Faridpur Med. Coll. J. 2025;20(2):44-53 DOI: https://doi.org/10.3329/fmcj.v20i2.83147

Reveiw Article

"New Horizons in T2DM Management: A Review of Emerging Antidiabetic Medications"

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Abstract:

T2DM mellitus continues to pose a significant global health challenge, with rising prevalence and associated complications necessitating novel therapeutic strategies. The emerging pharmacotherapies offer a new hope that focuses on recent advancements beyond traditional glucose-lowering medications to address not only glycemic control but also the broader range of complications and comorbidities associated with diabetes mellitus.

An optimal treatment for T2DM should address insulin resistance, obesity, and hyperglycemia. The next-generation GLP-1 receptor agonists, amylin analogues, and dual and triple incretin co-agonists targeting GLP-1, GIP, and glucagon receptors are effective for better glycemic control and weight loss. SGLT2 inhibitors show extended cardiometabolic and renal benefits, and the novel agent like imeglimin modulate mitochondrial dysfunction and improve insulin signaling pathways.

The purpose of this article is to review the existing literature and current clinical trials showing the effectiveness and safety of these newer agents individually, as well as to explore areas of future development in the field of T2DM management.

Keywords: T2DM, Emerging pharmacotherapy, Incretin co-agonist.

1. Introduction:

T2 Diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by a complex interplay of insulin resistance, progressive beta cell dysfunction, and impaired glucose homeostasis.[1] In the preceding decades, the prevalence of diabetes mellitus has been increasing exponentially, leading to significant economic burdens on health systems around the world. The estimated prevalence of diabetes in 2021 was 537 million worldwide, which is anticipated to grow by 46% to 783 million by 2045. In 2021 statistics, it is projected that 541 million individuals had impaired glucose tolerance.[2] Of all the instances of diabetes, >90 % are T2DM and pre-diabetes to T2DM development per year ranges from 5 to 10 %.[3]

Traditionally, a combination of lifestyle changes, insulin therapy, and oral anti diabetic drugs such as sulfonylureas (SU), biguanides, thiazolidinediones, and alpha-glucosidase inhibitors have been used to treat T2DM. However, their inherent limitations, including adverse effects, a gradual decline in effectiveness, and a neglect of the disease's complex pathophysiology, have accelerated the development of new pharmacotherapeutic approaches[4].

T2DM is associated with an increased incidence of major adverse cardiac events (MACE), cerebrovascular and peripheral vascular disease, and the development of diabetic kidney disease (DKD) because of hyperglycemia and the metabolic syndrome[5]. Approximately 70–75% of patients with established coronary artery disease (CAD) have coexisting overt diabetes or glucose dysregulation,

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significantly increasing the rate of hospitalization and death.[6] So, there is a clear need to develop medications that enhance contemporary strategies, offering superior safety and better outcomes for these patients.

Over the last decade, advances in the development of novel antidiabetic agents have revolutionized the treatment of diabetes, with enhanced metabolic control and fewer side effects on the horizon. Glucagon-like peptide-1 receptor agonists (GLP1-RAs) and dual GIP/GLP1 RAs particularly control hyperglycemia and obesity. Medications like SGLT-2 inhibitors also reduce the risk and improve the outcomes of cardiovascular diseases, including coronary artery disease and heart failure with reduced or preserved ejection fraction, as well as diabetic kidney disease.[7] In addition to this, novel treatments like imeglimin, amylin analogues, dual and triple receptor (GLP-1, GIP, glucagon) agonists, once weekly basal insulin and gene therapy are being explored for more individualized and efficient management of diabetes, improving patient outcomes and quality of life.

This article aims to provide a comprehensive and up-to-date overview of these newer anti-diabetic drugs, approved in recent times by regulatory authorities like the FDA, European Medicines Agency (EMA), or Japanese PMDA, elucidating their mechanisms of action, clinical efficacy, safety profiles, and their potential role in personalized diabetes management.

