A Review of the Use of Angiotensin Receptor Blockers for the Prevention of Cardiovascular Events in Patients with Essential Hypertension Without Compelling Indications

Kathy Zaiken, Timothy R Hudd, Judy WM Cheng

OBJECTIVE: To review the role of angiotensin receptor blockers (ARBs) for the prevention of cardiovascular events in patients with essential hypertension without other compelling indications.

DATA SOURCES: Peer-reviewed clinical trials, review articles, and relevant treatment guidelines were identified from MEDLINE and Current Content database (both 1966-November 15, 2012) using the search terms angiotensin receptor blockers (ARBs), azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, hypertension, myocardial infarction, stroke, heart failure, and cardiovascular outcomes. Results were limited to human trials published in English. Citations from articles were also reviewed for additional references.

STUDY SELECTION AND DATA EXTRACTION: The focus was on clinical trials evaluating cardiovascular end points of ARBs used in patients with essential hypertension without compelling indications.

DATA SYNTHESIS: Data supporting the use of ARBs for reducing cardiovascular events in patients with essential hypertension without compelling indications are inconsistent. To date, only candesartan and losartan have shown a significant reduction in cardiovascular morbidity within this sizable subgroup of patients. In the Study on Cognition and Prognosis in the Elderly (SCOPE) trial, candesartan showed a 27.8% reduction in nonfatal stroke versus placebo (95% CI 1.3-47.2; p = 0.04). Moreover, losartan demonstrated a decrease in all cardiovascular events compared to atenolol in the Cardiovascular Morbidity and Mortality in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study (RR 0.87; 95% CI 0.77-0.98; p = 0.021).

CONCLUSIONS: Data supporting the use of ARBs for reducing cardiovascular events in patients with essential hypertension without compelling indications are limited and inconclusive. More studies are needed before ARBs can be routinely recommended as first-line therapy for hypertension management in patients without other compelling indications.

Ann Pharmacother 2013;47:686-93.

Published Online, 11 Apr 2013, *theannals.com*, doi: 10.1345/aph.1R273

Hypertension, as defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7), the National Institute for Health and Care Excellence Clinical Management of Primary Hypertension in Adults, and the Canadian Hypertension Education Program, is blood pressure (BP) >140/90 mm Hg in adults aged 18 years or older.[1-3] One in 3 adults in the US has hypertension. To date, the American Heart Association estimates that 76.4 million Americans aged 20 years or older have hypertension.[4] According to the National Health and Nutrition Examination Survey/National Center for Health Statistics 2005-2008, 79.6% of patients with hypertension were aware of their diagnoses, 70.9% were taking antihypertensive medications, and only 47.8% of those being treated had their BP controlled.[4] By 2030

Author information provided at end of text.

it is projected that an additional 27 million people could have hypertension, which is an estimated 9.9% increase in prevalence from 2010.[5] Hypertension is a major risk factor for cardiovascular diseases.[6] Therefore, one of the fundamental goals in the management of hypertension is to reduce overall cardiovascular morbidity and mortality.[1]

The pathophysiology of essential hypertension is multifaceted. Malfunctions in either neurohormonal or vasodepressor mechanisms, defects in peripheral BP autoregulation, and disturbances in sodium, calcium, and natriuretic hormone balance can lead to the development of hypertension.[7,8]

The renin-angiotensin-aldosterone system (RAAS) is a neurohormonal system that is activated and regulated by the kidneys. The RAAS regulates sodium, potassium, and blood volume, thereby making it an influential contributor to the homeostatic regulation of BP.[9] Angiotensin II is the main effector hormone in the RAAS. Angiotensin receptor blockers (ARBs) exert most of their effects by blocking the angiotensin II type I (AT_1) receptor. In turn, vasoconstriction and aldosterone secretion are inhibited, resulting in an effective pharmacologic approach in the management of hypertension, cardiovascular disease, and renal disease.[10] It has been consistently demonstrated that blockage of the RAAS using angiotensin-converting enzyme (ACE) inhibitors in patients with essential hypertension without a compelling indication, diabetes, or heart failure, as well as in patients who have experienced a myocardial infarction (MI), not only decreases the risk of cardiovascular events and stroke, but also provides renal protection.[1,11] Various ARBs have demonstrated equivalent efficacy in BP control when compared to other classes of antihypertensives, including diuretics, ACE inhibitors, β-blockers, and calcium channel blockers.[12-18] Some also have similar benefits in improving cardiovascular outcomes when compared to ACE inhibitors in many patient populations (diabetes, heart failure, post-MI) with less incidence of cough.[19,20] Therefore ARBs alone or in combination are considered among the first-line agents for BP management of patients with specific compelling indications, including heart failure and diabetes, as well as patients who are post-MI.[1-3] However, whether ARBs possess similar benefits in reducing cardiovascular morbidity and mortality in patients with primary hypertension alone, without compelling indications, is less well defined. Notwithstanding, all 3 hypertension management guidelines (US, British, and Canadian) have recommended the use of ARBs as a potential first-line option for hypertension management in patients without compelling indications.[1-3]

This article reviews available evidence evaluating the effectiveness of ARBs in improving cardiovascular outcomes in patients with essential hypertension without other compelling indications.

