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REVIEW

Valsartan and Amlodipine: Safety and Efficacy in Stroke Prevention

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Abstract: Stroke is one of the leading causes of death and disability worldwide. Controlling hypertension is known to be the most important treatment in preventing stroke. Reduction of blood pressure (BP) even below the normal range continues to reduce stroke risk. However, there are also thought to be blood pressure-independent effects of antihypertensive treatments, which differ between antihypertensive classes. Calcium channel blocker, amlodipine, and angiotensin receptor blocker, valsartan, represent the two antihypertensive drugs with supportive evidence for the prevention of stroke. Amlodipne and valsartan have favorable effects on stroke outcome as monotherapy, particularly in patients with high cardiovascular risk. There has been no study in which evaluated the effectiveness of the combination of these two agents, however, the combination of amlodipine and valsartan is well tolerated and the large BP reductions with this combination therapy would suggest that this might be an effective approach for stroke prevention.

Keywords: calcium channel blocker, angiotensin receptor blocker, hypertension, cerebrovascular disease

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Introduction

Stroke is one of the leading causes of death and disability worldwide. Controlling hypertension is known to be the most important treatment in preventing stroke. This review will examine the evidence available for the use of calcium channel blocker, amlodipine and renin angiotension receptor blocker, valsartan in the primary and secondary prevention of stroke, and explore whether there is benefit in this regard for the combination therapy with these two agents.

Hypertension and Stroke

Hypertension serves as the most prevalent and powerful risks among the modifiable risk factors.[1] People with hypertension are 3 to 4 times more likely to suffer a stroke than those without hypertension.[2]

There are strong and consistent evidence that lowering elevated blood pressure (BP) is an important therapeutic target in the primary and secondary prevention of stroke. Although the J-curve debate has been going on, many examples of the J-curve relationship between blood pressure and cardiovascular/noncardiovascular events are due to reverse causality, where underlying disease is the cause of both the low blood pressure and the increased risk of both cardiovascular and noncardiovascular events. From the full publication of Hypertension Optimal Treatment (HOT) study database, it can be now concluded that for nonischmeic hypertensive subjects the therapeutic lowering of diastolic blood pressure to the low 80s mmHg is beneficial, but it is safe to go lower. In the presence of coronary artery disease, there is a J-curve relationship between treated diastolic blood pressure and myocardial infarction, but not for stroke. For patients, whose dominant risk is stroke, it is appropriate to be more aggressive in lowering blood pressure. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, also showed that in patients with type 2 diabetes at high risk for cardiovascular events, targeting systolic blood pressure of less than 120 mmHg, as compared with less than 140 mmHg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events, however, the annual rates of stroke significantly decreased in the intensive therapy group.[3] Studies demonstrated a strong log-linear relationship without threshold between stroke mortality and blood pressure.[1,4] Throughout middle and old age, usual blood pressure is strongly and directly related to vascular mortality, including stroke, without any threshold down to at least 115/75 mmHg. This means that reduction of blood pressure even below the normal range continues to reduce stroke risk.

Mechanism of Action

In hypertensive patients, cerebral blood flow is impaired, not only by the pressure-induced vascular wall stress but also as the result of inflammation and oxidative stress in the vascular wall, induced by angiotensin II.[5,6] The renin angiotensin system (RAS) has been linked to the development and progression of cerebrovascular disease in patients with hypertension.[7,8] Angiotensin II is thought to induce crebrovascular hypertrophy and remodeling, inhibit endothelium-dependent relaxation and disrupt the blood-brain barrier.[7] RAS blockade might provide cerebroprotection. There is one study which noted that differences in BP do not fully account for differences in stroke risk and that the relative risk of stroke was 17% greater with agents that potentially decrease angiotensin II levels, such as β-blockers and angiotensin converting enzyme inhibitors (ACEIs) compared with those that increase angiotensin II levels, such as thiazide diuretics, dihydropyridine CCBs and ARBs.[9] It was hypothesized that increased angiotensin II may act on angotensin type 2 (AT2) receptors and mediate protective effects such as improving collateral circulation and neuronal resistance to anoxia. Therefore, in addition to BP lowering effect, ARBs might help protect against stroke, by inhibiting the negative effects of angiotensin type 1 receptors in the cerebral circulation, but allow angiotensin to mediate stroke-protective effects through the AT2 receptor.