2. Emerging Drugs for T2DM:

Insulin was initially used to great success in humans in 1922 by Frederick Banting and Charles Best, in what constituted a diabetes breakthrough. Previously, type 1 diabetes had been recognized as an inevitable killer, but with the invention of insulin therapy, it has been reduced to a chronic, treatable condition. In under a century, the therapeutic potential in diabetes treatment has increased manifold. However, the search for more effective, safer, and targeted treatments continues. New medications such as GLP-1 receptor agonists, dual and triple incretin receptor agonists (e.g., tirzepatide and retatrutide), next-generation SGLT2 inhibitors, long-acting amylin analogues, and newer insulin analogues have offered new tools for improving not only glycemic control but also cardiovascular and kidney outcomes, addressing obesity, and also helping in beta-cell preservation. Imeglimin, which is a novel agent approved in some countries, also improves mitochondrial function and insulin sensitivity. Investigations are expanding to gut microbiota modulators with the perspective to manage glucose metabolism naturally. Oral and intelligent once weekly insulin formulations are under investigation to improve patient safety and convenience.

2.1 Glucagon-like Peptide-1 Receptor Agonist

Glucagon-like peptide-1 (GLP-1) secreted by intestinal L-cells act as a strong endogenous insulinotropic incretin hormone. The production of synthetic agents contended at its receptors in order to treat T2DM signified a significant advance in the quest for new antidiabetic agents. GLP-1 RA includes a range of drugs utilized in worldwide clinical practice, such as exenatide, lixisenatide, liraglutide, dulaglutide, albiglutide and semaglutide.[8]

In patients with T2DM, incretin effect is disrupted and there exists a relative deficiency of GLP-1. GLP-1 stimulates insulin secretion in a glucose dependent way, thereby lowering blood sugar levels, reduces glucagon secretion, reduces appetite and delay gastric emptying aiding in weight management.[9] Notably, these receptors have also been found to be expressed in the gastric mucosa, renal tissue, skin, immune cells, and the hypothalamus probably explaining the appetite-suppressing characteristics of this category of medications. GLP-1 RAs have demonstrated effectiveness in diminishing HbA1c with minimal hypoglycemia risk, unless combined with other agents. Central mechanisms in the hypothalamus and gastrointestinal tract contribute to weight loss. Higher GLP-1 levels also enhance insulin sensitivity via different mechanisms, including reducing oxidative stress, minimizing inflammatory responses and straining endoplasmic reticulum stress.[10]

Semaglutide, one of the recent glucagon-like peptide-1 (GLP-1) receptor agonist medication, has been FDA-approved for treating T2DM in 2018 and obesity in 2021, improving glycemic control and potentially reducing the risk of cardiovascular events with specific formulations and indications.[11] The starting dose is 0.25 mg once a week subcutaneously. Four weeks after initiation, dose increments can be done of 0.5 mg on a weekly basis (up-titrated to a FDA-approved maximum dosage of 2 mg per week as of March 2022). Semaglutide at a dosage of 2.4 mg once a week received approval from the FDA in June 2021 for chronic weight management in individuals with overweight or obesity associated with increased cardiovascular risk factors.[12]

The series of SUSTAIN trials demonstrated that, in comparison to placebo and other comparators (such as exenatide extended-release), Semaglutide (0.5 mg and 1.0 mg) significantly lowered glycated hemoglobin and body weight. The 1.0 mg dose of semaglutide showed an HbA1c decrease by 1.5% from the baseline, accompanied by a weight loss of 4.3 kg.[13] Semaglutide 2.4 mg (once weekly) in adults with obesity or overweight (BMI ≥30 kg/m² or ≥27 kg/m² with comorbidities) without diabetes led to loss of 14.9% of their body weight over 68 weeks, compared to a 2.4% loss in the placebo group.[14] It also lowers systolic blood pressure and improves lipid profiles (reduces triglycerides and increases HDL cholesterol), reduced the risk of major adverse cardiovascular events (MACE) by 26%, cardiovascular mortality by 42%, and non-fatal strokes by 39%. SUSTAIN-6 Results showed there was significant reduction of sustained increase in albuminuria, development of new or worsening nephropathy, a doubling of serum creatinine, the need for renal replacement therapy, or renal death by 39% compared to placebo.[15]

