Therapeutic Inertia in People With Type 2 Diabetes in Primary Care: A Challenge That Just Won't Go Away

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Therapeutic inertia is a prevalent problem in people with type 2 diabetes in primary care and affects clinical outcomes. It arises from a complex interplay of patient-, clinician-, and health system–related factors. Ultimately, clinical practice guidelines have not made an impact on improving glycemic targets over the past decade. A more proactive approach, including focusing on optimal combination agents for early glycemic durability, may reduce therapeutic inertia and improve clinical outcomes.

Type 2 diabetes is a complex chronic disease process that occurs because of relative insulin deficiency secondary to progressive β-cell loss over time and insulin resistance. The foundation of management includes lifestyle change and pharmacotherapy. Because of the progressive nature of the disease, many patients will require escalation of pharmacotherapy to achieve and maintain glycemic targets. The complications of long-term hyperglycemia in patients with type 2 diabetes are well established, and delays in treatment intensification can lead to tangible harm to patients (1,2).

"Clinical inertia" was originally defined by Phillips et al. (3) as "the failure of health care providers to initiate or intensify therapy when indicated." "Therapeutic inertia" was more recently defined by Khunti et al. (4) as "the failure to advance therapy or to deintensify therapy when appropriate to do so." A number of studies have tried to quantify the prevalence of therapeutic inertia in patients with type 2 diabetes (5). One major limitation of the available literature is a lack of standardization regarding how therapeutic inertia is measured. Various measures used by individual studies have included median time between A1C above target and treatment intensification, proportion of patients with A1C above target who have treatment intensification, or total length of time when A1C is above target (glycemic burden) (5). Regardless of the method of quantification, the common theme is that therapeutic inertia in diabetes is prevalent in clinical practice.

In the United States, a retrospective cohort study of 11,525 patients with type 2 diabetes and an A1C ≥8.0% after >3 months of medical therapy found that 52% of patients did not have treatment intensification within 12 months of the index date (6). In 2017, a National Health and Nutrition Examination Survey study examined the percentage of patients with type 2 diabetes from 2007 to 2014 who achieved the glycemic target (A1C <7%). Of the 2,677 patients in the study, only 50.9% achieved this target (7).

In Canada, studies have produced similar results. Leiter et al. (8) conducted the Diabetes Mellitus Status in Canada (DM-SCAN) study, a survey of 5,123 patients with type 2 diabetes from 479 primary care physicians (PCPs). Only 50% of patients met the glycemic target (A1C ≤7.0%). Not only were glycemic targets unmet, but the percentage of patients achieving global vascular protection (i.e., target control of A1C, blood pressure, and LDL cholesterol) was only 13%. In another survey of 379 patients with type 2 diabetes from 109 PCPs, Harris et al. (9) found a high prevalence of diabetes complications and a mean A1C of 9.5% at time of insulin initiation. These results suggest a period of time (of unknown duration) of marked hyperglycemia with a detrimental impact on patient outcomes (9).

Although therapeutic inertia is most commonly seen at insulin initiation, it can occur at any point in the disease process. A study of patients newly diagnosed with type 2 diabetes who took metformin monotherapy for 3 months without sufficient A1C lowering found a significant proportion (28–38%) for whom therapy was not escalated within 6 months of metformin failure (10). Early therapeutic inertia was also seen in a large retrospective cohort study by Khunti et al. (11) of >80,000 patients with type 2 diabetes on

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oral antidiabetic agents (OADs). This study looked at time to treatment intensification based on A1C and baseline number of OADs. For patients with an A1C ≥7.5% on one OAD, median time to intensification with an additional OAD was almost 2 years. These findings are striking considering the multitude of options, including oral agents that are safe and well tolerated, available to treating clinicians. Khunti et al. (11) also found that, for patients on two OADs, the median time to intensification with an additional OAD was 7.2 years. The median time to intensification with insulin was >6 years. The mean A1C at the time of intensification was markedly higher than the current guideline-recommended targets, at 8.7–9.1%.

Titration inertia is also an issue in patients already on basal insulin who are not at target. In a retrospective cohort study, only 30.9% of patients on basal insulin with A1C ≥7.5% had treatment intensification, with a median time to intensification of 3.7 years (12).

Therapeutic inertia is a prevalent problem. However, the management of patients with type 2 diabetes is not always straightforward. Patient-related factors, comorbidities, overall frailty, risk of polypharmacy, and duration of disease are some issues that may influence clinical decisions regarding setting specific glycemic targets and intensifying treatment. Appropriate inaction based on any of the above factors should be considered distinct from therapeutic inertia. However, even when individualized targets are accounted for, studies have still found a high rate of therapeutic inertia in patients with type 2 diabetes (7,13).

