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Commentary

Management and prevention of cardiovascular disease for type 2 diabetes: Integrating the diabetes management recommendations of AACE, ADA, EASD, AHA, ACC, and ESC☆

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With the recognition from recent cardiovascular outcome trials that two classes of glucose-lowering agents for type 2 diabetes (T2D), the sodium-glucose linked transporter inhibitors (SGLT2i) and the glucagon-like peptide-1 receptor agonists (GLP-1RA) are associated with cardiovascular (CV) outcome benefit, there has been increasing effort to sort out the implications for clinical practice. A number of major professional organizations and societies involved in the care of diabetes and of CVD have produced recommendations to address these outcomes. Differences result from the burgeoning clinical trial reports of CV outcomes and the fact that the mode of action of the various treatments of T2D are largely not known, leading to differences in interpretation and consequent evolution of treatment recommendations. As would be expected, the documents show various degrees of overlap in the clinical trials cited and more so in the conclusions. The present analysis should be seen as a review of these practice recommendations, selectively integrating and highlighting areas of agreement, specific suggestions, and the differences between the organizations.

An important distinction emerges this year in the recommendations separating the prevention of the next CV event from management of hyperglycemia. The European Society of Cardiology (ESC)/European Association for the Study of Diabetes (EASD) guidelines gives explicit comments on goals for glycemic treatment, stating they recognize HbA1c<7% "for most adults," and that HbA1c<6.5% "may be suggested on a personalized basis" for some. The glucose tolerance test is noted to be useful in diabetes diagnosis, and necessary for the diagnosis of prediabetes [1]. Self-monitoring of blood glucose and/or continuous glucose monitoring are suggested to "facilitate optimal glycemic control, [and are] recommended to avoid hypoglycemia." The ESC/EASD suggests that patients with established or high risk for CVD should be treated first with a GLP-1RA or an SGLT2i, only adding metformin if there is also a need to control hyperglycemia. The American Association of Clinical Endocrinologists (AACE) further observes that HbA1c $\leq$ 6.5% should be considered optimal. The notion that lower HbA1c led to increased mortality in the ACCORD trial is specifically refuted, with the observation that the group of persons randomized to intensive glycemic management who experienced higher mortality in this study comprised those who failed to attain HbA1c <7%. AACE also recommends that, "independent of glycemic control," if a person has diabetes with established atherosclerotic CVD (ASCVD) or high risk of ASCVD, or has chronic kidney disease (CKD), treatment with a long-acting GLP1-RA or a SGLT2i with "proven efficacy" should be initiated. AACE further recommends SGLT2i with proven benefit to patients with moderate to severe CKD, or heart failure with reduced ejection fraction (HFrEF) (with or without T2D) [2]. Although in the 2019 update of the American Diabetes Association/EASD recommendations and the 2020 ADA Standard of care these organizations also suggest that GLP-1RA or SGLT2i be given to reduce major adverse cardiovascular events (MACE), hospitalization for heart failure, CV death, and/or CKD progression, independently of HbA1c or HbA1c target, they still require that metformin be prescribed first [3]. The American College of Cardiology (ACC) suggests considering the use of a GLP-1RA or SGLT2i for patients with T2D and clinical ASCVD, whether at follow-up visits, in a person with ASCVD at a time that diabetes is diagnosed, or in a person with T2D who is subsequently hospitalized with ASCVD or HF. For glucose management the ACC position recommends following the ADA standard of Care [4]. Addressing primary CVD prevention, the ACC/American Heart Association (AHA) guidelines suggest that persons with T2D and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin be considered for SGLT2i and GLP-1RA "to improve glycemic control and reduce CVD risk." [5].

☆ AACE, American Association of Clinical Endocrinologists, ADA, American Diabetes Association, EASD, European Association for the Study of Diabetes, AHA, American Heart Association, ACC, American College of Cardiology, and ESC, European Society of Cardiology.

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All the groups discuss use of metformin, the ESC/EASD "in overweight patients with T2DM without CVD and at moderate CV risk," AACE not specifically addressing its use in persons with or at risk of CVD, recognizing its role, efficacy and safety in managing hyperglycemia but mentioning potential CV benefit, and also emphasizing limitations to its use with eGFR<45. AACE mentions the potential of metformin to cause vitamin B12 deficiency, suggesting screening for this in persons with neuropathy. The ADA/EASD and ACC/AHA recommend that metformin treatment be initiated at the time of T2D diagnosis for glucose control, though not proven suggest that there may be ASCVD benefit, and note that metformin is neutral in terms of HF outcome.

