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Medical Bulletin

EXCEL Division of Blue Cross Laboratories Pvt Ltd.

ATORVASTATIN FOR NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD), a prevalent condition, is projected to surpass alcoholic-related liver disease as the primary cause of liver transplants by 2030. NAFLD is defined by the presence of at least 5% of fat accumulation in the liver without significant alcohol consumption and absence of other etiologies causing liver injuries. It is a spectrum of liver disorders starting from fat deposition in the liver (steatosis), developing to inflammation of the liver (non-alcoholic steatohepatitis or NASH), leading to scarring of the liver (fibrosis and cirrhosis) and eventually progressing to liver cancer (hepatocellular carcinoma).

Dyslipidemia is frequently observed in NAFLD patients and excessive cholesterol accumulation in the liver can precipitate hepatic steatosis and atherosclerosis. Impaired hepatic cholesterol homeostasis may be a common cause of both NAFLD and atherosclerosis, as disrupted hepatic cholesterol equilibrium and free cholesterol aggregation are linked to NASH/NAFLD pathogenesis. Lipid-lowering capabilities of statins therefore holds promise for conferring beneficial effects in NAFLD. Recent studies have also suggested that statins may have potential benefits in reducing the risk and progression of NAFLD.

The use of Atorvastatin in NAFLD management offers several potential benefits;

i. Research indicates that Atorvastatin, when used at low-to-moderate doses, is generally safe and well-tolerated in patients with NAFLD.

ii. Atorvastatin may also lead to a decrease in liver enzyme levels, potentially enhancing liver function.

iii. Atorvastatin's cardioprotective effects are particularly relevant in patients with NAFLD, as they often have an increased risk of cardiovascular disease.

iv. Atorvastatin, known for its anti-inflammatory properties, may be beneficial in treating NAFLD, as inflammation is a significant factor in the progression of liver disease.

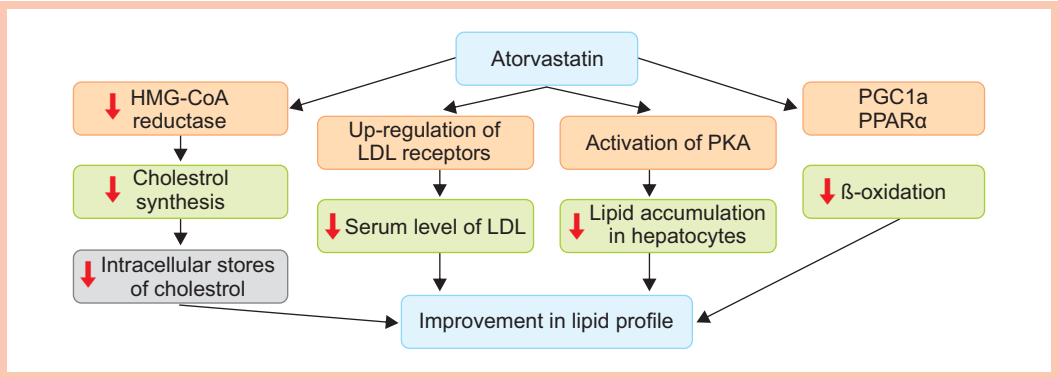
v. Atorvastatin may reduce the risk of hepatocellular carcinoma (HCC) in NAFLD patients by reducing inflammation and improving liver function.

Below is a brief summary on the possible beneficial mechanism of Atorvastatin in NAFLD;

✤ Atorvastatin & Lipid Profile

Atorvastatin effectively decreases cholesterol levels by variety of intricate mechanisms.

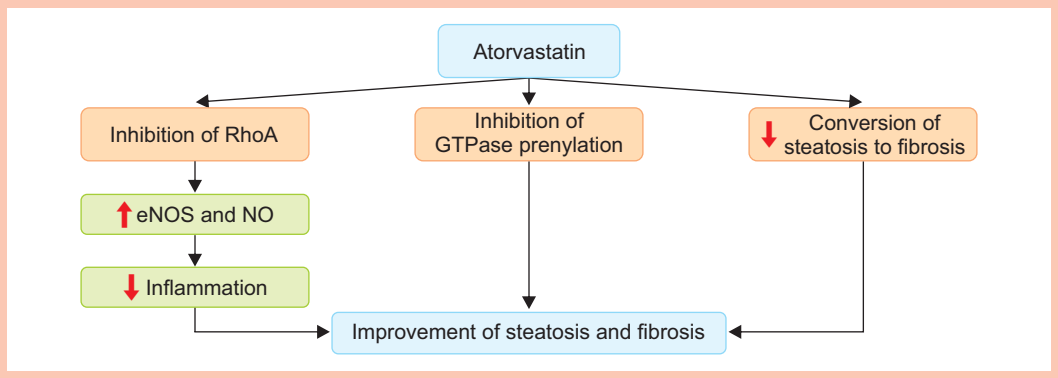
- One of its key actions involves the inhibition of HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase.
- Atorvastatin upregulates LDL (low-density lipoprotein) receptors, enhancing cholesterol clearance and improving overall lipid profile through a complex cascade of molecular events.
- Atorvastatin also activates the protein kinase pathway via AMPK (AMP-activated protein kinase), preventing lipid accumulation in hepatocytes and improving liver health by protecting against lipid build-up.
- Atorvastatin regulates beta oxidation through two key transcription factors - peroxisome proliferator-activated receptor alpha (PPARα) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α). The



interaction between Atorvastatin, PPARα and PGC1α, along with their target genes, significantly influences the expression of genes involved in beta oxidation and lipid metabolism.

