Significance of BP Control in Reducing Stroke Events: Role of Amlodipine in an Indian Perspective

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Abstract
While the incidence and prevalence of stroke is gradually decreasing in the western world, a parallel increase is seen in the developing world. It is a matter of special concern to us as approximately 20-30% of stroke occur in people younger than 45 years in India. Indians are prone to higher stroke risk because of urbanization, diabetes, cigarette smoking and high incidence of hypertension. Unfortunately, there is an inadequate awareness about the risk of stroke with hypertension among general public. Hypertension is considered to be the most important risk factor for stroke, and all forms of hypertension are associated with an increased risk of both ischemic and haemorrhagic stroke. The presence of hypertension also worsens mortality in stroke. Recently, it has been increasingly observed that controlling blood pressure variability (BPV) is equally important as achieving BP reduction, and an increased BPV has been shown to increase stroke risk. Thus, effective treatment option for stroke prevention should include drugs which can reduce BPV as well. The landmark ASCOT-BPLA trial reported that the calcium channel blocker amlodipine decreases stroke risk in hypertensive patients, and attributed this beneficial effect to its effective lowering of BPV. Such beneficial effects of amlodipine were replicated in other trials as well and thus it becomes an important drug from an Indian perspective. In this review, we analyse published literature and present a picture on the effect of amlodipine in the stroke prevention in hypertensive patients.

Introduction
The American Stroke Association defines stroke as clinical, radiological, or pathological evidence of ischemia or haemorrhage, involving a defined cerebral vascular territory.¹ Though country-wise statistics are often inconsistent, stroke is recognized as a major cause of mortality worldwide. In the US, stroke is the topmost cause of disability and the fifth leading cause of death.² Recent studies have noted that while there is a gradual reduction in the incidence of stroke in the developed countries, its incidence in low-to-middle-income countries is gradually increasing. It is estimated that up to 85% of the stroke is contributed by the developing countries.³ Compared to the Western statistics, though the Indian data is not consistent, it is clear that there is a steady increase in the incidence and prevalence of stroke.⁴ The estimated adjusted prevalence rate of stroke in India ranges from 334 to 424 (per 100,000) in urban areas, and from 84 to 262 (per 100,000) in the rural areas. Based on the recent population-based epidemiological studies, the incidence rate of stroke is estimated to be between 119 and 145 (per 100,000) in India. The case fatality rate reports range between 27% in Kerala, to 42% in Kolkata.⁵,⁶ It is reported that stroke results in a loss of 797.57 Disability Associated Life Years (DALYs) per 100,000 person-years: thus, stroke is also a major burden on morbidity. Sixty percent of stroke patients either die or become dependent. The outcome is worse because of poor treatment compliance and risk factors control along with lack of rehabilitation and treatment facilities. Out of stroke survivors, only one third are fully independent in their daily activities whereas one fourth of patients remain bed-ridden.⁷ Stroke is also associated with high treatment costs, acting as burden on both the family as well as society.⁸ A major concern in the stroke epidemiology from an Indian perspective is that, approximately 20-30% of strokes occurs in people younger than 45 years, and is more frequently seen in India.⁸ This has been further linked to an increase in the absolute number of stroke cases, secondary to the increased life span, and

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more importantly, the poor control of contributing risk factors to stroke. Unfortunately, the public awareness in this direction is still inadequate.

**Stroke and Hypertension: The role of Blood Pressure Variability (BPV)**

Various community-based and hospital-based studies have identified various risk factors associated with stroke; the most important of these include hypertension, diabetes, tobacco consumption, alcohol consumption, lower levels of HDL cholesterol, lower haemoglobin levels, and presence of heart disease. However, it is widely accepted that the most important risk factor among these is hypertension. The appropriate control of blood pressure is considered to be an essential step involved in stroke prevention, along with other measures such as avoidance of smoking, excessive alcohol intake, glycaemic and other biochemical factor control.

