Putting Heart (and Kidneys) Into Diabetes Care

Stephen Brunton, Editor-in-Chief

Historically, a glucocentric approach has been the foundation of our clinical management of diabetes. An A1C goal of ≤7% was assumed to optimize outcomes for our patients no matter how we got there. The U.K. Prospective Diabetes Study informed us that an A1C reduction of just 1% yielded significant improvements in microvascular endpoints (1). Pharmacological therapy started with metformin and then, based on efficacy, tolerability, cost, and availability, we determined the best choices of medications to add thereafter as needed.

Times have changed, however, and that foundation is no longer stable. We now have an evidence-based paradigm that should determine our choice of medication based on improvements in cardiovascular (CV) and renal outcomes.

In 2008, in response to concerns that rosiglitazone may cause more CV deaths than other available drugs (2), the U.S. Food and Drug Administration required all new medications for the treatment of type 2 diabetes to undergo specific trials to ensure that they were noninferior to placebo in terms of CV safety (3). Initially, this requirement was seen as unduly burdensome and likely to be very costly, time-consuming, and arduous.

However, the initial CV outcomes trials (CVOTs) were reassuring, demonstrating that dipeptidyl peptidase 4 inhibitors did not increase patients' mortality risk, although saxagliptin therapy did somewhat increase the incidence of heart failure (4).

Agents in the sodium–glucose cotransporter 2 (SGLT2) inhibitor and glucagon-like peptide 1 (GLP-1) receptor agonist drug classes were the next to undergo CVOTs, and the results of those trials shocked the diabetes community. The landmark EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial not only offered assurances that the SGLT2 inhibitor empagliflozin was noninferior to placebo in terms of CV safety, but also demonstrated a decrease in mortality and thus superiority versus placebo (5). Attendees at the 2015 European Association for the Study of Diabetes meeting in Stockholm, Sweden, where the trials results were initially announced, were so impressed they gave a standing ovation.

Since then, several additional CVOTs of SGLT2 inhibitors and GLP-1 receptor agonists have demonstrated not only improved CV outcomes, but also a positive impact of treatment on the progression of renal disease.

Although the designs of these trials have differed in terms of study populations and endpoints, the majority yielded results significant enough to prompt the American Diabetes Association (ADA) to revise its type 2 diabetes treatment algorithm. The ADA's *Standards of Medical Care in*

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Diabetes—2019 includes separate recommendations for patients with atherosclerotic CV disease (ASCVD) or renal disease that emphasize the appropriateness of using these newer therapies in such instances (6).

In this issue of *Clinical Diabetes* (p. 316), Robert H. Eckel and his colleagues provide an extensive review of the CVOTs involving SGLT2 inhibitors and GLP-1 receptor agonists, in which they highlight the methodologies, patient populations, and data from these trials, as well as the clinical implications of their results. In this new era of diabetes management, this article offers important perspectives on modern diabetes management by carefully reviewing the key CVOT findings.

In 2019, it is no longer sufficient to achieve glucose reduction. We must now consider the greater good for our patients and act accordingly by initiating pharmacological therapies that are proven to reduce CV and renal risk in patients with or at risk of ASCVD or renal disease.

Duality of Interest

S.B. serves on advisory boards and/or speakers bureaus for AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Janssen Pharmaceuticals, Novo Nordisk, and Sanofi.

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