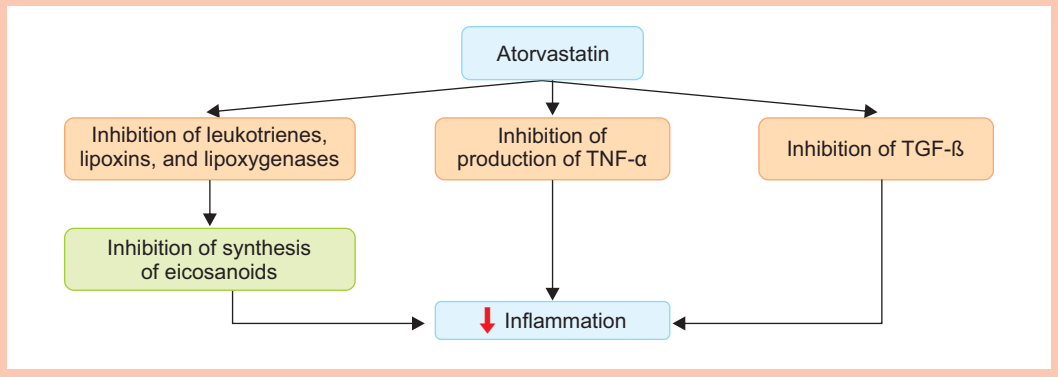
✤ Atorvastatin & its role in Liver Steatosis, Necrosis & Fibrosis

- Atorvastatin exerts its beneficial effects on the oxidative stress induced by angiotensin II by means of inhibiting RhoA - a small GTP-binding protein essential to many cellular functions and concurrently upregulating the expression and activity of endothelial nitric oxide synthase (eNOS), a powerful vasodilator and anti-inflammatory molecule.
- By inhibiting GTPase prenylation, a post-translational modification essential for the localization and function of numerous proteins involved in cell signaling and cytoskeletal architecture, Atorvastatin also ameliorates the harmful effects linked to fibrosis and cirrhosis.



✤ Atorvastatin & Liver Inflammation

- Atorvastatin effectively reduces hepatic inflammation caused by NAFLD by inhibiting leukotrienes, lipoxins and lipoxygenases and preventing the synthesis of eicosanoids, which are crucial in inflammatory processes.
- Its anti-inflammatory effect is also exhibited through its inhibitory action on the production of tumor necrosis factor



alpha (TNF-α), a potent pro-inflammatory cytokine, effectively diminishing the inflammatory response.

- Additionally, Atorvastatin exerts its anti-inflammatory effect by impeding the activity of transforming growth factor beta (TGF-ß), a cytokine involved in various physiological processes, including inflammation.

Atorvastatin, through its inhibitory effects on these key inflammatory mediators, effectively reduces tissue damage and improves clinical outcomes by mitigating the inflammatory cascade.

The above outcomes are derived from two studies, the 1st involved 57 patients with NAFLD who were administered Atorvastatin 20 mg for 32 weeks and the 2nd involved 40 patients with NAFLD who were administered Atorvastatin 20 mg for 3 months. It was found that there was a noticeable and statistically significant amelioration in the inflammatory condition of the liver, as well as in the overall CRP (C-reactive protein) index. The lower dosage and monitoring of liver enzymes is recommended to alleviate any associated side effects.

By integrating Atorvastatin into the treatment plan for NAFLD patients, healthcare providers can address both dyslipidemia and liver disease, with further clinical exploration.

Sources: *Zhang S, et al. Molecules 2024; 29(8): 1859, Eslami Z, et al. Chonnam Med J. 2024; 60(1): 13-20, Ho A, et al. J Clin Lipidol. 2024; 18(4):e501-e508.*

PROTON PUMP INHIBITORS IN CARDIAC PATIENTS

Dual-antiplatelet therapy (DAPT) is recommended as a long-term measure for patients with acute coronary syndrome (ACS) and coronary artery disease (CAD). DAPT comprises of low-dose aspirin along with inhibitors of the P2Y12 receptor such as prasugrel, ticagrelor, or clopidogrel, however, these antiplatelet drugs significantly increase the risk of gastrointestinal (GI) bleeding. To prevent GI bleeding, proton pump inhibitors (PPIs) are advised in addition to DAPT, yet concerns persist regarding their prolonged use and potential adverse effects like elevated risk of cardiovascular disease (CVD) events and higher mortality among patients with a prior history of CVD. This is believed to be due to the drug-drug interactions (DDI) between the PPIs and Clopidogrel caused by competition for the same pathway (cytochrome P450). Although all studies have not demonstrated an elevated risk of major adverse cardiovascular events (MACE) associated with PPI use, yet concerns persist regarding their prolonged use and potential adverse effects.

