Take 3 – Practical Practice Pointers© February 17, 2020 Edition

Diabetes Standards of Care 2020 – Part 2, Flozin Deep Dive

From the Guidelines and the American Diabetes Association (ADA)

1) ADA Diabetes Pharmacotherapy Standards of Care 2020

The Standards are developed by the ADA's multidisciplinary Professional Practice Committee, which comprises physicians, diabetes educators, and other expert diabetes healthcare professionals. The Standards include the most current evidence-based recommendations for diagnosing and treating adults and children with all forms of diabetes. ADA's grading system uses A, B, C, or E to show the evidence level that supports each recommendation.

Pharmacotherapy Recommendations – Prediabetes:

- Metformin therapy for prevention of T2D should be considered in those with prediabetes, especially for those with BMI ≥35, age <60, and/or hx of GDM. **A**

Pharmacotherapy Recommendations- Type 2 Diabetes (T2D):

- Metformin is the preferred initial pharmacologic agent for the treatment of T2D. **A**
- Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. **A**
- Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. **A**
- Those with T2D who have kidney disease, HF, and/or established ASCVD or are at high risk for it, a sodium–glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist with demonstrated CVD benefit is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors. **A**
- Those with T2D who need greater glucose lowering than can be obtained with oral agents, GLP-1 receptor agonists are preferred to insulin when possible. **B**
- Intensification of treatment for patients T2D not meeting treatment goals should not be delayed. **B**
- The early introduction of insulin should be considered when A1C levels (>10%) or blood glucose levels (≥300) are very high. **E**
- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include CV comorbidities, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences. **E**
- The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment. **E**

ASCVD Risk and T2D – Recommendations

- For established ASCVD **or** established kidney disease, an SGLT2 inhibitor or GLP-1 receptor agonist with demonstrated CVD benefit is recommended as part of the glucose-lowering regimen. **A**

- For established ASCVD, multiple CVD risk factors, **or** established kidney disease, an SGLT2 inhibitor with demonstrated CV benefit is recommended to reduce the risk of major adverse CV events and HF hospitalization. **A**
- For established ASCVD or multiple risk factors for ASCVD, a GLP-1receptor agonist with demonstrated CV benefit is recommended to reduce the risk of major adverse CV events. **A**
- For stable HF, metformin may be continued for glucose lowering if eGFR remains > 30 but should be avoided in unstable or hospitalized patients with HF. **B**
- For established HF, an SGLT2 inhibitor may be considered to reduce risk of HF hospitalization. **C**

Statin Treatment in T2D – Recommendations:

- For age 40–75 without ASCVD, use moderate-intensity statin therapy in addition to lifestyle therapy. **A**
- For all ages with ASCVD, high-intensity statin therapy should be added to lifestyle therapy. **A**
- For ASCVD and considered very high risk using specific criteria, if LDL cholesterol $\geq$70 on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor). **A** - Ezetimibe may be preferred due to lower cost.
- For those at higher risk, especially with multiple ASCVD risk factors or aged 50–70, it is reasonable to use high-intensity statin therapy. **B**
- For age >75 already on a statin, it is reasonable to continue statin treatment. **B**
- For age 20–39 years with additional ASCVD risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. **C**
- For those with a 10-year ASCVD risk of $\geq$20%, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL cholesterol levels by 50% or more. **C**
- For age >75, it may be reasonable to initiate statin therapy after discussion of potential benefits and risks. **C**
- For those who do not tolerate the intended intensity, the maximally tolerated statin dose should be used. **E**

Pharmacotherapy for Obesity/Weight Loss – Recommendations:

Nearly all FDA-approved medications have been found to improve glycemic control in patients with T2D and delay progression to T2D in patients at risk.

- Weight-loss medications are effective as adjuncts to diet, physical activity, and behavioral counseling for selected patients with T2D and BMI $\geq$ 27. Potential benefits must be weighed against potential risks of medications. **A**
- If a patient's response to weight-loss medications is <5% weight loss after 3 months or if there are significant safety or tolerability issues at any time, the medication should be discontinued, and alternative approaches should be considered. **A**

My Comment:

Despite the aggressive nature in which the newer diabetes medications have been advertised and detailed, metformin continues to be the first-line treatment based on the evidence. The SGLT2 inhibitors and GLP-1 receptor agonists have a specific indication for those patients with diabetes who have established ASCVD or are at very high risk for it or have kidney disease. Note the SGLT2 inhibitors also have an indication for those with diabetes and HF.

The Standards abridged document also includes 3 very helpful algorithms/summaries for prescribing/intensifying non-insulin medications, for prescribing/intensifying insulin, and a wonderful table of all the medications with their indications, strengths, and limitations. I have included this as a separate attachment in the e-mail version of Take 3 this week for your reference. Reviewing these 3 pages and keeping them close for reference during clinical care would likely be worthwhile until you feel familiar/comfortable with the recommendations. Next week we'll take a "deeper dive" into continuing glucose monitoring and the associated technology.

