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EXCEL Medical Bulletin

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AMLODIPINE FOR HEART FAILURE PATIENTS WITH DILATED CARDIOMYOPATHY

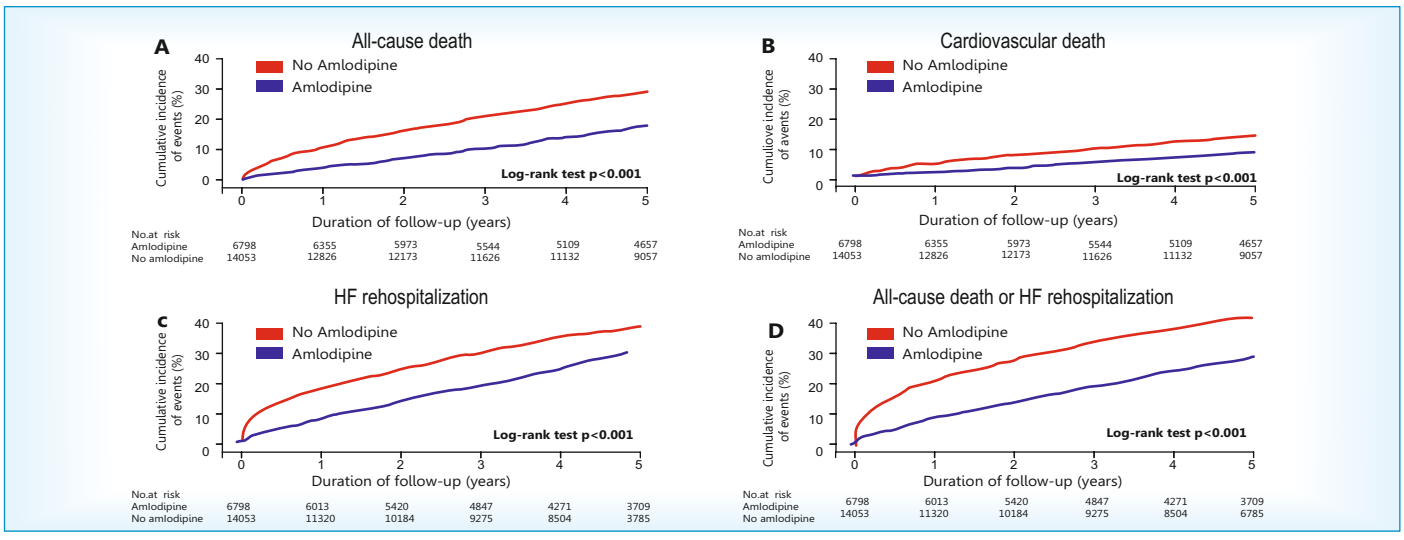
Heart failure (HF) remains a major cause of morbidity and mortality globally despite advancements in medical therapy. It is a rapidly growing public health issue with an estimated prevalence of 64 million people globally.

Amlodipine, a long-acting calcium channel blocker (CCB) is commonly used for hypertension & angina with demonstrated safety and efficacy. Evidence of its effectiveness in patients with HF and non-ischemic cardiomyopathy is inconclusive in previous studies. The PRAISE 1 (The Prospective Randomised Amlodipine Survival Evaluation) trial demonstrated Amlodipine's efficacy in lowering risk of death in patients with severe chronic HF and non-ischemic cardiomyopathy, whereas the PRAISE 2 trial did not show any clinical benefit. However, the different results may be due to differences in patient characteristics, particularly the proportion of patients with hypertension between the two trials (56% in PRAISE 1 vs. 17.4% in PRAISE 2).

To clear this inconsistent outcomes, a recent study explored the clinical efficacy of long-term (5-year follow-up) Amlodipine treatment on mortality after HF in patients (n=20,851) with dilated cardiomyopathy (DCMP) and found significantly ($p<0.001$) positive results.

Key results:

- Patients receiving amlodipine had a significantly lower risk of all-cause death than those not receiving amlodipine (32.0 vs. 56.6 per 100,000 person-years).
- The amlodipine group had better clinical outcomes of cardiovascular (CV) death and HF rehospitalisation (CV death: 12.2 vs. 22.4 per 100,000 person-years; HF rehospitalisation: 66.4 vs. 90.5 per 100,000 person-years).
- The composite of all-cause death or HF rehospitalisation was lower in the amlodipine group than non-users (81.1 vs. 123.8 per 100,000 person-years)
- In addition, the outcomes were consistent among different subgroups, particularly among those with an older age (≥60 years), a higher systolic blood pressure, and fewer comorbidities.



