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Superiority of Angiotensin II Receptor Blockers over Angiotensin Converting Enzyme Inhibitors in Stroke Prophylaxis

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Abstract

Angiotensin II receptor blockers provide better protection against stroke than Angiotensin converting enzyme inhibitors among the elderly population suffering from systolic hypertension. This research paper examines a series of published studies examining the superiority of angiotensin receptor blockers in stroke prophylaxis.

The study designs identified during the research include clinical studies and systematic reviews. An evidence table was made to analyze the researched data. A thorough analysis was performed of the angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, and their mechanism of action as well as their pathophysiological effects.

The results of the clinical trials demonstrated that angiotensin II receptor blockers indeed reduce stroke incidence in hypertensive patients. Angiotensin converting enzyme inhibitors were found to have no effect on stroke incidence, while two studies showed that they increased the incidence of stroke in hypertensives compared to a conventional anti-hypertensive therapy.

After a head-to-head comparison of the two-drug regimen, with substantial clinical and experimental evidence supporting the research hypothesis, it can be concluded that angiotensin II receptor blockers are indeed a superior choice in stroke prophylaxis in the elderly population suffering from isolated systolic hypertension.

Keywords: *Isolated systolic hypertension; Elderly; Angiotensin II receptor blockers; Angiotensin converting enzyme inhibitors; Stroke*

Introduction

Hypertension is a widespread problem among North Americans; it is defined as a systolic blood pressure of 140 mmHg or greater, or a diastolic blood pressure of 90 mmHg or greater. According to Centers for Disease Control and Prevention (CDC), 1 in 3 American adults or nearly 70 million adults suffer from hypertension, and only about 52% of these people have their high blood pressures under control. Known as the “silent killer”, hypertension does not present with any obvious symptoms or warning signs [1].

The prevalence of hypertension increases significantly with age. In the Framingham Heart study, approximately 90% of the participants who had a healthy blood pressure at the age of 55 eventually developed hypertension. Before the age of 55, most adults suffering from hypertension have elevated diastolic pressures; however diastolic pressures begin to fall while systolic pressures rise over the age of 55, eventually developing isolated systolic hypertension. With increasing age, there is a deposition of collagen and calcium that is seen within the arteries, accompanied by atherosclerosis which causes the arteries to stiffen leading to a decline in arterial compliance. Elastin, present within these arterial

layers, is also degraded causing a decline in arterial elasticity contributing to hypertension. Any pre-existing condition that increases cardiac output such as hyperthyroidism, can also lead to isolated systolic hypertension [2].

Hypertension increases the risk of stroke. Chronic hypertension causes vascular remodelling of the brain, retina, and kidney, with the brain being the early target for damage; this is a risk factor for both ischemic and haemorrhagic strokes [3,4]. According to the CDC, stroke is the fifth leading cause of death among Americans, and it is a major cause of disability in adults; antihypertensive therapy helps reduce this risk. Antihypertensive pharmacotherapy includes a wide variety of drugs including diuretics, Angiotensin converting enzyme (ACE) inhibitors, Angiotensin II receptor blockers (ARBs), and dihydropyridine calcium channel blockers. Of the existing pharmacotherapy used by the elderly in targeting isolated systolic hypertension, ARBs and ACE inhibitors are the most effective and more popularly used.

Angiotensin II receptor blockers selectively bind and inhibit AT1 receptors, lowering blood pressure, both diastolic and/or systolic pressures. Blocking the AT1 receptors upregulates the AT2 receptor expression (especially in endothelial cells), and the free angiotensin II binds to the unoccupied AT2 receptors providing additional benefits in cardiovascular remodelling, and stroke prevention. ACE inhibitors on the other hand inhibit the conversion of angiotensinogen to angiotensin I by blocking the activity of the ACE enzyme, therefore angiotensin II is not produced at all.

