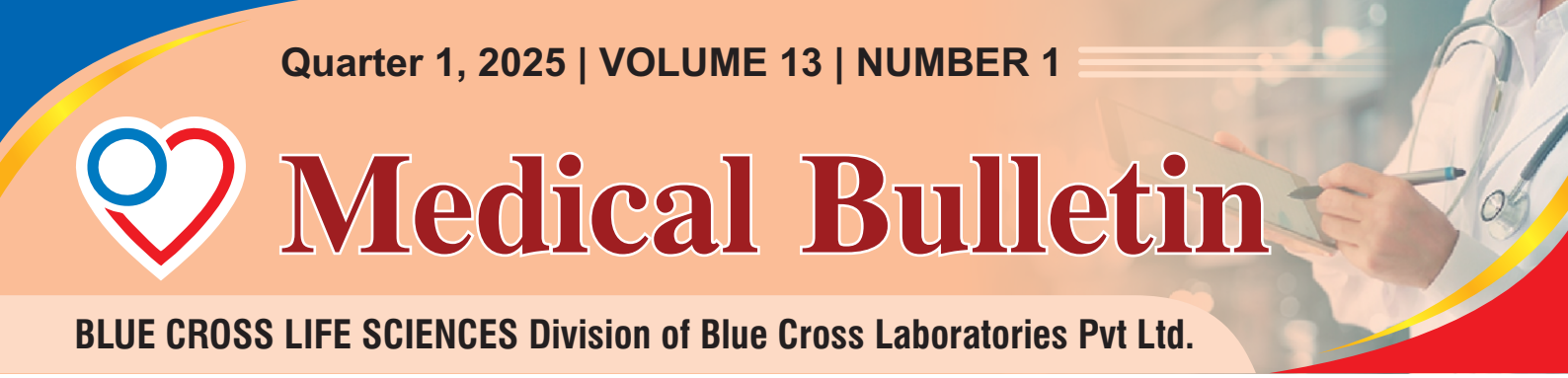
Quarter 1, 2025 | VOLUME 13 | NUMBER 1



Medical Bulletin

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

CLINICAL EFFICACY AND IMPACT ON BODY COMPOSITION OF DIABETIC PATIENTS TREATED WITH DAPAGLIFLOZIN

Dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, is approved globally & is widely used for treating of type 2 diabetes mellitus (T2DM), heart failure (HF) and chronic kidney disease (CKD). While its efficacy is well established, concerns remain regarding its impact on muscle mass and function, especially in elderly patients.

Patients with T2DM are at increased risk of sarcopenia, and skeletal muscle deterioration is accelerated compared with age-matched euglycemic individuals. Skeletal muscle deterioration during T2DM results in resistance to insulin action on skeletal muscle and impaired glucose uptake, which in turn impair myofibrillar renewal and muscle building, lipid accumulation, mitochondrial dysfunction, and oxidative stress. These effects lead to direct injury to muscle cells, the accumulation of advanced glycation end-products and pro-inflammatory cytokines, intestinal dysbiosis, and hormonal imbalances, in particular related to growth hormone-insulin-like growth factor 1 and the hypothalamic–pituitary–gonadal axes. Overall, patients with T2DM are at high risk of sarcopenic obesity, and this risk increases with aging and also increasing the cardiovascular mortality. Glycemic control, particularly by treatment with insulin, increases muscle glucose disposal and mitigates the development or intensification of sarcopenia.

Dapagliflozin is a drug that has the potential to not only halt this progression, but also to improve organ functions through an aggressive therapeutic approach.

The mechanism of action for its use as a diabetes treatment involves the excretion of large amounts of glucose in the urine. However, there are concerns about potential long-term adverse effects on the body's nutritional and metabolic systems, particularly in the elderly population, due to these changes. One of the main concerns is the potential impact on muscle mass. The human body maintains a daily nitrogen balance by breaking down muscle into glucose when glucose is unavailable, such as during the night, and then resynthesizing muscle fibers when glucose intake resumes, thereby maintaining a certain level of muscle mass. There is concern that the excessive glucose excretion of dapagliflozin could significantly shift this balance to a negative state, where muscle breakdown exceeds resynthesis. This raises the question of whether the drug could cause iatrogenic loss of muscle, reduced strength, and sarcopenia, particularly in elderly individuals with limited muscle mass reserves, paradoxically.

