



Editorial

Changing the diabetes treatment paradigm from glucose control to cardiorenal protection

Diabetes is an ancient disease and the first description of this disease has been attributed to Hesy Ra, the chief physician to the Egyptian Pharaoh Djoser, nearly 5000 years ago¹. Through the centuries, various herbs, chemicals and extreme carbohydrate-restricted diets were used to treat the symptoms of the disease². Sadly, the prognosis for patients remained uniformly grim until the discovery of insulin by Banting *et al*³ in Toronto, Canada, 100 years ago in 1921⁴. The introduction of insulin led to a paradigm shift in the management of diabetes and a shift in focus from extreme dietary carbohydrate restriction to effective lowering of blood glucose with the use of insulin. This not only improved glycaemia and ameliorated symptoms but also increased the life span of patients with diabetes. However, it soon became apparent that as patients with diabetes began to live longer, they began to manifest the classic microvascular and macrovascular complications of diabetes⁵. This occurred despite the introduction of several new classes of effective anti-hyperglycaemic agents and newer insulin preparations into clinical practice.

In the 1990s, several large trials such as the Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that tight glucose control has beneficial effects on the microvascular complications of diabetes (retinopathy, nephropathy and neuropathy)^{6,7}. However, tight glucose control has marginal effects on macrovascular disease and unexpectedly increases cardiovascular (CV) and all-cause mortality, as seen in the Action to Control Cardiovascular Risk in Diabetes (ACCORD study group) study⁸. This is counter-productive since diabetes is itself associated with pre-mature CV disease. An alternative definition of diabetes proposed by Fisher⁹ states that diabetes is a

state of pre-mature CV death which is associated with chronic hyperglycaemia and also with blindness and renal failure.

Clearly, the microvascular complications of retinopathy, nephropathy and neuropathy cause considerable morbidity in patients with diabetes, and early and optimal glucose control greatly reduces the severity and burden of these complications. However, the vast majority of patients with diabetes may die from pre-mature CV disease¹⁰. Unfortunately, tight glucose control has marginal or even detrimental effects on CV disease. Concerns regarding the CV safety of anti-diabetic agents were intensified when a meta-analysis suggested that the widely used insulin sensitizer rosiglitazone was associated with an increase in the risk of myocardial infarction (MI) and CV death¹¹. This led to the Food and Drug Administration (FDA) guidance in 2008, under which any new anti-diabetic therapy had to demonstrate that the therapy would not result in an unacceptable increase in CV risk¹².

Following the FDA guidance, several large cardiovascular outcomes trials (CVOTs) were conducted, and the results of these studies have truly transformed the landscape of diabetes treatment¹³. Initially, the results from the CVOTs with the dipeptidyl-peptidase-4 (DPP-4) inhibitors were neutral with regard to CV benefits. However, in 2015, results from the EMPA-REG OUTCOME trial demonstrated that empagliflozin, compared to placebo, significantly reduced the incidence of major adverse cardiovascular events (MACEs) comprising non-fatal MI, stroke and CV death in patients with type 2 diabetes and established CV disease¹⁴. These results, which occurred with optimal use of statins, blood pressure agents and renin angiotensin - aldosterone system (RAAS)

This editorial is published on the occasion of World Diabetes Day-November 14, 2021.

blockers, surprised many in the diabetes community and were felt to be chance findings. However, the replication of the CV benefits with other compounds in the same class alleviated these concerns¹³. Further, almost simultaneously, CV benefits were also seen in the CVOTs conducted with the glucagon-like peptide-1 (GLP-1) receptor agonists, which have a significantly different mechanism of action. The first positive CV results with GLP-1 receptor agonists were reported in the LEADER trial with liraglutide and have been subsequently confirmed with other agents in this class^{15,16}.

In addition to the CV benefits noted above, another serendipitous finding seen in the CVOTs was the ability of the sodium-glucose transport protein 2 (SGLT2) inhibitors and GLP-1 receptor agonists to improve renal function¹⁶. Thus, both classes of medications, in addition to effectively lowering blood glucose levels, also improved clinically significant CV and renal outcomes. In this context, it is important to note that there appear to be differences in the CV and renal benefits seen with SGLT2 inhibitors and the GLP-1 receptor agonists. In the CVOTs to date, the GLP-1 receptor agonists have demonstrated consistent effects to reduce atherosclerotic CVD (ASCVD) events of non-fatal MI, stroke and CV death in patients with and without established ASCVD¹⁷. Their effect on renal disease is confined to improvements in albuminuria without preventing progression to end-stage renal disease (ESRD). Further, the GLP-1 receptor agonists do not have beneficial effects on heart failure (HF) in diabetes. In contrast, the SGLT2 inhibitors have modest benefits on atherosclerotic MACE that seems confined to patients with established ASCVD¹³. More importantly, the SGLT2 inhibitors, unlike GLP-1 receptor agonists, reduce hospitalization for HF and progression to ESRD in those with and without diabetes, as seen in the DAPA HF, DAPA CKD, CREDENCE and the EMPEROR PRESERVED/REDUCED studies¹⁶.