There are supportive potential mechanisms that may explain the beneficial effects of Amlodipine in patients with HF through both non-clinical and clinical studies;

I. Left ventricular (LV) remodelling and diastolic dysfunction are strong predictors of worsening prognosis in patients with DCMP and HF. Amlodipine reduces LV mass and volume and improves left diastolic function, which could potentially lead to clinical improvements in HF patient outcomes. This has been proved in a previous clinical study, where Amlodipine improved diastolic and long axis functions of the left ventricle in patients with arterial hypertension and stable angina pectoris.

ii. Amlodipine have been reported to have antioxidant properties and this characteristic may help protect against oxidative stress and inflammation, both of which are known to play a role in the development and progression of HF. It also has been found to inhibit the production of reactive oxygen species and increase the activity of antioxidant enzymes, which could also contribute to its beneficial effects in patients with HF.

iii. Amlodipine with its vasodilatory effect potentially improves myocardial perfusion and oxygen supply hence improving clinical results.

iv. Further to the above, it has been revealed that Amlodipine may decrease peripheral resistance, increase cardiac output and reduce myocardial oxygen demand, all of which may contribute to its beneficial effects in patients with HF.

Thus through various potential mechanisms explained and clinical evidence, Amlodipine may be an effective medication for the treatment of HF.

Source: Bae S. et.al; Front. Cardiovasc. Med.; 2023; 10:1305824, Shahim B, et al. Cardiac Failure Review. 2023; 9:e11, Zaliunas R, et al. Acta Cardiol. 2005; 60(3):239-46.

SAFETY OF PROTON-PUMP INHIBITORS

Proton-pump inhibitors (PPIs) have been the mainstay for treatment of acid-peptic diseases. PPIs have demonstrated patient tolerance, excellent safety, and superior acid suppressing capability than other agents.

They are also frequently prescribed for prophylactic purposes and in conjunction with non-steroidal anti-inflammatory drugs. Generally prescribed for four to eight weeks, it may be also prescribed for a longer period of time in patients with comorbidities and multiple medications. This led to conduction of studies that have shown an association between long-term use of PPIs and risk of pneumonia, major cardiovascular (CV) events, dementia, electrolyte disturbances, bone fractures, gastric cancer and kidney injury.

However, the evidence generated for the risks mentioned above were reported to be inconclusive and contradictory.

Below is a summary of clinical data supporting the long-term use of PPIs (Omeprazole, Esomeprazole, Pantoprazole, and Rabeprazole):-

- ***Electrolyte abnormalities:*** A retrospective data showed no vitamin B12 deficiency in patients receiving concomitant metformin and Pantoprazole for 1 to 4 years which was corroborated from another study for iron malabsorption as well as, in patients with Zollinger-Ellison syndrome on chronic PPI therapy.
- ***Bone fracture:*** A large-scale case control study & recent 2018 meta-analysis (12 studies) studies found no dose dependent relationship between PPI use and the risk of bone fracture. No significant difference was observed comparing Pantoprazole and placebo for fracture rate after a follow-up of 3 years.
- ***Dementia:*** The largest trial with Pantoprazole (>17,000 patients from 33 countries, follow up of three years) showed no significant difference between Pantoprazole and placebo for dementia. Similar results were obtained in 2019 meta-analysis of 6 studies.
- ***Community-acquired pneumonia (CAP):*** PPIs have been reported as possible contributors to ventilator associated pneumonia, but the quality of evidence is low. A study conducted for a 5-year period in patients with gastrointestinal (GI) symptoms and diagnosis of chronic kidney disease (CKD) showed that patients on long-term use of Pantoprazole reported a lower risk of developing CAP. A meta-analysis (7 studies) failed to show a conclusive association between PPIs and respiratory infections.

- ***CV risk:*** PPIs are frequently used in patients with CV disease as prophylaxis to mitigate the risk of GI bleeding due to antithrombotic or antiplatelet medications. Guidelines from the European Society of Cardiology, the American College of Cardiology, and the American Heart Association have recommended PPIs to reduce the risk of GI bleeding in CV patients treated with dual antiplatelet therapy (DAPT). Evidences from multiple meta-analysis also highlighted no increased CV risk in patients taking long-term aspirin with PPI. A study demonstrated that Pantoprazole can be safely used as a PPI in patients receiving DAPT of aspirin and clopidogrel. Clopidogrel requires activation by CYP2C19 and Pantoprazole does not reduce the antiplatelet effect since Pantoprazole is metabolized by CYP2C9 and has low affinity for CYP2C19.
- ***Kidney injury:*** It is demonstrated that use of PPI in a chronic kidney disease population was not associated with increased mortality or progression to end-stage. There is no clear guideline yet available so clinicians can choose to routinely monitor creatinine levels and/or obtain urinalysis testing in high-risk patients on PPI therapy to assess for kidney disease progression.
- Only one study, spanning 15 years, comprising of 142 patients on initiation for continuous maintenance treatment of severe acid-peptic disease have assessed the long-term safety of Pantoprazole. Out of the initial, a total of 99 patients completed 10 years of the study, with 39 patients completing 15 years of treatment. The study concluded Pantoprazole to be effective and well-tolerated, with no identified safety concerns.

However, while considering the potential administration of PPIs, its appropriate indications of therapy should be confirmed as a first step and long-term PPI should be used judiciously and with high clinical vigilance.

Source: Bhatnagar MS, et al. Cureus. 2024; 16(1): e52773, Turshudzhyan A, et al. World J Gastroenterol 2022; 28(24): 2636-2781

ASSOCIATION OF STATIN WITH REDUCED RISK OF DEMENTIA IN HEART FAILURE PATIENTS

Heart failure (HF) and dementia are common comorbidities in the older people with HF affecting more than 64 million individuals worldwide and its prevalence continuing to rise, attributable to a growing and ageing population.