The PIONEER trial assessed the efficacy and safety of oral semaglutide at doses of 3, 7, and 14 mg in patients with T2DM and demonstrated that the 14 mg dose of oral semaglutide led to a notable 1.3% drop in HbA1c levels (compared to 0.1% with placebo, $p<0.0001$) and a reduction of weight was 4.3 kg (versus 1.6 kg with placebo, $p<0.0001$). Semaglutide demonstrated superior efficacy compared to sitagliptin, exhibiting a larger decrease in HbA1c of 1.1% and enhancing significant weight loss ($p<0.0001$)[16].

Efpeglenatide, the latest member of GLP-1 RA, is a modified exendin-4 molecule coupled with an immunoglobulin G4 at the fragment crystallizable region (IgG4 Fc) level, which comprises a protein or peptide to prolong the drug's half-life from once a week to once a month and is not yet FDA-approved for the management of obesity or T2DM, but it is being investigated in phase III clinical trials.[17]

Efpeglenatide showed positive impacts on glycemic control observed in phase-II studies with HbA1c reduction 1.61% at 4mg weekly subcutaneous dose in comparison to 1.38% for Liraglutide at a daily dose of 1.8 mg. Moreover, the A1C level was reduced by 1.2% with efpeglenatide 8mg monthly dose compared to placebo at 0.3%.[18] This medication can also be used as an anti-obesity treatment in addition to the anti-diabetic drug because the most significant weight reduction may be practical for patients with obesity without diabetes, where adults lost 7.3 kg with efpeglenatide 6 mg weekly and 7.1 kg with efpeglenatide 8 mg every two weeks.[19] Efpeglenatide also significantly lowers the incidence of cardiovascular events, which happen in 7.0% of those assigned to efpeglenatide and in 9.2% of individuals getting placebo (hazard ratio, 0.73; 95% CI, 0.58-0.92; P=.007 for superiority). The composite renal outcome event also happened less often with efpeglenatide than with placebo (13.0% vs. 18.4%), but this difference was driven more by progression of albuminuria than by decline in GFR.[20]

GLP-1 RAs are generally well-tolerated, but some common side effects, like gastrointestinal in nature, including nausea, vomiting, diarrhea, and abdominal pain, less commonly gallbladder disease and allergic reactions, often occur when initiating treatment and could improve over time. Serious side consequences comprise pancreatitis and thyroid C-cell tumors, advising caution for patients with a history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia (MEN2). Renal impairment, especially in patients with pre-existing CKD, and hypoglycemia are observed when GLP-1 RAs are used alongside insulin or sulfonylureas.[21]

2.2 GLP-1 and GIP Dual Agonist

Tirzepatide, a revolutionary drug, is an agonist for two hormones that are critical in the regulation of glucose and weight: glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). Its innovative mechanism of action with dual activation of GLP-1 and GIP receptors distinguishes tirzepatide from other medications used in the management of T2DM and obesity. It was approved by the U.S. Food and Drug Administration (FDA) to treat T2DM on May 13, 2022, and for the treatment of obesity on June 30, 2023, in adults with a BMI of 30 or higher or 27 or higher with at least one obesity-related comorbid condition.[22]

Tirzepatide activates the GLP-1 receptors, enhances glucose-mediated insulin release, and reduces the secretion of glucagon. Activation of GIP receptors augments insulin sensitivity and secretion and thereby assists in the reinforcement of the mechanisms that regulate blood glucose levels. Owing to the drug's additional effects, such as prolonged gastric emptying time and enhanced satiety after nutrient consumption, promoting lipolysis (fat breakdown) and inhibiting fat accumulation, its use is additionally linked to diminished food consumption and weight loss.[23]

