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Medical Bulletin

BLUE CROSS LIFE SCIENCES Division of Blue Cross Laboratories Pvt Ltd.

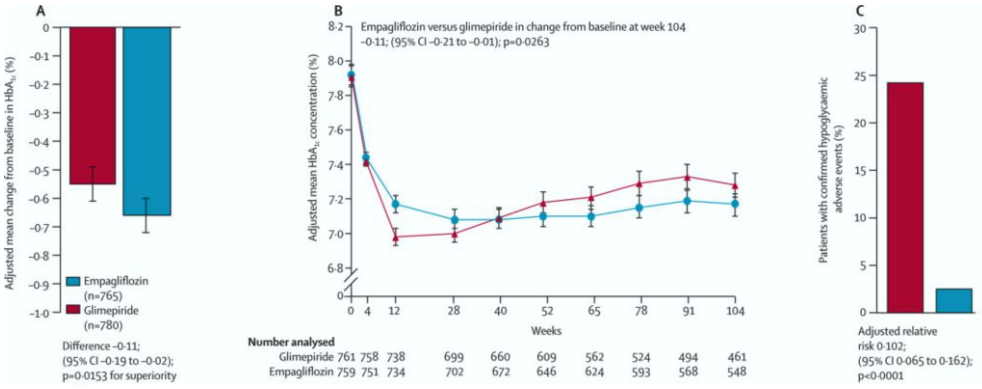
EXTENDED SAFETY EVALUATION OF EMPAGLIFLOZIN: IMPLICATIONS FOR LONG-TERM MANAGEMENT OF DIABETES AND CARDIO-RENAL RISKS

Type 2 diabetes mellitus (T2DM) is a chronic disease that results from a combination of insulin resistance and insulin deficiency caused by progressive beta-cell failure. Treatment of T2DM should aim to control glycemia to preserve quality of life and reduce the risk of the microvascular and macrovascular complications of diabetes. Metformin, the most used anti-diabetes agent, is recommended as first-line therapy for patients with T2DM. However, many patients eventually require **additional glucose-lowering agents** due to disease progression and inadequate glycemic control with monotherapy. Given the long duration of treatment, **the long-term safety and tolerability** of add-on therapies are of critical clinical importance.

Sulfonylureas, such as glimepiride, have traditionally been used as second-line agents because of their efficacy and low cost. However, their use is limited by **weight gain, increased risk of hypoglycemia, and concerns regarding long-term cardiovascular and metabolic safety.** These limitations have driven the search for alternative therapies that provide effective glycemic control while offering a more favorable safety profile.

Empagliflozin is a selective sodium-glucose cotransporter-2 (SGLT2) inhibitor that lowers blood glucose through an **insulin-independent mechanism** by promoting urinary glucose excretion. In addition to improving glycemic control, empagliflozin has been shown to provide **beneficial effects on body weight and blood pressure,** with a low intrinsic risk of hypoglycemia. These properties make it an attractive option for long-term treatment of T2DM. Furthermore, due to body weight and blood pressure lowering properties, in addition to its effects on glycemic control, treatment with empagliflozin has a beneficial effect on CV risk.

While short- and medium-term studies have established the efficacy and general safety of empagliflozin, **long-term safety data are essential** to fully assess its risk–benefit profile. The 4-year (208-week) trial on empagliflozin demonstrated that it has a favorable and durable safety profile in patients with type 2 diabetes mellitus.



Long term use (104 weeks) & glycemic parameter analysis along with adverse effects

For Patients with Type 2 Diabetes

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Empagliflozin 10 mg. / 25 mg. **Tablets**

Overweight and obesity are common comorbidities in patients with type 2 diabetes and contribute to insulin resistance and worsening of glucose control. Evaluating the long-term safety of empagliflozin over an extended treatment period allows for assessment of sustained tolerability, incidence of adverse events, hypoglycemia risk, effects on body weight and blood pressure, and overall clinical safety. Such evidence is crucial to inform therapeutic decision-making and support the use of empagliflozin as a preferred long-term add-on therapy to metformin in patients with type 2 diabetes mellitus.

