Quarter 4, 2025 | VOLUME 13 | NUMBER 12

EXCEL

Medical Bulletin

EXCEL Division of Blue Cross Laboratories Pvt Ltd.

LOSARTAN AS A NEUROPROTECTIVE AGENT AGAINST EARLY HYPERTENSIVE BRAIN INJURY

Pre-hypertension was first introduced in Joint National Committee (JNC)-7 in 2003 to define individuals whose systolic blood pressure (BP) levels are between 120 and 139 mmHg or diastolic BP between 80 and 89 mmHg. The purpose of this definition was onto the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in the target population with hypertension who has a higher-than-normal BP and is at a higher-than-normal risk of developing cardiovascular disease. Results of previous studies have shown that individuals with pre-hypertension had an increased risk of developing hypertension compared with the normotensive population and had an increased age-related risk of cardiovascular and cerebrovascular diseases including stroke and carotid atherosclerotic plaque.

As with hypertension, one of the target organs for pre-hypertension is brain. Findings of the Framingham Heart Study suggested that pre-hypertension caused impairment on the structural integrity of white matter and shrinkage of gray matter in young populations even before these individuals developed hypertension, and the damage was associated with premature aging but not stroke. Thus, it appears that BP-associated brain damage may start at a relatively younger age than expected and may continue over a long period of time if the abnormal BP is not controlled or corrected in time.

Recently researchers reported that key brain cells linked to thinking and memory show early signs of stress within just three days of exposure to angiotensin II, a hormone involved in human hypertension. This could probably help explain why hypertension is a major cause of cognitive decline and why many blood pressure medicines do not prevent brain problems.

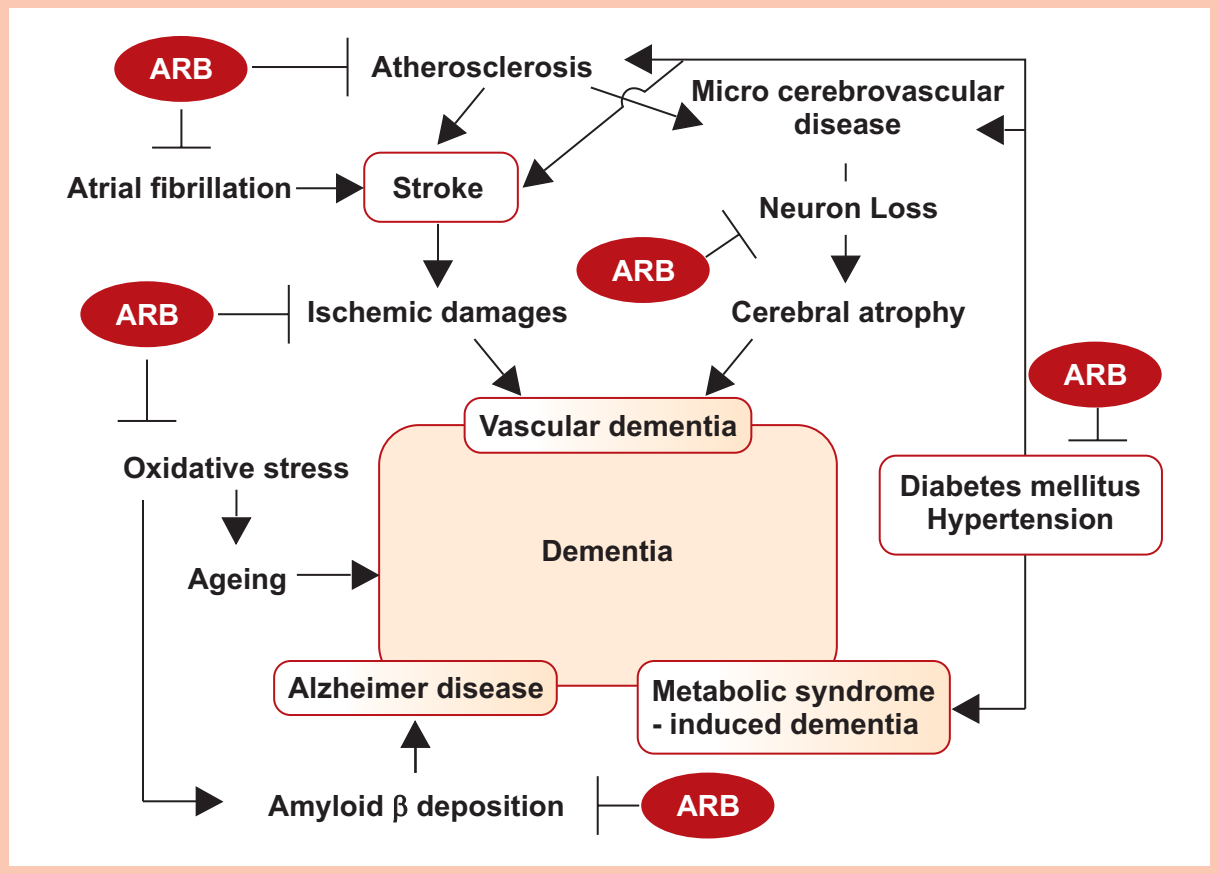
Losartan, a non-peptide angiotensin II receptor antagonist with high affinity and selectivity to receptor type I, is extensively used to treat arterial hypertension. The results from clinical trials such as LIFE (Losartan Intervention for Endpoint) and SCOPE (The Study on Cognition and Prognosis in the Elderly) have suggested that in a background of equally reduced blood pressure, angiotensin II type 1 receptor antagonist offered additional benefits over other blood pressure control in stroke reduction, suggesting that the benefits of angiotensin II type 1 receptor antagonist were due to effects beyond blood pressure control. Losartan showed evidence of protecting the brain from early damage in several contexts including brain injury, hypertension-induced damage, and ischemic stroke models. It works through mechanisms such as blocking harmful signaling pathways, reducing inflammation, oxidative stress, and neuronal apoptosis, and improving cerebral blood flow and barrier integrity.

