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Shifting The Paradigm: Early Intensive Combination Therapy In Newly Diagnosed Type 2 Diabetes

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Abstract*— *Type 2 diabetes mellitus (T2DM) is a progressive chronic metabolic disorder affecting approximately 537 million people worldwide, with severe hyperglycemia being prevalent at the time of diagnosis in nearly half of all newly identified patients. Despite the well-documented "legacy effect" of early glycemic control on long-term complications, traditional stepwise treatment escalation approaches frequently fail to achieve timely glycemic targets. This review examines the pathophysiological rationale, clinical efficacy, safety profile, and implementation framework supporting early intensive combination therapy in newly diagnosed T2DM. Evidence from the landmark VERIFY trial, the EDICT study, and recent "Intense-Simplified" protocols demonstrates that initial multi-agent regimens produce superior and more durable HbA1c reductions, attenuate β-cell decline, and induce remission in a substantial proportion of patients. These benefits are achieved without a proportional increase in hypoglycemia risk when modern agents with complementary mechanisms (metformin, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and pioglitazone) are employed. Current ADA/EASD consensus recommendations endorse early combination therapy for patients presenting with HbA1c levels exceeding individualized targets by 1.5–2.0%. The shifting paradigm thus reframes T2DM management as proactive disease modification rather than reactive symptom control.

Keywords*— *Early Intensive Combination Therapy, Type 2 Diabetes, B-Cell Preservation, Legacy Effect, Verify Trial, Disease Modification and Remission etc

I. INTRODUCTION

Type 2 diabetes mellitus has emerged as one of the most consequential non-communicable diseases of the modern era, currently affecting an estimated 537 million people globally and projected to rise further in parallel with the worldwide obesity epidemic. The disorder is characterized by a complex path physiological interplay between progressive β-cell dysfunction and chronic insulin resistance, producing the inexorable rise in glycemia that defines its natural history [1].

A particularly concerning observation is the prevalence of severe hyperglycemia at the time of diagnosis. A retrospective study conducted in China revealed that 44.5% of newly diagnosed patients present with HbA1c levels exceeding 9%. Globally, fewer than half of patients with T2DM achieve the recommended HbA1c target of less than 7%, reflecting the limitations of conventional management strategies. The persistence of inadequate glycemic control is consequential: every 1% reduction in HbA1c is associated with approximately a 35% decrease in the risk of micro vascular complications, and maintaining HbA1c below 6.0% has been shown to prevent the development of retinopathy [2].

Perhaps most critically, the long-term follow-up of the United Kingdom Prospective Diabetes Study and the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study has established that early glycemic exposure exerts a durable and frequently irreversible impact on subsequent vascular complications, a phenomenon described as the "legacy effect" or "metabolic memory". Individuals whose HbA1c was intensively controlled during the early years of the disease derived enduring protection against micro vascular and macro vascular events even when subsequent glycemic control diverged from the originally intensively treated group. These historical observations establish an unequivocal mandate for early therapeutic intervention that is both aggressive and effective.

The traditional "step-care" paradigm initiating metformin monotherapy and sequentially intensifying treatment in response to progressive hyperglycemia has been characterized by high rates of clinical inertia and treatment failure . In response, the contemporary approach of early intensive combination therapy has emerged as a rational strategy to address the multiple concurrent path physiological disturbances present at diagnosis, accelerate attainment of glycemic targets, and preserve residual β-cell secretory capacity. This review synthesizes the evidence supporting this paradigm shift, examines the clinical efficacy and safety of relevant regimens, and discusses the implications for current practice guidelines and future research [5].

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II. PATHOPHYSIOLOGICAL MECHANISMS

A. Beta Cell Function

A central pathophysiological feature of T2DM is the progressive decline in insulin secretory capacity, frequently already evident at the time of diagnosis. This decline reflects a cascade of cellular insults triggered by chronic hyperglycemia and glucolipotoxicity, including β-cell dedifferentiation, endoplasmic reticulum stress, oxidative stress, and accelerated apoptosis. The resulting loss of functional β-cell mass undergirds the characteristic clinical course of progressive glycemic deterioration despite ongoing therapy.

