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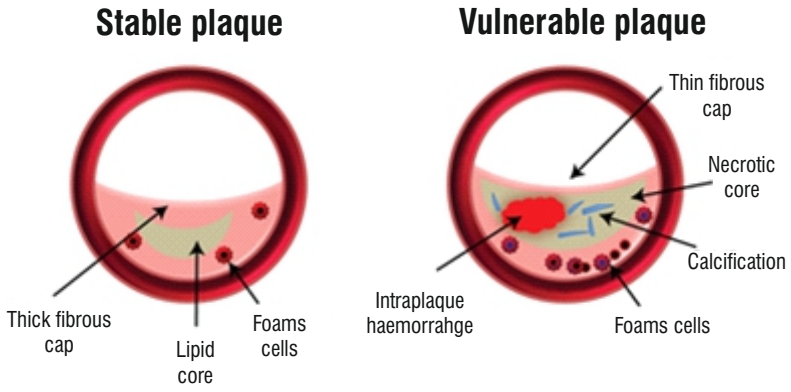
BLUGLIP-M (VILDAGLIPTIN AND METFORMIN) MAY IMPART STABILITY TO THE VULNERABLE PLAQUES

Vulnerable atherosclerotic plaque rupture is the principal mechanism that accounts for myocardial infarction and stroke. The plaque morphology and stability depend on the cellular components present within the plaque and associated inflammatory response.

Vulnerable plaques are characterized by fragile, thin fibrous caps, massive lipid cores, inter-plaque hemorrhage, immune activations and increased levels of macrophages, proinflammatory mediators like chemokines, cytokines and matrix metalloproteinases (MMPs) and fewer smooth muscle cells.



Type 2 diabetes mellitus (T2DM) is a recognized risk factor for coronary atherosclerosis and subsequent major acute cardiovascular events (MACE) which usually arise from the rupture of the coronary vulnerable plaques resulting in a 2-3 fold higher mortality risk compared to patients without T2DM.

