Therapeutic Inertia and the Legacy of Dysglycemia on the Microvascular and Macrovascular Complications of Diabetes

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Type 2 diabetes is characterized by a continuous decline in β-cell function with the resultant progressive loss of glycemic control over time (1). The hyperglycemic burden is associated with longer-term microvascular and macrovascular complications. Early diagnosis and intensive glycemic control has conclusively demonstrated a reduction in microvascular complications (2,3) and possibly macrovascular complications over a long period of observation (4), the so-called legacy effect (5). Even though there have been improvements in survival from cardiovascular disease in the general population, people with type 2 diabetes remain at increased risk of cardiovascular mortality compared with matched population control subjects (6). A very high proportion of patients fail to reach the recommended glycemic targets for a considerable period of time after the diagnosis of diabetes (7–9), thus leading to the complications. Guidelines for the treatment of patients with type 2 diabetes suggest that tight glycemic control (defined as glycated hemoglobin [HbA_{1c}] $<$7.0% [53 mmol/mol]) should be maintained from diagnosis through active titration of combinations of antihyperglycemic medications and lifestyle modification, as appropriate (10). Modeling studies suggest that when this is done through an individualized approach, it leads to reduced costs and increased quality of life (11).

Besides patient-level characteristics such as multimorbidity and poor adherence to treatment recommendations, clinical inertia has been suggested as one key reason for not achieving glucose targets. The term "clinical inertia" in most instances has been used in relation to failure to advance therapy when appropriate to do so (12). However, the definition of therapeutic inertia is now also accepted to reflect the failure to de-intensify treatment when appropriate to do so (12). A number of studies have shown that therapeutic inertia is associated with worse microvascular and macrovascular outcomes. In a cohort study of 105,477 patients, mean HbA_{1c} was 8.1% (65 mmol/mol) at diagnosis, 22% remained under poor glycemic control over 2 years, and 26% never received intensive treatment. A delay in intensive treatment by 1 year in conjunction with poor glycemic control significantly increased the risk of myocardial infarction, heart failure, stroke, and composite cardiovascular events (hazard ratio 1.62 [95% CI 1.46–1.80]) (7). In another study using a computer simulation model designed to translate surrogate end points into long-term health and economic outcomes (the IMS CORE Diabetes Model [13]) in a representative cohort of adults with type 1 or type 2 diabetes from the U.K. primary care patient database, significant cost avoidance of about £340 million was apparent in the first 5 years, rising to about £5.5 billion after 25 years of sustained improvement in control. Reductions in microvascular complications were the main factors driving the cost savings, with 74% of cost avoidance from prevention of renal disease in people with type 1 diabetes and 57% of cost avoidance from reductions in foot ulcers, amputations, and neuropathy in people with type 2 diabetes (14).

In the study in this issue of *Diabetes Care* using routine real-world data to explore the concept of legacy effects of tight glycemic control on complications of diabetes, Laiteerapong et al. (15) focused on newly diagnosed patients who had poor glycemic control and 10 years of survival. They demonstrated that HbA_{1c} levels ≥6.5% (≥48 mmol/mol) for the first year after diagnosis were associated with worse outcomes. They showed that there was a relative increase in mortality of 29% in patients with a dysglycemic burden of HbA_{1c} 7% to $<$8% in the first year of diagnosis compared with HbA_{1c} maintained at $<$6.5%. This increase rose to 32% if the dysglycemic legacy was HbA_{1c} ≥9% in the first year of diagnosis. The achievement of glycemic control after diabetes diagnosis is therefore sufficient to establish remedial long-term risk of complications (15).

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See accompanying article, p. 416.

Laiteerapong et al. (15) assessed the associations between HbA_{1c} <6.5% (<48 mmol/mol), 6.5% to <7.0% (48 to <53 mmol/mol), 7.0% to <8.0% (53 to <64 mmol/mol), 8.0% to <9.0% (64 to <75 mmol/mol), or ≥9.0% (≥75 mmol/mol) for different periods of early exposure (0–1, 0–2, 0–3, 0–4, 0–5, 0–6, and 0–7 years) to demonstrate the remedial long-term legacy benefits. HbA_{1c} levels of ≥6.5% in the first year of the early exposure period carried a higher risk for microvascular and macrovascular complications than HbA_{1c} <6.5% in the first year of glycemic exposure. For example, for HbA_{1c} <7%, the hazard ratio was 1.24 (95% CI 1.06–1.37) (15). This is a generous span of the whole spectrum of poor glycemic control and allows for adequate evaluation of the effects of good early control on glycemic legacy. The UK Prospective Diabetes Study (UKPDS) demonstrated the legacy effects of HbA_{1c} reduction below 7% (3). Additionally, the American Diabetes Association–European Association for the Study of Diabetes position statement also recommended HbA_{1c} targets of 6.5% in newly diagnosed patients (10).