Angiotensin II has proven to have a cerebroprotective effect through studies performed throughout history. It was first proposed in the Medical Research Council (MRC) Study in 1986, and further studied since [3]. Angiotensin II is a peptide hormone responsible for peripheral vasoconstriction increasing blood pressure, stimulating aldosterone secretion, sodium and water retention, cardiac contractility, and stimulation of the sympathetic nervous system. Several experimental studies using animals have been done in the past few decades that support the cerebroprotective actions of angiotensin II. Fernandez et al. [5] used rats to demonstrate the role of angiotensin II against transient ischemia and limb paralysis. The aorta was ligated between the two kidneys leaving the left kidney ischemic. Once the left ischemic kidney in these rats was surgically removed, and left for 24 hours, exogenous angiotensin II was injected. The angiotensin II increased blood flow, restoring the blood to the ischemic limb. In another later study using gerbils, Fernandez et al. [6] demonstrated the role angiotensin II plays in a unilateral carotid occlusive event. Once these gerbils experienced cerebral ischemia, they were infused with doses of angiotensin II while the control group of gerbils was injected with either equipressor doses of metaraminol or normal saline. The angiotensin II decreased mortality post cerebral ischemia in the treatment group of gerbils. In another experimental study, the gerbils were pre-treated with losartan or a selective AT2 agonist PD-123319 and demonstrated a reduced mortality with cerebral ischemia. However, the control group of gerbils which was pretreated with the ACE inhibitor enalapril or normal saline did not demonstrate any reduction in mortality in a cerebral ischemic event. When these gerbils were pre-treated with enalapril before being given losartan, losartan had no effect and there was no decrease seen in mortality. Other animal studies using rats have been used to demonstrate the anti-adhesive properties of the ARB Losartan. The rats treated with Losartan demonstrated a reduced adhesive activity of the platelets to the endothelial surfaces [3]. The anti-adhesive ability of Losartan prevents the formation of thrombi reducing the risk of stroke.

Several experimental evidence using animal studies strongly suggests that angiotensin II plays an important role in stroke prevention. For this reason, ARBs provide better protection against stroke then ACE inhibitors, and this paper further examines the two approaches and discusses the superiority of ARBs in stroke prophylaxis using clinical trials.

Methods

A retrospective study design was adapted to produce this paper. The databases used to conduct the research included ProQuest, Medline, and PubMed. Most of the articles obtained were published between 2005 to the current date. These articles include randomized clinical trials testing ARBs, as well as ARBs against ACE inhibitors, and other antihypertensive therapy placebos. Centers for Disease Control and Prevention (CDC) was referred for the most recent statistics.

The main data search terms were systolic hypertension, stroke, elderly, ARBs, ACE Inhibitors, antihypertensive drug therapy, cerebrovascular events.
All studies included were relatively recent between the last 10 to 11 years and any studies done before 2005 were excluded; this does not include the animal studies mentioned in the introduction. All clinical trials included were testing ARBs and/or ACE inhibitors and stroke incidence, ARBS compared to ACE inhibitors. Combinations of ACE inhibitors or ARBs with diuretics, calcium channel blockers and/or beta blockers were also included. However, clinical trials testing diuretics, beta blockers or calcium channel blockers alone were excluded.
Throughout the research, study designs identified included clinical studies and systematic reviews. The quality of the study was evaluated and maintained by using only peer reviewed and published journals. These journals were considered and checked to see if there are any potential risks to the validity and to see if any other explanations can be attributable to the outcomes obtained.
Data was analyzed by forming an evidence table that emphasized the key findings of the articles found through the research. This table was used to compare the stroke incidence in ARBs treated groups with the ACE inhibitor treated groups. Diuretics or beta blockers in combination with these drug therapies and its effect on stroke incidence was also assessed.

Results

This section will briefly state the results from the research conducted. Summary of study designs reviewed (Table 1). The drugs discussed in this section are listed in Table 2 in the Appendix.

Table 1: Summary of study designs reviewed.

Study design	Number of studies
Clinical trials	4
Systematic Reviews	2

Table 2: Drugs discussed in the results.