Atherosclerosis has a long clinically silent period lasting many years before the manifestation of overt disease, such as stroke. Carotid artery intima-media thickness (CIMT) is considered to be an early marker of atherosclerosis, and it is associated with an increased risk for stroke, even after statistical adjustment for hypertension. Reduction in CIMT may result in reduction of stroke risk. ARB and ACEI have been shown to inhibit balloon-injury-elicited neointima formation in the carotid arteries of rat models.[10]

Increased left ventricular mass (LVM) is known as a risk factor for stroke. It has been suggested that

individuals with LVH may be predisposed to ischemic stroke to owing to the association of LVM with atrial fibrillation (AF). ARB (candesartan) has been shown to significantly attenuate left ventricular remodeling (mass and wall thickness) in spontaneously hypertensive rats without affecting pressure.[11] A meta-analysis of 11 randomized, controlled, parallel-design clinical trials evaluating effect of ACEIs or ARBs on the development of AF showed that treatment with ACEIs or ARBs reduced the relative risk of AF in patients with hypertension by 23% [RR 0.769, $P < 0.001$, 95% CI 0.686–0.862].[12]

Inflammation in cerebral microvessels and impaired cerebral blood flow are also risk factors for stroke. Experiments in animals suggest that ARBs and CCBs might have BP-independent effects on stroke outcomes. Studies in rats have shown that ARB can reduce inflammation in cerebral microvessels and normalize the cerebral blood flow following stoke.[13] Also, in rat model of brain ischemia, ARB reduced middle cerebral artery (MCA) media thickness and infarct area following occlusion of MCA.[6] Moreover, in rats, protection in cerebral circulation by improving cerebral blood flow autoregulation and reducing supreoxide production, occurred with doses that do not decrease BP.[14] A similar result was observed with amlodipine in ApoE knockout mice model of stroke.[15]

Clinical Studies

Efficacy

Amlodipine

As shown in Table 1, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared amlodipine, chlorthalidone, lisinopril, and doxazosin mesylate in 33357 patients with stage 1 or 2 hypertension and at least one other risk factor for coronary artery disease.[16] There were significantly more strokes for lisnopril compared with amlodipine (RR 1.23 [1.08–1.41]; $P < 0.003$).[17] However, there was no significant difference in stroke incidence between amlodipine and chlorthalidone (RR 0.93 [0.82–1.06]; $P = 0.28$) in this study.[16]

The Comparison of AMlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study[18] compared amlodipine with enalapril or placebo in patients with angiographically documented coronary artery disease and diastolic BP < 100 mmHg. Amlodipine reduced the risk of stroke or TIA by 50% compared with placebo (HR 0.50 [0.19–1.32]) and 24% compared with enalapril (0.76 [0.26–2.20]), although these reductions did not achieve statistical significance ($P = 0.15$ and $P = 0.61$, respectively), possibly due to the small numbers of events.[18] The same result was shown in the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT)[19] which compared amlodipine with placebo in similar group of patients.

In the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA),[20] amlodipine-based treatment reduced fatal and nonfatal stroke by 23% (HR 0.77 [0.66–0.89]; $P < 0.0003$) compared with atenolol-based treatment in a range of high cardiovascular risk patients with uncontrolled blood pressure (BP).[21] However, second drugs were not allocated randomly or consistently, a definitive comparison cannot be made between second drugs. Although BP was the largest contributor to stroke events (average difference 2.7/1.9 mmHg), peripheral BP measurements could not fully account for the treatment differences in stroke.[22] Changes in central aortic pressure may explain some differences between CCBs and other agents. Despite similar peripheral BP, amlodipine-based treatment reduced central systolic BP more than atenolol-based treatment in the ASCOT Conduit Artery Function Evaluation (CAFE) substudy.[23]

The Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial compared benazapril/hydrochlorothiazide and amlodipine besylate/benazapril in hypertensive patients (systolic BP ≧ 160 mmHg or currently on antihypertensive therapy) with risk factors for cardiovascular events (prior events, target organ damage, kidney disease, or diabetes).[24] There was no significant difference in fatal of nonfatal stroke incidence between two groups (HR 0.84 [0.65–1.08]); $P = 17$). Also, in the Irbesartan in Diabetic Nephropathy Trial (IDNT),[25] which compared amlodipine with placebo in type 2 DM patients with nephropathy, and in the African American Study of Kidney Disease and Hypertension (AASK) trial,[26] which compared amlodipine with metoprolol and ramipril in patients with chronic kidney disease, there were no significant differences in the incidence of stroke between groups.

Table 1. Trials involving amlodipine or/and an ARB.

Trial	Masking	Total no. of patients	Disease or risk factors	Primary outcome	Antihypertensive treatment
					Control, mg
PREVENT[18] placebo	Double	825	CAD (≥30% stenosis)	Rate of coronary atherosclerosis	Placebo
IDNT[24] placebo	Double	1,715	2DM + nephropathy	All cause death + ESRD + DBSC	Placebo
ALLHAT[15] chlorthalidone	Double	33,357	1 risk factor	Coronary death + MI	Chlorthalidone (12.5–25)
ALLHAT[15] lisinopril					Lisinopril
CAMELOT[17] enalapril	Double	1,991	CAD (>20% stenosis)	CV death + MI + RCA + AP + CR + HF + stroke + PAD	Enalapril (10–20)
CAMELOT[17] placebo					Placebo
ASCOT[19] atenolol	Open	19,257	3 risk factors	Coronary death + MI	Atenolol (50–100)
AASK[25] metoprolol	Double	1,094	GFR 20–65 mL/min/1.73 m^2	CV death + MI + stroke + HF+ CR	Metoprolol (50–200)
AASK[25] ramipril					Ramipril (2.5–10)
ACCOMPLISH[23] HCTZ	Double	11,506	CVD or renal disease of target organ damage	CV death + MI + stroke + UA + CR + RCA	Benazapril/HCTZ (40/12.5–25)
Trials involving an ARB					
ELITE captopril	Double	3,152	HF (NYHAII-IV + LVEF <40%)	All cause death	Captopril
SPICE placebo	Double	270	LVEF < 35%		Placebo
RENAAL placebo	Double	1,513	2DM + nephropathy	All cause death + ESRD + DBSC	Placebo
IDNT placebo	Double	1,715	2DM + nephropathy	All cause death + ESRD + DBSC	Placebo
LIFE[27] atenolol	Double	9,913	ECG LVH	CV death + MI + stroke	Atenolol (50–100)
OPTIMAAL[35] captopril	Double	5,477	MI + HF	All cause mortality	Captopril (37.5–150)
SCOPE[39] placebo	Double	4,964	MMSE ≥ 24	CV death + non-fatal stroke + non-fatal MI	Placebo
ACCESS[40] placebo	Double	342	Early treatment of stroke	Fatality and disability (Barthel index)	Placebo
CHARM-Preserved[29] placebo	Double	3,025	HF (NYHAII-IV + LVEF > 40%)	CV death + admission for HF	Placebo + conventional therapy
CHARM-Alternative[30] placebo	Double	2,028	HF (NYHAII-IV + LVEF < 40%)	CV death + admission for HF	Placebo