Tirzepatide is commenced with a dose of 2.5 mg weekly with a 2.5-mg dose increment every 4 weeks until reaching the maintenance dose, and depending on efficacy and tolerability, the dose is increased to a maximum of 15 mg weekly.[24]

The SURPASS-1 trial shows that tirzepatide is effective when compared to a placebo in individuals with T2DM patients who are solely managed with exercise and medical nutrition therapy, and HbA1c mean change from baseline was the endpoint at 40 weeks of follow-up. A1C decreased to -1.87%, weight reduced by -7.0 kg, and 87% of patients achieved A1C <7% with the 5 mg dose of tirzepatide. With an A1C drop of -1.89%, weight loss of -7.8 kg, and 92% achieving A1C <7%, the 10 mg dose showed similar benefits. The 15 mg dose produced the most noticeable improvements with -2.07% A1C reduction, -9.5 kg of weight loss and 52% of participants achieving an A1C of <5.7%, the target for normal glucose levels.[25]

All other SURPASS trial series studies also found that tirzepatide treatment significantly reduced HbA1c levels and weight in individuals with established T2DM and advanced T2DM with cardiovascular risk factors, compared to semaglutide, insulin degludec, and glargine.[26] The SURPASS-4 trial found that tirzepatide had a significant effect in lowering the relative risk of major adverse cardiovascular events in T2DM patients by 18% with a hazard ratio (HR) of 0.82 (95% CI: 0.66 to 1.02) and reduced the risk of cardiovascular death by 21%. It has been demonstrated to reduce blood pressure and improve lipid profiles, markers of atherosclerosis, and endothelial function, which are essential for lowering cardiovascular risk.[27] Additionally, tirzepatide reduced albuminuria by 44% and improved eGFR with a relative risk reduction of end-stage kidney disease by 35% with a hazard ratio of 0.65 (95% CI: 0.54 to 0.78) compared to placebo in individuals with T2DM who are at higher risk of renal complications.[28]

Tirzepatide demonstrated substantial weight loss benefits over a period of 72 weeks. Dose of 15 mg had an average weight loss of 13.4%, compared to 2.4% with placebo in patients with obesity and T2DM (SURMOUNT-2).[29] While in patients with obesity without diabetes, tirzepatide 15 mg resulted in an average reduction in weight of 15.0%, compared to 3.1% with placebo, and 56.3% of patients achieved at least 20% weight loss (SURMOUNT-1).[30]

The safety profile of tirzepatide is satisfactory, and the most common side effects are dose-related gastrointestinal effects like diarrhea, vomiting, and nausea. Pancreatitis and worsening of diabetic retinopathy are very rare adverse events. Hypoglycemia is increased with the use in combination with insulin or sulfonylureas, while reactions at the injection sites are minimal and short-lived.[31]

2.3 SGLT-2 Inhibitor

An innovative class of antidiabetic medications is the sodium-glucose co-transporter-2 (SGLT-2) inhibitors. SGLT-2, situated in the kidneys' proximal tubules, plays a key role in renal glucose reabsorption. Similar to GLP-1 RAs, SGLT-2 inhibitors have also shown notable renal and cardiovascular benefits. Cardiovascular outcome trials have demonstrated that empagliflozin, dapagliflozin and canagliflozin reduce the risk of death from cardiovascular disease and hospitalization for heart failure.[32,33] Moreover, SGLT-2 inhibitors have been demonstrated to impede the advancement of chronic renal disease in patients with T2DM, emphasizing the renoprotective benefits.[34]