Name of Drug	Class of Drug
Omalsartan, Candesartan, Losartan, Eprosartan	ARBs
Ramipril, Enalapril, Perindopril, Lisinopril	ACE inhibitors
Nitrendipine	Calcium Channel Blockers
Hydrochlorothiazide, Indapamide, Chlothalidone	Diuretics
Atenolol	Beta Blockers

A side-by-side comparison was done with angiotensin II receptor blockers and ACE inhibitors. Two studies were used which followed the same protocol design: two weeks of placebo washout period, followed by 12 weeks of double-blind treatment with the ARB omalsartan or the ACE inhibitor Ramipril. The ESPORT study included 102 centres in Italy and a parallel multinational study used 31 centres across Europe. Both studies confirmed a greater blood pressure reduction (both systolic and diastolic pressures) with omalsartan, providing a more sustained control of the blood pressure within a 24-hour period. Omalsartan also provided a larger decrease in blood pressure within the last 6 hours of the 24-hour period. People suffering from metabolic syndrome were at a greater risk of cardiovascular complications. Pooled data from the two studies also showed that omalsartan provided a significant reduction in blood pressure in those patients suffering from metabolic syndrome compared to the ACE inhibitor Ramipril [7,8].
A Study on Cognition and Prognosis in the Elderly (SCOPE) trial demonstrates the relationship of ARBs and stroke. This was a double-blinded clinical trial with 4,964 patients between ages 70 and 89 years old that were randomly assigned to Candesartan (ARB) treatment group or an antihypertensive placebo therapy group. Of these 4,964 patients, 1,518 had isolated systolic hypertension, and a subgroup analysis was done to determine the outcomes in ISH patients. A total of 20 strokes occurred in the candesartan treated subgroup, while 35 strokes in the control group. The relative risk was 0.58 with a confidence interval of 95% with 0.33 to 1.00. The relative risk reduction was 42% with an adjusted p-vale of 0.049 [7]. There was little difference in blood pressure reduction between

the two groups. This finding was also supported by the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) pilot study which demonstrated a 52% reduction in stroke and mortality in hypertensive patients who have suffered a previous stroke compared to a placebo treatment [3].

A meta-analysis of previously done studies was examined, regarding stroke prevention in hypertensive elderly. The following table was taken from Current Hypertension Reports by Springer Science, written by Aronow W. This table is a compilation of studies conducted in the past that are supportive to the discussion of this paper [9].

To gather more details on a few of the trials mentioned in the table above, the meta-analysis done by Pedelty, et al. was examined. The Swedish Trial investigated the efficacy of conventional treatment of Beta-Blockers versus the newer drugs such as ACE inhibitors and Calcium channel blockers. A subsequent analysis in a subgroup of 2,280 Swedish patients suffering from isolated systolic hypertension was conducted to determine the relationship of conventional versus newer drugs therapy on stroke. There was no significant difference in blood pressure reduction in the treatment groups, however a 25% reduction in stroke was found in the patients receiving the newer drug therapy. The Systolic Hypertension in Europe trial also used 4,695 patients aged ≥60 years with isolated systolic hypertension; however, this trial examined the efficacy of a further adjusted regimen consisting of nitrendipine (a calcium channel blocker) with enalapril (an ACE inhibitor) with or without hydrochrlothiazide (a diuretic). There was a 42% reduction in all strokes and a 44% reduction in nonfatal strokes compared to the placebo group.

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study compared the efficacy of losartan (ARB) based treatment with atenolol (beta blocker)-based treatment in 9,193 patients between the ages 55 to 80 years old with hypertension and left ventricular hypertrophy. The ARB-treated group had a decreased cardiovascular mortality with a 25% reduction in fatal and nonfatal strokes. Further analysis of a subgroup of these patients suffering from isolated systolic hypertension demonstrated a greater reduction in the relative risk for stroke of approximately 0.60 with a 95% confidence interval of 0.38 to 0.92 and a p-value of 0.02 [10]. Another sub-study involved 8851 of the patients who did not have any baseline atrial fibrillation. During a 1 year follow up, 150 of the 4298 patients in the losartan treatment group developed atrial fibrillation, while 221 of the 4182 patients in the atenolol treated group developed atrial fibrillation, which was statistically significant. A sub-study also demonstrated that baseline uric acid levels were associated with cardiovascular complications and stroke, especially in the female study population. Losartan is the only ARB that has the ability to reduce uric acid levels and the incidence of stroke in hypertensive patients [3].

Data published in the Morbidity and Mortality after Stroke; Eprosartan Study (MOSES) provides additional evidence that ARBs are superior in prevention of stroke. A trial conducted on high-risk patients including elderly with hypertension and post-stroke patients over a 24 month period compared eprosartan (an ARB) and nitrendipine (calcium channel blocker). Eprosartan demonstrated a decreased recurrence of stroke by 25% compared to nitrendipine [9].

