

Diabetes Guidelines: Where Do the Old and New Agents Fit?

By Mark Molitch

The treatment landscape of management of type 2 diabetes has changed substantially over the past few years. Before the various cardiovascular outcome trials (CVOT) for the dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 receptor analogs (GLP-1RA) and the sodium glucose co-transporter 2 (SGLT-2) inhibitors (reviewed in other articles in this issue), it was generally recommended that metformin should be the initial treatment along with lifestyle modifications for people with type 2 diabetes. The choice of second agent was left open, with little apparent benefit of one drug class over another, even in patients with known cardiovascular disease (CVD) or chronic kidney disease (CKD) (1–3).

However, it has now been shown that for patients with preexisting heart disease, there are clear differences between classes of medications. For such patients, DPP-4 inhibitors provide no cardiovascular or kidney benefit over and above their efficacy in improving glycemic control; they also cause no harm and are generally well tolerated, although saxagliptin may increase heart failure risk. In CVOTs, the GLP-1RAs liraglutide, semaglutide, and dulaglutide showed clear CVD benefit, with exenatide showing a borderline positive result. However, with respect to kidney findings, there is a lowering of urinary albumin excretion, but none have shown a reduction in the rate of fall of estimated GFR (eGFR) in these GLP-1RA CVOTs. By contrast, the CVOTs for the SGLT-2 inhibitors empagliflozin, canagliflozin, and dapagliflozin have shown not only CVD benefit but also very significant reductions in albumin excretion and in the rate of fall of eGFR. The CVD benefit was most impressive for patients with heart failure. Interestingly, the CVD and kidney benefits, blood pressure reduction, and weight loss found with the SGLT-2 inhibitors remained even in patients with eGFR levels <60 mL/min per 1.73 m², despite minimal blood glucose-lowering effects at that degree of CKD. The details of these studies are outlined in other articles in this issue.

These CVD benefits for GLP-1RA and CVD and CKD benefits for SGLT-2 inhibitors were so robust that the guidelines for the management of type 2 diabetes by various organizations and expert panels were recently revised. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommended in 2018 that in patients with type 2 diabetes and known CVD, GLP-1RA and SGLT-2 inhibitors should be added to metformin as second-line therapy for patients not at glycemic goals, with a specific preference for SGLT-2 inhibitors for patients with heart failure (4). Because the CVOTs did not show statistically significant similar benefits for patients at high risk for CVD, the ADA/EASD guideline did not make a specific recommendation for such individuals (4). The ADA/

EASD guideline also recommended using SGLT-2 inhibitors for patients with type 2 diabetes and CKD with or without CVD (4). These recommendations were then incorporated into the American Diabetes Association 2019 Standards of Medical Care in Diabetes (5).

Guidelines from other groups have similarly been modified. The 2019 diabetes guideline of the American Association of Clinical Endocrinologists has moved the GLP-1RAs and the SGLT-2 inhibitors to the top of the list of drugs to be added if glycemic control is not achieved by metformin and lifestyle changes for all patients with type 2 diabetes (6). Furthermore, they state that “certain GLP-1RAs and SGLT-2s have shown CVD and CKD benefits and are preferred in patients with those complications,” implying an equal benefit of the two classes on CKD (6). However, as noted from the discussion above, the SGLT inhibitors have been shown to reduce albuminuria and slow loss of GFR progression, whereas the GLP-1RAs have only been shown to reduce albuminuria.

The American College of Cardiology Task Force on Expert Consensus Decision Pathways recommended both GLP-1RAs and SGLT-2 inhibitors for patients with type 2 diabetes and CVD who are already taking metformin, with a preference for the latter in patients with heart failure (7). This cardiology guideline did not address the issue of progression of CKD.

In its 2018 Clinical Practice Guidelines, the Diabetes Canada Clinical Practice Guidelines Expert Committees have also recommended GLP-1RAs and SGLT-2 inhibitors as second line therapy in patients with clinical CVD (8, 9). The Canada guidelines also recommended using SGLT-2 inhibitors to retard the progression of CKD (10).

The Taiwan Society of Cardiology and the Diabetes Association of the Republic of China (Taiwan) came up with different recommendations for patients with type 2 diabetes with known CVD, recommending thiazolidinediones as the best class to add after metformin, with SGLT-2 inhibitors and GLP-1RA coming in third, except for patients with heart failure, for whom SGLT-2 inhibitors were recommended as second-line therapy after metformin (11). They also recommended SGLT-2 inhibitors as second-line therapy for patients with CKD (11).

In the recent Endocrine Society Clinical Practice Guideline for the Treatment of Diabetes in Older Adults, the CVD and CKD benefits of GLP-1RAs and SGLT-2 inhibitors were discussed, but these benefits did not rise to the level of being specific recommendations (12). The same is true of the 2019 standards of medical care for type 2 diabetes in China (13).

Overall, these changes in guidelines are generally consistent with one another (except for the recommendation from Taiwan to start thiazolidinediones) with respect to adding a GLP-1 receptor agonist or an SGLT-2 inhibitor to metformin in patients with type 2 diabetes with established CVD inadequately controlled on metformin plus lifestyle change, with the additional recommendation that SGLT-2 inhibitors would be favored in patients with heart failure. In patients with CKD, SGLT-2 inhibitors also slow down the rate of progression of GFR loss, whereas this was not demonstrated for any other class of drugs. These beneficial CVD and CKD effects of SGLT-2 inhibitors are independent of glucose lowering, and these agents can be used at GFRs below 60 mL/min per 1.73 m², where they have little glycemic efficacy. Whether these classes should be used in patients at high risk for CVD and/or CKD but without

overt disease is not established from clinical trials, but many clinicians might extrapolate these findings to this larger group of patients as well. ■

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