The concept of "glucotoxicity" is fundamental to understanding the rationale for early intervention. Sustained hyperglycemia directly impairs β-cell function through multiple mechanisms, including the induction of ER stress within the islets of Langerhans, which in turn activates apoptotic signaling pathways and exacerbates secretory failure. Even mild, persistent hyperglycemia can trigger β-cell dedifferentiation and phenotypic switching, leading to a self-perpetuating vicious cycle in which worsening glycemia begets further β-cell deterioration.

Early intensive combination therapy disrupts this deleterious cycle by leveraging pharmacological agents with complementary mechanisms of action to achieve rapid near-normoglycemia. Clinical evidence indicates that aggressive early glycemic normalization may facilitate the recovery of dormant β-cell subpopulations, potentially inducing a period of remission. The underlying mechanism appears to involve relief of glucotoxicity-mediated ER stress, attenuation of the inflammatory milieu associated with insulin resistance, and protection of the vascular endothelium through durable epigenetic and metabolic changes. This physiological "reset" not only halts the immediate progression of hyperglycemia but also modulates the "metabolic memory" of target tissues, potentially conferring sustained reductions in long-term cardiovascular morbidity.

B. Insulin Resistance Patterns

Insulin resistance represents the other major pathophysiological axis of T2DM and is typically present years before clinical hyperglycemia manifests. In 1987, DeFronzo described what he termed the "triumvirate" of T2DM pathophysiology: moderate-to-severe muscle and hepatic insulin resistance, combined with progressive β-cell failure. In the prediabetic state, normoglycemia is maintained through compensatory hyperinsulinemia; with time, however, the β-cell is unable to sustain the increased secretory demand, and fasting and postprandial hyperglycemia emerge .

Contemporary understanding has expanded this framework to recognize additional defects, including altered adipocyte fat metabolism, incretin deficiency or resistance in the gastrointestinal tract, hyperglucagonemia from pancreatic α-cells, enhanced renal glucose reabsorption, and central nervous system insulin resistance. The result is a multiorgan pathophysiological disturbance requiring a therapeutic strategy that addresses several mechanistic targets simultaneously.

The choice of agents in early intensive combination therapy is informed by this pathophysiological logic. Metformin principally targets hepatic glucose overproduction and modestly improves peripheral insulin sensitivity; thiazolidinediones such as pioglitazone ameliorate muscle and adipose tissue insulin resistance; GLP-1 receptor agonists and DPP-4 inhibitors enhance insulin secretion in a glucose-dependent manner and suppress glucagon; and SGLT2 inhibitors promote urinary glucose excretion through an insulin-independent mechanism. By combining agents with complementary mechanisms, early intensive regimens simultaneously target multiple components of the pathologic process rather than addressing them sequentially.

III. CLINICAL EFFICACY

A. Glycemic Control Outcomes Multiple randomized controlled trials have demonstrated that initial combination therapy achieves greater and more durable glycemic control compared with the conventional stepwise approach. The VERIFY trial, the first large-scale prospective study of its kind, randomized 2,001 patients with newly diagnosed T2DM (mean baseline HbA1c of 6.5–7.5%) to either initial combination therapy with metformin plus the DPP-4 inhibitor vildagliptin or to metformin monotherapy with sequential addition of vildagliptin upon loss of glycemic control. The early combination strategy demonstrated significantly greater durability of glycemic control over 5 years, with a slower decline in the proportion of patients maintaining HbA1c below 7.0% .The rationale underlying this finding is straightforward: rather than allowing patients to "lose control" under stepwise intensification, early combination therapy targets glycemic control from the outset, shifting the patient expectation.

The benefits of early combination therapy appear particularly pronounced in patients with more severe hyperglycemia at diagnosis. The EDICT (Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes) study evaluated a triple-therapy regimen of metformin, pioglitazone, and exenatide in patients with newly diagnosed T2DM and reported that 78% of participants achieved HbA1c less than 6.5% over 3 years, with the combination producing significantly fewer hypoglycemic events than sequential add-on therapy with metformin, sulfonylurea, and basal insulin. These findings highlight the capacity of pathophysiological-based initial combination regimens to outperform conventional strategies in both efficacy and safety.

