Quarter 4, 2024 | VOLUME 12 | NUMBER 11

# Medical Bulletin

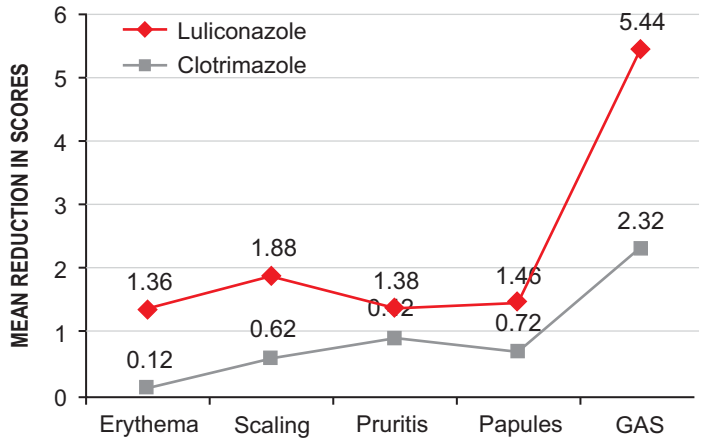
EXCEL Division of Blue Cross Laboratories Pvt Ltd.

## MULTIPOTENTIALITY OF LULICONAZOLE AGAINST VARIOUS FUNGAL STRAINS

Dermatophytosis is the most common type of superficial fungal infection that affects as many as 20–25% of the world's population. It is a significant health issue, particularly in tropical nations like India because of the hot and humid weather. Dermatophytosis is classified into three generations Epidermophyton, Trichophyton, and Microsporum. Tinea corporis and tinea cruris refer to the dermatophytic infections of the glabrous skin of the body (excluding palms and soles) and groins respectively. Tinea corporis (36–59%) and tinea cruris (12–27%) are the two clinical types of dermatophytosis that are most frequently seen in India. Dermatophytosis does not prove fatal, but it does interfere with everyday life, lead to a poor quality of life, and increase medical costs. The advantages of topical therapy over oral therapy, however, include fewer side effects, the avoidance of drug-drug interactions, better compliance, and lower costs.

The increase of drug-resistant fungi is one of the greatest challenges in a clinical setting and may affect the disease outcome. Due to the emergence of multi-drug resistant C. albicans, rational drug prescription based on the anti-fungal stewardship strategy and therapeutic drug monitoring is warranted.

The introduction of newer broad-spectrum antifungals like Luliconazole (LLCZ) has created new treatment options to address the increasing pathogenicity of superficial fungal infections. Luliconazole is a broad-spectrum antifungal agent with impactful fungicidal and fungistatic activity. It has shown exceptional potency against miscellaneous fungal strains like Candida, Aspergillus, Malassezia, Fusarium species and various dermatophytes. The in-vitro antifungal activity of LLCZ against dermatophytes is reportedly superior to that of other topical antifungal agents. Luliconazole is one among those topical antifungal agents, which offers a good efficacy and tolerability with a short duration of treatment. In one of the comparative study the short course (2 weeks) once daily topical luliconazole cream regimen was more effective achieving complete clearance, faster clinical cure, and mycological cure than standard 4 weeks twice daily clotrimazole cream.




*Comparisons of mean scored from baseline to end of treatment*

In one of the pooled prevalence of antifungal resistance ranged from 0% to 26%. The lowest resistance levels among azoles were observed in luliconazole with a frequency of 0%.

Infections with Scedosporium spp. and Lomentospora prolificans have become a serious threat in clinical settings. Lomentospora prolificans and S. apiospermum/P. boydii are opportunistic, multidrug-resistant pathogens causing invasive infections in immunosuppressed patients and sometimes in healthy persons. The high mortality rates associated with these infections can be correlated with their multidrug resistance. Recent study demonstrating LLCZ activity against Lomentospora prolificans in-vitro and in-vivo and the first study showing the antibiofilm effect of LLCZ in Scedosporium spp. It represents an extension of the literature regarding azole-resistant fungi and could potentially lead to the development of future treatment strategies against these opportunistic fungal pathogens. In another in-vitro evidence potent efficacy of luliconazole at low concentrations on Leishmania major makes it a good candidate for treatment of leishmaniasis, although clinical trials are warranted in this condition.

Luliconazole represents a significant advancement in antifungal therapy, offering a potent and targeted option for dermatophytosis treatment. Its broad-spectrum activity, combined with favorable pharmacokinetic properties, underscores its potential as a first-line treatment for various dermatophyte related infections.