Data Sources and Selection

Peer-reviewed clinical trials, review articles, and relevant treatment guidelines were identified from MEDLINE and Current Content database (both 1966-November 15, 2012) using the search terms angiotensin receptor blockers, azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, hypertension, myocardial infarction, stroke, heart failure, and cardiovascular outcomes. Results were limited to human trials published in English. Citations from articles were reviewed for additional references. This article focuses on the discussion of clinical trials that measure the effectiveness of ARBs in reducing cardiovascular end points when used in patients with hypertension without other compelling indications.

Clinical Trials

There are no published clinical trials to date evaluating the impact of azilsartan, eprosartan, and olmesartan in terms of mortality and end organ damage in patients with hypertension. Clinical trials evaluating cardiovascular outcomes (fatal and nonfatal MI, fatal and nonfatal stroke, and heart failure) with candesartan, irbesartan, losartan, telmisartan, and valsartan in hypertensive patients are discussed here. Table 1 also summarizes the results of these studies.

SCOPE (the Study on Cognition and Prognosis in the Elderly) was a randomized, double-blind, placebo-controlled trial that enrolled 4964 hypertensive elderly patients (aged 70-89 years) with systolic BP of 160-179 mm Hg and/or diastolic BP of 90-99 mm Hg.[21] Patients were randomized to receive candesartan (8 mg daily titrated to 16 mg daily) or placebo, with open-label active antihypertensive therapy added as needed to both groups (if BP was 160/90 mm Hg or higher with maximum treatment doses). The recommended second-line antihypertensive was hydrochlorothiazide. The choice of the third antihypertensive, if needed, was up to the discretion of the patients' primary care physicians. The primary outcome of the study was major cardiovascular events, a composite of cardiovascular death, nonfatal stroke, and nonfatal MI. Patients' baseline BPs were 166/90 and 167/90 mm Hg in the candesartan and control groups, respectively. BP was reduced by 21.7/10.8 mm Hg in the candesartan group and by 18.5/9.2 mm Hg in the control group ($p < 0.001$). A first major cardiovascular event occurred in 242 candesartan patients and 268 control patients. This equated to a nonsignificant risk reduction with candesartan by 10.9% (95% CI −6.0 to 25.1; $p = 0.19$). However, candesartan-based treatment reduced nonfatal stroke significantly by 27.8% (95% CI 1.3-47.2; $p = 0.04$) and all strokes (fatal and nonfatal) by 23.6% (95% CI −0.7-42.1; $p = 0.056$). Treatments were well tolerated and adverse events occurred in similar incidence in both groups. The most common adverse event re-

ported was dizziness (candesartan 20.9%, placebo 20%; p > 0.05). Despite reducing BP to a greater extent, candesartan did not demonstrate statistically significant improvements in cardiovascular outcomes when compared to standard treatment. Most patients in the comparison group were prescribed medications that have been proven to improve cardiovascular outcomes in patients with hypertension, including hydrochlorothiazide, calcium channel blockers, and ACE inhibitors. Thus, it cannot be conclusively determined whether candesartan is superior to other agents in reducing cardiovascular outcomes or if it just reduces cardiovascular outcomes to a similar extent. This study enrolled primarily relatively healthy elderly patients (aged 70-80 years, with no other significant medical problems or compelling indications beside hypertension), so these results may not be applicable to other patient populations.

Suzuki and Kanno performed a single-blind, randomized, prospective study in 2048 Japanese patients with essential hypertension (BP >140/90 mm Hg), aged 35-79 years, with or without history of cardiovascular disease.[22] Subjects were randomly assigned to receive candesartan 2-12 mg daily or conventional antihypertensive drugs other than an ACE inhibitor or other ARB. In Japan, the conventional antihypertensive used was primarily a calcium channel blocker. The primary outcome assessed was hospitalization due to stroke, MI, and congestive heart failure. Baseline BP values were 166/96 and 162/91 mm Hg in the candesartan and conventional treatment groups, respective-

Table 1. Pertinent Clinical Trials of Effectiveness of Angiotensin Receptor Blockers Used in Hypertension and Clinical Outcomes