Indications for use of SGLT2i highlighted by the ESC/EASD are for reduction in HF-hospitalization, as well as use in CKD with eGFR 30 to <90. The CV effects are noted to be "mostly unrelated to the extent of glucose lowering" and the document recommends use of any of the drugs in the class in patients with T2D and CVD or high CV risk. AACE suggests that the SGLT2i reduce HF hospitalization in patients with established CVD and that dapagliflozin, specifically, is effective for primary prevention of HF hospitalization. Further, AACE points out that dapagliflozin demonstrated efficacy in patients who have HFrEF with and without diabetes. AACE notes that empagliflozin is FDA approved to reduce CV mortality and that canagliflozin is FDA approved to reduce MACE and to manage moderate to severe CKD with proteinuria, and is the only SGLT2i approved for eGFR between 30 and < 45. The AACE report addresses ketoacidosis as a potential serious adverse effect of SGLT2i, and outlines mitigating strategies like stopping SGLT2i 24–48 hours prior to scheduled surgery or other anticipated stress, also suggesting that persons taking SGLT2i with insulin avoid both very-low-carbohydrate diets and excess alcohol. . The ADA/EASD notes empagliflozin and canagliflozin as having benefit for ASCVD, and both, along with dapagliflozin, as having benefit for HF. Use is particularly suggested in patients with HFrEF, and with CKD, particularly with macroalbuminuria. The ACC and AHA suggest that persons with T2D and high CVD risk be considered for addition of SGLT2i after use of metformin, and that persons with T2D and existing CVD may have reduction in CV outcomes from use of these agents. The ACC and AHA, addressing patient-specific characteristics that affect tolerability of SGLT2i, suggests that genital mycotic infections usually are of minor import, that urinary infections are not associated with SGLT2i, and that there is little evidence of causal relationship of peroneal fasciitis to SGLT2i treatment.

The GLP-1RA are recommended by ESC/EASD to be indicated for prevention of ASCVD-related events, with liraglutide and semaglutide suggested as options even with eGFR<30. AACE suggests CV benefit with long acting GLP1ra, particularly with liraglutide and semaglutide in patients with established CVD, and notes dulaglutide to also have evidence of such effects in primary prevention. The ADA/EASD document addresses CV outcome benefits of GLP-1RA in detail, noting the greatest evidence of benefit with liraglutide, but also evidence of benefit among persons with T2D and existing CVD with semaglutide and albiglutide, and of benefit with dulaglutide among persons with T2D not only having clinical CVD but also in those having increased risk for CVD. The ACC/AHA document suggests that pancreatitis appears not to be caused by GLP-1RA (though other documents mention a small increase in risk), and suggests, without substantiation, that the increase in diabetic retinopathy in the semaglutide trial could have been a function of rapid improvement in glycemia.

As far as other glucose-lowering agents, ESC/EASD states that in persons with HF thiazolidinediones not be used, and that the dipeptidyl peptidase 4 inhibitor saxagliptin not be used, but that both sitagliptin and linagliptin should be considered reasonable for such patients if otherwise indicated. AACE notes two further agents potentially benefiting persons with ASCVD: pioglitazone [6–8], and also the rapidly absorbed preparation of bromocriptine [9,10].

For the clinician, many additional questions may need to be addressed prior to initiating T2D treatment based on the existence of CVD or increased CV risk. In particular, it is unclear what patient characteristics need be considered when choosing one of these new drugs beyond their evidence of CV risk modification. Because the mode of action of these agents in reducing CV outcomes is not known, there is some difficulty identifying a specific patients' potential for benefit with a given agent. As such we are witnessing a paradigm shift in managements: prescribing medications to prevent the next CV event independent of an intended CV risk modification, such as the degree of reduction in glycemia. We anticipate that eventually patient characteristics such as age, diabetes duration, CKD, the other "microvascular" complications of neuropathy and retinopathy, and bio markers will potentially contribute to our ability to match the appropriate drug to the right patient. This will help managed the expense as the cost of the newer T2D medications often poses a barrier. Knowing which drug will help which patient will improve our ability to help make shared decisions with our patients as to which of the newer agents might be reasonable choices.

References

[1] Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al., ESC Scientific Document Group. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2019; 41(2):255–323. 2020 Jan 7.

[2] Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement by the American association of clinical Endocrinologists and American College of endocrinology on the comprehensive type 2 diabetes management algorithm - 2019 executive summary. Endocr Pract 2019 Jan;25(1): 69–100.

[3] Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. Update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). Diabetes Care 2019;43(2):487–93. 2020 Feb.

[4] Das SR, Everett BM, Birtcher KK, Brown JM, Cefalu WT, Januzzi Jr JL, et al. ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology task force on expert consensus decision pathways. J Am Coll Cardiol 2018;72(24):3200–23. 2018 Dec 18.

[5] Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines. Circulation 2019;140(11):e596–646. 2019 Sep. 10.

[6] Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): a randomised controlled trial. Lancet 2005 Oct 8; 366(9493):1279–89.

[7] Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. IRIS trial investigators. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016 Apr 7;374(14):1321–31.

[8] Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. J Am Med Assoc 2007 Sep 12;298(10):1180–8.

[9] Gaziano JM, Cincotta AH, O'Connor CM, Ezrokhi M, Rutty D, Ma ZJ, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. Diabetes Care 2010 Jul; 33(7):1503–8. https://doi.org/10.2337/dc09-2009.

[10] Gaziano JM, Cincotta AH, Vinik A, Blonde L, Bohannon N, Scranton R. Effect of bromocriptine-QR (a quick-release formulation of bromocriptine mesylate) on major adverse cardiovascular events in type 2 diabetes subjects. J Am Heart Assoc 2012 Oct;1(5):e002279.

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