***Sources:*** *Ayushi Mahajan et.al; benthamscience journal, Volume 16, Issue 3, 2021, Kermani F et.al; Iran J Public Health, Vol. 52, No.2, Feb 2023, pp.290-305.*

## BENEFICIAL EFFECTS OF FENOFIBRATE WITH ATORVASTATIN IN THE TREATMENT OF COMBINED HYPERLIPIDEMIA

Dyslipidemia refers to plasma lipid abnormalities including elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) or triglycerides (TG), and reduced levels of high-density lipoprotein cholesterol (HDL-C), or a combination of these attributes. Hypertriglyceridemia is among the most common dyslipidemias observed in clinical practice and is characterized by increased plasma TG levels (fasting state, >150 mg/dL; fed state, >175 mg/dL). Elevated TG either independently or together with low levels of HDL-C and high levels of small, dense LDL poses a high cardiovascular (CV) risk as part of atherogenic dyslipidemia. Additionally, diabetes and hyperlipidemia are linked with significant complications, thereby emphasizing lipid-modifying agents as potential medical options.

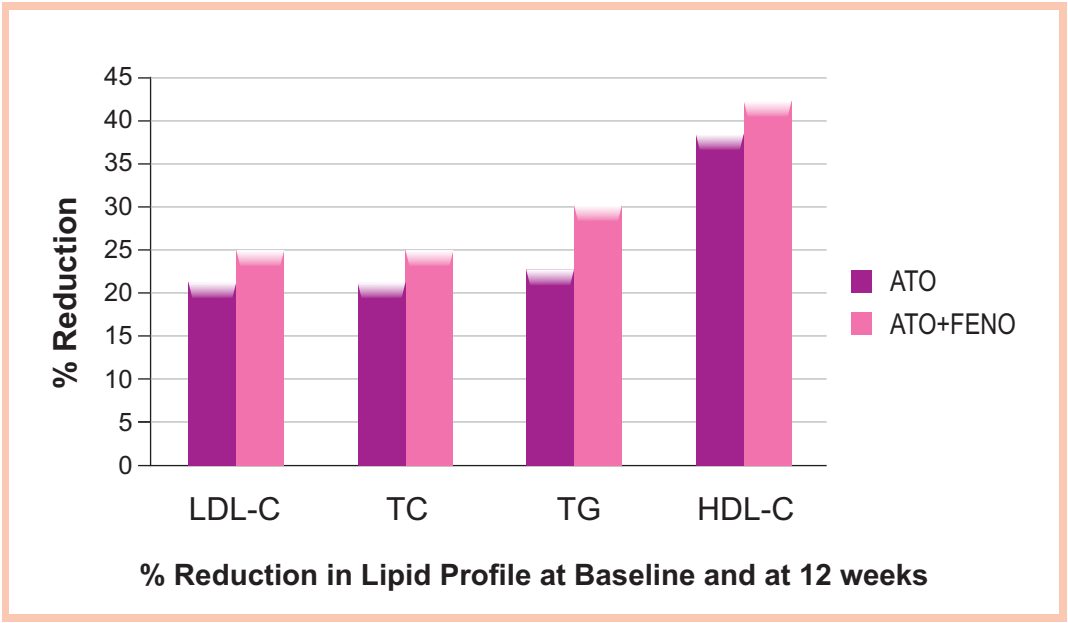
High serum cholesterol and elevated low-density lipoprotein (LDL) cholesterol are important risk factors for coronary heart disease. Many patients on statin therapy have initial or recurrent coronary heart disease events despite reductions in LDL cholesterol. Interestingly, fibrate therapy, which significantly decreases triglycerides and increases high-density lipoprotein (HDL) cholesterol without reducing LDL cholesterol, is associated with significant decreases in coronary events.

Recent studies showed that statin or fibrate monotherapies can improve the lipid profile in patients with type 2 diabetes and combined hyperlipidemia (CHL); however, these affect different aspects of lipoprotein (LP) metabolism. Hence, it is difficult to modify the lipid profile of patients with type 2 diabetes and CHL using monotherapy with either a statin or a fibrate, according to the recent suggestions of the American Diabetes Association (ADA).

Moreover, combined therapy with statins and fibrates is more effective in controlling atherogenic dyslipidemia in patients with combined hyperlipidemia than the administration of either drug alone.

Recognizing that statin and fibrate therapies affect different aspects of lipoprotein metabolism, combination therapy with these two classes of drug is emerging as a possible therapeutic approach for many high-risk patients, especially those with atherogenic dyslipidemia. The additive effects of statin-fibrate combinations on lipid profiles have been documented. The atorvastatin-fenofibrate combination has been shown to have a highly beneficial effect on lipid parameters in patients with type 2 diabetes and combined hyperlipidemia (CHL).