Empagliflozin for 104 weeks resulted in sustained reductions in bodyweight, whereas glimepiride was associated with weight gain. Nearly 90% of the weight loss with empagliflozin was due to a reduction in fat mass like the results of body composition studies with other SGLT2 inhibitors. Treatment with empagliflozin for 104 weeks also resulted in sustained and significant reductions in systolic and diastolic blood pressure compared with glimepiride. The favorable effects of empagliflozin on glycemic control, bodyweight, and blood pressure might reduce cardiovascular risk in patients with type 2 diabetes. Empagliflozin was well tolerated over 104 weeks & demonstrated its long-term safety. Although the percentage of patients with serious adverse events was slightly higher with empagliflozin than with glimepiride, there was no pattern in the type of serious adverse events. Events consistent with urinary tract infection were reported in a similar percentage of patients in the empagliflozin and glimepiride groups, but empagliflozin was associated with an increased risk of events consistent with genital infection, as has been noted in other studies of SGLT2 inhibitors. Assessment of eGFR over time indicated that renal function was preserved with empagliflozin even after 104 weeks.

Substantial cardiovascular benefit associated with SGLT2 inhibitors, which has been consistently demonstrated across multiple large-scale clinical trials.

For instance, the **EMPA-REG OUTCOME** trial showed a significant 38% reduction in cardiovascular death among high-risk patients with T2DM treated with Empagliflozin. The cardioprotective effects of SGLT2 inhibitors seem to extend beyond glycemic control, suggesting potential benefits through mechanisms such as improved myocardial metabolism, reduced oxidative stress, and favorable hemodynamic effects such as blood pressure and volume reduction. Also, Multiple trials have shown that these agents slow the progression of chronic kidney disease and reduce the risk of end-stage renal disease in patients with T2DM.The renoprotective effects of SGLT2 inhibitors appear to be independent of their glucose-lowering action, suggesting a direct effect on kidney function. Key trials **EMPEROR-Reduced** confirmed these renal benefits, demonstrating empagliflozin's role in slowing CKD progression and reducing kidney-related events, thus making it a cornerstone treatment for cardio-renal protection.

Empagliflozin demonstrates **good long-term safety and tolerability**, with clinically meaningful advantages, particularly regarding hypoglycemia risk, weight control, and overall metabolic safety.

Source: *Herrington W,et.al; Lancet Diabetes Endocrinol. 2025 Oct 10.; Farhan Khan et.al; Cureus 16(11): e74400,2024; Ridderstråle M et.al; Cardiovasc Diabetol. 2013 Sep 5;12:129.*

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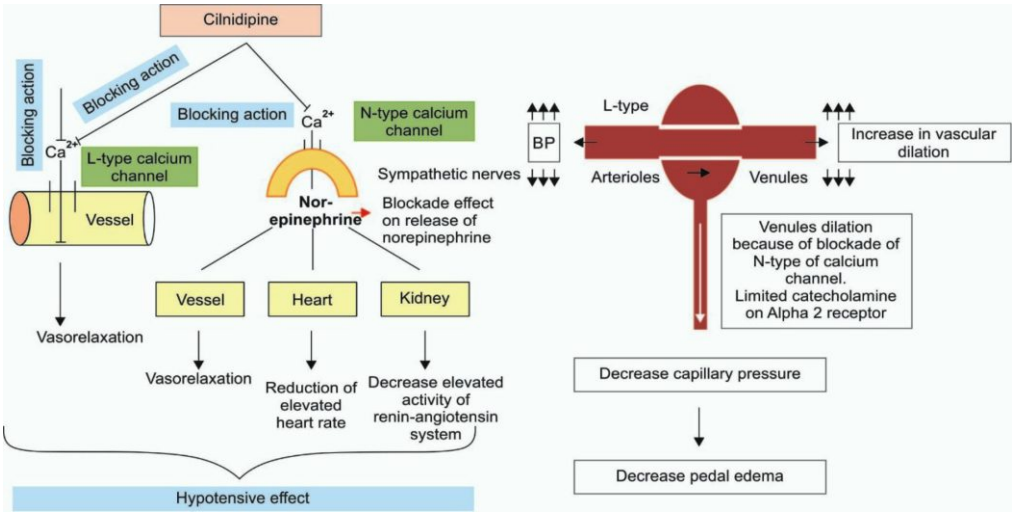
CILNIDIPINE – A NOVEL CALCIUM CHANNEL BLOCKER REDUCING BLOOD PRESSURE, HEART RATE, AND PROTEINURIA IN INDIAN HYPERTENSIVE PATIENTS

