EDITORIAL

"Type 2 diabetes is not easy to manage, and many find changing lifestyle difficult. Clinical inertia in managing diabetes among health professionals and consumers is common. The array of new therapies has resulted in new treatment algorithms advocating a patient-centered approach to guide the choice of therapies, taking into consideration efficacy, presence of cardiovascular disease, unwanted and potential side effects, cost, and patient preferences."

The evolving landscape of type 2 diabetes

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Diabetes is a serious, chronic disease that now affects 425 million people globally, and it is projected that by 2045 there will be 629 million living with diabetes throughout the world. Factors driving this increase include population growth and aging and an increase in diabetes risk factors. While every country is affected, 4 out of 5 people with diabetes live in low- or middle-income countries, which often do not have adequate resources to provide appropriate care.[1] Type 2 diabetes accounts for around 90% of diabetes and is linked to rapid urbanization, unhealthy diets, and a sedentary lifestyle and consequent obesity. Although type 2 diabetes occurs most commonly in older adults, it increasingly presents at a younger age, including children and adolescents.[2]

Diabetes is associated with significant premature mortality and morbidity, which impacts not only the individual with diabetes but also their family and the whole of society, and it has been described as a global societal catastrophe.[1] Global health care expenditure on treatment of diabetes and its complications reached USD 727 billion in 2017, an 8% increase from 2015.[1] The cost of diabetes is affecting socioeconomic development in many countries,[1] and heath care expenditure and loss in family income associated with disability and premature death can push families into poverty.[3]

Nearly 4 million deaths each year are attributed to diabetes, with half occurring in people under the age of 60.[1] In addition, diabetes results in a range of complications and significant morbidity. Compared with adults without diabetes, end-stage renal disease is up to 10 times higher and rates of amputation are typically 10 to 20 times higher. Retinopathy affects an estimated 35% of people with diabetes and may result in severe visual loss and blindness. Adults with diabetes have two- to threefold increased rates of cardiovascular disease.[2] Complications are a particular problem in young-onset type 2 diabetes, which is associated with greater mortality rates, more diabetes complications, and unfavorable cardiovascular disease risk factors compared with type 1 diabetes of similar duration.[4,5]

There is strong evidence that diabetes, especially when detected early, can be successfully managed and complications prevented, but there is an appreciable evidence-practice gap in implementing proven clinical care programs. Multifactorial intervention including control of blood glucose, blood pressure, and lipids can reduce the broad range of diabetes-related microvascular and macrovascular complications and premature mortality.[6] The beneficial effects of relatively short-term improved glycemic control on reducing microvascular complications was clearly demonstrat-

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ed in the UKPDS trial (United Kingdom Prospective Diabetes Study) in newly diagnosed people with type 2 diabetes,[7] whereas the beneficial effect on macrovascular complications takes longer.[8]

More recent studies comparing intensive and standard glycemic control in people with long-standing type 2 diabetes have failed to show a beneficial effect on cardiovascular disease and mortality,[9-11] with one, the ACCORD study (Action to Control Cardiovascular Risk in Diabetes), reporting an increase in mortality with aggressive blood-glucose lowering.[9] The benefit on microvascular outcomes was confirmed in the studies ACCORD[12] and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN Controlled Evaluation).[10]

Adopting a healthy lifestyle remains the cornerstone of type 2 diabetes treatment; however, many also require oral or injectable blood-glucose–lowering therapies to control hyperglycemia. There is now a wide and increasing range of available therapies. Insulin has been available since the early 1920s and sulfonylureas and metformin since the 1950s. Over the last 20 or so years, α-glucosidase inhibitors, thiazolidinediones, glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose transport protein 2 (SGLT-2) inhibitors have been added to the blood-glucose–lowering armamentarium. This proliferation of therapies for type 2 diabetes has been helpful in stimulating a push to individualize treatment. However, our current limited ability to identify an individual's underlying pathogenetic mechanisms that cause their diabetes has made individualizing therapy challenging.

A series of randomized studies mandated by the US Food and Drug Administration has examined the cardiovascular safety of newer blood-glucose–lowering therapies in people with or at high risk of cardiovascular disease. Three focused on DPP-4 inhibitors and confirmed the safety of these agents compared with placebo,[13-15] although one showed an increase in hospital admissions for heart failure.[13] Three large randomized controlled studies have reported significant reductions in cardiovascular events for two SGLT-2 inhibitors (empagliflozin and canagliflozin) and one GLP-1 receptor agonist (liraglutide).

The EMPA-REG study ([Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) reported benefits of empagliflozin in reducing cardiovascular and total mortality and heart failure.[16] The CANVAS program (CANagliflozin CardioVascular Assessment Study) integrated data from two trials in people with type 2 diabetes and high cardiovascular risk. People treated with canagliflozin had a lower risk of death from cardiovascular events and hospitalization for heart failure than those who received placebo, but a greater risk of amputation, primarily at the level of the toe or metatarsal.[17] The LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results) reported major cardiovascular benefits, reduced major cardiovascular events, and reduced total mortality with the GLP-1 receptor agonist liraglutide.[18] However, two other studies with GLP-1 receptor agonists have not shown cardiovascular benefits. The ELIXA study (Evaluation of LIXisenatide in Acute coronary syndrome) in people with type 2 diabetes and recent acute coronary syndrome showed that the addition of lixisenatide to usual care did not significantly alter the rate of major cardiovascular events or other serious adverse events.[19] The EXCEL study (EXpanded Clinical Evaluation of Lovastatin) in people with type 2 diabetes with or without previous cardiovascular disease showed that the incidence of major adverse cardiovascular events did not differ significantly between patients who received long-acting exenatide and those who received placebo.[20]

Regrettably, poorly controlled diabetes remains common, with many contributing factors. Type 2 diabetes is not easy to manage, and many find changing lifestyle difficult. Clinical inertia in managing diabetes among health professionals and consumers is common. The array of new therapies has resulted in new treatment algorithms advocating a patient-centered approach to guide the choice of therapies, taking into consideration efficacy, presence of cardiovascular disease, unwanted and potential side effects, cost, and patient preferences. Although increasing choice, this approach is arguably less practical in guiding primary care physicians about specific therapeutic pathways. In addition, the limited availability and cost of these newer medications make them less relevant to people with diabetes living in low- or middle-income countries, with none being added to the most recent World Health Organization essential medicines list.[21]

This edition of *Medicographia* is devoted to revisiting the role of sulfonylureas in the management of type 2 diabetes. Although sulfonylureas were the first class of oral agents introduced for the treatment of diabetes, there have been many advances with these agents, which remain a commonly used, safe, and cost-effective global treatment for type 2 diabetes. This issue explores the role of sulfonylureas in the contemporary and evolving landscape of type 2 diabetes and includes a special focus on a number of important challenges, including management of people with coexisting renal impairment, treatment of the elderly, people observing Ramadan, and the increasing number of people diagnosed with maturity-onset diabetes of the young (MODY). ■

Keywords: *elderly; MODY; Ramadan, renal impairment; sulfonylurea; type 2 diabetes*

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