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Medical Bulletin

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$SGLT_2$ INHIBITORS: BEYOND GLUCOSE LOWERING TO CARDIOVASCULAR, KIDNEY AND METABOLIC PROTECTION

Sodium-glucose cotransporter-2 inhibitors ($SGLT_2$i) have undergone one of the most important therapeutic evolutions in modern cardiometabolic medicine. Originally developed to improve glycaemic control in type 2 diabetes mellitus (T2DM), the class is now positioned prominently in the management of heart failure (HF), chronic kidney disease (CKD), and T2DM with cardiovascular or renal risk.

The recently published American Diabetes Association (ADA) & the European Association for the Study of Diabetes (EASD) 2026 consensus report shifts the focus from glucose control to the comprehensive, holistic management of T2DM & its associated long-term cardiovascular, renal and metabolic complications. It specifically highlights earlier use of $SGLT_2$ inhibitors & GLP-1-based therapies, with treatment selection individualized according to cardiovascular & CKD risks.

Why Do the Benefits of $SGLT_2$ Inhibition Extend Beyond HbA1c Lowering?

$SGLT_2$ mediates much of the glucose and sodium reabsorption in the proximal renal tubule. Inhibiting it promotes glucosuria and natriuresis, lowering glucose independently of insulin. However, the clinical benefits of $SGLT_2$ inhibition extend beyond glycaemic control and include several important physiological effects:

Renal effects include increased distal sodium delivery, restoration of tubuloglomerular feedback, reduced intraglomerular pressure, a possible initial reversible decline in eGFR after treatment initiation, and long-term preservation of kidney function. It may also reduce renal tubular workload and hypoxic stress and favourably influence metabolic substrate utilization.

Cardiovascular effects include mild natriuretic and osmotic diuretic actions, reduced haemodynamic stress, while additional proposed pleiotropic mechanisms include improved myocardial energetics, modulation of cellular sodium and calcium homeostasis, reduced oxidative stress and inflammatory signalling, and attenuation of adverse cardiac fibrosis and remodelling offering clinically meaningful benefits in heart failure.

Metabolic effects include modest reductions in plasma glucose, body weight & blood pressure, with a low intrinsic risk of hypoglycaemia when used without insulin or insulin secretagogues, explaining benefits of $SGLT_2$ inhibitors extending beyond HbA1c lowering.

From Antidiabetic Drug to Organ-Protective Therapy

Collectively, these haemodynamic, metabolic, renal and cellular actions provide a mechanistic basis for the clinically demonstrated reductions in heart-failure events and slowing of CKD progression observed with $SGLT_2$ inhibitors.

The 2026 ADA/EASD consensus marks a therapeutic shift toward earlier use of $SGLT_2$ inhibitors and GLP-1-based therapies based on cardiovascular and CKD risks, prioritising organ protection beyond HbA1c control; therefore, treatment choice in T2DM with cardiorenal disease should not depend solely on baseline HbA1c.

$SGLT_2$ Inhibitors in Heart Failure

Landmark trials such as DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER have established $SGLT_2$ inhibitors (Dapagliflozin & Empagliflozin) as heart-failure therapies across the ejection-fraction spectrum, with benefits beyond glucose lowering.