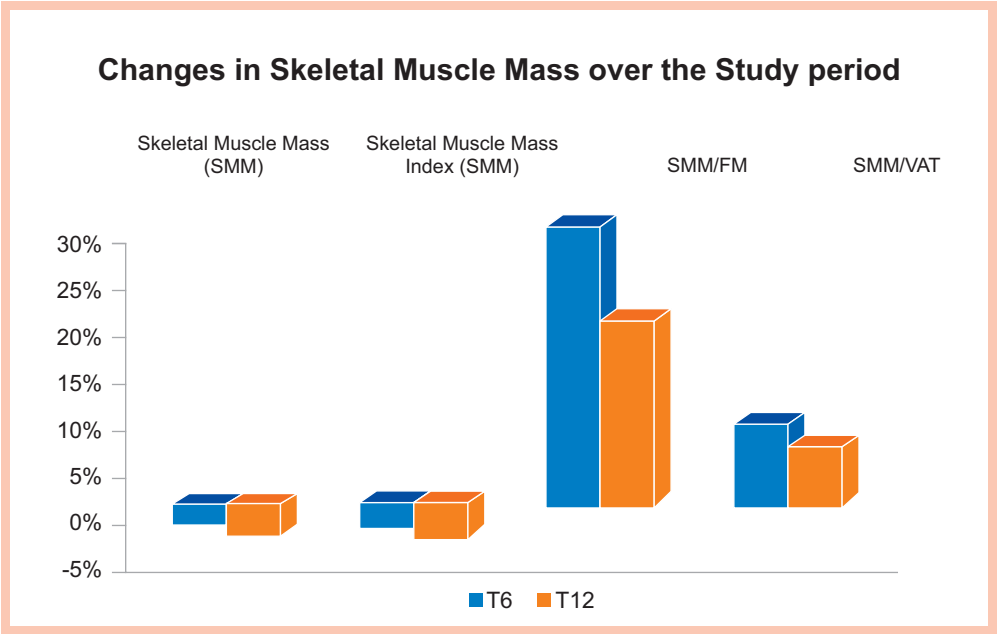
Upon the administration of SGLT2 inhibitors, a decline in body weight is expected during the first two to four weeks due to caloric loss and excess body water loss, followed by a reduction in fat mass and small reductions in lean mass that persist in the long term with an average two-thirds of weight loss is derived from adipose tissue, which corresponds to approximately 2 to 3 Kg.

The fat mass reduction may be attributable because SGLT2i increases the gluconeogenesis, at least in part, by increasing glucagon levels and shifting substrate utilization from carbohydrates to lipids and ketone bodies.

In another study administration of dapagliflozin for 24 weeks was associated with significant decreases in body mass index, waist circumference, and waist-to-hip ratio. Changes in body composition were driven by reductions in body fat mass and percent body fat, without changes in lean mass or total body water.

Several prospective studies have suggested that glycemic control, reduction of insulin resistance, and adiponectin have been associated with reduced risk of muscle loss in T2DM individuals and also with improved muscular function. These effects were due to increased insulin sensitivity, reduction of intramuscular lipids, oxidative stress, and improvement of peripheral microvascular function.

An important finding from the available clinical evidence confirms that the weight loss by dapagliflozin in T2DM patients is primarily the result of a reduction in fat mass rather than in soft lean mass. Changes in body composition, being more relevant on the Fat Mass (FM) and Visceral Adipose Tissue (VAT) than the Skeletal Muscle Mass (SMM), consequently induced a beneficial increase in the SMM/FM and SMM/VAT ratios as suggested by the statistically significant increase in the SMM/ FM ratio after 6 and 12 months of treatment.