Importance of Addressing Therapeutic Inertia

The benefit of achieving glycemic targets in people with type 2 diabetes has long been established based on the results of the U.K. Prospective Diabetes Study (UKPDS) (14). The UKPDS found that every 1% reduction in A1C was associated with significant reductions in the rates of diabetes complications, death related to diabetes, myocardial infarction, and microvascular complications (2). In addition, the long-term observational study that followed the original UKPDS trial found persistent benefit with regard to diabetes-related complications, including important cardiovascular (CV) outcomes (1). This benefit persisted even after the initial difference in A1C was lost between the intervention and control groups (1). Another cohort study of patients newly diagnosed with type 2 diabetes found that the A1C achieved during the first year after diagnosis was strongly associated with the risk for future diabetes-related complications and mortality (15). The legacy benefit of achieving glycemic targets early on cannot be overstated. Finally, a cohort study of >100,000 patients newly diagnosed with type 2 diabetes in the United Kingdom found that a 1-year delay in treatment intensification when A1C was ≥7.0% was associated with significant increases in myocardial infarction, heart failure, stroke, and a composite of CV outcomes (16). These increases were significant for patients with and without baseline CV disease (16). Thus, there is compelling evidence that therapeutic inertia can lead to worse outcomes for patients.

Factors Contributing to Therapeutic Inertia and Strategies to Address Them

Therapeutic inertia arises from a complex interplay of a number of factors. These factors can be broadly categorized as patient-, clinician-, and health system–related factors and are reviewed extensively elsewhere (5,17–21). Here, we will emphasize a select number of factors that we encounter frequently in the primary care setting. Table 1 provides a summary of the key findings.

Patient-Related Factors

Hypoglycemia is a common fear expressed by patients and clinicians alike. In a survey of 708 insulin-naive patients with type 2 diabetes, 43.3% endorsed "problematic hypoglycemia" as one of the reasons that contributed to insulin avoidance (22). Likewise, a survey of 1,250 clinicians (600 specialists and 650 PCPs) worldwide found that the majority (75.5%) would be more aggressive with insulin treatment if not for the risk of hypoglycemia (23).

Fear of insulin injections is also a well-documented barrier for patients (22,24). However, clinicians may be more concerned than patients about the physical discomfort of injections (25).

Clear communication can help to allay fears of hypoglycemia and injection pain. Recent innovations in both oral and injectable pharmacotherapies have yielded a much lower risk of hypoglycemia compared with older treatments. For example, prefilled insulin pens are easier to manage than vials and syringes, and the needles are smaller and finer than ever before. Demonstrating the use of insulin pens and supervising patients' first injection in the clinic can be effective ways to increase patients' confidence.

Self-blame is also an important factor to consider when initiating insulin therapy. In the DAWN (Diabetes, Attitudes, Wishes, and Needs) study, half of participants expressed the negative belief that insulin therapy meant they had failed to follow previous treatment recommendations properly (26). Because diabetes is known to be a progressive disease, many patients will require exogenous insulin therapy through no fault of their own. Thus, clear

TABLE 1 Summary of Key Points

Therapeutic inertia in type 2 diabetes is a prevalent problem in clinical practice regardless of duration of disease.
Therapeutic inertia in type 2 diabetes leads to worse clinical outcomes.
Clear communication, expectation-setting, and shared decision-making are crucial to address patient-related factors, including fear of hypoglycemia, fear of injection pain, and fear of weight gain, and to mitigate negative beliefs such as self-blame.
It is crucial to engage and educate primary care practitioners on novel therapies and the importance of early intensification. Clinical practice guidelines have failed to affect the prevalence of therapeutic inertia through the years.
The lack of time and resources is a significant barrier. Strategies with proven glucose-lowering benefit include providing self-management education, incorporating more allied health support in the clinic, and using telehealth remote monitoring.
Clinical practice guidelines have not affected the prevalence of therapeutic inertia. A new approach focusing on optimal combination agents for early glycemic durability may reduce therapeutic inertia and improve clinical outcomes. More randomized clinical trials investigating combination options are needed.

communication to set expectations early in the disease course is crucial for success (26).