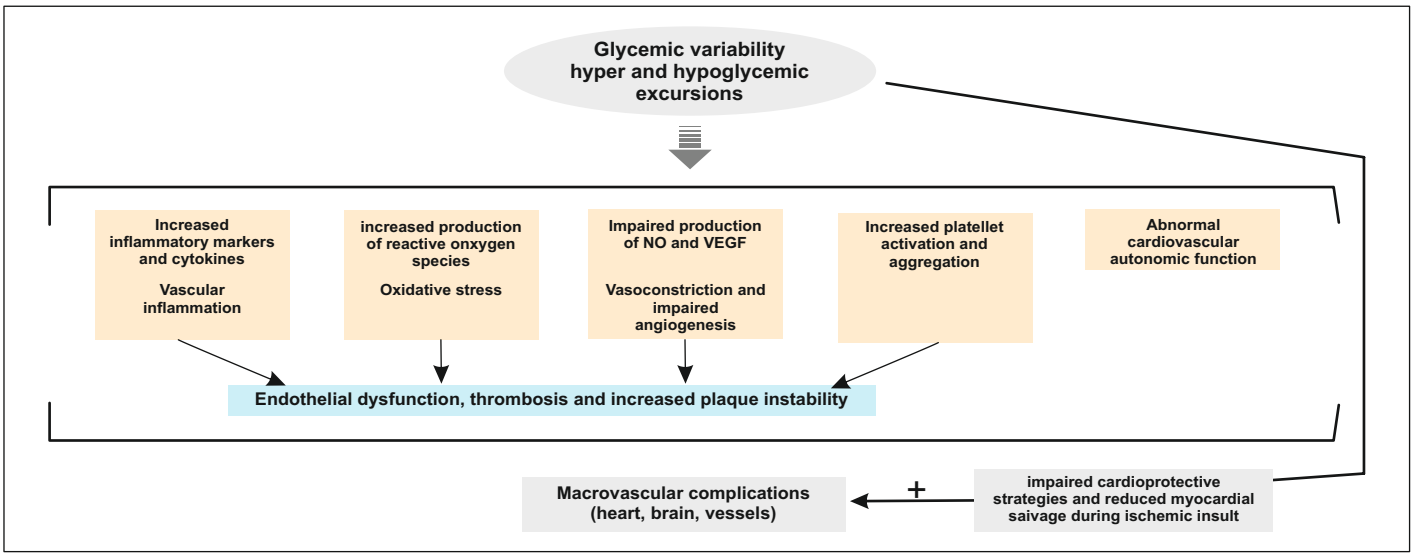
GLYCEMIC VARIABILITY AND PLAQUE VULNERABILITY

Glycemic variability represented by Mean Amplitude of Glycemic Variation (MAGE) and measured by the continuous glucose monitor (CGM) has been shown to be associated with coronary plaque vulnerability.

Glycemic variability refers to the blood glucose oscillations that occur throughout the day and both long-term glycemic variability and short-term glycemic variability are known to be deleterious.

High glycemic variability is an independent determinant of increased lipid and decreased fibrous contents with larger plaque burdens.

The higher glycemic variability has been shown to be closely linked with markers of oxidative stress and inflammation, vasoconstriction and impaired angiogenesis and increased platelet activation and aggregation that add to plaque vulnerability. This suggests that poor management of daily glycemic variability could adversely affect the endothelial function promoting atherosclerosis progression and the advancement of plaque vulnerability, leading to fatal cardiovascular events.



The glycemic variability could alter the balance of monocyte subsets, excessive formation of advanced glycation end products AGEs via the activation of Nuclear factor kappa B (NF-kB) and protein kinase C pathway promoting the expression of atherogenic genes causing damage to the coronary artery endothelium leading to changes in coronary lesion morphology and favoring plaque vulnerability.

Additionally, the coronary lesions of T2DM patients are characterized by a thinner minimal fibrous cap with a larger lipid core. Also, the presence of macrophages in the microvessels of T2DM patients indicate the presence of a coronary inflammatory process.

Oral anti-diabetic drugs like vildagliptin and metformin have been shown to be beneficial in impaired plaque stability.

VILDAGLIPTIN

Vildagliptin, a DDP-4 inhibitor is widely used for the treatment of T2DM. Recent studies have revealed that the effect of vildagliptin in lipid-controlled patients with coronary artery disease causes:

- An absolute decrease in the MAGE representing lower glycemic variability.
- An absolute increase in the fibrous cap thickness along with a decrease in the lipid arc.

This suggests that vildagliptin reduces glucose fluctuations and simultaneously stabilize coronary plaque morphology in patients with impaired glucose tolerance. Additionally, vildagliptin is also known to reduce the proinflammatory activation of macrophages, an important cell type in atherogenesis.

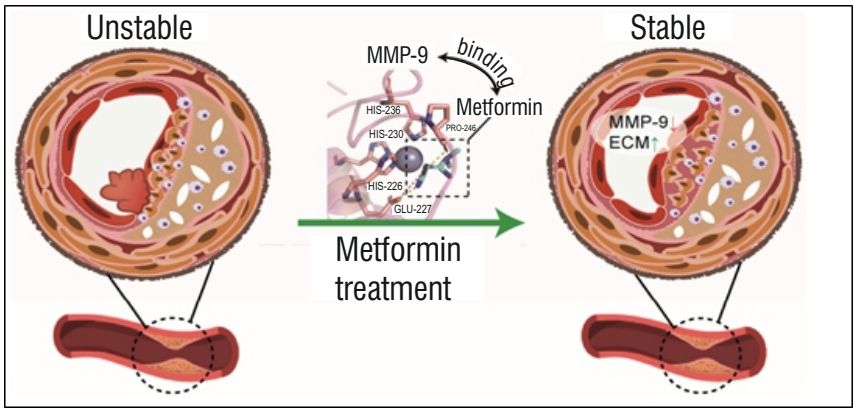
Based on the findings, it can be deduced that vildagliptin has a potential benefit to stabilize the plaque vulnerability even in thin-cap fibroatheromas, which are a main cause of MACE.