Reference	Design	Pts.	Intervention	Primary End Point	Results
Lithell (2003)[21]	R, DB, PC	4964 hypertensive pts. (aged 70-89 years); SBP 160-179 mm Hg and/or DBP 90-99 mm Hg	Candesartan (8 mg/day titrated to 16 mg/day) or placebo	Composite of cardiovascular death, nonfatal stroke, and nonfatal MI	Primary end points: candesartan 242 pts., placebo 268 pts. (p = 0.19)
Suzuki (2005)[22]	R, OL, controlled	2048 hypertensive pts. (aged 35-79 years); SBP 140-180 mm Hg and/or DBP 90-110 mm Hg	Candesartan (two 12-mg doses/day) or conventional antihypertensive therapy	Hospitalization due to stroke, MI, heart failure	39% reduction in hospitalization for stroke (RR 0.61; 95% CI 0.41-0.84; p < 0.05); 57% reduction in hospitalization for MI (RR 0.44; 95% CI 0.21-0.84; p < 0.05) with candesartan vs conventional treatment; no significant differences in heart failure
Dahlof (2002)[24]	R, DB	9193 pts. (aged 55-80 years); essential hypertension (BP 160-200/95-115 mm Hg) and left ventricular hypertrophy	Losartan 50 mg/day titrated to 100 mg/day or atenolol 50 mg/day titrated to 100 mg/day	All cardiovascular events	Primary end points: losartan 508 pts., atenolol 588 pts. (RR 0.87; 95% CI 0.77-0.98; p = 0.021)
Julius (2004)[25]	R, DB, controlled	15,245 pts. (aged 50 years or older) with treated or untreated hypertension and high risk for future cardiovascular events (current smoker, diabetes, high total cholesterol, left ventricular hypertrophy, proteinuria)	Valsartan 80 mg/day or amlodipine 5 mg/day	Time to first cardiac event (composite of sudden cardiac death, fatal MI, death during or after percutaneous coronary intervention or coronary artery bypass graft, death due to heart failure, and death associated with recent MI, heart failure requiring hospital management, non-fatal MI, or emergency procedures to prevent MI)	Primary end points: valsartan 810 pts., amlodipine 789 pts. (HR1.04; 95% CI 0.94-1.15)
Kjeidsen (2010)[27]	Epidemiologic study (from prescription database)	14,100 pts. diagnosed with hypertension (6771 prescribed losartan, 7329 prescribed candesartan)	Losartan vs candesartan	Total cardiovascular disease	Candesartan had lower adjusted HR for total cardiovascular disease (0.86; 95% CI 0.77-0.96; p = 0.0062), heart failure (0.64; 95% CI 0.50-0.82), cardiac arrhythmias (0.80; 95% CI 0.65-0.92), and peripheral artery disease (0.61; 95% CI 0.41-0.91) vs losartan

BP = blood pressure; DB = double-blind; DBP = diastolic BP; HR = hazard ratio; MI = myocardial infarction; OL = open-label; PC = placebo-controlled; R = randomized; SBP = systolic BP.

ly. BP levels after treatment were similar between groups (candesartan 140/79 mm Hg, conventional treatment 138/81 mm Hg). There was a 39% reduction in hospitalization due to stroke (5.8 vs 9.4 cases; RR 0.61; 95% CI 0.41-0.84; $p < 0.05$) and a 57% reduction in hospitalization due to MI (RR 0.44; 95% CI 0.21-0.84; $p < 0.05$) in patients receiving candesartan-based treatment compared to those receiving conventional treatment. However, there was no significant reduction in the incidence of heart failure (15% reduction: 4.3 vs 5.0; RR 0.85; 95% CI 0.57-1.26). Further analysis in stratifying the subjects with or without a history of cardiovascular diseases, including stroke and MI, revealed that candesartan reduced the incidence of stroke (61% reduction; RR 0.39; 95% CI 0.15-0.43; $p < 0.01$) and congestive heart failure (49% reduction; RR 0.51; 95% CI 0.23-0.92; $p < 0.05$) but not MI (RR 0.74; 95% CI 0.36-1.48; $p = 0.1$) in hypertensive patients with a history of cardiovascular diseases. However, conventional treatment was superior to candesartan-based treatment in reducing the incidence of stroke in patients without a history of cardiovascular diseases (66% reduction; RR 0.34; 95% CI 0.16-0.69; $p < 0.05$). The authors concluded that candesartan may improve cardiovascular outcomes in patients with a history of cardiovascular disease, but not in those without. However, another large study, the TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Diseases) study, which enrolled more than 5000 patients with a history of cardiovascular disease, did not demonstrate any benefits of telmisartan compared to placebo in terms of improving cardiovascular outcomes.[23] Therefore, it is difficult to conclude whether the benefits seen in patients with cardiovascular diseases in the Suzuki study occurred by chance.[22] Because this population was Japanese, its results may not be applicable to other patient populations. This study also demonstrated that candesartan may be inferior to conventional treatment options in improving cardiovascular end points in patients without a history of cardiovascular diseases. Larger studies are needed to confirm this trend. Most (90.5%) patients in the conventional treatment group received a calcium channel blocker. It is difficult to determine whether candesartan is inferior to calcium channel blockers or inferior to true placebo.