It is also important to ensure that patients understand the benefits of achieving glycemic targets. A Brazilian study showed that patients were more concerned about complications with significant quality-of-life impact, including blindness from retinopathy and dialysis with nephropathy. These complications resonated more with patients than did the CV complications on which clinicians tended to focus (27). Patients should also understand the short-term benefits of achieving euglycemia. In our clinical practice, we see patients with chronic hyperglycemia and A1C values markedly above target who have felt unwell and tired for a long time. In addition, these patients may feel dejected when they see fasting and postprandial glucose numbers that are constantly elevated. It can be helpful for these patients to understand the benefits of achieving glycemic targets in the short term, including urinating less, having more energy, and seeing better blood glucose readings throughout the day (28). These simple, short-term outcomes can be incredibly powerful motivators for individual patients.

Fear of gaining weight also can be a powerful barrier, especially with regard to insulin therapy. The foundation of diabetes management (as with the management of all chronic diseases) is healthy lifestyle change with an emphasis on eating whole, nutritious foods and engaging in regular exercise to promote a healthy body weight. In addition to lifestyle coaching, medication options that promote weight loss should be optimized if possible. These agents include sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists. In addition, the new fixed-ratio combination products combining a GLP-1 receptor agonist with a basal insulin can lead to robust A1C lowering with less weight gain compared with intensive insulin therapy (29).

Clinician-Related Factors

Clinician-related factors can influence therapeutic inertia as well. As clinicians, we tend to overinflate the quality of care that we provide and consequently underestimate the number of patients who are not at target in our own practice. This was evidenced by the DM-ACTION survey of general practitioners in Canada (30). Although 98% of practitioners reported that they would adjust pharmacotherapy within 3 months if A1C goals were not met, practice audits found that the mean A1C was 8.2% and the median time between A1C tests was 5 months, suggesting glycemic instability in a significant proportion of patients.

Another potential barrier is the ever-evolving armamentarium of glycemic management options at our disposal. The therapeutic options for type 2 diabetes have increased significantly over the past 10 years. With the rapid development of novel agents, it is no wonder that some physicians feel overwhelmed with the magnitude of choice (31). The myriad of combination products can be easily overlooked even though they can be excellent options when it comes to reducing patients' prescription burden. In a survey of 600 physicians, 49% noted that one of the main challenges was the inability to stay current with advances in diabetes therapy (31). There is also a knowledge gap and differing comfort levels between family physicians and diabetes specialists. In a study of clinicians in France, specialists were 9.9 times more likely than primary care providers to prescribe early insulin therapy (32). Another study of patients with type 2 diabetes treated by specialists and family physicians found that therapeutic inertia was prevalent in both groups. More than half of patients with an elevated A1C did not have therapy escalated. However, specialists overall were less prone to therapeutic inertia and were more likely to intensify treatment (45.1 vs. 37.4%, $P = 0.009$) and to initiate insulin therapy (8.6 vs. 1.7%, $P < 0.0001$) (33). Type 2 diabetes is increasingly managed in the primary care setting given its rising prevalence worldwide. It is crucial therefore to engage and educate primary care practitioners on novel therapies and on the importance of early intensification.

Clinical practice guidelines have recommended when and where to use glucose-lowering agents for decades. Unfortunately, recent data have shown that the number of

patients achieving target A1C levels has essentially plateaued since the 1999–2006 period, despite the plethora of novel agents available for the treatment of type 2 diabetes (7). The current approach of stepwise therapy, through which glycemic medications are intensified only after treatment failure, may lead to periods of sustained hyperglycemia and worse outcomes.

Health System–Related Factors

Lack of time and resources is a frequently cited barrier to appropriately escalating therapy. Primary care visits can be complex and touch on a variety of acute and chronic issues. These visits are finite, and visits dedicated to diabetes management can be easily taken over by other patient concerns. One study looked at the relationship between escalating therapy in patients with type 2 diabetes and elevated A1C and the number of additional concerns patients brought to their visits. Not surprisingly, the likelihood of treatment intensification decreased as the number of patient complaints increased (34).

Strain et al. (35) observed that therapeutic inertia does not appear to affect clinical trials. This is likely because of the high numbers of visits during which clinicians are able to reinforce to patients the importance of escalating therapy, have the ability to troubleshoot problems on a routine basis, and can also continuously reinforce to patients the seriousness of their condition. In addition, the highly regimented protocols in clinical trials leave no room for ambiguity about treatment intensification (35).

However, increasing the number of clinic visits is likely not feasible for many PCPs. Instead, patients need to be empowered to learn self-management skills. A systematic review found that diabetes self-management education delivered in a group setting was associated with a significant reduction in A1C at 6 months (0.44%, $P = 0.0006$). This reduction was durable and was maintained at 2 years (36). In addition to empowering patients, we need to engage other allied health professionals. A study in the United States found that a program combining a nurse practitioner and physician versus usual care by a physician alone was more effective in lowering A1C (37). This finding was similar to that of a cluster-randomized controlled trial in Australia that evaluated a model called "Stepping Up." This model was essentially the incorporation of practical nurses with family physicians supported by endocrinologists and certified diabetes educators. It resulted in higher insulin initiation rates and greater reductions in A1C compared with standard care (38).

