., 2008). There is a growing need to update the JNC7 guidelines (Messerli & Bangalore, 2009), and in particular, the placement of diuretics as first-line therapy has been called into question.

Although diuretics may serve as useful complementary treatment with an ACEI, ARB, or DRI, other combinations with these agents are also being explored. The ACCOMPLISH trial demonstrated that first-line treatment with an amlodipine/benazepril combination or an HCTZ/benazepril combination produced similar BP control rates and only small differences (< 1 mmHg) in systolic BP over the course of the trial. However, the CCB/ACEI treatment regimen was associated with significantly reduced cardiovascular morbidity and mortality compared with the HCTZ/ACEI regimen (20% relative risk reduction), suggesting cardioprotective benefits beyond BP-lowering effects with CCB/ACEI (Jamerson et al., 2008).

Hypertension often occurs in the presence of other disease, and one of the most common and clinically challenging comorbidities is with diabetes. There is a complex interaction between hypertension and diabetes; RAAS stimulation of inflammatory mediators may precipitate insulin resistance. Routine screening and subsequent monitoring of changes in surrogate markers of kidney function, including serum creatinine and albuminuria, which is also a marker of generalized endothelial dysfunction (Paisley et al., 2003), can help guide treatment of patients with hypertension to prevent microvascular disease progression. Novel biomarkers such as cystatin C, which is a cysteine protease produced in almost all cells and secreted into the bloodstream, may be a more accurate measure of glomerular filtration rate than creatinine and a stronger predictor of death and cardiovascular events (Shlipak et al., 2005). Early diagnosis and treatment of the microvascular complications of hypertension are as imperative as the management of macrovascular complications (Patel et al., 2007; Tatti et al., 1998). For example, UK Prospective Diabetes Study (UKPDS 36), a prospective observational study, demonstrated a correlation between each 10-mmHg reduction in mean systolic BP with increasing average reductions in risk rates for diabetes-related mortality (by 17% [95% CI, 13–21]), macrovascular complication (myocardial infarction by 12% [95% CI, 7–16]; $p < .001$), and microvascular complication (retinopathy and nephropathy by 13% each; $p < .001$ for all; Adler et al., 2000).

In addition to investigation of ACEI or ARB therapy in patients with diabetes and associated complications, the effects of combining agents that affect different elements of the RAAS on outcomes has also been investigated. The Valsartan in Acute Myocardial Infarction (VALIANT) study compared the effects of valsartan, captopril, or the combination in 14,703 patients with myocardial infarction complicated by left ventricular dysfunction, heart failure, or both. Patients receiving the combination therapy had greater reductions in BP compared with those receiving either agent alone, but had significantly more adverse events ($p < .05$), particularly hypotension and renal events, than patients receiving captopril alone (Pfeffer et al., 2003).

The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) sought to assess the effects of dual RAAS blockade (with the ARB telmisartan plus the ACEI ramipril) versus either agent alone on outcomes in a large hypertension population ($n = 25{,}620$; Yusuf et al., 2008). The primary outcome measure was a composite of myocardial infarction, stroke, cardiovascular death, and hospitalization for heart failure, which occurred in 16.5% of the ramipril-treated patients, 16.7% of the telmisartan-treated patients, and 16.3% of the patients receiving the dual RAAS combination. Treatment with either agent alone produced similar reductions in BP; however, the combination resulted in a higher incidence of adverse events without additional benefit in cardiovascular risk reduction, despite a greater reduction in BP. Because of the significant increase in the relative risk of renal impairment with the dual RAAS combination (1.33 [95% CI, 1.22–1.44]) compared with monotherapy (1.04 [95% CI 0.96–1.14]; $p < .001$), the use of ACEI/ARB (Mann et al., 2008) dual RAAS combinations has been challenged (Messerli, 2009). However, considering that there are different agents and classes of agents that act on the RAAS, these findings may not represent results that could be expected for all dual RAAS blockade combinations.

Direct renin inhibition

The newest class of antihypertensive therapy is represented by the DRI aliskiren. Based on the unique

mechanism of action of aliskiren, it can be useful as part of dual RAAS combination therapy with an ACEI or ARB, likely mitigating the incidence of adverse events and providing improved outcomes compared with those seen with ACEI/ARB combinations (Fisher & Hollenberg, 2005). The effect of each agent that interferes with the RAAS is achieved by a distinct mechanism of action (Figure 2). DRIs inhibit the enzymatic activity of renin, which is the first and rate-limiting step in the RAAS cascade. ACEIs block the formation of ANG II from ANG I while ARBs block the action of ANG II at the receptor level. ACEIs and ARBs achieve their BP-lowering effects by inhibiting the formation and action of ANG II, respectively, disrupting the normal negative feedback by which ANG II inhibits renin release. This results in a reactive increase in plasma renin activity (PRA; Azizi, Webb, Nussberger, & Hollenberg, 2006; Fisher & Hollenberg, 2005), which is associated with increased cardiovascular risk, morbidity, and mortality (Tami et al., 2009; Vasan, 2006). Since ANG II may be formed from ANG I by pathways independent of ACE, such as chymase (Figure 2; Hollenberg, Fisher, & Price, 1998), ANG II levels may actually increase over the long term in patients treated with ACEIs, a phenomenon known as "ACEI escape" (Roig et al., 2000). ARBs also increase PRA by inhibiting the ANG II-renin release negative feedback loop (Azizi & Menard, 2004). Therefore, with ACEIs and ARBs, the increase in PRA may limit the degree of RAAS inhibition produced by these drugs.