References:

- ADA Standards for Medical Care in Diabetes – 2020: Abridged for Primary Care Providers. Clinical Diabetes published ahead of print December 20, 2019. Link
- ADA Standards of Care 2020: Diabetes Care. January 1, 2020; volume 43 issue Supplement 1. Link

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From a Deeper Dive into the Literature

2) Making Sense of "Flozins" and Their Effect on CV Outcomes

Much has been published and written about the sodium-glucose cotransporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, empagliflozin, and a couple of new ones) and their "benefits in heart disease." This is an area that's a setup for misinformation and confusion. There's heavy pharmaceutical industry marketing, the science is a bit complex and is evolving, and we're unsure of WHY the flozins might produce their CV benefit. In addition, "hospitalizations for heart failure" got introduced as a major outcome for these medications, and in this era of accountable care and a focus on reducing hospitalization, this outcome has attracted a lot of interest.

In the last year, four systematic reviews have looked at SGLT2 inhibitors and their impact on cardiovascular events. Each had a slightly different perspective – e.g., looking at different CKD stages and established CVD vs. only risk factors for CVD. While there was a decent amount of competing (industry) interest in the authorship lists for these reviews (except for Lo 2020), all reviews used established and clear methods. The appropriate searches were performed, inclusion and exclusion criteria were clear and well-specified, there was quality assessment of all the included studies, and the heterogeneity of the evidence was assessed appropriately. Creating a valid review on this topic isn't too hard, since there are now only four trials that exist in the literature that measure the relevant outcomes. Each of these reviews included all three of the earlier trials (called CANVAS, EMPA-REG and DECLARE-TIMI), and Lo 2020 included the most recent study (CREDENCE).

The included studies were generally valid themselves and were large – almost 40,000 subjects in total. However, the relevant outcomes are rare overall, so this literature is full of "composite outcomes" used to increase the power of the studies. Any one of the components of the composite outcomes would qualify as "the outcome" for the study. For example, major adverse cardiovascular events (MACE) is a popular composite outcome in cardiovascular research. In the case of these studies, a MACE can be any one of "death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke." Sometimes other outcomes get thrown in there – often ones that are not as

serious or may not be as “patient-oriented” as morbidity and mortality. For instance, the composite outcome for renal events in these studies included “doubling of creatinine” and “40% decrease in eGFR” in addition to “renal death” and “dialysis”. It’s important to unpack these composite outcomes when you’re reading these studies.

From the Lo 2020 study (the most recent and inclusive review), over an average of 3 years of follow up, flozins decreased MACE in patients with diabetes and cardiovascular disease (NNT ~ 167). Flozins were associated with a small reduction in all-cause mortality (NNT ~ 143) and reduced hospitalizations from heart failure (NNT~91). They seemed to reduce renal events (NNT ~67) too, though this result should be viewed with some skepticism because of the composite outcome issue (see above). Across the four reviews, the results varied concerning the significance of any of the individual outcomes (MI, dialysis, death, etc.) In these reviews, there was a general trend toward these medications working better for those at higher risk – i.e., those with established CVD vs. those with just the risk factors for CVD. The safety outcome data (best reported in Toyama 2019) is generally reassuring but does note an increase in “genital infections.” In all these reviews, there could be high levels of heterogeneity for some outcomes.

John’s Comments:
This area is rapidly evolving, and I don’t think we have the final answer about these medications yet, especially when I see the heterogeneity and the short follow up durations. This meta-analysis suggests that the benefits associated with flozins are a class effect, but this study included data about canagliflozin, empagliflozin and dapagliflozin only. The makers of those drugs have each sought slightly different FDA indications based on the individual study data and promote them differently. When I need another medication beyond metformin to treat poorly controlled diabetes in patients with CVD, I can reach for one of the flozins with some reassurance that they will help, although cost is a significant barrier for many patients.

Of note, for the goal of better 2° prevention of CVD, we should ensure that we’re providing aspirin, statins, smoking cessation and adequate BP control before we devote a significant amount of energy to fine-tuning our diabetes medications. The NNT for each of these interventions is generally smaller than for flozins.

References:

- Zelniker TA et al. SGLT2-I for 1° and 2° prevention of CV and renal outcomes in T2D: a systematic review/meta-analysis. Lancet. 2019 Jan 5;393(1):31–9. Article
- Toyama T et al. Effect of SGLT2 inhibitors on CV, renal and safety outcomes in patients with T2D and CKD: A systematic review and meta-analysis. Diabetes Obes Metab. 2019 May;21(5):1237–50. Article
- Hussein H et al. CV efficacy and safety of SGLT2 inhibitors and GLP-1 receptor agonists: a systematic review/meta-analysis. Diab Med. 2019;36(4):444–52. Article
- Lo KB et al. The Effects of SGLT2 Inhibitors on CV and Renal Outcomes in DM. A Systematic Review and Meta-Analysis. Cardiorenal Med. 2020;10(1):1–10. Article

Feel free to forward Take 3 to your colleagues. Glad to add them to the distribution list.

Mark and John

Carilion Clinic Department of Family and Community Medicine