The recently reported "Intense-Simplified" strategy provides additional compelling evidence derived from an open-label, multicenter, randomized controlled trial conducted across 15 hospitals in China. Participants had a mean age of 46.8 years, a baseline BMI of 25.8 kg/m², and notably severe hyperglycemia at entry: mean baseline HbA1c of 11.0% ± 1.9%, fasting plasma glucose of 11.4 mmol/L, and 2-hour postprandial glucose of 20.5 mmol/L; 76% of participants presented with classic symptoms of severe hyperglycemia including polydipsia, polyuria, and weight loss. Following initial short-term intensive insulin therapy to relieve glucotoxicity, patients were randomized to maintenance

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therapy with linagliptin plus metformin (LIN+MET), linagliptin alone, metformin alone, or standard care. At 48 weeks, the LIN+MET group achieved HbA1c less than 7.0% in 80% of participants (85.9% in the per-protocol analysis) — significantly higher than the 60% rate observed in the control group (p = 0.003) (Liu & Li, 2024). For the more stringent target of HbA1c less than 6.5%, the LIN+MET group achieved 70%, compared with 48% in controls (p = 0.005). The mean HbA1c reduction from baseline in the LIN+MET group was 4.8%, reaching a final mean of 6.2%, significantly lower than all other groups (p = 0.004).

Notably, the glycemic outcomes observed in the Intense-Simplified strategy were strikingly superior to those reported in other studies employing similar oral regimens in less hyperglycemic populations. For example, in a post hoc analysis of two randomized trials, linagliptin combined with metformin at 1000 mg/day in early T2DM patients with moderate hyperglycemia (mean baseline HbA1c 8.7%) reduced HbA1c by 1.67%, achieving HbA1c < 7.0% in only 51.4% and HbA1c < 6.5% in just 40.1% of patients (Liu & Li, 2024). This apparent disparity underscores the unique disease-modifying properties of the Intense-Simplified approach, in which initial remission-inducing therapy establishes a robust metabolic foundation upon which simplified maintenance therapy can sustain long-term benefits.

B. Durability of Remission

A particularly compelling dimension of early intensive combination therapy is its potential to induce remission rather than merely achieve control. The feasibility of remission through intensive intervention was first established by short-term intensive insulin therapy studies. Liu and colleagues have demonstrated that SIIT effectively alleviates glucotoxicity and induces diabetes remission lasting over one year in more than 50% of patients with newly diagnosed T2DM. However, the remission rate after SIIT declines progressively over time: from 70% immediately post-therapy to approximately 50% by the end of the first year and around 40% by the end of the second year.

These temporal patterns provide two key insights. First, the reversal of hyperglycemia and β-cell dysfunction achieved through SIIT establishes a robust foundation for long-term glycemic control. Second, sustained glucose-lowering strategies following intensive therapy are essential to prevent recurrent hyperglycemia and to protect β-cell function over the long term. The Intense-Simplified model operationalizes this insight by combining intensive remission induction with simplified, well-tolerated maintenance therapy to extend the durability of remission. Recent data confirm that oral hypoglycemic agents facilitate SIIT implementation and enhance transient improvements in glycemic control, though similar 12-month diabetes remission rates suggest that prolonged sequential therapy may be required to translate these transient improvements into durable benefit.

The mechanisms underpinning durable remission include the continuous improvement in β-cell secretory capacity that follows glucotoxicity relief. In the Intense-Simplified trial, the LIN+MET group exhibited sustained improvement in the Insulin Secretion-Sensitivity Index-2 throughout the 48-week follow-up period, significantly superior to the control group. Similarly, HOMA-B levels in the subsequent intervention groups were significantly higher than in controls, confirming the strategy's capacity to preserve β-cell function. Importantly, a 24-week clinical trial found that the sitagliptin-and-metformin combination produced better β-cell responsivity to a mixed meal tolerance test than either monotherapy, with changes in β-cell function significantly correlated with changes in HbA1c.