Ertugliflozin is the fourth SGLT2 inhibitor with remarkable selectivity for SGLT2 over SGLT1 (>2000-fold) approved by the US Food and Drug Administration in December 2017 for the management of T2DM. Being a strong SGLT2 inhibitor, ertugliflozin prevents glucose reabsorption from kidney tubules and re-entering into the bloodstream, leading to increased urinary glucose excretion while avoiding excessive insulin secretion from pancreatic beta cells in patients with T2DM.[35]

The recommended starting dose of ertugliflozin for most patients with T2DM is 5 mg once daily and can be increased to 15 mg once daily after 4-8 weeks of treatment for additional glycemic control. Ertugliflozin consistently showed a 1.3% reduction in HbA1c, 2.4 kg of average weight loss, consequently increasing the rate of patients achieving target HbA1c (< 7). There is also a significant reduction in systolic blood pressure by 3.3 mmHg ($p = 0.02$). In combination with sitagliptin (VERTIS SITA-ER Trial), ertugliflozin demonstrated a reduction of HbA1c by 1.8% and had positive effects on weight and blood pressure ($p < 0.001$).[36]

The VERTIS CV trial did not reveal a significant decrease in major adverse cardiovascular events (HR 0.97 (95% CI, 0.85-1.10, $p = 0.58$), but it reduced the risk of hospitalization for heart failure by 30% (HR 0.70,

95% CI, 0.59-0.83, $p < 0.001$) and significant renal benefits.[37] The ERASER Trial (Renal Outcomes) demonstrates a 39% reduction in the risk of the renal composite endpoint (sustained decline in eGFR, end-stage renal disease, or renal death) (HR 0.61, 95% CI, 0.47-0.80, $p < 0.001$) and reduced albuminuria by 27% compared to placebo ($p < 0.001$).[38]

Its safety profile, however, warrants a cautious assessment. Due to glucose excretion through urine, it may promote fungal growth in genitourinary tract. Common side effects include urinary tract infections and genital mycotic infections. Ertugliflozin can also cause hypotension, volume depletion, electrolyte imbalances, polyuria, especially in elderly patients or those taking diuretics, and hypoglycemia when used with other glucose-lowering agents. Euglycemic diabetic ketoacidosis and acute kidney injury (AKI), although less frequent, are significant risks that require immediate mitigation. Though it leads to the reduction of albuminuria with retard the progression of kidney disease cautiousness is advised in patients with pre-existing kidney disease and contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1.73m²).[39]

2.4 Imeglimin

Imeglimin is a novel anti-diabetic drug containing tetrahydrotriazine, known as the "glimins" which offers a new approach to treating T2DM due to its exceptional dual mode of action, possessing both insulinotropic and insulin-sensitizing properties.[40] Its mechanism of action involves amplifying glucose-stimulated insulin secretion while preserving functional β-cell mass and enhancing insulin sensitivity, including the potential to inhibit hepatic glucose output and improve insulin signaling in both the liver and skeletal muscles mediated by its inhibitory action on mitochondrial oxidative phosphorylation with the improvement of mitochondrial dysfunction. Imeglimin was first approved in 2021 in Japan and China and has now also been available in India and Bangladesh since 2022.[41]

Comprehensive studies with imeglimin monotherapy led to a dose-dependent response in glycemic control in T2DM patients. Japanese T2DM patients participated in a randomized double-blind, placebo-controlled study, and after 24 weeks of clinical trial, the study demonstrated that participants receiving imeglimin 1,000 mg daily experienced a significant reduction in HbA1c by 0.72% (95% CI -0.86 to -0.58, $p < 0.0001$). An increment of daily doses of 2,000 mg gives rise to a fall of 0.94% (95% CI, -1.19 to -0.68), and 3,000 mg daily leads to a drop of 1.0% (95% CI, -1.26% to -0.75%; $P < 0.0001$ for both).[42]

Imeglimin has shown improvements in cardiac function, and it decreases cardiac hypertrophy, fibrosis, and left ventricular dysfunction. AST and ALT levels also dramatically decreased in patients with stage B heart failure. Furthermore, it enhanced left ventricular function and myocardial perfusion, and a notable decrease in albuminuria suggested possible renal protective effects.[43]