Experimental, mg	Mean Age, y	Mean SBP/DBP, mmHg		DM	Follow up, y	Stroke outcome (Favor, RR, significance)
		Mean at entry	Difference during follow up			
Amlodipine (5–10)	57	129/79	+6.8/+3.7*	0	3.0	NS
Amlodipine (2.5–10)	59	159/87	+4/+3*	100	2.6	NS
Amlodipine (2.5–10)	67	146/84	–1.1/+0.6*	36	4.9	NS
Amlodipine (2.5–10)	67	146/84	+1.5/+1.1*	36	4.9	Amlodipine, 0.81, S
Amlodipine (5–10)	58	129/77	-0.1/+0.1	17	2.0	NS
Amlodipine (5–10)	57	129/78	+4.1/+1.9*	19	2.0	NS
Amlodipine (5–10)	63	164/95	+2.7/+1.9*	27	5.5	Amlodipine, 0.77, S
Amlodipine (5–10)	55			0	4.1	NS
Amlodipine (5–10)				0	4.1	NS
Amlodipine/ benazapril (5–10/40)	68	145/80	–0.9/+1.1	60	2.9	NS
Losartan	71	138/78	NS between groups	24	1.5	NS
Candesartan (4–16)	66	130/75	–10/–6	19	12 weeks	NS
Losartan (5–100)	60	153/82	+1*/0	100	3.4	NS (Morbidity + mortality from CVD)
Irbesartan (75–300) or Amlodipine (2.5–10)	59	159/87	+6/+3*	100	2.6	NS
Losartan (50–100)	67	174/98	+1.1*/+0.2	13	4.8	Losartan, 0.75, S
Losartan (12.5–50)	67	123/71		17	14,866 patient-years	NS
Candesartan (8–16)	76	166/90	3.6/1.6*	12	3.7	NS
Candesartan (4–16)	68	189/99	NS	37	1.1	Candesartan, 0.475, S (vascular events)
Candesartan (4–32)	67	136/78	–6.9*/–2.9*	28	3.1	NS
Candesartan (4–32)	66	130/77	–4.4*/–3.9*	27	2.8	NS

(*Continued*)

Table 1. (*Continued*)

Trial	Masking	Total no. of patients	Disease or risk factors	Primary outcome	Antihypertensive treatment
					Control, mg
DETAIL[37] enalapril	Double	250	2DM + nephropathy	Change in GFR	Enalapril (10–20)
MOSES[42] nitrenidipine	Open	1,352	CBV	All cause death + MI + HF + CBV	Nitrendipine (10)
VALIANT[34] captopril		1,146	Acute MI	All cause mortality	Captopril (–150)
Jikei heart[26] convetional therapy	Double	3,081	HTN + CAD + HF	CV death + morbidity (hospital admission for stroke or TIA; MI, etc.)	Conventional therapy
ONTARGET[33] ramipril	Double	25,620	High CV risk	CV death + MI + stroke + hospitalization for HF	Ramipril (5–10)
PRoFESS[41] placebo	Double	20,332	Ischemic stroke within the last 120 days	Recurrent stroke	Placebo
TRANSCEND[32] placebo	Single	5,926	High CV risk	CV death + MI + stroke + admission for HF	Placebo
KYOTO HEART[31] conventional therapy	Open	3,031	Uncotrolled HTN + CV riskl	Fatal and non-fatal CVD	Conventional therapy
Trials involving amlodipine and an ARB					
IDNT[24]	Double	1,715	2DM + nephropathy	All cause death + ESRD + DBSC	Amlodipine (2.5–10)
VALUE[43]	Double	15,245	CVD or risk factors	MI + HF	Amlodipine (5–10)
CASE-J	Open	4,703	1 disease or risk factor	CV death + MI + AP + CR + HF + CBV + VE + ESRD	Amlodipine (2.5–10)

Patient preference

Taken together, no study has indicated beneficial effects of amlodipine on incidence of stroke as primary outcome in hypertensive patients with several risk factors. In some trials however, amlodipine had favorable effects on stroke as secondary outcome particularly in patients with high cardiovascular risk.