The actions of ACE inhibitors were compared to diuretics. In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), the ACE inhibitor perindopril was given to hypertensive patients who have suffered a stroke and this intervention showed merely a 5% stroke reduction for a 5 mmHg decrease in systolic blood pressure, while adding a diuretic (indapamide) to the ACE inhibitor resulted in a 43% reduction in stroke with a 7 mmHG decrease in systolic blood pressure. In another study, the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) study, the ACE inhibitor lisinopril increased the incidence of stroke by 15% in hypertensive patients compared to the diuretic chlorthalidone treatment group which did not show any increase in stroke incidence. Augmenting the results found by the ALLHAT study, another experimental study called the Captopril Prevention Project (CAPP) done with hypertensive patients further shows that the group treated with ACE inhibitor captopril had a 43% higher incidence of stroke then the control group that was treated using conventional hypertensive therapy.

According to the study done by Heart Outcomes Prevention Evaluation (HOPE) in normotensive patients with pre-existing coronary artery disease, peripheral vascular disease, and/or diabetes, ACE inhibitors proved to be beneficial in stroke prevention. The treatment group was given the ACE inhibitor Ramipril in high doses (10mg/day) compared to the placebo-controlled group, and the results showed a 32% reduction in stroke incidence [3].

Discussion

Angiotensin II Receptor Blockers (ARBs) and Angiotensin Converting Enzyme (ACE) inhibitors are

the most widely used pharmacotherapy to treat isolated systolic hypertension as well as hypertension in general. To understand these drugs, it is necessary to understand the production and role of angiotensin II in the human body. Angiotensin II production is regulated by the Renin-Angiotensin System (RAAS). The RAAS is depicted in the diagram below:

Angiotensinogen→Angiotensin I →Angiotensin II

The conversion of angiotensinogen to angiotensin I is regulated by renin, while Angiotensin I is converted to angiotensin II by the angiotensin converting enzyme (ACE).

Angiotensin II binds to two types of receptors: Type 1 (AT1) and Type 2 (AT2) receptors; these two receptors have opposing effects. AT1 receptors are found in adult tissues of the heart, kidney, lungs, brain and blood vessels, and their function is to cause vasoconstriction, resulting in an increased blood pressure, catecholamine release and cardiac contractility. The AT2 receptors are expressed majorly in foetal tissue, however their expression and role is limited in adult tissue. During an ischemic or stressful event, or in damaged tissues, the expression of AT2 receptors is upregulated. Stimulation of AT2 receptors improves overall endothelial function, resulting in vasodilation through nitric oxide and prostacyclin production modulating the actions of AT1, decrease inflammation, modulate neuronal apoptosis and facilitate collateral circulations serving an important role in neuroprotection and regeneration. Angiotensin II also constricts the proximal cerebral arteries, preventing rupture of any Charcot-Bouchard microaneurysms and developing any cerebral haemorrhage [3]. ARBs have a dual effect by inhibiting AT1 and indirectly stimulating AT2 via angiotensin II which is the cause of its superiority over ACE inhibitors in preventing stroke.

ACE inhibitors do not have any protective effect against stroke due to the inhibition of angiotensin II production causing a blunted AT1 response. ACE inhibitors when paired with calcium channel blockers, can have a prophylactic effect against stroke. Calcium channel blockers inhibit voltage-gated L-type calcium channels on cardiac and smooth muscle, decreasing muscle contractility. As mentioned in the Results, the Swedish Trial and the Systolic Hypertension Trial support the beneficial effect of using calcium channel blockers. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) also supported this finding that ACE inhibitors alone do not provide any sufficient reduction in stroke incidence, but when combined with a diuretic, there is a significant reduction in stroke. However, the exact mechanism involved in stroke prevention with these drug regimens is unknown but both calcium channel blockers (dihydropyridines more specifically) and diuretics stimulate angiotensin II formation.

ACE inhibitors when used alone can increase the risk of stroke in some hypertensive individuals. As discussed in the paragraph above, this class of drugs do not produce angiotensin II and thus do not have any cerebroprotective effect, but studies have shown that if given alone, they can promote cerebrovascular events. The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) study and the Captopril Prevention Project (CAPP) both reported significant increases in stroke incidence in those groups being treated with an ACE inhibitor. This suggests that ACE inhibitors may actually work to promote strokes in some people; however, there is no substantial information or evidence available on the mechanism by which this can occur.

