Metabolism Clinical and Experimental 99 (2019) 113–115

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Beyond glycemic control: New guidance on cardio-renal protection

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ARTICLE INFO

Article history:
Received 17 February 2019
Accepted 18 February 2019

Keywords:
Diabetes mellitus
Cardiovascular
GLP-1 receptor agonist
SGLT-2 inhibitor
Limb amputation

1. Commentary

The global prevalence of Type 2 diabetes mellitus (T2DM) has dramatically increased over the past 3 decades, due to the impact of obesity and prolonged life expectancy, with the consequent increase in morbidity and mortality. Persistent deficiencies in glucose and metabolic control associated with considerable residual cardiovascular (CV) risk, as well as cardio-renal (CR) and other risks such as increased risk for malignancies and non-alcoholic fatty liver disease (NAFLD), have engendered advances in the pharmacologic management of T2DM yielding several new agents with elegant mechanisms of action [1]. As new evidence regarding the efficacy and safety of these novel agents is accumulated, timely updates of the management guidelines for T2DM are required. A joint ADA and EASD expert panel has recently published a consensus statement [2] and updated 2019 clinical guidelines incorporating evidence from recent clinical trials.

A major difference from previous guidelines [3] is the recommendation for early use of a sodium–glucose cotransporter 2 inhibitor (SGLT-2i) or a glucagon-like peptide 1 receptor agonist (GLP-1 RA) with proven CV benefit in patients with established atherosclerotic cardiovascular disease (ASCVD) and inadequate glycemic control (HbA1c > 7%) on metformin. Both of these drug classes probably exhibit their cardioprotective effect not only by direct lowering of glucose levels but also through the favorable metabolic effects of the associated weight reduction [4–6]. However, similar benefits of weight reduction are recognized to occur with the administration of metformin, an antidiabetic agent of considerably lower cost and well-established safety profile [1], which has also been shown to reduce CV morbidity and mortality [7], and justifiably remains the first line of pharmacologic treatment for patients with T2DM [2]. Of note, metformin increases endogenous GLP-1 levels [8].

A reasonable question arising from the above consensus recommendation is why limit its guidance only to patients with established ASCVD. While the GLP-1 RAs liraglutide [9], semaglutide [10] and albiglutide [11] demonstrated CV benefit in high CV risk patients, dulaglutide showed CV benefit in patients without CVD (https://www.medscape.com/viewarticle/904373), implying the broader value of these agents to all T2DM patients. In specific, in its large REWIND CV outcomes trial (CVOT) in which the majority of the participants did not have prior CVD, dulaglutide significantly reduced the risk of major adverse cardiovascular events (MACE), including a composite of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke. Of note, trials on dulaglutide are based on a much more representative and much larger segment of the population [12]. Thus, dulaglutide, a compound administered once a week, may offer advantages over other GLP-1 RAs. In this respect, it would be tantalizing to speculate on the CV outcome of dual GLP-1 and GIP (or other in the future [13])

Abbreviations: CV, cardiovascular; CR, cardio-renal; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; SGLT-2i, sodium–glucose cotransporter 2 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; ASCVD, atherosclerotic cardiovascular disease; SVOT, cardiovascular outcomes trial; MACE, major adverse cardiovascular events; MI, myocardial infarction; CKD, chronic kidney disease; HF, heart failure; eGFR, estimated glomerular filtration rate; GIP, gastric inhibitory polypeptide.

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https://doi.org/10.1016/j.metabol.2019.02.004

inhibitor(s), which in phase 2 trials has shown greater effects than dulaglutide in glucose lowering and weight loss [14].