Patients with T2DM typically tolerate Imeglimin well. Mild gastrointestinal side effects like nausea, abdominal pain, and diarrhea are common. Imeglimin is thought to be safe in patients with mild to moderate renal impairment and does not raise the risk of hypoglycemia but is used with caution in patients with severe renal impairment (eGFR <30 mL/min/1.73 m²). Further advanced research is necessary to assess its long-term cardiovascular and renal safety.[44]

3. Novel agents that are in development

3.1 GLP-1, GIP and Glucagon Triple Receptor Agonist

A new, groundbreaking triple receptor agonist, retatrutide, is still in the experimental phase for the treatment of obesity, T2DM, non-alcoholic fatty liver disease, and related indications, currently undergoing phase 3 clinical trials and expected to be finished by February 6, 2026. However, the phase 1 to 3 clinical trials have provided expectant data regarding effective glycemic control and obesity management.[45]

It enhances the glucose-dependent insulin secretion, slows the emptying of the stomach, and promotes appetite modulation by activating the GLP-1 receptor, while the GIP receptor activation boosts insulin secretion and enhances fat metabolism. The activation of the glucagon receptor increases energy expenditure and lipolysis, thereby contributing to weight loss. Retatrutide's unique mechanism, with the synergistic action of three receptor activations, offers better blood sugar regulation and increased insulin sensitivity, encourages weight loss, and strengthens overall metabolic health, making it a promising treatment for obesity and T2DM.[46]

In a Phase 2 trial, retatrutide was compared between various dosages in adults with T2DM (0.5 mg, 4 mg, 8 mg, 12 mg) against a placebo and dulaglutide (1.5 mg). The change in HbA1c at 24 weeks was the primary endpoint, while the secondary endpoint focused on body weight reduction at 36 weeks. The 12 mg dose of retatrutide achieved an HbA1c reduction of maximum -2.02% ($p<0.0001$) over 24 weeks, and significantly better than placebo (-0.01%). Dulaglutide, in contrast, demonstrated a lesser HbA1c decrease of -1.41, which was less effective than the 12 mg retatrutide ($p=0.0019$). Concerning body weight, the use of retatrutide showed a dose-dependent decrease in weight, which was substantial. Dose of 12 mg was linked to a 16.94% loss of weight at 36 weeks ($p<0.0001$ vs placebo), and the 8 mg slow dose escalation group to a 16.81% loss. In order to relate to these impacts, placebo caused a loss of a negligible 3.00%, and dulaglutide led to a change of -2.02%.[47]

In a separate Phase 2 obesity trial conducted in the United States with 338 obese participants, after 48 weeks, retatrutide 12 mg dose showed a mean weight loss of approximately 17.5 kg (about 24.2% reduction in body weight). Indeed, in individuals receiving 12 mg of retatrutide, 26% reported a 30% or greater reduction in body weight and also experienced reductions in blood pressure and improvement of other cardiometabolic parameters.[48]

Experiencing just slight side effects, including nausea, diarrhea, vomiting, constipation, tachycardia, and brief elevations of liver enzymes retatrutide had a great safety profile. Importantly, there were no fatalities or severe hypoglycemic incidents. Further evaluation of the long-term safety and efficacy, as well as possible benefits in conditions like osteoarthritis and sleep apnoea, is being continued with ongoing phase 3 trials.[49]

3.2 Amylin analogue

Pramlintide, an injectable anti-diabetic drug, available in the United States since 2005, is a synthetic analogue of the hormone amylin, co-secreted with insulin from the pancreas, used as an adjunctive treatment to insulin for managing both Type 1 and T2DM. Similar to endogenous amylin's activity, pramlintide helps to improve glycemic control and weight management in diabetic patients by decreasing glucagon secretion, slowing gastric emptying, and inducing satiety.[50]