There was an interesting finding about ACE inhibitors used in patients who do not suffer from isolated systolic hypertension or any other form of hypertension. According to the HOPE Study discussed in the Results, ACE inhibitors can have a prophylactic effect against cerebrovascular events if used by a healthy individual. The mechanism by which ACE inhibitors cause such an effect in a normotensive individual is unknown, however if given in high doses to normotensive patients, ACE inhibitors can in fact have a protective effect against stroke.

Angiotensin II receptor blockers are the only drug type that upregulate AT2 receptors directing all the produced angiotensin II to exclusively act on these receptors. Angiotensin II increases blood flow and restores blood to ischemic tissues by stimulating the development of collateral circulation via stimulation of AT2 receptors and development of collateral circulation [3]. For this mechanism alone, ARBs have superiority over ACE inhibitors and other diuretics against stroke. A large number of clinical trials mentioned in the Results section above, as well as the Evidence table depicted in the appendix, support this

finding. ARBs are not only prophylactic in stroke patients but also in post-stroke patients. Candesartan-based regimen in the SCOPE Trial has shown to reduce stroke incidence in the elderly population suffering from isolated systolic hypertension as well as providing secondary protection in those patients who have previously suffered from stroke. This is evidently supported by the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) pilot study.

Unlike the calcium channel blocker and ACE inhibitor combined drug regimen, the dihydropydridine calcium channel blockers alone do not provide any substantial protection against stroke when compared to ARBs. The Morbidity and Mortality after Stroke, Eprosartan Study (MOSES) demonstrated this finding by comparing eprosartan treatment group with nitrendipine treated group of post-stroke hypertensive patients. Even though the dihydropyridines stimulate angiotensin production, their effect is far less compared to that of ARBs and their AT2 response.

Not all cerebroprotective effects of angiotensin II receptor blockers are attributable to angiotensin II. ARBs aid in glucose metabolism, preventing the development of diabetes mellitus similarly to ACE inhibitors. This antidiabetic prophylaxis effect is very important because diabetes mellitus increases the risk of stroke significantly in hypertensives. Recent studies suggest that angiotensin II interferes with the signalling of insulin, preventing or slowing glucose metabolism. Thus, the inhibitory effect of ARBs on the actions of angiotensin II favors glucose metabolism.

Increased platelet aggregation and high serum uric acid levels have been associated with increased cerebrovascular events. When platelets are activated, they release ADP, thromboxane A2 (TXA2) and P-selectin, which initiate platelet aggregation. Of the existing ARBs, Losartan has antiplatelet aggregating effects. Losartan interacts with the receptor TXA2/PGH2 on the platelets inhibiting aggregation. Platelet adhesion is also inhibited by losartan through its actions against P-selectins; Losartan decreases P-selectin expression. Hyperuricemia is also a risk factor for cardiovascular events, stroke, and hypertension. Hypertensive patients who also have high serum uric acid levels are at a significant risk of stroke in comparison to those hypertensive patients with normal serum uric acid levels. Hyperuricemia triggers an increased inflammatory response with oxidative stress, resulting in endothelial dysfunction with platelet adhesion and aggregation. These pathological changes eventually lead to cardiovascular and cerebrovascular events. Losartan is the only ARB that has the ability to reduce uric acid levels and the incidence of stroke in hypertensive patients; these results were also consistent with the LIFE Study.

The risk of developing a stroke from atrial fibrillation increases with advancing age. ARBs have atrial anti-fibrillatory effects, and this has been studied in a subsequent analysis of the LIFE study discussed in the Results. The decreased incidence of new onset atrial fibrillation in the losartan treatment group is attributable to the remodelling of the atria by the ARB [3]. Therefore, independent of angiotensin II effects, ARBs also have the ability to structurally remodel the atrial tissue to serve cardiovascular benefits, preventing any future cerebrovascular events that can result due to ischemic complications as a result of atrial fibrillation.