In pre-hypertensive preclinical models, losartan treatment protected against stroke-induced brain damage more effectively than other blood pressure drugs by reducing local renin-angiotensin-aldosterone system activity and protecting brain structure and function. Mechanistically, the short- and long-term treatments with losartan reduced the activity of the local renin-angiotensin-aldosterone system (RAAS) in a time-dependent manner mainly by decreasing AT1R levels and increasing AT2R levels in the cerebral cortex.

TROPHY (TRial of Preventing Hypertension) study demonstrated that an angiotensin receptor blocker (ARB), had a preventing effect on the progression of pre-hypertension to hypertension.

Mechanisms of Protection

- ***Renin-Angiotensin-Aldosterone System (RAAS) Modulation:*** Losartan decreases AT1R levels and increases AT2R levels in the cerebral cortex. This reduces the harmful impacts of local RAAS activation, which is known to promote inflammation, oxidative stress, and apoptosis in neural tissues.
- ***Neuroplasticity Enhancement:*** Chronic losartan treatment improves neuroplasticity by increasing dendritic and spine density in cortical areas, which correlates with cognitive improvement and greater structural resilience to hypertension-induced damage.
- ***Cerebral Blood Flow Improvement:*** Losartan restores and maintains baseline cerebral blood flow and cerebral autoregulation, supporting neuronal survival and function even as it lowers systemic blood pressure.
- ***Endothelial and Cellular Protection:*** In preclinical studies losartan reversed early damage to endothelial cells and interneurons, indicating a direct cellular neuroprotective effect beyond simply lowering blood pressure.



In summary, losartan's brain-protective mechanisms against hypertension-induced damage include RAAS suppression, restoration of cerebral blood flow, neuroplasticity enhancement, and direct cellular protection, making it a promising option for early intervention in pre-hypertensive or hypertensive patients at risk of brain injury.

Source: *Oku et al: Hypertens Res Vol. 28, No. 1 (2005); Mogi M., et.al; Hypertens Res 32, 738–740 (2009).; Heriberto Coatl-Cuaya, et.al; Jour of Chemical Neuroanatomy Vol. 120, Mar 2022.*

PROTON PUMP INHIBITORS (PPIs): GLOBAL USE, CLINICAL GUIDANCE AND STEWARDSHIP APPROACHES

Proton pump inhibitors (PPIs) are widely prescribed for acid-related disorders such as gastroesophageal reflux disease (GERD), peptic ulcer disease, Helicobacter pylori eradication, functional dyspepsia, and gastroprotection in high-risk patients. Since their introduction in 1989, PPIs have become a mainstay of therapy due to their superior acid suppression compared to H2 receptor antagonists & increasing their global utilization significantly. However, concerns about inappropriate initiation & prolonged use have prompted regulatory agencies to issue safety warnings. Observational data links long-term PPI therapy to potential adverse effects, reinforcing the need for stewardship. Current guidelines advocate regular review and deprescribing when appropriate, supported by tools as Beers Criteria, STOPP/START, National Institute for Health and Care Excellence (NICE) recommendations,& Choosing wisely campaigns.

Indications of PPIs

The indications of PPI therapy depend on the underlying condition, treatment duration, and goals of therapy. In clinical practice, many acid-related disorders are initially managed with a finite course of PPIs (*"treatment phase"*) followed by reassessment. For example, uncomplicated gastro-esophageal reflux disease (GERD) or peptic ulcer disease is typically treated with a 4-8-week course to achieve mucosal healing and symptom resolution. After this induction period, clinicians should reassess the need for continued therapy. If symptoms have resolved and no high-risk features are present, PPIs can often be tapered, discontinued, or switched to on-demand use.