Another novel avenue that requires further study is the use of telehealth remote monitoring. A randomized clinical trial compared telehealth remote monitoring and usual care and found that the telehealth group had greater A1C lowering at 6 months (–1.11 vs. –0.70%). Reduced therapeutic inertia was also seen, with the telehealth group having more medication changes versus the usual care group (39).

Medication costs and access to care remain major barriers for patients, clinicians, and the health care system. In the United States, where direct health care costs of diabetes were estimated to be $237 billion in 2017 alone, the costs of prescription medications have steadily risen (40). From 2002 to 2013, the mean price of insulin increased 197%, and the mean price of dipeptidyl peptidase 4 (DPP-4) inhibitors increased by 34% (41). Not surprisingly, higher out-of-pocket costs to patients are associated with lower medication-taking and persistence (42,43). Cheaper alternatives also tend to have high risks of hypoglycemia and negatively affect weight, with the exception of metformin. This situation plays into patients' and clinicians' fears and will only enhance both parties' reluctance to escalate therapy.

It Is Time for a New Approach

The pathophysiology of diabetes is a complex interplay of a number of metabolic defects affecting numerous organ systems. Ultimately, the hallmark of the disease is declining β-cell function. At the time of diagnosis, patients have already lost a significant portion of their β-cell mass, with further loss anticipated in many patients (44). The ability of medications to limit β-cell decline has become an area of intense interest. Striving for normoglycemia at disease onset with insulin therapy has been shown to result in disease remission in small clinical trials (45). Previous studies have described the durability of the effects of thiazolidinediones, and animal models have shown some durability of effects with the incretin family as well (46). Currently, the optimal agent for limiting β-cell decline is unknown.

Clinical practice guidelines worldwide are updated frequently to reflect new treatments and innovations. However, this practice has not made any impact in overall glycemic levels over the past decade, despite the availability of novel agents (7). The current approach of stepwise therapy with treatment intensification only after persistent elevated A1C may lead to inadvertent periods of sustained hyperglycemia and worse clinical outcomes.

Therefore, a more proactive approach early in the disease process that addresses the different metabolic defects may lead to sustained A1C targets. Although guidelines recommend combination agents in patients with markedly

elevated A1C and also recommend using agents with proven CV benefit as a second line after metformin, there is a paucity of data to help determine which combination is best for glycemic durability. A recent randomized trial (VERIFY) compared early combination of vildagliptin and metformin versus metformin with stepwise introduction of vildagliptin if glycemia deteriorates in treatment-naive type 2 diabetes (47). The study was completed in April 2019, with results pending as of this writing. The goal is to determine whether the combination approach would result in more durable glycemic levels (47). Results from VERIFY will help clinicians decide whether initial combination therapy with a DPP-4 inhibitor would be a worthwhile option in patients with type 2 diabetes, although vidagliptin itself is currently not available in the United States. Similar trials should be conducted for SGLT2 inhibitors and GLP-1 receptor agonists.

It should be noted that the benefit of intensive management early in the disease process applies to lifestyle modification as well. Recent data showed the durability of weight management in sustaining diabetes remission in one-third of patients with type 2 diabetes (48). As one of the two pillars of diabetes management, escalation in pharmacotherapy must be balanced with an equal degree of emphasis on the other, namely lifestyle modification.

Additional strategies to overcome therapeutic inertia include self-examination of performance by health care professionals, education of health care professionals on new and evolving therapies, and use of allied health professionals as case managers (49,50).

Conclusion

Therapeutic inertia is a common problem in primary care that can lead to worse clinical outcomes. It can arise at any point in the disease process and results from a complex interplay of patient-, clinician-, and health system–related factors. Setting expectations, communicating clearly, and adopting a patient-centered approach are crucial in addressing patient-related factors. Strategies highlighting a multidisciplinary approach can be effective as well. Ultimately, guidelines have not made an impact on glycemic targets over the past decade. A proactive approach early in the disease process targeting the metabolic defects of diabetes may be beneficial. More randomized clinical trials are required to study which agents, likely in combination, can lead to glycemic durability in patients with early type 2 diabetes.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

N.A.Z. wrote the manuscript. S.B.H. reviewed and edited the manuscript. N.A.Z. is the guarantor of this work and, as such, had full access to all of the references cited and takes responsibility for the integrity of the review.

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