The LIFE (Cardiovascular Morbidity and Mortality in the Losartan Intervention for Endpoint Reduction in Hypertension) study was a randomized, double-blinded trial that enrolled 9193 patients aged 55-80 years with essential hypertension (BP 160-200/95-115 mm Hg) and left ventricular hypertrophy diagnosed by electrocardiography.[24] Patients were randomized to receive losartan 50 mg daily titrated to 100 mg daily or atenolol 50 mg daily titrated to 100 mg daily. If the target BP (<140/90 mm Hg) was not achieved, the addition of hydrochlorothiazide 12.5-25 mg daily was permitted. Additional antihypertensives were permitted if required thereafter. The choice of antihypertensive was at the discretion of the patients' primary care physician. Primary end points consisted of all cardiovascular events (death, MI, or stroke). Baseline BP was 174/98 mm Hg in both the losartan and the atenolol groups. Similar reductions in BP were seen in the losartan (30.2/16.6 mm Hg) and atenolol (29.1/16.8 mm Hg) groups. The primary composite end point occurred in 508 losartan (23.8 per 1000 patient-years) and 588 atenolol patients (27.9 per 1000 patient-years; RR 0.87; 95% CI 0.77-0.98; $p = 0.021$). Two hundred four losartan and 234 atenolol patients died from cardiovascular disease (RR 0.89; 95% CI 0.73-1.07; $p = 0.206$) and 232 losartan patients and 309 atenolol patients experienced fatal and nonfatal stroke (RR 0.75; 95% CI 0.63-0.89; $p = 0.001$). Fatal and nonfatal MI occurred in 198 losartan patients and 188 atenolol patients (RR 1.07; 95% CI 0.88-1.31; $p = 0.491$). Overall, patients who received atenolol experienced more drug-induced adverse events than did losartan patients ($p < 0.05$). Cardiovascular morbidity and mortality was lower in those receiving losartan compared to those receiving atenolol.

The VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) study was a randomized, double-blind, parallel group trial evaluating 15,245 patients aged 50 years or older with treated or untreated hypertension (>140/90 mm Hg).[25] Patients enrolled in this trial were considered to be at a relatively high risk for developing a future cardiovascular event (ie, current smokers and patients with diabetes, high total cholesterol, left ventricular hypertrophy, or proteinuria). Patients already receiving antihypertensive treatment discontinued their previous treatment and were randomized to receive either valsartan 80 mg daily or amlodipine 5 mg daily. Hydrochlorothiazide was added if another agent was needed. If necessary, choice of a third agent was left to the discretion of the patients' primary care physicians. The primary end point of the study was time to first cardiac event (a composite of sudden cardiac death, fatal MI, death during or after percutaneous coronary intervention or coronary artery bypass graft, death due to heart failure, and death associated with recent MI, heart failure requiring hospital management, nonfatal MI, or emergency procedures to prevent MI). Baseline BP was 155/87 mm Hg in both groups. The amlodipine-based regimen reduced BP to a significantly greater degree than the valsartan-based regimen (BP 4.0/2.1 mm Hg lower in amlodipine group after 1 month; 1.5/1.3 mm Hg lower after 1 year; $p < 0.001$ between groups). The primary composite end point occurred in 810 patients in the valsartan group (10.6%) and 789 in the amlodipine group (10.4%; HR 1.04; 95% CI 0.94-1.15; $p = 0.49$) and failed to reach statistical significance. Most secondary end point analysis also demonstrated no difference between the 2 treatments, except for a higher incidence of MI in the valsartan group (HR 1.19; 95% CI 1.02-1.38; $p = 0.02$) and lower incidence of new-onset diabetes in the valsartan group (HR 0.77; 95% CI 0.68-0.86; $p < 0.0001$). The trend of increasing MI may be worrisome and future larger studies will be needed to confirm the findings.

