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How does Angiotensin II Receptor Blocker (ARB) Therapy Compare to Angiotensin Converting Enzyme (ACE) Inhibitor Therapy in Prevention of Long-Term Complications in Idiopathic Hypertension?

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How does Angiotensin II Receptor Blocker (ARB) Therapy Compare to Angiotensin Converting Enzyme (ACE) Inhibitor Therapy in Prevention of Long-Term Complications in Idiopathic Hypertension?

By

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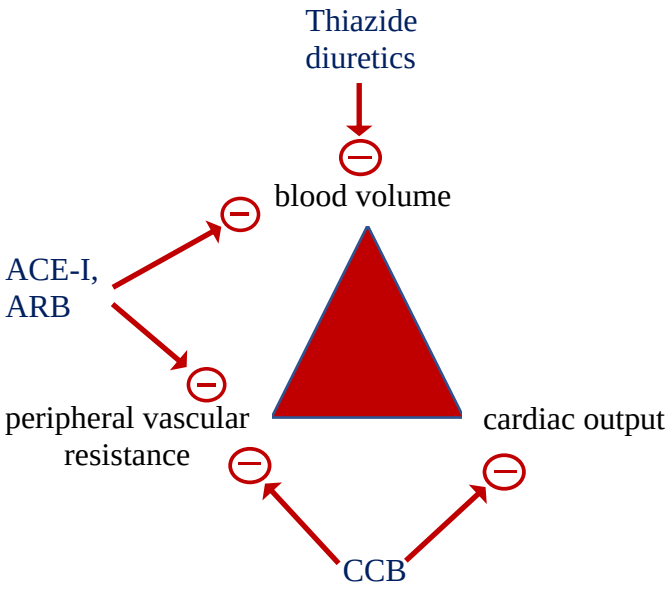
Introduction

Approximately one third or 75 million adults in the US have idiopathic hypertension,[1] also known as essential hypertension (HTN). Hypertension, a common cause of kidney disease, is also a known cause of heart disease and stroke, both of which are leading causes of death in the United States.[2] Therefore, controlling hypertension is vital for prevention of complications, which can make it challenging to treat due to patient compliance issues. Nonetheless, long-term control of blood pressure decreases adverse cardiovascular, cerebrovascular and renal outcomes. According to the American College of Cardiology (ACC) and the American Heart Association (AHA) define stages of hypertension, Stage 1 (systolic: 130-139 mm Hg or diastolic: 80-89 mm Hg) and Stage 2 (systolic ≥140 mm Hg or diastolic ≥90 mm Hg) as shown in **Table 1**.[3] The JNC 8 treatment guidelines recommend a target blood pressure of less than 130/80mmHg. Beyond lifestyle management, many medications are available to treat hypertension and, thus, lower the risk of long-term complications. First line therapy for essential hypertension includes four classes of drugs: calcium channel blockers (CCBs), thiazide diuretics, angiotensin converting enzyme inhibitors and angiotensin type 2 receptor blockers,[4] see **figure 1** for mechanisms of action.[5] Two well-known and widely used treatment options are Angiotensin Converting Enzyme Inhibitors, or ACE inhibitors, and Angiotensin II Receptor Blockers, also known as ARBs. Historically, these medications have been used interchangeably, often initiating therapy with an ACE inhibitor and switching to an ARB if the patient does not tolerate the ACE inhibitor. As most providers know, ACE inhibitors are associated with increased risk of cough and angioedema when compared to ARBs.[6,7] When compared to ACE inhibitors, ARBs are more selective and potentially exert more complete blockade of angiotensin II. This is due to blockade

of other enzymes apart from ACE which produce angiotensin and their lack of effect on bradykinin, unlike ACE-inhibitors.[5]

However, many studies have confirmed that both exert equivocal control on blood pressure.[6,8,9] Currently, another factor that affects choice of prescription is the higher cost associated with ARBs compared to ACE inhibitors. Nonetheless, cost is becoming less of an issue due to generic availability of most medications in each class. If cost is no longer a barrier, then determining whether an ACEI or an ARB is superior in preventing long-term complications will change clinical practice.

Figure 1: First Line Treatments for Essential Hypertension and their effects on Basic Components of Blood Pressure



Calcium Channel Blockers (CCB): inhibits Ca^{2+} into the arterial smooth muscle resulting in peripheral vasodilation and decreased cardiac contractility
Thiazide Diuretics: Inhibits Na^+/Cl^- transporter in the distal convoluted tubule resulting in increased Na^+ and H_2O excretion
Angiotensin Converting Enzyme Inhibitors (ACE-I): prevent conversion of angiotensin I to angiotensin II resulting in peripheral vasodilation and inhibition of aldosterone secretion
Angiotensin Type 2 Receptor Blockers (ARB): block angiotensin II resulting in peripheral vasodilation and inhibition of aldosterone secretion

This review examines the relevant question: in adult patients with idiopathic hypertension how does Angiotensin II Receptor Blocker therapy compare to Angiotensin Converting Enzyme Inhibitor therapy for prevention of adverse cardiovascular, renal or cerebrovascular outcomes?