Type of Indication	Long-Term PPI (>8 Weeks)		Short-Term PPI (<8 Weeks)	
	Definite	**Conditional**	**Definite**	**Conditional**
Therapeutic	- GERD with erosive oesophagitis - Peptic stricture - Eosinophilic oesophagitis with histological response - Barrett's oesophagus - Zollinger-Ellison syndrome	- GERD with incomplete response to short-term PPI - GERD with recurrence of symptoms on PPI cessation - Eosinophilic oesophagitis (maintenance) - Idiopathic chronic cough (GORD-confirmed)	- GERD - *H. pylori* eradication (combination therapy) - Non-erosive GERD (symptom relief) - Peptic ulcer disease - Mild peptic inflammation	- Functional dyspepsia - Laryngopharyngeal reflux (LPR) - Mild gastritis
Prophylactic	- Chronic NSAID/Aspirin use + high GI risk - Antiplatelet therapy post-bleeding ulcer - Systemic sclerosis with reflux	- Long-term corticosteroids + GI risk factors	- NSAID/Aspirin use (short course + risk factors) - Post-endoscopic ulcer therapy - Stress ulcer prophylaxis (ICU only)	- NSAID/Aspirin use (short course + risk factors) - Post-endoscopic ulcer therapy - Stress ulcer prophylaxis (ICU only)

PPI, Proton pump inhibitors; GERD, Gastro-oesophageal reflux disease; NSAID, Non-steroid anti-inflammatory drug

In contrast, “maintenance therapy” refers to long-term PPI use aimed at preventing relapse or complications and should be prescribed at the lowest effective dose or on-demand dosing. Continuous daily PPI therapy is indicated in patients with high-risk conditions such as severe erosive esophagitis, Barrett's oesophagus, active peptic ulcer bleeding, recurrent ulcer disease, or Zollinger–Ellison syndrome.

According to the recommendations of the American Gastroenterology Association (AGA), proton pump inhibitors (PPIs) should be avoided in certain conditions to minimize the risk of long-term harms. In the short-term setting, PPIs are not advised for isolated throat symptoms, acute undifferentiated upper gastrointestinal complaints such as pain, nausea, or vomiting that are not clearly attributable to gastro-oesophageal reflux disease (GERD) or peptic ulcer disease, and isolated lower gastrointestinal symptoms. For long-term use, PPIs should be avoided in patients with non-erosive reflux or functional dyspepsia who fail to respond to high-dose therapy, as well as in those with peptic ulcer disease including gastric or duodenal erosions. From a prophylactic perspective, long-term PPI therapy is not recommended for patients receiving steroid treatment without concomitant NSAID or antiplatelet therapy, nor for the prevention of recurrent gastrointestinal bleeding when the cause is unrelated to peptic ulcer disease. These restrictions highlight the importance of tailoring PPI therapy to well-defined indications, thereby reducing unnecessary exposure and mitigating potential adverse effects associated with prolonged use.

NICE recommends routine PPI prophylaxis in patients over 45 years of age on long-term NSAIDs for chronic conditions, while the American College of Gastroenterology (ACG) advises PPI use in high-risk groups such as those over 60 years, with prior ulcers, or taking corticosteroids/anticoagulants. Mortality from GI bleeding is significantly higher in NSAID users, highlighting the importance of co-prescription. For dual antiplatelet therapy, the European Society of Cardiology (ESC) supports routine PPI use, whereas American societies recommend a selective approach based on risk factors. PPIs are also advised for patients on warfarin or direct oral anticoagulants (DOACs), and guidelines from NICE, ACG, and European Alliance of Associations of Rheumatology (EULAR) support PPI use in corticosteroid-treated patients with additional GI risks, especially when combined with NSAIDs. Thus, the stewardship framework stresses the importance of appropriate initiation, duration, and deprescribing to avoid overuse

PPIs are highly effective but overprescribed globally. Clinical guidelines recommend short-term use for most acid-related disorders and long-term therapy only for high-risk conditions. Stewardship focuses on appropriate prescribing, minimizing duration, and deprescribing when possible, to reduce long-term harms.

Source: *Andrawes M, et.al; Medicina 2025, 61,1569.*

EXCEL

Dr. Prabhu Kasture (MD, DPH)
Director Medical Services & Pharmacovigilance
Phone No.: 022-66638043
Email: prabhu.k@bluecrosslabs.com
Correspond: Blue Cross Laboratories Pvt Ltd., Peninsula Chambers, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013.
Website: http://www.bluecrosslabs.com