The "legacy effect" observed in long-term follow-up of UKPDS and DCCT/EDIC implies that the benefits of early intensive control will persist for years. Lind and colleagues have demonstrated using UKPDS data that historical HbA1c values have a greater impact than recent values on long-term clinical outcomes, and that early detection combined with intensive glucose control from the time of diagnosis is essential to maximize the long-term reduction of glycemic complications. Early intensive combination therapy is uniquely positioned to exploit this phenomenon.

IV. Safety and Tolerability

A. Hypoglycemia Risk Analysis

A primary concern regarding any intensive glucose-lowering strategy is the corresponding risk of hypoglycemia. Modern combination regimens incorporating agents with glucose-dependent mechanisms of action have largely mitigated this concern. GLP-1 receptor agonists stimulate insulin secretion only in the setting of elevated glucose and appropriately preserve glucagon counter regulation during hypoglycemia; thus, their inherent hypoglycemia risk is low when used as monotherapy or in combination with other non-insulin secretagogues. DPP-4 inhibitors similarly enhance endogenous incretin action in a glucose-dependent fashion and have a safety profile frequently indistinguishable from placebo (Davies et al., 2020). A meta-analysis examining incretin-based agents in T2DM patients at cardiovascular risk found that incretin-based therapy overall was not associated with any increase in hypoglycemia (RR = 1.05, 95% CI 0.96–1.15) or severe hypoglycemia (RR = 0.97, 95% CI 0.74–1.26), though DPP-4 inhibitors modestly increased the overall risk of hypoglycemia while GLP-1 agonists decreased the risk of severe events.

The favorable comparative safety of GLP-1 receptor agonists versus DPP-4 inhibitors has been confirmed in head-to-head analyses. Among older adults stratified by frailty status, GLP-1 receptor agonist initiators demonstrated an overall rate of the primary composite safety outcome of 51.9 per 100 person-years compared with 57.5 for DPP-4 inhibitor initiators (HR 0.90, 95% CI 0.87–0.94), with significant rate reductions observed in non-frail and pre-frail populations (Kutz et al., 2023). GLP-1 receptor agonists were also associated with significantly lower rates of acute kidney injury and hypoglycemia.

The Intense-Simplified strategy, which combined SIIT with maintenance therapy primarily using the DPP-

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4 inhibitor linagliptin, maintained hypoglycemia rates at acceptably low levels, with patient compliance exceeding 85% across all maintenance groups and drug discontinuation rates below 5% due to gastrointestinal events. These findings indicate that contemporary early intensive combination regimens can achieve aggressive glycemic targets without incurring disproportionate hypoglycemia risk.

B. Adverse Event Profiles

Beyond hypoglycemia, the broader adverse event profile of early intensive combination therapy varies according to the specific agents employed. Metformin, the foundation of most combination regimens, is principally associated with gastrointestinal intolerance, which can be minimized by gradual titration and the use of extended-release formulations. In the Intense-Simplified trial, gastrointestinal adverse events were primarily reported in the metformin-containing groups, but most patients tolerated these events well.

Pioglitazone, a component of the EDICT triple-therapy regimen, is associated with weight gain, fluid retention, and a modestly increased risk of bone fracture, though these concerns have been substantially mitigated by appropriate patient selection. The EDICT trial reported that the metformin/pioglitazone/exenatide combination resulted in fewer hypoglycemic events than the sequential comparator regimen, with favorable cardiovascular and weight profiles attributable to the inclusion of exenatide.

GLP-1 receptor agonists are predominantly associated with transient gastrointestinal effects (nausea, vomiting, early satiety), which typically attenuate over time and are counterbalanced by clinically meaningful weight loss. SGLT2 inhibitors carry a small risk of genitourinary infections and, in rare cases, euglycemic diabetic ketoacidosis, though their cardiovascular and renal protective benefits frequently outweigh these concerns in appropriate patients.