This underscores the importance of careful consideration when prescribing PPIs along with DAPT, especially in situations where potential interactions may impact patient outcomes.

✤ Similarities and Differences of Individual PPIs and its Effect in Patients on Clopidogrel

All PPIs, except Rabeprazole are extensively metabolized via the hepatic CYP2C19 and CYP3A4 enzymes. Clopidogrel is also transformed to its active metabolite by the CYP2C19 enzyme. Hence, there is competitive behaviour between clopidogrel and PPIs for the CYP2C19 enzyme. The impact of each PPI on CYP metabolism varies, leading to potential differences in clopidogrel metabolism and subsequent cardiovascular outcomes.

- Omeprazole is almost completely metabolized by CYP3A4 and CYP2C19; however, the role of CYP2C19 is predominant.
- Esomeprazole undergoes relatively lower metabolism by CYP2C19 as opposed to Omeprazole. CYP2C19 is responsible for around 70% clearance of Esomeprazole and approximately 90% of the clearance of Omeprazole.
- Pantoprazole is primarily metabolized by CYP2C19, which accounts for more than 80% of its metabolism, with the remaining portion metabolized by CYP3A4.
- Rabeprazole is primarily metabolized through non-enzymatic reduction to a thioether metabolite and is a weak competitive CYP2C19 inhibitor. Thus, it has negligible impact on the metabolizing process of Clopidogrel when compared to the other PPIs.

Therefore, owing to the Clopidogrel-PPI interaction and risk of bleeding with DAPT, a combination of guideline recommendations (Table 1) and practical approach is required to balance the need for compliance with DAPT and minimize the risk due to the said interaction.

Guideline	PPI Recommendation with DAPT
ACCF/ACG/AHA (2010, 2016)	• PPI only for high-risk bleeding patients (prior GI bleeding, advanced age and concomitant use of warfarin, steroids or non-steroidal anti-inflammatory drugs). • Routine use of either a PPI or an H2RA (Histamine-2 receptor antagonist) is not recommended for patients at lower risk of upper GI bleeding, who have much less potential to benefit from prophylactic therapy.
ESC (2018)	• Routine use of PPI for all patients on DAPT.
International consensus (2020)	• Management of patients with non-variceal upper GI bleeding, patients with a history of ulcer bleeding who are on cardiovascular prophylaxis with either single- or DAPT should receive PPI medication.
AIGO, ANMCO (2020)	• In patients taking one antiplatelet agent, standard dose of PPIs should be used if GI risk factors are present [history of Peptic Ulcer Disease (PUD), receiving antiplatelet therapy, concomitant use of vitamin K-antagonists (VKAs), concomitant use of another antiplatelet agent, non-steroidal anti-inflammatory drugs (NSAIDs), direct-acting oral anticoagulants (DOACs), or steroids]. • In patients receiving clopidogrel, choosing PPI lacking interference with the hepatic CYP450 enzymes might be preferred. • There are no restrictions on the choice of PPIs with prasugrel and ticagrelor.

ACCF: American College of Cardiology; ACG: American College of gastroenterology; AHA: American Heart Association; ESC: European Society of Cardiology; ANMCO: National Association of Hospital Cardiologists; AIGO: Italian Association of Hospital Gastroenterologists and Endoscopist.

✤ Practical approaches to address the concern of bleeding;

1. Present regulations for stable CAD suggest a minimum 6-month DAPT for patients receiving drug-eluting stents (DES) and a minimum 1-month DAPT for patients receiving bare-metal stents.
2. The suggested duration of DAPT for patients with ACS receiving PCI is at least 12 months.
3. DAPT may be prolonged to >12 months in patients who have minimal bleeding risk or it may be limited to 6 months in patients with an elevated bleeding risk (or to 3 months in extremely elevated bleeding-risk patients).

The shortened duration of DAPT also reduces the duration of concomitant PPI intake.

Still, it is imperative to regularly review and document the indications for long-term PPI use in cardiac patients.

A judicious approach involves selecting a PPI with minimal inhibitory effects on CYP2C19, such as ***Rabeprazole owing to its unique metabolic profile*** which helps to optimize gastro-protection while minimizing potential drug interactions.

Source: *Kahali D, et al. IJCC. 2024, Ogawa R, et al.Clin Pharmacokinet. 2010; 49(8):509-533, Niu Q, et al. J Cardiovasc Pharmacol Ther. 2017; 22(2):142-152, El Rouby N, et al. Expert Opin Drug Metab Toxicol. 2018; 14(4):447-460, Andersson T, et al. Br J Clin Pharmacol. 1998; 45(4):369-375.*

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