Hypertension is a major public health challenge in India, contributing significantly to cardiovascular morbidity and mortality. It is closely associated with complications such as coronary artery disease, stroke, chronic kidney disease (CKD), and heart failure. Despite the availability of multiple antihypertensive drug classes, optimal blood pressure (BP) control remains suboptimal in a large proportion of Indian patients, especially those with associated metabolic disorders, renal impairment, and proteinuria. About 36% of the Indian population suffers from hypertension, with many patients having uncontrolled blood pressure [BP] despite treatment. Calcium Channel Blockers [CCB] are widely prescribed in India and Southeast Asia, either as monotherapy or in combination with other AHDs, and have proven efficacy and safety. Cilnidipine, a newer generation CCB, has emerged as a promising alternative with unique pharmacological properties that offer additional cardiovascular and renal benefits.

Cilnidipine is a dual L-type and N-type calcium channel blocker, distinguishing it from traditional dihydropyridine CCBs such as amlodipine, which primarily block L-type calcium channels.

- **L-type calcium channel blockade** results in vasodilation of peripheral arteries, leading to effective reduction in blood pressure.
- **N-type calcium channel blockade** inhibits calcium influx into sympathetic nerve terminals, thereby suppressing excessive norepinephrine release.

This dual mechanism results in reduced sympathetic activity, prevention of reflex tachycardia, and improved cardiovascular stability. These properties are particularly beneficial in Indian hypertensive patients, who often exhibit heightened sympathetic tone due to stress, lifestyle factors, and metabolic syndrome.



Pharmacological profile of Cilnidipine

In management of Hypertension

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Cilnidipine 5 mg. / 10 mg. **Tablets**

Blood Pressure Reduction

Multiple Indian clinical studies have demonstrated that cilnidipine effectively lowers both systolic and diastolic blood pressure in patients with mild to moderate hypertension. Its antihypertensive efficacy is comparable to that of amlodipine and other standard CCBs. However, cilnidipine offers the advantage of more stable BP control throughout the day, including early morning hours when cardiovascular events are more frequent. Additionally, cilnidipine has been shown to maintain antihypertensive efficacy in elderly patients and those with diabetes, making it suitable for the diverse demographic profile of Indian hypertensive populations.

Effect on Heart Rate

One of the major limitations of conventional dihydropyridine CCBs is **reflex tachycardia,** which may increase myocardial oxygen demand and worsen cardiovascular outcomes. Cilnidipine, through N-type calcium channel blockade, suppresses sympathetic nerve activity and thereby **reduces heart rate or prevents reflex tachycardia.** Indian studies have consistently reported that cilnidipine either maintains or modestly reduces heart rate, unlike amlodipine, which may cause a compensatory increase. This effect is particularly beneficial in patients with ischemic heart disease, heart failure, or those at risk of arrhythmias.

Renoprotective Effects and Reduction of Proteinuria

Proteinuria is a well-established marker of renal damage and an independent risk factor for cardiovascular disease. In Indian hypertensive patients, especially those with diabetes or CKD, proteinuria is highly prevalent. Cilnidipine has demonstrated significant **renoprotective effects,** including reduction in proteinuria.

The mechanism underlying this benefit involves: Dilatation of both **afferent and efferent glomerular arterioles,** leading to reduced intraglomerular pressure, suppression of sympathetic overactivity, which otherwise contributes to glomerular injury & improved renal hemodynamics.

Several Indian clinical trials have shown that cilnidipine significantly reduces urinary albumin excretion compared to amlodipine, particularly in patients with diabetic nephropathy and hypertensive nephropathy. This makes cilnidipine an attractive option for hypertensive patients with early renal involvement. Moreover, cilnidipine does not adversely affect lipid or glucose metabolism, making it suitable for patients with diabetes and metabolic syndrome conditions highly prevalent in India.

Clinical Relevance in Indian Hypertensive Patients

The Indian hypertensive population often presents with multiple comorbidities such as diabetes, obesity, CKD, and cardiovascular disease. Cilnidipine's ability to simultaneously reduce blood pressure, control heart rate, and protect renal function aligns well with the therapeutic needs of these patients. Its efficacy in reducing proteinuria further supports its use as a preferred CCB in patients with hypertension complicated by renal disease.

Source: *Mehta K,et.al; Journal of the Association of Physicians of India, Volume 72 Issue 4 (April 2024) ;Naik A et.al; Kidney International Reports Volume 10, Issue 2, Supplement, February 2025, Page S348*

In management of Hypertension

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