A valid argument is why to limit these novel agents only to patients needing glucose lowering since their CV effects are, at least partly, independent of glucose reduction. This is analogous to the use of statins which have shown CV risk reduction in T2DM patients regardless of their glucose levels [15]. Whether SGLT-2i and/or GLP-1 RA provide CV benefit in non-diabetic patients or patients without CVD has not been established to date. However, the recent CVD-REAL 2 trial demonstrated that treatment with 6 different SGLT2i reduced endpoints such as all-cause death, heart failure (HF), stroke and MI compared with other antihyperglycemic medications and that 74% of patients did not have established CVD [16]. Improved adipose tissue function and reduced inflammation with these agents could contribute to the favorable CV outcomes [17]. Why should the early use of a SGLT-2i or GLP-1 RA be considered? Besides glucose lowering and weight loss, other mechanisms could contribute to the CV benefit which may differ between the two classes. GLP-1RA may exert predominantly anti-thrombotic/antiatherogenic effects: liraglutide significantly reduced CV death with a trend towards a reduction in non-fatal MI/stroke [9] while semaglutide significantly reduced strokes with a trend towards a reduction in MI events [10]. On the other hand, SGLT-2i seems to have modest effects on hallmark atherosclerotic events (MI, stroke) but appears to reduce CV death in diabetic patients primarily through reduced hospitalization for HF [18–20]. HF is highly prevalent in patients with T2DM and also associated with a poor prognosis [21,22]. Whether SGLT-2i may improve outcome in HF patients without DM is currently under investigation [23]. Conversely, existing data suggest that GLP-1RA do not positively affect HF outcomes [24]. Another difference between the two classes is their effect on renal function. Both classes reduce albuminuria but only the SGLT-2i have been shown to reduce the decline in estimated glomerular filtration rate (eGFR), the onset of end-stage renal disease and the rate of renal transplantation [18–20]. Based on the existing published evidence, the consensus recommendation advocates administration of a SGLT-2i over a GLP-1 RA in chronic kidney disease (CKD) or clinical HF if eGFR is adequate (>45 mL/min/1.73 m^2) [2]. Of note, FDA does not recommend SGLT-2i use in significant renal impairement and warns that they may cause intravascular volume contractions and could cause or aggravate renal impairment. A re-evaluation of metformin treatment in T2DM patients with CKD or stable HF has shown evidence of a favorable effect [25] with updated guidelines permitting its use with dose reduction in diabetic patients with an eGFR >30 mL/min.

In contrast with the CV and renal benefits SGLT-2i have shown in large CVOTs, a currently unexplained increased risk of lower limb amputation (especially toe) has been reported primarily with canagliflozin [18], prompting both Food and Drugs Administration (FDA) and European Medicine Association (EMA) to issue a warning against canagliflozin and all SGLT-2i, respectively. The highest risk was observed among patients who had a history of amputation or peripheral vascular disease. In a subsequent meta-analysis of four observational databases including several hundred thousands of T2DM patients, no short-term (median 60–100 days on-treatment) increase in the risk of lower limb amputation was found in canagliflozin or other SGLT-2i treated patients compared with patients treated with other antidiabetic agents [26]. However, in the canagliflozin CANVAS study, the amputation risk began to emerge after the first 6–12 months [18]. Additionally, patients included in the above meta-analysis were relatively younger and therefore, had a lower risk of amputation. In another study evaluating real-world data, initiation of a SGLT-2i was associated with a significantly greater risk of amputations compared with initiation of sulfonylureas, metformin, and thiazolidinediones, and a non-significantly higher risk compared with dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 RA [27]. In support of the above, in a Scandinavian registry based cohort study, initiation of a SGLT-2i (dapagliflozin or empagliflozin in 99% of the patients) was associated with a two-fold increased risk of lower limb amputation compared to initiation of GLP-1 RA [28], providing evidence that these complications may be associated with all members of the class and complications may extend beyond amputation to a broader increased risk of peripheral vascular disease and venous ulcerations. However, a very recent expert panel overview of the evidence has concluded that the risk of amputation in relation to SGLT2i use seemed to be limited to canagliflozin and that this adverse event may not represent a class effect [29].

New diabetes pharmacotherapies offer more than glucocentric benefits, with a promise for lower rates of complications and thus lower morbidity and mortality. Furthermore, these medications seem to improve other conditions associated with metabolic dysregulation, such as NAFLD [6]. We are in the midst of a paradigm shift in T2DM management, expanding the primary objective of glucose control to a comprehensive lifestyle and pharmacologic management program that addresses existing CV and renal disease [30]. Emerging data have suggested that novel agents such as GLP-1 RA and SGLTi provide CV protection with existing CVD and CKD, and clinical trials are currently underway to evaluate primary CV and renal protection of these agents and to better define their complication profile in larger populations and for additional indications e.g. NAFLD. These are exciting times that hold major promise that new additions to our therapeutic armamentarium will soon be providing better and broader tangible benefits to our patients.

Conflicts of Interest/Financial Disclosure Statement

ADA and ES have nothing to declare in regard to this work. CSM is consultant to Intarcia and shareholder, grant recipient through BIDMC and advisor to Novo Nordisk.

Acknowledgements

None.

Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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