Hypertension increases the risk for ischemic stroke, haemorrhagic stroke, and silent brain infarcts. All subtypes of hypertension, including isolated systolic hypertension or diastolic hypertension, or a combination of systolic and diastolic hypertension, have been shown to increase the risk of stroke. More than 50% of the stroke patients have elevated BP at the time of presentation, which is associated with poorer outcomes, including fatal or nonfatal neurological complications. Subjects with hypertension are at 3-4 times higher risk of developing stroke than normotensive subjects. Thus, elevated BP is a direct, independent, and continuous risk factor for development of stroke, and the risk of stroke increases continuously when the BP is 115/75 mmHg or above.

The presence of hypertension also worsens mortality in stroke.

A 2003 meta-analysis reported that in patients aged 40-69 years, each elevation of 20 mmHg of systolic blood pressure or 10 mmHg of diastolic blood pressure was associated with over two-fold increase in stroke death rate. It has been estimated that the elimination of this single risk factor, namely normal to severe hypertension would prevent stroke incidence by 64% in men and 50% in women, and would also reduce stroke mortality by 67% in men and 29% in women. In a recently published meta-analysis involving 123 studies and 613,815 participants, it was revealed that every 10 mmHg reduction in SBP significantly reduced the risk of stroke (relative risk 0.73, 95% CI 0.68-0.77), in addition to other cardiovascular events and heart failure.

It has also been found that intensive lowering of BP (i.e. SBP <120 mm Hg) significantly reduces the risk of stroke as compared to standard lowering of BP (140 mm Hg). The latest SPRINT study showed that intensive lowering (<120 mm Hg) of BP among adults with hypertension is associated with significantly lower rates of fatal and nonfatal cardiovascular events and death from any cause (HR 0.75; 95% CI, 0.64-0.89; p<0.001). Analysis of 14 trials by Xie et al. involving 43,483 participants further proved that intensive BP lowering was associated with a 22% reduction in the risk of stroke as compared to the less intensive regimen. Thus, hypertension control becomes a very important component of stroke prevention.

In addition to elevated blood pressure, it is being increasingly realised that blood pressure variability (BPV) is not simply a ‘background noise’ which dilutes the prognostic effects of average BP measurement, but is in fact an important predictor for cardiovascular events. The importance of BPV in stroke incidence has also been reported, although the degree of association between incidence of stroke and BPV may differ among study populations. A higher BPV was associated with a higher risk of cerebral infarction after adjustment for confounding factors including average BP level. With every 5 mmHg increase in night time SBP variability, the risk of stroke increased by as much as 80% in elderly hypertensive population.

In the BP lowering arm of the Anglo- Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA), it was reported that in addition to maximum SBP, visit-to-visit SBP variability was a strong predictor of stroke, and recommended that BP lowering drugs should not only reduce BP but also reduce BPV. A significant positive association between visit-to-visit BPV and stroke was also observed in post-menopausal women in the Women’s Health Initiative study. Thus, for effective prevention of stroke, drugs which reduce BPV in addition to reducing the BP would provide the best possible outcomes.

**Antihypertensive Drugs and Stroke Prevention: The Role of Amlodipine**

The recently published JNC-8 guidelines recommend four antihypertensive drug classes for initial treatment of hypertensive patients, namely angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide-type diuretics. However, with regards to BPV, the CCBs and thiazide diuretics have a distinct advantage over the other two classes and over the β blockers as well. In a meta-analysis published in Lancet in 2010, it was reported that the inter-individual SBP variation was reduced by CCBs and non-loop diuretics (p<0.0001 and 0.007 respectively), whereas it was increased by ACEIs and ARBs (p=0.008 and 0.0007 respectively). When compared with placebo,
the maximum reduction in inter-individual SBP variation was observed with the CCBs (p=0.0001). This effect was consistently observed in different types of study designs, including parallel group and crossover design trials.29 Similar results were reported in another study published in 2014, where CCBs and diuretics were associated with lower BPV when compared to ACEIs, ARBs or β blockers.30