METFORMIN

Matrix metalloproteinases (MMP) have a specific proteolytic activity against the extracellular matrix (ECM) which results in the thinning of the fibrous cap and plaque instability. MMP-9, is a widely studied member of the MMP family and is mainly distributed in the fibrous cap area of atherosclerotic plaques, and the level and activity of MMP-9 in unstable plaques are higher than those in stable plaques.

Many studies have shown that high MMP-9 expression can be used as a predictor of atherosclerotic plaque instability, whereas its overexpression may lead to plaque instability. Therefore, MMP-9 can be a potential target for improving atherosclerotic plaque stability.

Preclinical studies have shown that metformin directly binds to MMP-9, and significantly downregulates MMP-9 expression/activity in local plaques and circulation, which may explain the role of metformin in improving plaque stability.



Metformin also has an anti-inflammatory effect and has shown to reduce the macrophage infiltration in the plaque which is one of the important pathological effects predisposing the plaque to vulnerability.

Additionally, metformin has been reported to promote macrophage cholesterol efflux thus decreasing the lipid content of the atherosclerotic plaque and increasing its stability.

Since diabetics are more prone to atherosclerotic cardiovascular disease and the progression to MACE, a combination of the anti-diabetic agents, vildagliptin and metformin through their action in preventing glycaemic variability and their molecular actions on the plaque, may be a potential therapeutic intervention for improvement of plaque stability and prevent the occurrence of acute cardiovascular events in T2DM patients.

Source: Milzi A et al. Cardiovasc Diabetol 2017; 16(152): 1-9; Ito T et al. J od Cardiology 2022; 79(1): 58-64; Ambrees S et al. Nutrients 2022; 14(10): 1991; Yamamoto H et al. BMC Cardiovasc Disorders 2021; 21(92): 1-9; Alfieri V et al. Int J Mol Sci 2021; 22(16): 8393; Dettori R et al. Cardiovasc Diabetol 2020; 19: 192; Chen X et al. J od Cardiovasc Devp & Disease 2023; 10(54): 1-14.

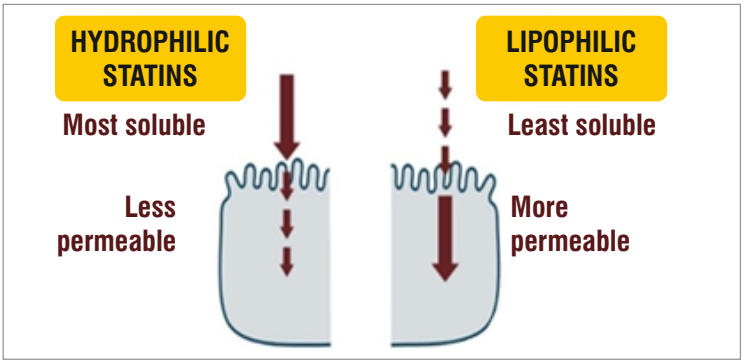
LIPONORM (ATORVASTATIN) BEING LIPOPHILIC MAY OFFER BETTER CARDIOPROTECTION

Drugs can be classified as hydrophilic or lipophilic depending on their ability to dissolve in water or in lipid-containing media.

Statins are similar in mode of action, however, they differ in their solubility owing to the presence/absence of polar moieties on the largely hydrophobic backbones.

According to their solubility, statins are either Hydrophilic or Lipophilic:

- Lipophilic statins like Atorvastatin can easily pass more deeply into the membranes and therefore get widely distributed in different tissues.
- Hydrophilic statins like Rosuvastatin remain attached with the polar surface of the membrane and require protein transporters to enter the cell. They may be less able to have non-lipid effects on extra hepatic tissues due to the liver-specific, carrier-mediated mechanisms needed for their uptake.
- Thus, the ability of lipophilic statins to reach extra hepatic tissues could account for the more favorable cardiovascular outcomes.