Both atorvastatin and fenofibrate significantly improved the lipid profile, each in different aspects, in this group of patients with type 2 diabetes and CHL. However, both monotherapies were not able to induce the maximum global change in patients' CAD risk profile. Conversely, combined therapy had a concurrent beneficial effect on all lipid parameters, changing the CAD risk status of these patients from high to low. These two hypolipidemic drugs used in the present study have complementary modes of action. Atorvastatin is a potent inhibitor of hydroxymethylglutaryl-CoA reductase, which decreases LDL cholesterol in plasma by upregulating LDL receptor activity. It has been shown that atorvastatin significantly reduced circulating levels of all major LDL subspecies: light, intermediate, and dense; however, in terms of absolute LP mass, the reduction in small dense LDL particles and atherogenic LDL particles, characteristic of CHL, was predominant . Atorvastatin also reduces the secretion of apo B-containing LPs. This is believed to account for its TG-lowering effect, which is more profound at higher doses. Effects on apo E, apo C-II, and apo C-III and a dose-dependent reduction in cholesteryl ester transfer protein activity by atorvastatin have also been suggested. Fenofibrate activates peroxisome proliferator-activated receptors, which induce an increase in LP lipase activity, a reduction in apo C-III, an increase in apo A-I, as well as a reduction in cholesterol ester transfer protein activity. These result in TG level reduction, redistribution of LDL particle size, and an HDL cholesterol increase. The significant reduction of apo B, with "low or normal" LDL cholesterol, seen in various trials with atorvastatin, fenofibrate, and mainly with their combination is indicative of a beneficial increase in LDL particle size. Combination treatment seems to be the optimal therapeutic approach.

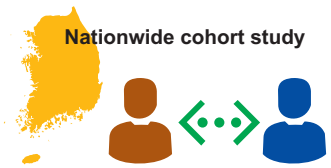



**% Reduction in Lipid Profile at Baseline and at 12 weeks**

As clinical data from one of the Indian study population, significantly showed greater reduction in TG, also decreases in non-HDL-C, LDL-C, TC and increases in HDL-C than those treated with atorvastatin 10 mg alone. The combination therapy also shows less adverse effects than atorvastatin monotherapy.

# Fenofibrate's impact on cardiovascular risk in patients with diabetes: A nationwide propensity-score matched cohort study

***Method and cohort***




**From 2010 to 2019**
**Mean follow-up: 4.03 years**

**Primary outcome :** Myocardial infarction (MI), stroke, both (MI and/or stroke), and all-cause death

***Exposure***

Individuals with diabetes, TG levels ≥ 150 mg/dL, no prior diagnoses of ASCVD and statins plus fenofibrate

***Control***

Individuals with diabetes, TG levels ≥ 150 mg/dL, no prior diagnoses of ASCVD and statins only

***Outcomes***

| *Outcomes* | Statins plus fenofibrate comparing statin only |
|---|---|
| MI | 12.2% ↓ |
| Stroke | 9.9% ↓ |
| Both (MI and/or stroke), | 10.3% ↓ |
| All-cause death | 28.4% ↓ |

CONCLUSION: *The risk of all-cause death and ASCVD was significantly lower with fenofibrate use in conjunction with statin treatment compared to statin treatment alone.*

In a nationwide propensity-score matched cohort study from Asian region involving individuals with diabetes and TG ≥ 150 mg/dL, the risk of all-cause death and ASCVD was significantly lower with fenofibrate use in conjunction with statin treatment compared to statin treatment alone. These beneficial effects of fenofibrate were consistent across subgroups, including those with TG levels between 150 and 199 mg/dL.

Recent evidence supports the potential role of fenofibrate in residual CV risk management, especially in Asian patients with hypertriglyceridemia and/or low HDL-C level, despite appropriate statin therapy. However, the combination therapy with statins has potential risk of hepatic or renal side effects in vulnerable individuals that necessitate careful monitoring. Also, fenofibrate protects against prediabetes and diabetes-related CV complications by improving insulin sensitivity and β-cell function and has beneficial effects on microvascular complications (retinopathy and nephropathy).

Statin-fibrate combinations seem superior to high dosages of statins because they normalize all aspects of the lipid profile and further improve CAD risk status. The fibrate induced additional, but moderate, LDL cholesterol reduction, especially by fenofibrate, and the substantial reduction in TG levels, the shift to a less-dense and thus less-atherogenic LDL particle profile, as well as the significant increase in HDL cholesterol levels substantially improve the efficacy of combination treatment.

***Source:*** *Hong, S., et al. Cardiovasc Diabetol 23, 263 (2024). Chaicharn D;et.al. Diabetes & Metabolism Journal 2024;48(2):184-195.*



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