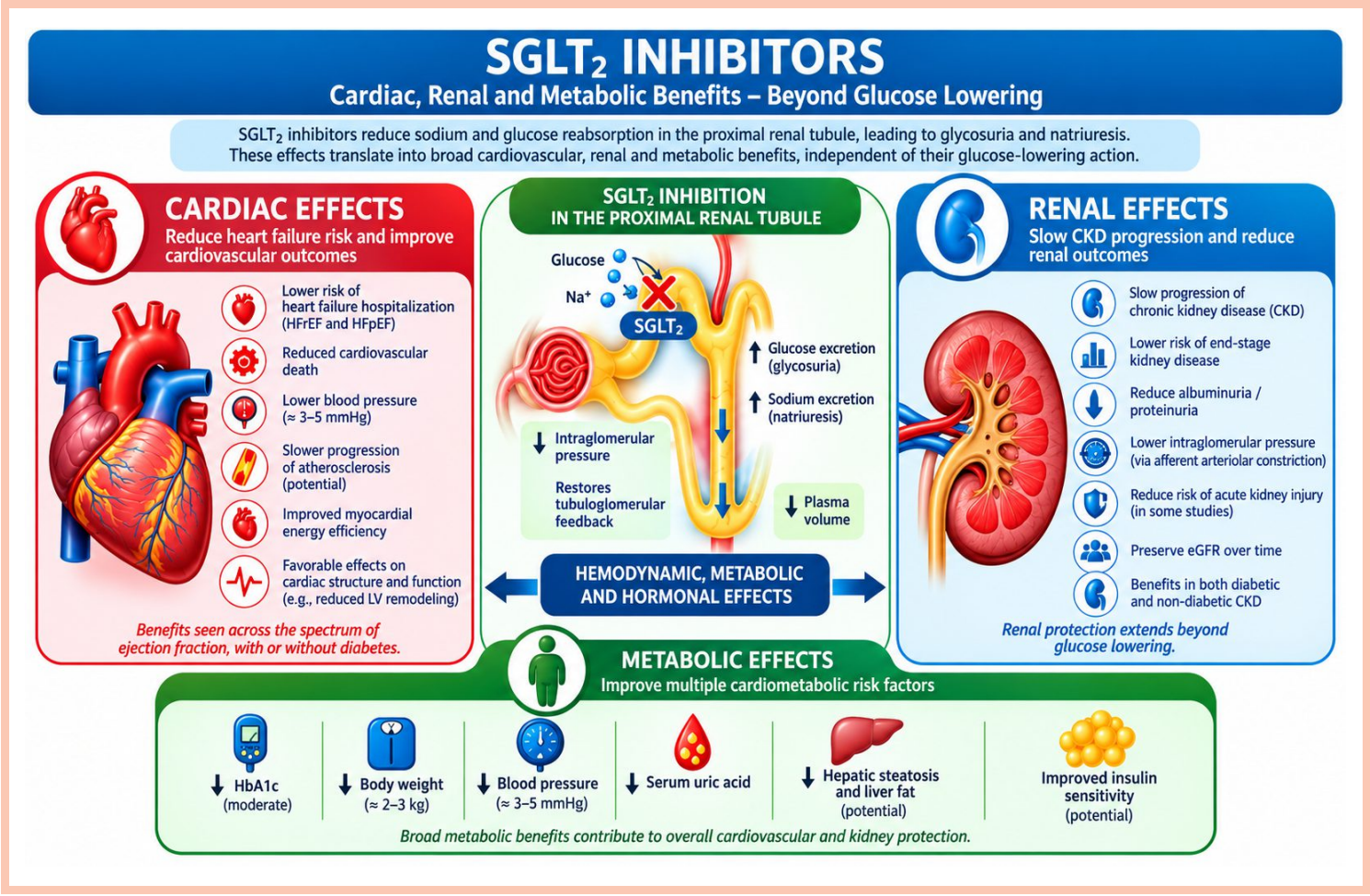
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$SGLT_2$ Inhibitors in Chronic Kidney Disease

CKD is now a major non-glycaemic indication for SGLT2 inhibitors, with landmark trials such as CREDENCE, DAPA-CKD, and EMPA-KIDNEY demonstrating their kidney protective benefits. In 2026, Kidney Disease: Improving Global Outcomes (KDIGO) announced that it was developing a focused update incorporating emerging evidence on $SGLT_2$ inhibitors, GLP-1-based therapies, and non-steroidal mineralocorticoid receptor antagonists such as finerenone.



Dapagliflozin and empagliflozin provide cardio-renal-metabolic benefits beyond glycaemic control, reducing heart-failure events and slowing CKD progression. Their use should align with approved indications and molecule-specific renal criteria. Before initiation, assess renal function, volume status, blood pressure, concomitant diuretic use, recurrent genital infections, and any planned surgery or acute illness.

$SGLT_2$ inhibitors are no longer viewed solely as HbA1c lowering drugs; their therapeutic value increasingly lies in providing integrated cardiovascular and renal protection for appropriately selected patients. The 2026 ADA/EASD consensus recommends earlier use of $SGLT_2$ inhibitors and GLP-1-based therapies to modify disease progression and reduce complications according to cardiovascular and CKD risks. Thus, management has shifted from adding an $SGLT_2$ inhibitor only after inadequate glycaemic control to identifying organ risk in patients with T2DM, CKD, or HF and selecting evidence-based therapy that provides cardiac, renal, and metabolic benefits while addressing glycaemic targets as appropriate. Thus, $SGLT_2$ inhibition represents a fundamental shift from glucose-centric management toward integrated organ protection.