Clinical evidences for Atorvastatin

1. The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study compared Atorvastatin 80 mg (intensive therapy) with Pravastatin 40 mg (moderate therapy) in patients (n=4162) with acute coronary syndrome. Atorvastatin significantly reduced the rate of hospitalization for heart failure (HF) and reduced the risk of HF compared with Pravastatin. Lipid lowering with lipophilic atorvastatin thus provided greater protection against death and cardiovascular events than hydrophilic pravastatin.
2. A meta-analysis of 13 studies (10,966 patients), reported superiority of lipophilic statins in all-cause mortality, cardiovascular mortality and hospitalization for worsening HF.
3. Superiority of lipophilic statins has also been observed when cardiac function and anti-inflammatory effects were evaluated in patients with established HF.
   - A meta-analysis with 19 trials (6,200 patients) obtained more favorable results with lipophilic Atorvastatin in improving cardiac function and reducing inflammation, with a greater rise in left ventricular ejection fraction (LVEF).
   - Atorvastatin was also superior in reducing B-type natriuretic peptide (BNP), C-reactive protein (CRP), interleukin 6 and tumor necrosis factor α compared to hydrophilic statins.
4. Effect of Atorvastatin (5 mg) in comparison to Rosuvastatin (2.5 mg) therapy on cardiac sympathetic nerve activity in patients with chronic heart failure (CHF) demonstrated Atorvastatin to be superior in improving LVEF and reducing BNP levels.

Thus, beyond improving lipid profile, these findings emphasise the role of lipophilic statins on inflammation response.

Possible superiority of lipophilic statins can be attributed to its solubility profile playing a beneficial role in the favorable cardiovascular outcomes.

Source: Climent E, et al. Front. Cardiovasc. Med. 2021; 8, Cannon CP, et al. N. Engl. J. Med. 2004; 350:1495-1504, Bonsu KO, et al. Cardiovasc Drugs Ther. 2016; 177-188, Bonsu, et al. Cardiovasc. Ther. 2015; 33(6): 338-346, Tsutamoto T, et al. Circulation Journal. 2011; 75(9): 2160-2166.

APPROPRIATE DOSING OF AZIBEST (AZITHROMYCIN) FOR TONSILLOPHARYNGITIS IN CHILDREN

Tonsillopharyngitis is one of the most common infectious diseases of childhood affecting about 15 to 30% of them. The condition is common in children between the ages of 5 and 15, peaking during the first few years of school. The most frequent bacterial cause of tonsillopharyngitis requiring antibiotic treatment is Group A beta-hemolytic Streptococcus (GABHS).

In Children above 6 months
60 mg/kg of Azithromycin is the effective dosage in eradicating GABHS
Azithromycin is a frequent choice for treatment of GABHS tonsillopharyngitis

In 2 regimens

- **12 mg/kg/day for 5 days**
- **20 mg/kg/day for 3 days**

*Dosage of Azithromycin in children should not exceed 500 mg per day.

Rationale for Dosage

- Unique pharmacokinetics (long half-life 68-79 hours) & better tissue penetration
- Convenient once daily dosing
- Higher dose (12 mg/kg) of Azithromycin results in higher concentrations in tonsillar tissue
- 12 mg/kg for 5 days dosage found to be superior to the 10-day comparators (Penicillin & Erythromycin)

Source: Casey JR, et al. Clin. Infect. Dis. 2005; 40: 1748-55, Doherty BO, et al. Clin. Infect. Dis. 1996; 15: 718-24, Cohen R, et al. Pediatr Infect Dis J. 2002; 21: 297–303, Cohen R, et al. Pediatr Infect Dis J. 2004; 23(2): 129-134, 5. https://www.ncbi.nlm.nih.gov/

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