A systematic review and meta-analysis of initial combination therapy in treatment-naïve T2DM patients demonstrated that compared with monotherapy, all initial combination regimens produced significant HbA1c reductions, and DPP-4 inhibitor-plus-metformin and SGLT2 inhibitor-plus-metformin combinations demonstrated hypoglycemia risk comparable to metformin monotherapy. In contrast, sulfonylurea-plus-metformin and thiazolidinedione plus metformin combi-nations were associated with significantly higher hypoglycemia risk. These findings reinforce the importance of selecting combination partners with complementary, glucose-dependent mechanisms when implementing early intensive treatment. 5. Therapeutic Implementation

V. THERAPEUTIC IMPLEMENTATION

A. Early Intervention Strategies

The conceptual foundation supporting early intensive combination therapy derives from the recognition that T2DM is a multiorgan, multi-mechanism disease in which delaying the initiation of effective therapy allows irreversible patho-physiological deterioration to occur. The patho-physiologic approach advocated by DeFronzo and colleagues recommends initial combination therapy with agents that correct the established patho-physiological defects in T2DM, using a framework that individualizes treatment based on general health status and associated medical disorders.

The selection of specific agents in early combination therapy should be informed by the severity of hyperglycemia at presentation, the presence of comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, obesity), and the patient's tolerability profile. For patients presenting with severe hyperglycemia (HbA1c > 9–10%), short-term intensive insulin therapy may be employed to rapidly eliminate glucotoxicity, followed by transition to an oral combination regimen to maintain the benefits achieved. For patients with milder hyperglycemia (HbA1c 1.5–2.0% above target), direct initiation of oral combination therapy with metformin plus a second agent (DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or pioglitazone depending on comorbidities) is appropriate.

Fixed-dose formulations can improve medication adherence when combination therapy is used and may help achieve glycemic targets more rapidly (Davies et al., 2018). The Intense-Simplified trial demonstrated that low-dose metformin (e.g., 1000 mg/day) combined with a DPP-4 inhibitor having a favorable safety profile (linagliptin) achieves excellent compliance exceeding 85%, with high tolerability reflecting the simplicity of the regimen (Liu & Li, 2024). Such simplified maintenance regimens are essential to translate the benefits of intensive initial therapy into long-term clinical gains.

B. Clinical Practice Guidelines

Contemporary international guidelines have increasingly endorsed early intensive combination therapy. The ADA Standards of Care in Diabetes—2024 state that "early combination therapy can be considered in adults with type 2 diabetes at treatment initiation to shorten time to attainment of individualized treatment goals". Furthermore, the Standards explicitly advise: "Initial combination therapy should be considered in people presenting with A1C levels 1.5–2.0% above target". The 2022 ADA/EASD consensus report on the management of hyperglycemia in T2DM identified four principal advantages of combination therapy: increased durability of the glycemic effect, addressing therapeutic inertia; simultaneous targeting of the multiple pathophysiological processes that characterize T2DM; improved medication-taking behavior and treatment persistence; and complementary clinical benefits on glycemic control, weight, and cardiovascular risk profiles.

The ADA Standards of Care in Diabetes—2023 reference the VERIFY trial as direct evidence that "initial combination therapy is superior to sequential addition of medications for extending primary and

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secondary failure". The Standards also note that incorporating high-glycemic-efficacy therapies or therapies for cardiovascular/renal risk reduction (e.g., GLP-1 receptor agonists, SGLT2 inhibitors) may allow for weaning of the current regimen, particularly of agents that may increase the risk of hypoglycemia.

These recommendations reflect a substantial evolution from the 2018 ADA/EASD consensus, which, while supportive of initial combination therapy in patients with HbA1c more than 17 mmol/mol (1.5%) above target, placed greater emphasis on stepwise intensification and the option of sequentially assessing each agent's individual efficacy and risk-to-benefit profile. The progressive shift toward endorsing earlier, more aggressive combination therapy reflects the accumulating evidence base supporting the clinical benefits of this approach.

VI. Future Research Directions

The shifting paradigm of early intensive combination therapy opens several important avenues for future investigation. While current evidence convincingly supports the early initiation of combination therapy in adult patients with newly diagnosed T2DM, several key questions remain.

First, the long-term impact of early intensive combination therapy on hard cardiovascular and kidney outcomes in newly diagnosed patients has not been fully elucidated. Most existing trials have focused on glycemic endpoints rather than macrovascular events. As the GRADE study has demonstrated, even long-term comparative effectiveness research has predominantly enrolled patients with established (not newly diagnosed) T2DM, limiting generalizability of cardiovascular findings to the early-disease population.