Table 1: AHA/ ACC HTN classification, adapted from American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines DETAILED SUMMARY FROM THE 2017 Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults[3]

BP Class	Systolic (mmHg)		Diastolic (mmHg)
Normal	<120	**And**	<80
Elevated	120-129	**And**	<80
Stage 1 HTN	130-139	**Or**	80-89
Stage 2 HTN	>140	**Or**	>90

Discussion

Medical evidence to date confirms that ACE inhibitors and ARBs provide equivalent blood pressure control[6,8,9]. However, for prevention of specific outcomes, the data show stronger support for ACE inhibitors than ARBs, and vice-versa. Nonetheless, there is no clear answer as to whether one of these drugs has overall superiority for prevention of long-term complications of hypertension.

Data in Favor of ACE inhibitors

ACE inhibitors are superior to ARBs for reducing morbidity and mortality from myocardial infarction when treating hypertension in type 2 diabetics and other high-risk populations, as was shown in a meta-analysis of placebo-controlled trials published in 2018[10].

This article discusses the ARB-MI paradox, which refers to the risk reduction of myocardial infarction (MI) and mortality seen with ACE inhibitors, not with ARBs[10]. The data are compelling because of the recency of the publication, the large sample size (n=128,680) and the convincing findings. However, the population was limited to patients with comorbidities or patients at high risk for cardiovascular events, and thus, does not directly answer whether ACE inhibitors are better in patients with hypertension without significant comorbid conditions. Additional research found secondary prevention/ risk reduction with ACE inhibitors for non-fatal MI, CV mortality and all-cause mortality.[11,7] In a meta-analysis of RCTs, Hoang et al analyzed the efficacy of ACE inhibitors versus ARBs for CV event reduction in patients with CAD without heart failure in the context of statin therapy. These findings support the hypothesis of ACE inhibitor's superiority in prevention of adverse cardiovascular events. The sample size was large (n=78,761) and the research is up-to-date, however, the article did not provide data on the dose or potency of concurrent statin therapy. Hence, it is difficult to extrapolate whether the cardiovascular risk reduction was secondary to statin therapy, ACE inhibitor therapy, a combination of the two or other components of coronary artery disease treatment. In 2018, Messerli et al conducted a literature review comparing outcomes and adverse events between ACE inhibitors and ARBs in patients with hypertension. Their review yielded equivalent outcomes for both groups except in patients with comorbid coronary artery disease, in which ACE inhibitors, once again, were found to be superior.

For adverse cerebrovascular outcomes, such as stroke (cerebrovascular accident or CVA), similar risk reductions were found by Hoang et al when hypertension was treated in patients with coronary artery disease but without heart failure[11]. This meta-analysis provides intriguing evidence. The sample was very inclusive; subjects included patients with a combination of

coronary artery disease risk factors (hypertension, dyslipidemia, diabetes or previous atheromatous conditions). Although the findings from this meta-analysis may not be exclusive to patients with isolated idiopathic hypertension, they may be even more compelling, given the variety of conditions treated and the lack of difference between ACE inhibitors and ARBs for cerebrovascular outcomes. However, as stated above, it is difficult to isolate Renin-Angiotensin-Aldosterone System (RAAS) blockade as the cause of cerebrovascular risk reduction due to the concurrent statin therapy.

Data in favor of ARBs

Although, ACE inhibitors and ARBs have been shown to have equivalent blood pressure control, azilsartan medoxomil had superior blood pressure reduction and lower discontinuation rates when compared to ramipril. This investigation was one of the few current randomized, controlled, double-blind trials comparing an ACE inhibitor and an ARB head-to-head[8]. Furthermore, the data was gathered from a large sample size (n=784) from patients at different sites throughout Europe and Asia. However, the sample only included patients with a recorded clinic systolic blood pressures of 150-180mm Hg.

Although, multiple sources have shown superior stroke risk reduction with ACE inhibitors, the 2016 retrospective cohort study on patients with hypertension and diabetes in Taiwan showed that ARBs provide a 35% higher reduction in ischemic stroke than ACE inhibitors, ACE inhibitors combined with ARBs, or neither[12]. Although these data were not derived from a randomized controlled trial, their significance still warrants further evaluation. The investigation extracted data from Taiwan's health insurance claims on all patients 18 years and older diagnosed with hypertension from 1997 to 2010. Limitations of this study included the distinct population studied, which may have had lifestyles, exposures, or genetic risk factors for

CVA that are different from other populations. The data also lacked measurement of medication non-compliance. Strengths of this article include its large sample size and the lengthy time period from which the data were collected, which distinguishes it from much of the literature available for analysis. It is also important to note that the data excluded patients who had pre-existing cardiovascular disease or arrhythmias.