These results indicate that SGLT2 inhibitors are effective and safe in patients with T2DM, regardless of baseline body weight and body composition. The use of this class of anti-hyperglycemic agents did not affect muscle mass and strength in a clinically significant manner, as the average loss of SMM after one year of therapy was only 3%. Overall, the weight loss induced by SGLT2 inhibitors was significant but “healthy” because it was mainly attributable to a decrease in fat mass and visceral adipose tissue with improvement in SMM/FM ratio.

Source: *Nomura A et.al; Journal of Diabetes and its Complications, Volume 39, Issue 2,2025. Volpe, S., et.al; Nutrients, 16(22), 3841. Wolf et.al;Nutr. Diabetes 11, 17 (2021).*

TELMISARTAN AND AMLODIPINE: PREFERRED INITIAL COMBINATION IN NEWLY DIAGNOSED INDIAN PATIENTS

Hypertension (HTN) remains one of the most important risk factors for cardiovascular (CV) diseases & a leading cause of mortality worldwide. The situation in India is alarming with only 22.5% of patients maintaining their BP under control. Initiating early and effective treatment for HTN helps control BP within normal limits and reduces associated health risks. In India, currently, there are no guidelines on the choice of dual combination treatment that can be considered an initial treatment for newly diagnosed HTN patients to achieve effective BP control & reduce CV risks.

HTN is treatable and needs to be managed with lifestyle measures and by introducing pharmacological interventions. However, the HTN diagnosis, treatment, and control continue to remain a challenge across sociodemographic groups and geographic areas within India. These poor control rates and lack of awareness are worrying and need immediate correction. It is of utmost necessity to bring the elevated BP to near normal at the earliest. All-cause and CV mortality in subjects with different grades of HTN has been well demonstrated in several research findings. The disease prevalence data shows that HTN seems to strike at a young age with an approximate prevalence of 12% population of aged between 30 and 40 years and 24% population of 41–50 years. Thus ~40% young Indian population below 50 years is hypertensive. HTN on average gets diagnosed at an average age of 51 years with almost 64% prevalence above 50 years of age. Association of both stages I and II HTN with CV mortality has been reported in India. The subsequent follow-up over 5 years has further demonstrated that the subjects with stage II HTN have had greater risk of death from hypertensive heart disease, ischemic heart disease and cerebrovascular diseases.

One of the important reasons is the “therapeutic inertia,” that is, unwillingness and/or apprehension by the clinicians to increase the dosage and/or to add an additional antihypertensive medication to the treatment. A few of the other reasons include the low efficacy of monotherapy and the underuse of combination therapies. Nonadherence to the treatment and compliance issues from the patients are also responsible for not achieving the target goal of controlling the elevated BP.