Cagrilintide is another long-acting amylin analogue that not only mimics the actions of native amylin but also has an agonistic effect on calcitonin receptors involved in regulating pain and calcium metabolism and has broader effects on the body compared to pramlintide. One of the trials discovered that a 4.5 mg cagrilintide injection led to a 6% greater reduction in body weight over 26 weeks compared to liraglutide. In addition, cagrilintide therapy also resulted in the lowering of HbA1c levels, an indicator of long-term blood glucose control, by an average of 1.2%.[51]

Cagrilintide, used in combination with semaglutide, is being studied in the REDEFINE phase 3 clinical development program for treating overweight or obesity in adults. REDEFINE 1, involving 3,417 adults with comorbidities but no T2DM, showed that once-weekly cagrilintide 2.4 mg and semaglutide 2.4 mg resulted in a 22.7% weight loss at 68 weeks, significantly outperforming cagrilintide (11.8%), semaglutide (16.1%), and placebo (2.3%). REIMAGINE phase 2 trial for T2DM and overweight, where it showed a higher reduction in HbA1c (2.18%) and body weight (15.6%) compared to its individual components, semaglutide and cagrilintide, which had reductions of 1.79% and 5.1%; and 0.93% and 8.1%, respectively.[52]

The most common adverse effects of cagrilintide were gastrointestinal discomfort, and nearly all were mild to moderate and reduced over time, as one would expect in the GLP-1 receptor agonist class.[53]

3.3 Once weekly basal insulin analogue

Novel antidiabetic therapies cause significant weight loss and organ protection but glycemic control is the first priority in the management of T2DM. Insulin plays a central role in the control of blood glucose that cannot be controlled using conventional antidiabetic agents for individuals with T2DM.

Insulin icodec is a structurally modified insulin analogue with a C20 fatty diacid side chain that promotes strong, reversible albumin binding, reducing receptor affinity and clearance. Its pharmacodynamic profile shows evenly distributed glucose-lowering effects throughout a full 7-day dosing interval, supporting its once-weekly insulin administration.[54] Insulin icodec is a once-weekly basal insulin analogue that has been evaluated in a number of phase 3 ONWARDS studies for the treatment of T2DM. In the ONWARDS 1 trial, 984 insulin-naive adults were randomized to once-weekly insulin icodec or once-daily insulin glargine U100. At week 52, insulin icodec

demonstrated a greater reduction in HbA1c (–1.55% vs. –1.35%) and time in the range of 70 to 180 mg per deciliter is significantly greater with icodec treatment than with glargine U100 treatment (71.9% vs. 66.9%). Safety profile was similar between groups, with no new safety concerns, although a slightly higher incidence of level 1 hypoglycemia was observed with icodec. In ONWARDS 4, in previously basal-bolus-treated patients, insulin icodec was non-inferior to glargine U100 regarding HbA1c reduction and had a comparable safety profile confirming its potential to simplify diabetes management with effective, sustained glycemic control.[55]

4. Conclusion:

The development of newer antidiabetic medications, including SGLT2 inhibitors, GLP-1 RAs, DPP-4 inhibitors, dual and triple incretin receptor co-agonists, imeglimin, amylin analogues and once weekly basal insulin represents a paradigm shift in T2DM management. These agents provide more effective glycemic control and address critical comorbidities such as obesity, cardiovascular disease, and CKD. As these drugs keep getting optimized and more and more becoming integral to clinical practice, they offer promise for more individualized, effective diabetes management, with undeniably improved outcomes beyond traditional therapies and reduced long-term burden of diabetes-related complications. Subsequent research must determine better outcome, long-term safety, cost-effectiveness, and individualized treatment strategies to maximize patient benefits.

Conflict of interest: There is no conflict of interest.

Acknowledgment:

Gratefully acknowledge the thoughtful comments of our teacher & colleagues.

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