These patients were considered at relatively high risk of developing cardiovascular diseases; 32% of the patient population had diabetes, which is a JNC7 guideline–compelling indication. In a follow-up prespecified subanalysis, primary outcomes did not differ between treatment in patients with or without diabetes.[26]

Kjeidsen and colleagues compared the antihypertensive effect of losartan to that of candesartan in hypertensive patients with no known cardiovascular disease.[27] Seventy-two primary care centers in Sweden were screened for patients who had been prescribed losartan or candesartan between 1999 and 2007. Among the 24,943 eligible patients, 14,100 patients were diagnosed with hypertension. Of those, 6771 were prescribed losartan and 7329 were prescribed candesartan. Patients were linked to the Swedish National Hospitalizations and Death Cause Register. There was no significant difference in BP reduction when comparing the losartan and candesartan groups during follow-up. Compared with the losartan group, the candesartan group had a lower adjusted hazard ratio for total cardiovascular disease (0.86; 95% CI 0.77-0.96; p = 0.0062), heart failure (0.64; 95% CI 0.50-0.82; p = 0.0004), cardiac arrhythmias (0.80; 95% CI 0.65-0.92; p = 0.0330), and peripheral artery disease (0.61; 95% CI 0.41-0.91; p = 0.0140). The authors concluded that no differences in BP reduction were observed, suggesting that other mechanisms related to different pharmacologic properties (eg, difference in receptor binding affinity) of the drugs may explain the differences in clinical outcomes. The clinical significance of variations in receptor binding properties within the ARB class in reducing cardiovascular outcomes remains to be determined.

Clinical Implications and Future Perspective

A limited number of clinical trials currently exist evaluating the effectiveness of ARBs in reducing cardiovascular events in hypertensive patients without compelling indications. The majority of these studies showed that there were no significant differences in the reduction of cardiovascular outcomes between ARBs and conventional treatments. Most of the studies, except the SCOPE trial, did not have a true placebo control group, understandably so, due to ethical reasons for not treating hypertension. In the SCOPE trial, candesartan did not significantly reduce the primary end point of combined cardiovascular death, nonfatal stroke, and nonfatal MI. Because other studies did not use noninferiority trial design, it is difficult to conclude whether a drug being not significantly different than other traditional treatment implies that it is equally effective in reducing cardiovascular outcomes or not. Some of the antihypertensives used in the control arm, such as thiazides, diuretics, and calcium channel blockers, have been demonstrated to reduce cardiovascular events.

The Agency for Healthcare Research and Quality performed a systematic review of 94 studies to compare the effectiveness of ACE inhibitors and ARBs in patients with essential hypertension.[28] BP lowering was found to be equivalent between the groups, but the incidence of cough was more frequently reported in patients receiving an ACE inhibitor (OR 4.74; 95% CI 3.56-6.31). Additionally, no consistent differential effects on other outcomes, including lipid levels, diabetes control, left ventricular mass/function, renal function, and cardiovascular outcomes, were found. However, outcomes assessed among these studies varied and significant differences existed among study protocols, which may limit the generalizability of these results. Law and colleagues performed a meta-analysis of 147 randomized trials on antihypertensives (4 of which evaluated ARBs) in the prevention of cardiovascular disease.[29] ARBs demonstrated no effects on improvement in cardiovascular outcomes. Further study is necessary to better define the role of ARBs when used in patients with uncomplicated essential hypertension to prevent adverse cardiovascular events. Again, because of ethical reasons of not being able to use true placebo, noninferiority studies comparing ARBs to other conventional antihypertensive agents with proven benefits related to cardiovascular outcomes may be one way to explore this question.

Candesartan, valsartan, and losartan have been evaluated in patients with hypertension without compelling indications. The impact of these agents on reducing cardiovascular outcomes may not necessarily imply the existence of a class effect. Structural differences among ARBs may inherently account for differing pharmacologic effects within the body. In general, the AT_1 receptors are more widely distributed and more strongly expressed than the AT_2 receptors and are concentrated primarily in the vascular smooth muscle, kidney, and adrenal glands.[30] Structurally, most of the ARBs (losartan, valsartan, candesartan, and irbesartan) include a biphenyltetrazole moiety. This moiety aids in positioning the molecule to present the active component to the AT_1 receptor. The biphenyltetrazole moiety is attached to different substituents in each of the agents. Telmisartan and eprosartan do not contain the biphenyltetrazole unit; hence, they are among the least selective ARBs. Additionally, fine variations between the active moiety among each ARB may account for slight differences in pharmacologic properties within this class. For example, losartan carries a heterocycle imidazole, which is replaced by a nonplanar acylated amino acid in valsartan.[30] Perhaps the most important pharmacologic contribution of these structural differences among the ARBs is their degree of selectivity for the AT_1 receptor.[31-38] Losartan and eprosartan have the lowest receptor affinity, followed by telmisartan. The other ARBs range in their receptor affinity from >8500- to 20,000-fold. Studies conducted to evaluate clinical outcomes on ARBs have mostly utilized agents with a

higher affinity and selectivity to the AT_1 receptor (eg, candesartan, valsartan), believing that high receptor affinity would not only make the agent more potent in lowering BP, but also in suppressing neurohormones that can lead to adverse cardiovascular outcomes. However, it is not yet known whether any benefit observed in clinical outcomes is a class effect or a specific agent effect.