In contrast, DRIs, such as aliskiren, reduce PRA because it directly inhibits the enzymatic activity of renin. As a result, it also reduces the production of ANG I, ANG II, and aldosterone (Azizi, 2006; Fisher & Hollenberg, 2005; Nussberger, Wuerzner, Jensen, & Brunner, 2002). This may result in a more complete inhibition of the RAAS compared with ACEIs or ARBs (Fisher & Hollenberg, 2005). The reduction of aldosterone levels is of particular importance. In addition to its well-established effect of promoting sodium retention by stimulating the reabsorption of this ion by the kidney, there is now clear evidence that aldosterone also activates a number of pathways in the heart, kidney, and vasculature that induce fibrosis (Epstein, 2001), oxidative stress, inflammation (Brown, 2008), and endothelial dysfunction (Farquharson & Struthers, 2000).

Studies comparing the BP-lowering effects of aliskiren to that seen with other antihypertensive agents have demonstrated that treatment with aliskiren had similar or greater reductions in BP (Gradman & Traub, 2007; Stanton, Jensen, Nussberger, & O'Brien, 2003). For example, aliskiren 300 mg monotherapy has been shown to result in greater BP reductions compared with HCTZ 25 mg monotherapy while causing fewer incidences of hypokalemia (.9%) than HCTZ (17.9%; Schmieder et al., 2009). Thiazide-induced hypokalemia is associated with impaired glucose tolerance and may lead to the development of diabetes (Zillich et al., 2006).

The incidence of hypertension increases with age, and two thirds of Americans aged $\geq$ 60 years are hypertensive (Ong et al., 2007). Yet, only 50% of those treated attained BP control (Ong et al., 2007). In the Aliskiren for Geriatric Lowering of Systolic Hypertension trial (AGELESS; Duprez, Munger, Botha, Keefe, & Charney, 2009), aliskiren monotherapy (150–300 mg) decreased mean sitting systolic and diastolic BP to a greater extent than did ramipril (5–10 mg) over a 12-week period in patients with hypertension with a mean age of 72 years. The percentage of patients achieving BP control during this period was also greater with aliskiren than with ramipril. A study on the safety and tolerability of aliskiren in pediatric and adolescent patients (6–17 years of age) with hypertension is ongoing (http://clinicaltrials.gov/ct2/show/NCT00834041). As with ACEIs and ARBs, aliskiren is contraindicated in pregnancy.

Benefits beyond BP reduction have been observed with combination therapy with aliskiren; in patients with type 2 diabetes and with proteinuria, the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial (Parving, Persson, Lewis, Lewis, & Hollenberg, 2008) demonstrated that aliskiren 300 mg added to losartan 100 mg plus optimal antihypertensive treatment resulted in a 20% reduction in the mean urinary albumin-creatinine ratio (UACR) versus placebo plus losartan after 6 months of treatment ($p < .001$), suggesting renoprotective effects of aliskiren beyond those seen with losartan (Parving et al., 2008). Rates of hyperkalemia were similar in the aliskiren (5.0%) and placebo (5.7%) groups. However, as with ACEIs and ARBs (Palmer, 2004), serum electrolyte levels including potassium need to be monitored in patients with impaired renal function when using aliskiren.

Studies with aliskiren suggest that it has the potential to provide cardiovascular risk reduction independent of BP reduction based on reported beneficial effects on surrogate endpoints of cardiovascular or renal decline. In the Aliskiren Observation of Heart Failure Treatment (ALOFT) study (Cleland, Abdellah, Khaleva, Coletta, & Clark, 2007), the between-group difference from baseline to 3 months in levels of N-terminal prohormone brain natriuretic peptide (NT proBNP) was assessed in patients with heart failure. NT-proBNP may be the most powerful indicator of outcomes in heart failure patients, with reductions in NT-proBNP consistently being associated with improved outcomes in heart failure (Daniels & Maisel, 2007). In the ALOFT study, patients who were already receiving standard care with an ACEI (or ARB) and

a β-blocker were randomized to aliskiren ($n = 156$) or placebo ($n = 146$). The data demonstrated that aliskiren provided favorable neurohormonal effects. Plasma NT proBNP rose by 762 pg/mL in the placebo group and fell by 244 pg/mL in the aliskiren group ($p = .0106$). Additional studies are ongoing and planned to further investigate the cardiac and renal protective benefits of aliskiren (Parving et al., 2009).

In the AVOID trial, 599 patients with hypertension and type 2 diabetes with nephropathy who were receiving losartan and optimal antihypertensive therapy were given add-on treatment with aliskiren or placebo. Reduction in the UACR was compared after 6 months (Parving et al., 2008). Despite relatively small additional reductions in BP, mean UACR was reduced by 20% with aliskiren compared with placebo ($p < .001$), suggesting that aliskiren may have renoprotective effects in these patients that are independent of BP effects.

Conclusions

Practical disease management of hypertension is a pervasive clinical challenge, particularly in patients at high risk for cardiovascular events. Issues concerning barriers to reaching BP goals were highlighted in this review to help clinicians promptly identify and minimize disease progression and its complications. Nurse practitioners play a vital role in helping patients reach their BP goals by overcoming barriers such as nonadherence to antihypertensive medication regimens. There are many antihypertensive agents and combinations available, and knowledge of and education regarding current guideline recommendations for patients at high risk of cardiovascular events is critical. Although most available antihypertensive agents provide similar levels of efficacy, combination therapy that includes an agent that inhibits the RAAS for initial treatment of hypertension provides a strategy for effective BP reduction that is generally well tolerated.

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