There are a number of strengths to this study. It is a population-based study with a large number (34,737) of participants included in the analysis. The analytical methodology was very thorough, capturing not just the raised levels of HbA_{1c} but also the periods of dysglycemic exposures. Another strength of this study was that it included an ethnically diverse population. Most studies on this subject are usually conducted in predominantly Caucasian populations, thus making the results less generalizable to other populations. The study also highlights in its analysis all diabetes complications, including microvascular complications, macrovascular complications, and mortality. Previous publications on this subject have usually just focused on macrovascular (7) or microvascular complications (16) or surrogate cardiovascular risk factors. The authors also focused mainly on the effect of glycemic control rather than the effects of specific antidiabetes medications. Hopefully, this approach ruled out potential confounding by the pleiotropic effects of newer glycemic agents with extraglycemic cardiovascular benefits (17–20).

Despite these strengths, the study is not without limitations. In the first instance, the analysis did not differentiate between patients with or without prior cardiovascular disease. As the UKPDS recruited newly diagnosed patients, most of whom had no prevalent cardiovascular disease, it would have been more informative to explore patients with and without prevalent cardiovascular disease in the current study. In a recent analysis of 15 years of follow-up results of the Veterans Affairs Diabetes Trial (VADT), patients with established cardiovascular disease recruited in that study did not demonstrate the legacy benefits (21) demonstrated in the UKPDS, although such benefits were demonstrated after 10 years (22). Another limitation is the sole emphasis on the early sustained intensive glycemic control. In real clinical practice, there are marked variations in care standards and patients' self-management, thus resulting in variation in HbA_{1c} levels, which has also been associated with poor outcomes (23). Also, even though this study is dubbed a real-world study, 34,737 of the eligible 44,763 patients were included in the analysis. The strength of real-world studies is the inclusion of patients with varying characteristics, reminiscent of those in real clinical practice, as opposed to the refined selection of patients in randomized controlled trials (24). In this instance, it is unclear whether the remaining 22.4% of the patients excluded would have behaved differently. Therefore, the exclusion of such a large proportion of the study population limits the generalizability of the results of this study. Finally, although the study population was ethnically diverse, the analysis could have been strengthened even more by examination of the outcomes by different ethnicities and levels of deprivation. In an observational study of this nature, the influence of many more confounding factors, known and unknown, cannot be completely excluded.

There is currently a lot of interest in real-world evidence. The findings in this study (15) support evidence from randomized controlled trials for the need to intensify blood glucose–lowering therapy in a timely manner to ensure that the benefits of reduced blood glucose are realized. It is expected that sustained reduced HbA_{1c} levels over a long period of time, achieved through the confines of the strict protocols of randomized control trials, will be associated with reduced microvascular and macrovascular events (Fig. 1). In addition to therapeutic inertia in glycemic control, recent studies have also revealed associations of long-term glycemic variability of HbA_{1c} with microvascular and macrovascular control (23). The mechanism for this is not entirely certain, but HbA_{1c} variability has been shown to increase urinary excretion of 8-iso-prostaglandin F2α, a marker of oxidative stress (25). Wide variations of HbA_{1c} could reflect poor adherence to therapeutic and lifestyle interventions, a more complicated clinical course, or a subpar organizational process of diabetes care. Figure 1 demonstrates the theoretical adverse effects of both a legacy of dysglycemia as a result of therapeutic inertia (potentially avoided through the confines of strict

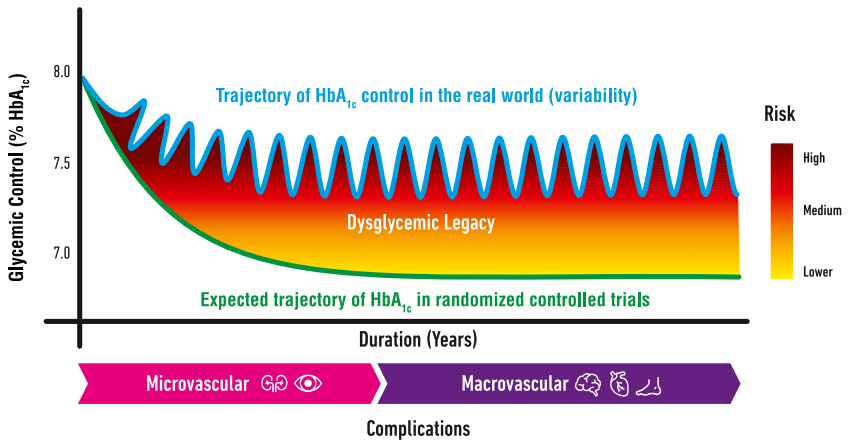

Figure 1—A schematic representation of the effects of early intensive glycemic control in preventing initial microvascular complications and then macrovascular complications several years later. Failure to initially control and maintain glycemia at diagnosis or sustained glycemic variability leads to the dysglycemic legacy of diabetes complications.

randomized controlled trial protocols) and variability of HbA_{1c} control. Future studies should be designed to determine outcomes in people intensified to individualized targets with reduced glycemic variability.

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