Valsartan

In the Japanese Investigation of Kinetic Evaluation in Hypertensive Event and Remodelling Treatment (JIKEI-HEART) study,[27] valsartan has been examined in a Japanese hypertensive population with heart failure or coronary artery disease, or a combination of these cardiovascular disorders who were receiving conventional treatment. Of patients who received

Experimental, mg	Mean Age, y	Mean SBP/DBP, mmHg		DM	Follow up, y	Stroke outcome (Favor, RR, significance)
		Mean at entry	Difference during follow up			
Telmisartan (40–80)	61	152/86	+4.0*/–	100	5.0	NS
Eprosartan (600)	68	151/87	–2.8/–0.8*	37	2.5	Eprosartan, 0.75, S
Valsartan (–320)	65	123/72	+0.9*/	23	2.1	NS
Valsartan (80–160)	65	139/81	–0.4/0.1	20	3.1	Valsartan, 0.60, S
Telmisartan (80)	66	142/82	–0.9/–0.6	37	4.7	NS
Telmisartan (80)	66	144/84	+3.8/+2.0	29	2.5	NS
Telmisartan (80)	67	141/82	+3.2/+1.3	36	4.7	NS
Valsartan (80–160)	66	157/88	0.0/0.0	27	3.3	Valsartan, 0.55, S
Irbesartan (75–300)	59	160/87	+2*/0	100	2.6	NS
Valsartan (80–160)	67	155/88	-2.2/–1.6*	32	4.2	NS
Candesartan (4–12)	64	163/92	–1.9*/0	43	3.2	NS

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; 2DM, type 2 DM; MI, myocardial infarction; CAD, coronary artery disease; CV, cardiovascular; RCA, resuscitated cardiac arrest; AP, angina pectoris; CR, coronary revascularization; HF, heart failure; PAD, peripheral artery disease; ESRD, end-stage renal disease; DBSC, doubling of baseline serum creatinine; HCTZ, hydrochlorothiazide; CVD, cardiovascular disease; UA, unstable angina; GFR glomerular filtration rate; ECG, electrocardiogram; LVH, left ventricular hypertrophy; CBV, cerebrovascular events including stroke and transient ischemic attack; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; MMSE, mini-mental state examination, HTN, hypertension; VE, vascular events; S, significant difference in stroke outcome between groups, $P < 0.05$; NS, no significant difference in stroke outcome between groups, $P \geqq 0.05$.
*Significant difference in achieved blood pressure between groups.

valsartan on top of conventional treatment, 29 had stroke (or TIA), compared with 48 in patients receiving non-ARB-based treatment (HR 0.60; $P = 0.0280$), suggesting that valsartan has beneficial effects on stroke outcome. However, in the Evaluation of Losartan in The Elderly (ELITE) study,[28] which also examined patients with heart failure, there was no difference in stroke outcome between groups who received losartan and captopril. Also, in the Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE),[29] and in the Candesartan Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) study,[30,31] which examined the effectiveness of candesartan on stroke outcome in patients with heart failure, there were no significant difference in stroke reduction compared with placebo or conventional therapy.

The KYOTO HEART Study[32] examined whether valsartan added to the conventional anti-hypertensive treatment influences cardiovascular events in the high-risk Japanese patients with uncontrolled hypertension. Twenty five patients given valsartan had stroke or TIA, compared to 46 in the control group (HR 0.55, $P = 0.01488$), suggesting that valsartan reduces stroke events significantly compared with the conventional therapy. However, in the Telmisartan Randomised AssessmeNt Study in ACE iNtolerant Subjects with Carediovascular Disease (TRANSCEND)[33] and the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET),[34] which examined effectiveness of telmisartan on stroke in patients with high CV risk, there were no significant differences in stroke outcomes between groups.

The Valsartan in Acute Myocardial Infarction Trial (VALIANT)[35] compared valsartan with captopril in patients who had recent acute MI with left ventricular systolic dysfunction or clinical evidence of heart failure. There was no significant difference in the incidence of stroke between both groups. Also, in the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL),[36] there was no significant difference in stroke outcome between losartan and captopril.