The understanding of the role of RAAS in the pathophysiology of cardiovascular diseases also continues to evolve. There is a growing body of evidence suggesting the RAAS may contribute to systemic inflammation and increase the risk for future cardiovascular events. ACE inhibitors and ARBs have been said to possess pleiotropic effects. In experimental trials, angiotensin II has been shown to play a role in regulating steps in the inflammatory process through its interaction with the nitric oxide pathway and via induction of proinflammatory cytokines.[39] Some also believe that differences in receptor affinities among the ARB class may lead to differences in pleiotropic effects with each agent.[38] Further understanding of these differences among different ARBs may allow for the development of regimens that would maximize the chances for improving cardiovascular outcomes in patients with hypertension.

Summary

Clinical trials evaluating the effectiveness of ARBs in reducing cardiovascular events in hypertensive patients without other compelling indications are limited. In elderly patients with primary hypertension, candesartan has been shown to reduce stroke, but not other cardiovascular events, when compared to placebo. In other hypertensive patients without other compelling indications, candesartan and valsartan do not appear to reduce cardiovascular events when compared to placebo. However, in patients with hypertension and left ventricular hypertrophy, losartan may reduce cardiovascular events more significantly than β-blockers.

The benefits of certain ARBs in terms of improving morbidity and mortality in patients with heart failure and those who are post-MI, and preventing diabetic nephropathy are well established. Further evaluation of such benefits in patients with essential hypertension without compelling indications is necessary.

Kathy Zaiken PharmD, Associate Professor of Pharmacy Practice, Massachusetts College of Pharmacy and Health Sciences (MCPHS University); and Clinical Pharmacist, Harvard Vanguard Medical Associates, Boston, MA

Timothy R Hudd BS PharmD AE-C, Associate Professor of Pharmacy Practice, Massachusetts College of Pharmacy and Health Sciences (MCPHS University); and Clinical Pharmacist, Greater Lawrence Family Health Center, Lawrence, MA

Judy WM Cheng BS PharmD MPH FCCP BCPS, Professor of Pharmacy Practice, Massachusetts College of Pharmacy and Health Sciences (MCPHS University); and Clinical Pharmacist, Brigham and Women's Hospital, Boston

Correspondence: Dr. Zaiken, kathy.zaiken@mcphs.edu

Reprints/Online Access: www.theannals.com/cgi/reprint/aph.1R273

Conflict of interest: Authors reported none

References

1. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf (accessed 2012 Feb 4).
2. NICE clinical guidelines 127. Hypertension: clinical management of primary hypertension in adults. www.nice.org.uk/guidance/CG127 (accessed 2012 Oct 6).
3. The Canadian Hypertension Education Program (CHEP) 2012 recommendations. www.hypertension.ca/chep-recommendations (accessed 2012 Oct 6).
4. Roger VL, Go AS, Lloyd-Jones D, et al. Heart disease and stroke statistics—2012 update. A report from the American Heart Association statistics committee and stroke statistics committee. Circulation 2012;125:e2-220.
5. Centers for Disease Control and Prevention. Compressed mortality file: underlying cause of death, 1979 to 2007. Atlanta: Centers for Disease Control and Prevention. http://wonder.cdc.gov/mortSQl.html (accessed 2012 Feb 4).
6. Centers for Disease Control and Prevention. High blood pressure facts. March 21, 2011. www.cdc.gov/bloodpressure/facts.htm (accessed 2012 Feb 4).
7. Staessen JA, Wang J, Bianchi G, Birkenhager WH. Essential hypertension. Lancet 2003;361:1629-41.
8. Kaplan NM. Kaplan's clinical hypertension. 9th ed. Philadelphia: Lippincott Williams & Wilkins, 2006.
9. Saseen JJ, Maclaughlin EJ. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: a pathophysiologic approach. 8th ed. New York: McGraw-Hill, 2011:101-35.
10. Ojima M, Hideki I, Masayuki T, et al. In vitro antagonistic properties of a new angiotensin type 1 receptor blocker, azilsartan, in receptor binding and function studies. J Pharmacol Exp Ther 2011;336:801-8.
11. Lip GY, Beevers DG. More evidence on blocking the renin-angiotensin-aldosterone system in cardiovascular disease and the long-term treatment of hypertension: data from recent clinical trials (CHARM, EUROPA, ValHeft, HOPE-TOO and SYST-Dur2). J Hum Hypertens 2003;17:747-50.
12. Center for Drug Evaluation and Research. Medical review of azilsartan. www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200796Orig1s000MedR. pdf (accessed 2012 Feb 7).
13. Easthope SE, Jarvis B. Candesartan cilexetil: an update of its use in essential hypertension. Drugs 2001;62:1253-87.
14. Plosker GL. Eprosartan: a review of its use in hypertension. Drugs 2009;69:2477-99.
15. Pouleur HG. Clinical overview of irbesartan: a new angiotensin II receptor antagonist. Am J Hypertension 1997;10:318S-24S.
16. Scott LJ, McCormack PL. Olmesartan medoxomil: a review of its use in the management of hypertension. Drugs 2008;68:1239-72.
17. Battershill AJ, Scott LJ. Telmisartan: a review of its use in the management of hypertension. Drugs 2006;66:55-83.
18. Taylor AA, Siragy H, Nesbitt S. Angiotensin receptor blockers: pharmacology, efficacy, and safety. J Clin Hypertension 2011;13:677-86.
19. Izzo AC, Zion AS. Value of angiotensin receptor blocker therapy in diabetes. J Clin Hypertension 2011;13:290-5.
20. Chrysant SG. Angiotensin II receptor blocker in the treatment of cardiovascular disease continuum. Clin Therapeut 2008;30(part 2):2181-90.
21. Lithell H, Hansson L, Skoog I, et al. for the SCOPE study group. The study on cognition and prognosis in the elderly (SCOPE): principal results of a randomized double-blind intervention trial J Hypertension 2003;21:875-86.