Second, the optimal composition of early combination regimens requires further investigation. The VERIFY trial results have not been generalized to oral agents other than vildagliptin, and head-to-head comparisons of DPP-4 inhibitor-, SGLT2 inhibitor-, and GLP-1 receptor agonist-based early combination regimens are needed. The emergence of dual and triple hormone agonists (e.g., tirzepatide) with greater glycemic and weight-loss efficacy than existing agents may further expand the therapeutic options available for early intensive intervention. Additional evidence is needed regarding the specific ability of initial combination therapy to impact β-cell function preservation; a 16-week alogliptin/pioglitazone combination study in recent-onset T2D showed a significant increase in insulin secretion rate compared with placebo, while alogliptin alone did not, illustrating that not all combinations produce equivalent mechanistic benefits.

Third, the applicability of early intensive combination strategies across diverse populations, ethnic groups, and cultural contexts warrants systematic evaluation. The Intense-Simplified trial was conducted exclusively in China; whether the strategy translates to populations with different genetic backgrounds, dietary patterns, and healthcare systems requires confirmation. Cost-effectiveness analyses will also be crucial to inform health policy decisions in resource-constrained settings.

Fourth, the role of disease-modifying therapies in T2DM is an emerging frontier. While immunomodulatory approaches such as teplizumab have demonstrated the capacity to delay the progression of type 1 diabetes by addressing the underlying autoimmune pathogenesis, analogous interventions for the glucolipotoxic, β-cell-directed pathophysiology of T2DM remain under investigation. Targeted pharmacological therapy capable of restoring β-cell function for diabetes remission — including the replenishment of functional β-cell mass through regenerative or anti-dedifferentiation approaches — represents a particularly promising research direction. Combination early intensive strategies may serve as a critical platform to enable such regenerative interventions by creating a low-glucotoxicity environment in which β-cell recovery can occur.

Fifth, the integration of stricter glycemic control metrics during intensive therapy merits further investigation. Evidence suggests that tighter glycemic control during SIIT — indicated by lower mean blood glucose and higher time in range— strongly predicts β-cell restoration and long-term glycemic outcomes. Establishing the optimal glycemic thresholds and monitoring strategies during the Intense phase of combination protocols will be essential to maximize the durability of benefits.

Finally, the question of whether sustained glycemic control in the early stages of T2DM can effectively reduce both microvascular and macrovascular complications — analogous to the legacy effect observed in UKPDS — when achieved through combination pharmacotherapy rather than insulin remains to be confirmed in adequately powered long-term trials. Incorporating agents with cardiovascular benefits, such as GLP-1 receptor agonists or SGLT2 inhibitors, into early maintenance regimens represents a particularly promising avenue, as these complementary purposes — cardiovascular protection and glycemic stability — are synergistic rather than competing.

VII. Conclusion

The accumulating evidence base supports a decisive shift away from the traditional stepwise approach and toward early intensive combination therapy as a foundational strategy for newly diagnosed T2DM. The pathophysiological logic is compelling: T2DM is a Multi mechanism disease in which simultaneous targeting of multiple defects is more rational than sequential monotherapy. The clinical outcomes — superior glycemic control, durable remission, and preserved β-cell function — are demonstrated across multiple landmark trials including VERIFY, EDICT, and the Intense-Simplified strategy. The safety profile is favorable when agents with complementary, glucose-dependent mechanisms are selected. And the international guideline community has progressively endorsed this approach, with the ADA Standards of Care

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in Diabetes—2024 explicitly recommending consideration of early combination therapy at treatment initiation to shorten the time to attainment of individualized glycemic goals. By prioritizing early metabolic stabilization, healthcare systems can mitigate the future burden of diabetes-related complications and exploit the legacy effect to confer durable protection against microvascular and macrovascular morbidity. The paradigm shift embodied in early intensive combination therapy represents more than an incremental refinement of existing practice; it reflects a fundamental reconceptualization of T2DM management — from reactive symptom control to proactive disease modification. As the field moves forward, the guiding principle articulated by Liu and Li remains apt: "No matter how advanced our research and approaches to diabetes care become, simplicity will always remain a fundamental guiding principle".

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