CCBs also have been shown to be associated with a reduction in stroke risk in many studies. In the landmark ASCOT-BPLA study, investigators observed that amlopidine was associated with a lower risk of stroke than atenolol (hazard ratio 0.78, 95% CI 0.67-0.90), and attributed it to the more effective lowering of BPV by amlopidine.26 An analysis of 12 trials involving 94,338 hypertensive patients, who were prescribed different antihypertensive medications, reported that amlopidine provided more protection against stroke when compared with placebo (-37%, P=0.06), and also when compared with other antihypertensive drugs including ARBs (-19%, P<0.0001) (Figure 1).31

A detailed analysis of stroke occurrence during in-trial and post-trial phase of Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), provided comparative results of chlorthalidone, amlopidine and lisinopril. During the 4.9 years of in-trial follow-up, it was found that the least percentage of patients in amlopidine arm had stroke (4.5%, 4.2% and 5.1% of patients of chlorthalidone, amlopidine and lisinopril groups respectively).32 In another meta-analysis published in 2016 involving 123 studies and 613,815 participants, it was revealed that the CCBs were superior to other drug classes for the prevention of stroke (relative risk 0.90, 95% CI 0.85-0.95).20 Another meta-analysis of large scale long term outcome studies involving 87,257 patients compared CV outcomes in amlopidine based regimens with non-CCB based treatment regimens. It was observed that there was a significant reduction of risk of stroke (OR, 0.84; 95% CI, 0.79-0.90; P<0.0001), a 10% reduction in risk of CV events and a significant decrease in total mortality in the amlopidine arm as compared to non-CCB treatments.33

The benefit of CCBs has also been studied in hypertensive patients who are already suffering from stroke. It has been repeatedly established that the control of BP is the most important aspect in this subset of patients, and amlopidine has been shown to be most consistently equal or superior when compared to any other agent.34 While it has been established that the beneficial effect of amlopidine on stroke is due to its BP-lowering effects, a study published in 2011 reported that amlopidine provided stroke protection beyond that conferred by BP reduction alone. While each 1-mmHg reduction in BP provided by amlopidine achieved a 6.1% (95% CI, 1.1–10.8; P=0.018) reduction in the stroke risk, it was found that at zero BP reduction, amlopidine achieved an estimated 10.3% (95% CI, 2.9–17.2; P=0.008) reduction in stroke risk. This suggests that the stroke risk protection provided by amlopidine has two components: one which is dependent on BP reduction, and another which is independent of BP reduction.35 It is known for some time that the calcium channel blockers have effects beyond BP reduction. Specifically, amlopidine is known to regulate membrane fluidity and cholesterol deposition, act as an antioxidant, stimulate NO production to recruit its biologic actions, and regulate matrix deposition.36 It appears plausible that some of these effects are responsible for the beneficial effects of amlopidine on stroke, over and above BP reduction. Appropriate studies are lacking in this direction.

### Conclusions

The increase in stroke burden in India parallels the changing lifestyle, urbanization and
increasing life expectancy among Indians. As per 2002 data, 771,067 Indians lost their lives to stroke, the second largest number worldwide.\textsuperscript{37} It is also reported that for every ten people who die of stroke, four could have been saved if their blood pressure had been regulated.\textsuperscript{37} This suggests the importance of BP control in the prevention of stroke. Role of BPV has further added a new dimension towards the outlook of preventive strategies for stroke. Recently published clinical evidence reinforces the role of CCBs, especially amlodipine as one of the most effective drugs to decrease the risk of stroke. Amlodipine has been consistently demonstrated to have a beneficial effect on lowering BP, BPV, and reducing stroke incidence in hypertensive patients. Amlodipine is also a useful drug in the treatment of hypertensive patients already suffering from stroke. Thus, amlodipine forms a valuable and powerful addition to the armamentarium for stroke prevention and treatment in hypertensive patients. This is especially important in India, where the incidence and prevalence of stroke is gradually increasing in contrast to the Western world. Further research to understand the unique properties of amlodipine will strengthen its role in prevention of stroke incidence.

References