Evidently, cardiovascular problems can lead to cerebrovascular events. Atrial fibrillation is associated with a cardioembolic stroke, which has higher mortality than atherosclerotic infarcts in the brain; the presence of other comorbidities such as isolated systolic hypertension increases the incidence and severity of such event. Age also plays a huge role in the severity of a cerebrovascular event although it is true that stroke can occur at any age. Older patients have more severe stroke deficits then the younger patients, and their recovery is much slower. This has been studied with aged animal models; in aged animals with Middle Cerebral Artery Occlusion (MCAO), the volume of cerebral infarction was far greater compared to younger animals and they had a higher mortality rate. The older animals showed poorer performances on functional tests compared to the younger animals; the younger animals also showed improvement in their neurological deficits within 24 hours of the MCAO. These animal model studies closely resemble the response of the elderly population upon suffering from a stroke.

The brain is constantly changing as age increases. Human post-mortem studies have proven that the weight of the brain decreases by 0.1% every year between the ages 20 and 60 years, and most of this loss occurs in the cerebral cortex and hippocampus. The leptomeninges thicken and the choroid plexus located

in the lateral ventricles also increases in size. The white matter undergoes moderate to severe change between the ages 65 to 84 years, and process is termed leukoaraiosi. Leukoaraiosis is most commonly seen in the frontal ventricular lobe and is responsible for the cognitive dysfunction seen with increasing age. The cause of leukoaraiosis is said to be the age-related changes seen in the microvasculature of the brain, and the degree of leukoaraoisis corresponds to the recurrence of stroke. The gradual process of aging also affects the cerebral vessels, decreasing the blood reserve of the brain and predisposing it to vascular insufficiency and ischemic injury [10]. These vascular changes increase morbidity and mortality of the aging population, especially following an ischemic stroke or vascular cognitive impairment following a transient ischemic attack. Thus, the process of aging itself increases the vulnerability of our aging population to any sort of cerebrovascular event and it is necessary to take precautionary measurements to prevent such events.

Large artery stiffness is a strong predictor of pulse pressure and in turn, systolic blood pressure. When arterial stiffness increases, there is greater interference with the aortic blood flow causing the velocity of the pulse wave to increase; this results in an increased systolic pressure. The systolic component of blood pressure has a greater impact on the development of cerebrovascular disease; the Multiple Risk Factor Intervention Trial (MRFIT) reported that increased systolic pressures were found to have a stronger deleterious effect on stroke [10]. As a result, controlling isolated systolic hypertension is necessary to reduce the vascular risk factors that predispose the aging population to cerebrovascular disease and stroke.

Conclusion

As the aging population increases, hypertension and more specifically, isolated systolic hypertension (ISH) have become a widespread concern among the elderly. A rising and alarming complication of chronic ISH and essential hypertension is stroke. Stroke is one of the major causes of death and disability among the elderly worldwide. The incidence of stroke is directly related to blood pressure and age, and effective blood pressure control is the key to stroke prevention. Antihypertensive therapies that stimulate angiotensin II production such as angiotensin II receptor blockers, diuretics, and calcium channel blockers provide an additional benefit to stroke prophylaxis, compared to ACE inhibitors and beta blockers which supress it. The most used antihypertensive drug therapy is ARBs and ACE inhibitors, and this paper examined the superiority of ARBs over the ACE inhibitors in preventing stroke.

Several clinical studies were discussed that provided evidence of the cerebroprotective role of angiotensin II, and its specific cerebroprotective mechanism of action through direct stimulation of AT2 receptors. In response to ischemic or stress injury in the brain, there is an overexpression of AT2 receptors to counteract the Renin-Angiotensin System and the effects of AT1 receptors. For this very cerebroprotective mechanism of AT2 receptors, ARBs are a superior choice of treatment for ISH and hypertension in the elderly. ARBs selectively inhibit AT1 and upregulate the expression of AT2 receptors. Several clinical trials were discussed examining the effects of ARBs on the incidence of stroke, as well as against ACE inhibitors, and other antihypertensive drugs. Apart from the production of angiotensin II, ARBs have several other mechanisms that aid in stroke prophylaxis such as their antiplatelet aggregation and adhesion effects, hypouricemic effect, and atrial anti-fibrillatory effect.