The above cardiorenal benefits have led to a major shift in the international treatment guidelines. The American Diabetes Association (ADA) now recommends the use of SGLT2 inhibitors and GLP-1 receptor agonists as the second-line treatment after metformin and lifestyle measures to reduce the risk of cardiorenal complications in individuals at high risk of CV disease, irrespective of baseline and target glucose control¹⁸. The European Society of Cardiology (ESC) guidelines recommend either an SGLT2 inhibitor or a GLP-1 receptor agonist as the first-line

treatment in people with type 2 diabetes at high or very high CV risk, even ahead of metformin¹⁹. However, it is important to note that in the CVOTs, most participants were on at least one glucose-lowering medication at baseline. Hence, the CV benefit of SGLT2 inhibitors or GLP-1 receptor agonists in treatment-naive individuals is uncertain²⁰.

In the context of the burden of CV disease in diabetes, it is ironical to recollect that in 1927 (just six years after the introduction of insulin), Joslin²¹, the Father of Modern Diabetology, prophetically wrote, "I believe the chief cause of premature development of arteriosclerosis in diabetes, save for advancing age, is an excess of fat, an excess of fat in the body (obesity), an excess of fat in the diet, and an excess of fat in the blood. With an excess of fat, diabetes begins, and from an excess of fat, diabetics die, formerly of coma, recently of arteriosclerosis". Clearly, we have come a long way from the 1920s. Today, diabetes has assumed epidemic proportions, especially in the developing world, and is still associated with increased morbidity and mortality. The devastating microvascular complications of diabetes are a major cause of blindness, kidney failure and non-traumatic amputations. Diabetes has been estimated to reduce average life expectancy by about 5-6 years²². However, this grim scenario for patients with diabetes may perhaps become a thing of the past. A hundred year ago, the discovery of insulin heralded a new dawn in the treatment of diabetes. At long last, we now have potent disease-modifying agents which not only improve glycaemia but provide additional robust CV and renal protection along with reduction in all-cause mortality. Cost however, remains a major barrier to the use of these disease-modifying drugs. There is a hope that with the introduction of generic and potentially less expensive SGLT2 inhibitors and GLP-1 receptor agonists, there will be more widespread use of these agents, along with more education of healthcare providers on the risks/benefits of these medications. In addition, dedicated trials will need to be conducted in patients with type 1 diabetes, who have as much to gain from using the SGLT2 inhibitors and GLP-1 receptor agonists as those with type 2 diabetes.

Financial support & sponsorship: None.

Conflicts of Interest: None.

Preethika Ekanayake^{1,2} & Sunder Mudaliar^{1,2,*}

¹Veterans Affairs Medical Center & ²Department of Medicine, University of California, San Diego School of Medicine, San Diego, California, USA

*For correspondence:
smudaliar@vapop.ucsd.edu

Received October 22, 2021

References

- Loriaux DL. Diabetes and the Ebers Papyrus: 1552 B.C. *The Endocrinologist* 2006; 16 : 55-6.
- Allen FM, Stillman E, Fitz R. Total dietary regulation in the treatment of diabetes. In: *Monographs of the Rockefeller Institute for Medical Research*. New York: The Rockefeller Institute for Medical Research; 1919.
- Banting FG, Best CM, Collip JB, Campbell WR, Fletcher AA. Pancreatic extracts in the treatment of diabetes mellitus preliminary report. *Can Med Assoc J* 1922; 12: 141-6
- Rydén L, Lindsten J. The history of the Nobel Prize for the discovery of insulin. *Diabetes Res Clin Pract* 2021; 175 : 108819.
- Forbes JM, Cooper ME. Mechanisms of diabetic complications. *Physiol Rev* 2013; 93 : 137-88.
- Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329 : 977-86.
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352 : 837-53.
- Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358 : 2545-59.
- Fisher M. Diabetes and atherogenesis. *Heart* 2004; 90 : 336-40.
- Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson A, et al. Risk factors, mortality, and cardiovascular outcomes in patients with Type 2 diabetes. *N Engl J Med* 2018; 379 : 633-44.
- Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; 356 : 2457-71.
- US Department of Health & Human Services, Food and Drug Administration. Center for Evaluation and Research. *Type 2 diabetes mellitus: Evaluating the safety of new drugs for improving glycemic control. Guidance for industry March 2020*. Available from: <https://www.fda.gov/media/135936/download>, accessed on October 11, 2021.
- Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019; 393 : 31-9.
- Zinman B, Wanner C, Lachin JM; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373 : 2117-28.
- Marso SP, Daniels GH, Brown-Frandsen K; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; 375 : 311-22.
- Brown E, Heerspink HJ, Cuthbertson DJ, Wilding JP. SGLT2 inhibitors and GLP-1 receptor agonists: Established and emerging indications. *Lancet* 2021; 398 : 262-76.
- Hupfeld C, Mudaliar S. Navigating the “MACE” in cardiovascular outcomes trials and decoding the relevance of atherosclerotic cardiovascular disease benefits versus heart failure benefits. *Diabetes Obes Metab* 2019; 21 : 1780-9.
- American Diabetes Association. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes-2021. *Diabetes Care* 2021; 44 (Suppl 1) : S111-24.
- Visseren FL, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur J Prev Cardiol* 2021; 42 : 3227-37.
- Zaccardi F, Khunti K, Marx N, Davies MJ. First-line treatment for type 2 diabetes: Is it too early to abandon metformin? *Lancet* 2020; 396 : 1705-7.
- Joslin EP. Arteriosclerosis and diabetes. *Ann Clin Med* 1927; 5 : 1061.
- Loukine L, Waters C, Choi BC, Ellison J. Impact of diabetes mellitus on life expectancy and health-adjusted life expectancy in Canada. *Popul Health Metr* 2012; 10 : 7.