Effectiveness of ARBs was also examined in other risk groups. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial,[37] the IDNT, and the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) trial,[38] effectiveness of losartan, irbesartan, and telmisartan was examined in type 2 DM patients, respectively. None of these ARBs showed favorable effect on stroke, compared to placebo or ACEI. The Losartan Intervention For Endpoint Reduction (LIFE) trial[39] compared losartan with atenolol in patients with left ventricular hypertrophy, and there was significant reduction in stroke incidence in losartan group. In the Study on Cognition and Prognosis in the Elderly (SCOPE),[40] effectiveness of candesartan on stroke prevention was examined in patients with cognition disorder, and there was no significant difference in stroke outcome compared with placebo. The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS),[41] the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS),[42] and the Morbidity and mortality after Stroke (MOSES) study[43] compared risk of recurrent stroke in patients with recent stroke or TIA. In the ACCESS study, there was significant reduction in vascular events in patients who received candesartan compared with placebo, and in the MOSES study, eprosartan significantly reduced stroke compared to nitredipine. However, in the PRoFESS study, which compared telmisartan with placebo, there was no significant difference.

Patient preference

Taken together, valsartan reduces stroke events in patients with high cardiovascular risk and heart failure. Losartan was effective in patients with LVH, candesartan as well as eprosartan were effective in preventing the recurrence of cerebrovascular disease. However, no study has shown effectiveness of ARBs on stroke events in patients with type 2 DM and cognition disorder.

Amlodipne vs. Valsartan

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial[44] which compared valsartan to amlodipine, was designed to investsigate the question of whether cardiovascular benefits of renin-angiotensin system (RAS) inhibitors can be detected beyond BP.[45] BP was 1/1 mmHg lower in the amlodipine arm and no statistical difference between the two agents in any primary or secondary outcomes was shown. For stroke, the hazard ratio slightly favored amlodipine (HR, 1.15; 95% CI, 0.98–1.35; $P = 0.08$), but there was no significant difference. Also, in IDNT, which compared irbesartan to amlodipine in type 2 DM patients with nephropathy, and in CASE-J trial, which compared candesartan to amlodipine in patients with high CV risk, there were no differences in stroke outcome.

Patient preference

Since as mentioned above, amlodipne and valsartan have favorable effects on stroke outcome as monotherapy, particularly in patients with high cardiovascular risk, these two agents may be equally effective in preventing stroke.

Combination therapy

Evaluation on the combination therapy of valsartan and amlodipine in the context of stroke prevention

has not been conducted to date. Studies have shown that a combination of valsartan and amlodipine is an effective antihypertensive strategy capable of reducing BP more effectively than either treatment alone.[46–48] Indeed, amlodipne (5 to 10 mg)/valsartan (160 mg) reduces BP across all stages of hypertension, with reductions from baseline in mean sitting systolic BP of 20, 30 and 36 to 43 mmHg, respectively, in patients with mild, moderate, and severe hypertension.[46,48,49]

Pulse wave velocity (PWV)[50] and albuminuria[51] are known as surrogate markers of stroke. One study has shown that by adding amlodipine on valsartan, PWV and urine albumin excretion decreased more, when compared with using valsartan alone.[52]

Presence of CCB/ARB combinations in single-pill formulation may have indirect benefits. It is known that the use of single-pill antihypertensive combinations can improve persistence with therapy beyond that provide by free combinations.[53] Patients who persist on antihypertensive therapy have been reported to have a 28% reduction in the relative risk of stroke compared with patients who do not persist with therapy.[54] Thus, the use of single-pill agents may help to reduce stroke through improvements in adherence.

Although there is no study which directly evaluated the efficacy of valsartan and amlodipine as a combination therapy, the large BP reductions and the reductions of surrogate markers with these two drugs as combination and RAS inhibition by each drug would suggest that the combination therapy might be an effective approach for stroke prevention. However, further evaluation is needed to confirm the efficacy of this combination therapy on stroke.

Safety

ARBs are generally considered to be tolerable, while amlodipine are capable to exert a dose dependent peripheral edema. Studies have shown that valsartan reduces the incidence of dose- related amlodipine-induced edema.[55,56] Other adverse event rates were low and the combination therapy was well tolerated.[46–48]

Conclusion

In conclusion, amlodipne and valsartan have favorable effects on stroke outcome as monotherapy, particularly in patients with high cardiovascular risk. There has been no study in which evaluated the effectiveness of the combination of these two agents, however, the large BP reductions with this combination therapy would suggest that this might be an effective approach for stroke prevention.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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