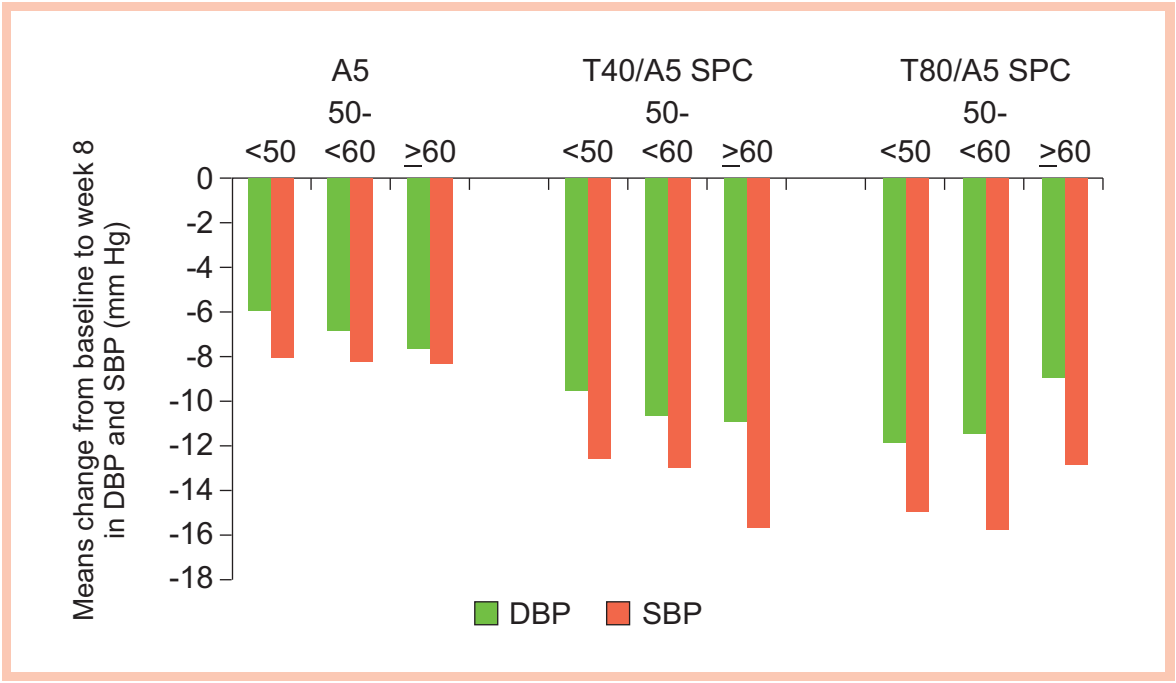
Combination treatment is endorsed by all global HTN treatment guidelines & is evidence based from various clinical trials .Initial combination therapy was found to be associated with a significant risk reduction of CV events or death. Achieving rapid BP reduction and achieving the target BP are the main factors in the estimated risk reduction lot of evidence is available today that endorses the use of combination therapy as it offers BP control and helps in preventing CV events among patients.

The European Society of Cardiology and European Society of HTN ESC/ESH 2023 as well as the International Society for Hypertension (ISH) guidelines 2020 provide clear guidance to start dual low-dose combination therapy as the first step toward pharmacological intervention for HTN management. These guidelines further advise the choice of pharmacological agents that can be considered between ACEIs, ARBs, CCBs, and Dus.

Cumulative evidence from LIFE, ASCOT, CAFE, ACCOMPLISH, and VALUE trials strongly support the view that in hypertensive patients, combination therapy with CCB/ARB or CCB/ACEI is likely to be associated with better CV outcomes including myocardial infarction (MI) and stroke than regimens containing BB and DU.

Cost-effectiveness analysis from the NICE guidelines clearly demonstrates that CCBs and ARBs or ACEIs are more cost-effective treatment choices than BB or thiazide DU.

Telmisartan plus amlodipine can be considered the preferred initial combination in the management of newly diagnosed Indian patients with HTN. Various landmark trials like ONTARGET, INNOVATION, CAMELOT, ACCOMPLISH, COACH, TEAMSTA-5, TACT have established the effectiveness of Telmisartan and Amlodipine and also as a single-pill combination of telmisartan 40/amlodipine 5 mg or telmisartan 80 /amlodipine 5 mg had been a better treatment option than up-titration to full-dose monotherapy with amlodipine 10 mg that was associated with side effects.



The advantages of switching patients from monotherapy to combination therapy with dual low-dose therapy, thereby achieving target BP control as well as lowering the side effects of high doses of monotherapy and improving compliance have been demonstrated in this study. Based on the current evidence, telmisartan and amlodipine can be considered the preferred first-line treatment for HTN in India.

The diversity of India requires customization and simplification of strategies that are easy to implement and follow. As observed with mean rating scores from experts for each recommendation, telmisartan plus amlodipine can be considered the preferred initial combination in the management of newly diagnosed Indian patients with HTN to achieve better control of BP and to reduce CV outcomes.

Source: *Source: Journal of the Association of Physicians of India, Volume 71 Issue 12 (December 2023) 5. Journal of The Association of Physicians of India, Volume 72 Issue 11 (November 2024).*

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