Source: *Davies, M.J.,et al., Diabetologia (2026). Thomas MC, et al., Endocr. Connect. 2023 Jul 31;12(8); Grigoriou, K, et al., Medicina 2025, 61, 1903*

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A COMPLEMENTARY APPROACH TO CARDIORENAL RISK MANAGEMENT WITH TELMISARTAN AND CILNIDIPINE

Hypertension remains one of the most important modifiable drivers of cardiovascular and renal disease. Contemporary management has therefore shifted from simply achieving a numerical blood pressure (BP) target toward early diagnosis, sustained 24-hour BP control, reduction of total cardiovascular risk, prevention of target-organ damage, and protection of the heart, kidneys and vasculature.

The 2024 European Society of Cardiology (ESC) guideline simplified office BP classification into three categories: non-elevated BP (<120/70 mmHg), elevated BP (SBP 120-139 / DBP 70-89 mmHg), and hypertension (≥140/90 mmHg).

Single agent therapy often fails to control BP because hypertension is driven by interacting mechanisms, including activation of the renin-angiotensin-aldosterone system, increased sympathetic activity, elevated peripheral vascular resistance, arterial stiffness and endothelial dysfunction, sodium and fluid retention, and metabolic and renal abnormalities. This provides a strong clinical rationale for combining antihypertensive agents with complementary mechanisms of action. The 2024 ESC guideline recommends an initial low-dose two-drug combination for most patients with hypertension, preferably as a single-pill combination. Recommended first-line drug classes include angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), dihydropyridine calcium-channel blockers (CCBs), and thiazide-like diuretics.

Telmisartan is an angiotensin II receptor blocker that selectively inhibits the angiotensin II Type 1 receptor (AT_1), thereby reducing angiotensin II mediated vasoconstriction and aldosterone driven sodium retention. In a randomised Indian study, telmisartan 40 mg once daily significantly reduced all assessed ambulatory BP parameters. A 2026 Indian study of 70 patients with newly diagnosed hypertension and type 2 diabetes further showed a lower median HOMA-IR after 12 weeks with telmisartan than with other antihypertensive therapies (1.79 vs 3.45; P<0.001), supporting its use when hypertension coexists with cardiometabolic risk.

Cilnidipine is a dihydropyridine CCB that blocks L-type calcium channels, reducing calcium influx and promoting arteriolar vasodilatation to lower peripheral vascular resistance and BP. It also blocks N-type calcium channels, thereby attenuating sympathetic activity. In the renal circulation, cilnidipine may dilate the efferent arteriole and reduce intraglomerular hypertension, making it a potentially useful partner for RAAS blockade.

Telmisartan and Cilnidipine lower blood pressure through complementary mechanisms: telmisartan blocks AT_1 receptors, reducing angiotensin II mediated vasoconstriction, aldosterone activity, and RAAS related organ stress, while cilnidipine blocks L-type calcium channels to promote arteriolar vasodilatation and N-type calcium channels to modulate sympathetic neurotransmission. This combined RAAS blockade, vasodilatation, and sympathetic modulation provides additive BP reduction, making the combination a rational option when monotherapy is inadequate, particularly in patients with associated renal or metabolic comorbidities.