22. Suzuki H, Kanno Y, for the Efficacy of Candesartan on Outcome in Saitama trial (E-COST) group. Effects of candesartan on cardiovascular outcomes in Japanese hypertensive patients. Hypertension Res 2005;28:307-14.
23. The Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial. Lancet 2008;372:1174-83.
24. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet 2002;359:995-1003.
25. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. Lancet 2004;363:2022-31.
26. Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial. J Hypertens 2006;24:2163-8.
27. Kjeidsen SE, Stalhammer J, Hasvold P, Bodegard J, Olsson U, Russell D. Effects of losartan vs candesartan in reducing cardiovascular events in primary treatment of hypertension. J Human Hypertens 2010;24:263-73.
28. Powers BJ, Crowley MJ, McCrory DC, et al. Future research needs for comparing angiotensin-converting enzyme inhibitors (ACEs), angiotensin receptor blockers (ARBs), and direct rennin inhibitors (DRIs) in the treatment of hypertension. (Prepared by the Duke Evidence-based Practice Center under contract No. 290-2008-10066-I). AHRQ Publication No. 12-EHC046-EF. Rockville, MD: Agency for Healthcare Research and Quality, March 2012.
29. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.
30. Siragy HM. Angiotension receptor blockers: how important is selectivity? Am J Hypertension 2002;15:1006-14.
31. Product information. Atacand (candesartan cilexetil oral tablets). Wilmington, DE: AstraZeneca LP, April 2012.
32. Product information. Avapro (irbesartan oral tablets). New York: Bristol-Myers Squibb/Sanofi-Synthelabo Partnership, September 2012.
33. Product Information. Benicar (olmesartan medoxomil oral tablets). New York: Sankyo Pharma, March 2012.
34. Product information. Cozaar (losartan potassium oral tablets). Whitehouse Station, NJ: Merck Sharp & Dohme Corp., November 2011.
35. Product information. Diovan (valsartan oral tablets). East Hanover, NJ: Novartis Pharmaceuticals Corp., October 2012.
36. Product information. Edarbi (azilsartan medoxomil oral tablets). Deerfield, IL: Takeda Pharmaceuticals America, Inc., July 2012.
37. Product information. Micardis (telmisartan oral tablets). Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc., September 2012.
38. Product information. Teveten (eprosartan mesylate oral tablets). Bridgewater, NJ: Biovail Pharmaceuticals, Inc., September 2012.
39. Dobrek L, Thor PJ. Future potential indications for pharmacotherapy using renin-angiotensin-aldosterone system inhibitory agents. Adv Clin Exp Med 2010;19:389-98.

EXTRACTO

Revisión del Uso de Bloqueadores del Receptor de Angiotensina Para la Prevención de Eventos Cardiovasculares en Pacientes con Hipertensión Esencial Sin Indicaciones Apremiantes

K Zaiken, TR Hudd, JWM Cheng

Ann Pharmacother 2013;47:686-93.

OBJETIVO: Analizar el rol de los bloqueadores del receptor de angiotensina para la prevención de eventos cardiovasculares en pacientes con hipertensión esencial sin indicaciones apremiantes.