Hypercholesterolemia may be positively correlated with dementia in middle-aged people. In fact, cognitive impairment is common in patients with HF, with estimates of its prevalence ranging from 10 to 68%.

For mild HF, the predominant morphological feature of brain injury includes atrophy of the medial temporal lobe, accompanied by significant cognitive declines in attention and memory. Other reports have also implicated multiple aspects of higher cerebral dysfunction in chronic HF, including domains of cognition, language, psychomotor function, and visuospatial acuity.

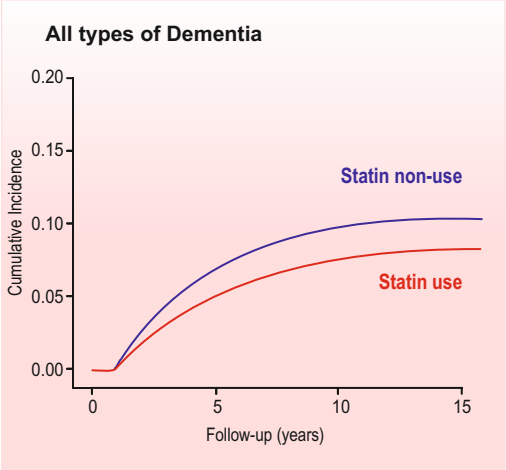
Although the precise pathophysiological processes involved are still under debate, events including poor perfusion, micro-embolism, ischaemic syndromes, cerebral inflammation and endothelial dysfunction have been proposed to play a role. Additionally, shared risk factors, including vascular comorbidities of atrial fibrillation and diabetes, may further predispose patients with HF to dementia.

Emerging evidence has suggested that higher LDL-C concentrations is associated with an increased dementia risk, independent of vascular risk factors.

Several studies conducted have showed protective effects of statins in cognitive function, dementia and Alzheimer disease (AD) in elderly patients summarized as below;

- A meta-analysis based on 31 studies supported that statins use was associated with decreased dementia risk, and a dose–response showed per 1 year of duration of statins use was associated with 20% reduced dementia risk.

- Another retrospective cohort study of 33,398 patients aged ≥ 60 years, found statin's association with a significantly lower risk of incident dementia in the elderly patients.
- A comprehensive meta-analytic (25 studies) evidence demonstrated the positive effects of statins on reducing risk of all-caused dementia, Alzheimer's disease (AD), vascular dementia (VaD) and mild-cognitive impairment (MCI). Therefore, a detailed evaluation of the association between statin use and dementia incidence in HF patients was recently conducted.



The results obtained corroborated the above outcomes and the added value obtained is such that,

1. Statin use was linked to a significantly 20% lower risk of all-cause dementia.
2. Specifically, it demonstrated a 28% risk reduction in AD, 18% risk reduction in VaD, and 20% risk reduction in unspecified dementia.
3. The results remained consistent across subgroups, including age, gender, comorbidities, indicating that the cognitive benefits of statin may extend to a broad population of HF patients.
4. Furthermore, lower serum LDL-C levels were associated with lower risk of dementia, suggesting a potential "dose response" benefit of LDL-C lowering in the prevention of incident dementia.

Mechanism of statins in reducing dementia risk:

The reduction of dementia risk is likely to be mediated through both LDL-C dependent and LDL-C-independent pleiotropic pathways.

Hypercholesterolemia in the brain can be deposited in the hippocampus, causing amyloid precursor protein to be degraded, which causes degeneration of neurons, resulting in AD.

➤ ***Statins may reduce the formation of β-amyloid peptide by decreasing cholesterol levels.***

I. Statins have a stable effect on the homeostasis of the nervous system cholesterol, inhibit the synthesis of cholesterol, lower its level, and thus inhibit the β metabolism of amyloid precursor protein.

ii. In addition, the intermediate product isoprene of cholesterol biosynthesis in dementia patients is often depleted, thus affecting cell growth, mitosis, and signal transduction. Statins have a regulatory role in the above intracellular mechanisms.

iii. Furthermore, apoE4, an important cholesterol transporter, is a risk factor and genetic marker of AD and plays an important role in Aβ deposition and the formation of senile plaques. Astrocytes and microglia secrete apoE, which requires the isoprenylation of key proteins, while mevalonic acid is the precursor of isoprene derivatives.

Statins inhibits the synthesis of mevalonate, inhibits apoE secretion, and reduces extracellular apoE levels, thereby preventing the formation of senile plaques and improving cognitive function.

➤ ***For LDL-C-independent pathways,*** statins may exert anti-oxidant and anti-inflammatory effects that may prevent cognitive impairment and dementia.

Therefore, these findings provide useful insights into the potential preventative role of statins and its association with lowered risk of dementia in patients with HF.

Source: Ren QW, et al. Lancet Reg. Health West. Pac. 2024; 44: 101006, Zhang X, et al. Medicine. 2018; 97:30 (e11304)

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