Overall, according to the Cochrane (systematic) Review published in 2014, ARBs are non-inferior, based on moderate-quality evidence, to ACE inhibitors for total mortality in the treatment of essential hypertension[13]. This review questioned whether ACE inhibitors were superior to ARBs for preventing mortality, cardiovascular events and withdrawal due to adverse events. The sample included 11,007 subjects with uncontrolled or controlled essential hypertension with or without risk factors.

Conclusion

According to the evidence in current medical literature, prevention of adverse cardiovascular, renal and cerebrovascular events in patients with idiopathic hypertension appears to depend on the patient's comorbid conditions. Data suggests ACE inhibitors are superior for prevention of adverse cardiovascular events, particularly non-fatal myocardial infarction, cardiovascular mortality and all-cause mortality, in high risk populations such as patients with type 2 diabetes or coronary artery disease without heart failure[7,10,11]. The evidence is conflicting on the topic of cerebrovascular risk reduction. Both ACE-inhibitors and ARBs reduced the risk of stroke in pts with HTN and CAD[11]. However, one article reflects superiority of ARBs to ACE inhibitors[12]. The data as a whole is lacking assessments for the prevention of adverse renal events; this potential adverse outcome is an important area for data collection given that hypertension is one of the main causes of chronic kidney disease. Direct head-to-head

comparison of ACE inhibitors to ARBs in patients with isolated idiopathic hypertension are lacking as well, which Strauss pointed out[10]. There are several barriers to further research on this topic. For example, research comparing drug classes as a whole are unlikely to be funded by pharmaceutical industries because these drugs are already available in generic formulations. Moreover, research in academia may be constrained by limited funds. For better analysis of long-term risk reduction in treatment of hypertension a randomized-controlled trial must be conducted to accurately compare ACE inhibitors to ARBs, possibly with placebo control if ethically approved.

References:

1. Merai R, Siegel C, Rakotz M, et al. CDC Grand Rounds : A Public Health Approach to Detect and Control Hypertension. 2016;65(45):1261-1264.

2. Lackland D. *Heart Disease and Stroke Statistics — 2017 Update A Report From the American Heart Association*.; 2017. doi:10.1161/CIR.0000000000000485.

3. DETAILED SUMMARY FROM THE 2017 Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults. *Am Coll Cardiol Am Hear Assoc Task Force Clin Pract Guidel*. 2017.

4. Carey MD RM, Whelton MB MD MSc PK. Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Synopsis of the 2017 American College of Cardiology/American Heart Association Hypertension Guideline. *Ann Intern Med*. 2018;168(5):351-358.

5. Benowitz NL. Antihypertensive Agents. In: Katzung BG, ed. *Basic & Clinical Pharmacology*. 14th ed. New York, NY: McGraw-Hill; 2017. http://accessmedicine.mhmedical.com/content.aspx?aid=1148434002.

6. AHRQ. *Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension – An Update*.; 2010.

7. Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-Converting Enzyme Inhibitors in Hypertension: To Use or Not to Use? *J Am Coll Cardiol*. 2018;71(13):1474-1482. doi:10.1016/j.jacc.2018.01.058.

8. Bönner G, Bakris GL, Sica D, et al. Antihypertensive efficacy of the angiotensin receptor blocker azilsartan medoxomil compared with the angiotensin-converting enzyme inhibitor ramipril. *J Hum Hypertens*. 2013;27(8):479-486. doi:10.1038/jhh.2013.6.

9. Matchar DB, Mccrory DC, Orlando LA, Patel MR, Patel UD. Review Annals of Internal Medicine Systematic Review : Comparative Effectiveness of Angiotensin- Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers for Treating Essential Hypertension. *Ann Intern Med*. 2007;(6).

10. Strauss MH, Hall AS. The Divergent Cardiovascular Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Type 1 Receptor Blockers in Adult Patients With Type 2 Diabetes Mellitus. *Can J Diabetes*. 2018;42(2):124-129. doi:10.1016/j.jcjd.2017.09.011.

11. Hoang V, Alam M, Addison D, Macedo F, Virani S, Birnbaum Y. Efficacy of Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blockers in Coronary Artery Disease without Heart Failure in the Modern Statin Era: a Meta-Analysis

of Randomized-Controlled Trials. *Cardiovasc Drugs Ther*. 2016;30(2):189-198. doi:10.1007/s10557-016-6652-7.

12. Pai PY, Muo CH, Sung FC, Ho HC, Lee YT. Angiotensin receptor blockers (ARB) outperform angiotensin-converting enzyme (ACE) inhibitors on ischemic stroke prevention in patients with hypertension and diabetes - A real-world population study in Taiwan. *Int J Cardiol*. 2016;215:114-119. doi:10.1016/j.ijcard.2016.04.096.

13. Eck L, Bs H, Jm W. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension (Review). *Cochrane Lib*. 2014;(8). doi:10.1002/14651858.CD009096.pub2.www.cochranelibrary.com.