EXTRACCIÓN DE DATOS: Estudios clínicos revisados por otros profesionales, artículos de revisión y guías de tratamientos relevantes fueron identificadas en MEDLINE y el banco de datos del Contenido Actual (desde 1966 hasta el 15 de noviembre del 2012) usando los términos: bloqueadores del receptor de angiotensina (ARBs), azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, hipertensión, infarto del miocardio, accidentes cerebro vasculares, y resultados cardiovasculares; limitado a estudios en humanos y publicados en inglés. Las citaciones de los artículos fueron revisadas como referencias adicionales.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Este artículo se enfocó en la discusión de estudios clínicos evaluando los puntos finales cardiovasculares de los ARBs en pacientes con hipertensión esencial sin indicaciones apremiantes.

RESUMEN DE DATOS: Los datos que apoyan el uso de los ARBs para reducir eventos cardiovasculares en pacientes con hipertensión esencial sin indicaciones apremiantes es inconsistente. Hasta la fecha, solamente cardesartan y losartan han demostrado tener una reducción significativa en la morbilidad cardiovascular. En el Estudio de Cognición y Pronóstico en Ancianos (SCOPE), candesartan demostró un 27.8% de reducción en accidentes cerebro vasculares no fatales contra placebo (95% CI, 1.3 a 47.2, p = 0.04). Por otra parte; losartan demostró una disminución en eventos cardiovasculares comparado con atenolol en el estudio de la Morbilidad y Mortalidad Cardiovascular con el Uso de Losartan para la Reducción de Hipertensión (Life) RR 0.87, (95% CI 0.77-0.98, p = 0.021).

CONCLUSIONES: Los datos que apoyan el uso de los ARBs para reducir eventos cardiovasculares en pacientes con hipertensión esencial sin indicaciones apremiantes es inconcluyente y limitada. Más estudios son necesarios para que los ARBs puedan ser recomendados como terapia de primera línea para el manejo de hipertensión esencial sin indicaciones apremiantes.

Traducido por Wilma M Guzmán-Santos

RÉSUMÉ

Revue de l'Utilisation des Antagonistes des Récepteurs de l'Angiotensine dans la Prévention des Evénements Cardiovasculaires chez les Patients atteints d'Hypertension Essentielle sans Autre Indication Etablie

K Zaiken, TR Hudd, JWM Cheng

Ann Pharmacother 2013;47:686-93.

OBJECTIFS: Faire le point sur le rôle des antagonistes des récepteurs de l'angiotensine (ARAII) dans la prévention des événements cardiovasculaires chez les patients atteints d'hypertension essentielle sans autre indication établie.

SOURCES DE DONNEES: Les essais cliniques publiés dans des revues à comité de lecture, les articles de synthèse, et les recommandations thérapeutiques appropriées ont été identifiés via MEDLINE et la base de données Current Contents (dans les 2 cas de 1966 au 15 novembre 2012), à l'aide des termes: antagonistes des récepteurs de l'angiotensine (ARAII), azilsartan, candésartan, éprosartan, irbésartan, losartan, olmésartan, telmisartan, valsartan, hypertension, infarctus du myocarde, AVC, insuffisance cardiaque, et effets cardiovasculaires, en se limitant aux essais chez l'homme publiés en anglais. Les références citées dans les articles retrouvés ont également été considérées.

SELECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Cet article porte sur la discussion des essais cliniques évaluant les effets cardiovasculaires des ARAII utilisés chez les patients atteints d'hypertension essentielle sans autre indication établie.

SYNTHÈSES DES DONNÉES: Chez les patients atteints d'hypertension essentielle sans autre indication établie, les données en faveur de l'utilisation des ARAII dans le but de réduire les événements cardiovasculaires ne sont pas concluantes. Jusqu'à présent, seuls le candésartan et le losartan ont montré une réduction significative de la morbidité cardiovasculaire au sein de ce sous-groupe mesurable de patients. Dans l'Étude Cognition et Pronostic chez la Personne Agée (SCOPE), le candésartan a montré une diminution de 27.8% des AVC

non mortels par rapport à un placebo (Intervalle de Confiance 95%: 1.3 à 47.2; p = 0.04). Et le losartan a montré une diminution de l'ensemble des événements cardiovasculaires par comparaison à l'aténolol dans l'étude LIFE de Morbidité et Mortalité Cardiovasculaire dans l'Hypertension: RR 0.87 (Intervalle de Confiance 95%: 0.77-0.98; p = 0.021).

CONCLUSIONS: Les données en faveur de l'utilisation des ARAII, dans le but de diminuer les événements cardiovasculaires chez les patients atteints d'hypertension essentielle sans autre indication établie, sont à la fois limitées et non concluantes. D'autres études sont nécessaires avant de pouvoir recommander en routine les ARAII en tant que traitement de première ligne de l'hypertension chez les patients sans autre indication établie.

Traduit par Michel Le Duff