This paper was limited to the existing literature and clinical studies that have been conducted in the past. The clinical studies comparing ARBs and ACE inhibitors solely together regarding cerebrovascular events were limited to a few. There was limited literature and studies available discussing the prophylactic mechanisms of ACE inhibitors in normotensive patients, however promoting cerebrovascular events when used alone in some hypertensive individuals. Future studies should focus on demonstrating whether ACE inhibitors do in fact have such effects as current studies are extremely limited and their mechanism of action in promoting or preventing strokes should also be investigated. Also, more clinical trials should be conducted that directly compare ARBs with ACE inhibitors and their effect on cardiovascular and cerebrovascular events.

Appendix

First Author	Date of Publication	Study Design	Level of Evidence	Study Population	Therapy or Exposure	Outcome/Results
Omboni et al. [7]	January 17, 2014	Two Clinical trials	1	Elderly hypertensives	Omalsartan and Rimipril	Omalsartan showed a greater efficacy then Rimipril and provided a longer lasting control.
Aronow et al. [9]	August 16, 2013	Retrospective Study	3	Elderly with Isolated Systolic Hypertension	Lifestyle modifications and antihypertensive drug therapy and stroke reduction	Lifestyle modifications and antihypertensive drug therapy should be used to prevent stroke and other cardiovascular events; however, additional clinical trials are needed to determine the efficacy.
Papademetriou et al. [7]	September 15, 2004	Clinical trial (the Study on Cognition and Prognosis in the Elderly (SCOPE) trial)	1	4964 men and women aged 70 to 89 years old with Isolated Systolic Hypertension	Candesartan or an open-label antihypertensive placebo	The elderly patients being treated with candesartan had a 42% relative risk reduction in stroke compared to the other antihypertensive therapy.
Chrysant [3]	2005	Systematic Review	3	Hypertensives who have previously suffered stroke – ACCESS study Hypertensives who have suffered a stroke – Progress.	Candesartan or a placebo – ACESS study Perindopril or perindopril and indapamide added to it – Progress.	- Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) pilot study which demonstrated a 52% reduction in stroke and mortality compared to placebo - PROGRESS Study: Perindopril intervention showed 5% stroke reduction for a 5 mmHg decrease in SBP, while adding indapamide resulted in a 43% reduction in stroke with a 7 mmHG decrease in SBP - ALLHAT Study: lisinopril increased the incidence of stroke by 15% in hypertensive

						patients compared to the chlorthalidone group - CAPP Study: captopril had a 43% higher incidence of stroke - Heart Outcomes Prevention Evaluation (HOPE): a 32% reduction in stroke incidence in the treatment group
				Hypertensive – ALLHAT Study	Lisinopril to the treatment group and chlorthalidone to the control group – ALLHAT Study	
				Hypertensives – CAPP Study	Captopril or conventional drug therapy –CAPP Study	
				Normotensive patients with pre-existing coronary artery disease, peripheral vascular disease, and/or diabetes - HOPE	Treatment group was given the ACE inhibitor Ramipril in high doses (10mg/day) compared to the placebo-controlled group - HOPE	
Heagerty et al. [11]	2009	Clinical trials	1	Two groups: males and females over 5 years old with essential hypertension, and those with isolated systolic hypertension	Olmesartan medoxomil with additional therapy of hydrochlorothiazide if blood pressure needed control.	Olmesartan medoxomil showed significant reduction in both DP and SP in those with essential hypertension, but significant reduction in SP with little or no effect on DP in those with isolated systolic hypertension.
Pedelty et al.	May 19,	Systematic	3	Previously	Antihypertensives,	- Studies demonstrate

[9]	2008	Review		done studies on the elderly with isolated systolic hypertension and/or essential hypertension 9,193 patients between the ages 55 to 80 years old with hypertension and left ventricular hypertrophy – LIFE Study. High-risk patients including elderly with hypertension and post-stroke patients – MOSES Study	specifically ARBs and stroke reduction Losartan for the treatment group and atenolol for the control group – LIFE Study Compared eprosartan and nitrendipine over a 24 month period	an increase in stroke risk reduction that extends beyond lowering blood pressure in the elderly patients being treated with ARBs. - Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study: ARB-treated group had a decreased cardiovascular mortality with a 25% reduction in fatal and nonfatal strokes Sub-studies of the LIFE study showed that Losartan reduced atrial fibrillation and uric acid levels in the treatment group. - Morbidity and Mortality after Stroke, Eprosartan Study (MOSES): Eprosartan demonstrated a decreased recurrence of stroke by 25% compared to nitrendipine

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