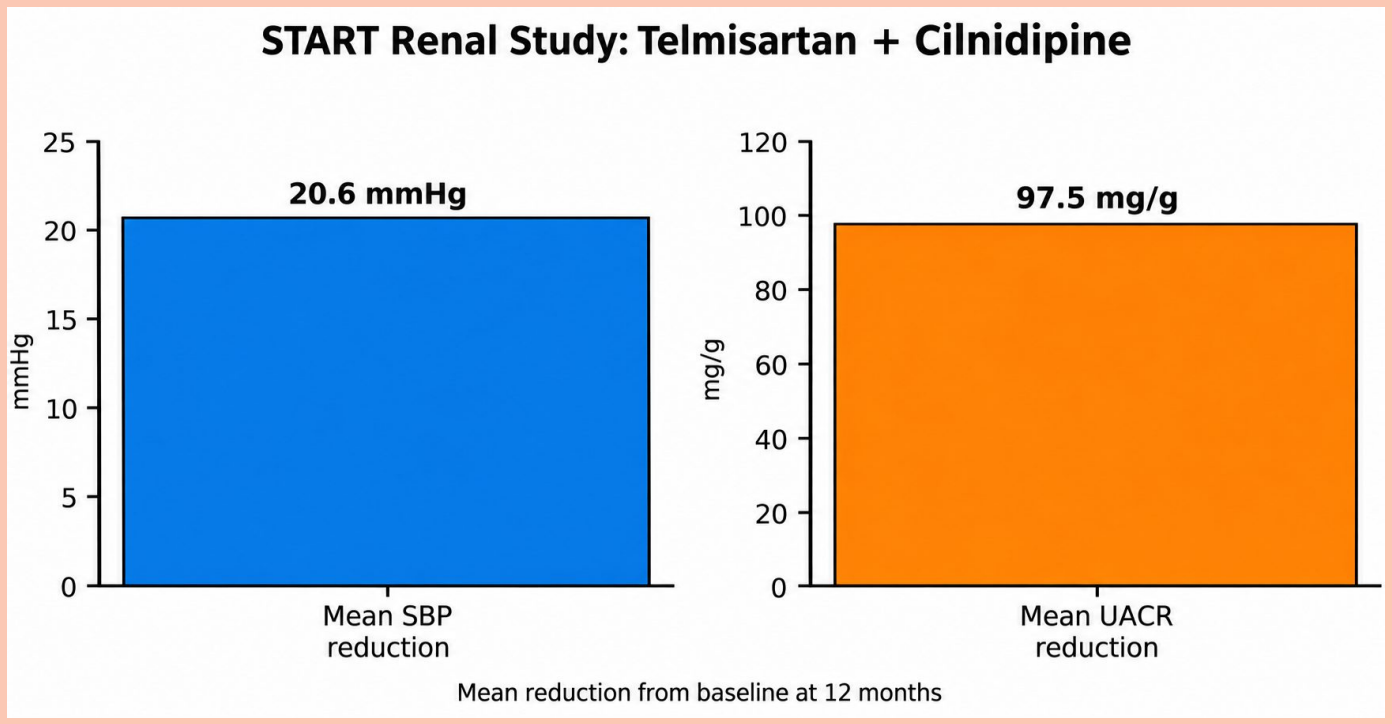
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*. Shinobu Nagahama et al. Hypertens Res. 2007;30(9): 815-822.

The START Renal study, published in 2026, was a randomised, open-label, multicentre Indian post-marketing study involving 188 adults with hypertension and renal impairment. Participants were randomised 1:1 to telmisartan plus amlodipine or telmisartan plus cilnidipine for 12 months; the telmisartan–cilnidipine regimen comprised telmisartan 40/80 mg plus cilnidipine 10 mg once daily.



In the telmisartan–cilnidipine group, urinary albumin-to-creatinine ratio (UACR) decreased from 143.8 mg/g at baseline to 46.28 mg/g at 12 months, a mean reduction of 97.5 ± 128.6 mg/g (P<0.0001). eGFR increased from 75.1 to 95.98 mL/min/1.73 m² over the same period with a mean SBP reduction of 20.6 mmHg at 12 months.
Based on pharmacology and the available clinical evidence, this combination of telmisartan-cilnidipine may be considered particularly relevant when:

- *Monotherapy provides inadequate BP control:* Combining an ARB and CCB targets different mechanisms and is consistent with the contemporary preference for combination treatment.
- *Hypertension coexists with renal impairment or albuminuria:* RAAS blockade is an important therapeutic strategy in renal disease, while the 2026 START Renal study demonstrated substantial UACR reduction during telmisartan-cilnidipine therapy.
- *Hypertension occurs with diabetes/metabolic risk:* Telmisartan has supportive emerging Indian evidence regarding insulin sensitivity in patients with hypertension and T2DM, although confirmation in larger studies is needed.
- *Sympathetic overactivity may be clinically relevant:* Cilnidipine L/N-type calcium channel pharmacology provides a mechanistic rationale for combining vascular calcium channel blockade with RAAS inhibition.

Source: *Uday Jadhav, et al., International Journal of Nephrology and Renovascular Disease, 2026:19 555573. Gomaz SM, et al., Indian J Med Res. 2026;163:41-8. McCarthy CP, et al., Eur Heart J Cardiovasc Pharmacother. 2025 Feb 8;11(1):7-9.*

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*. Shinobu Nagahama et al. Hypertens Res. 2007;30(9): 815-822.

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