CLOSER LOOK

MEMORANDUM

New ADA/EASD consensus report for managing hyperglycemia in type 2 diabetes released at EASD 2018 - October 4, 2018

Executive Highlights

- **A just-published joint consensus document from the ADA and EASD (*Diabetes Care*; *Diabetologia*)** calls for "a paradigm shift" to more patient-centered care for type 2 diabetes and makes groundbreaking recommendations for CVD, heart failure, and CKD, in an update to the associations' 2015 position statement. According to ADA Chief Science, Medical and Mission Officer Dr. Will Cefalu, this document has been endorsed by the ADA and incorporated into the "living" Standards of Care.
- **Patient-centricity underlies the entire set of recommendations,** and Dr. Cefalu emphasized that patient-centric care is an ongoing cycle - as reflected in the paper's leading figure, below. HCPs are advised to discuss treatment plan at least twice a year, and patient preferences and needs (e.g. cost, lifestyle, comorbidities, mental health, SES) are prominently considered.
- **In terms of specific recommendations,** the statement offers roadmaps for choosing therapy based on areas of particular concern, with specific algorithms focused on CVD, cost, minimizing hypoglycemia, and weight loss; we noticed a strong emphasis on cost and promoting adherence throughout the document. GLP-1 agonists are recommended as first-line injectable therapy (except in specific cases of catabolism or intolerance), and there is a clear preference for both GLP-1s and SGLT-2s.
- **The document emphasizes cardiovascular and kidney disease and specifically recommends GLP-1 agonists and SGLT-2 inhibitors for patients with ASCVD.** In the case that ASCVD predominates, either a GLP-1 or SGLT-2 with proven benefit should be considered; if either heart failure or CKD predominates, an SGLT-2 is preferred over a GLP-1. This reflects a notable change from the draft presented at ADA 2018.
- **A few areas where this document could improve?** We'd love to see stronger recommendations on tech (i.e. clear CGM recommendations for those with hypoglycemia risk - Medicare pays for this after all), more criticism of lackluster therapies (i.e. SUs), and perhaps a greater consideration of language (what might be the unintended impact of calling GLP-1 a "first injectable"? is "clinical inertia" really the term we want to use?).

A new joint consensus document from the ADA and EASD (*Diabetes Care*; *Diabetologia*) calls for "a paradigm shift" to more patient-centered care for type 2 diabetes. This document is an update to the associations' 2015 position statement. We see these new recommendations as critical in multiple respects and missing in a couple of other ways - we hope, always, that health care providers in the US and Europe will be supported as they move to use them for patients of all kinds. The session at EASD - over 1500 people! - just finished and we're excited to discuss this monumental milestone.

Presented Friday at EASD 2018 in Berlin (in a very well-attended session!), this ADA/EASD consensus report draws on 479 papers published over the past four years to develop strategies for health care providers in treating diabetes. See the ADA's Standard of Care, where there has already been an update from these guidelines - this is the first time that the guidelines are a "living document" where important events are updated real-time.

That these recommendations are explicitly emphasizing patient-centricity is a major positive. Patient preferences are fundamentally factored into treatment decisions; additionally, different adherence rates with

various medications - and the impact that can have on outcomes - is a prominent factor to consider. Cost has also become, in our observation, a much bigger point of concern.

We also perceived a strong focus of "closing the loop" per se; Dr. Cefalu described how patient-centered care is an ongoing cycle (below) in expressing his approval of the statement's recommendations. The repetition is key: The report suggests patient and provider should work on a new plan at least twice a year, in order to better match evolving treatment needs. Although we'd like to see a bigger technology orientation to help patients better guide themselves, we are grateful to EASD and ADA for working together on this plan.

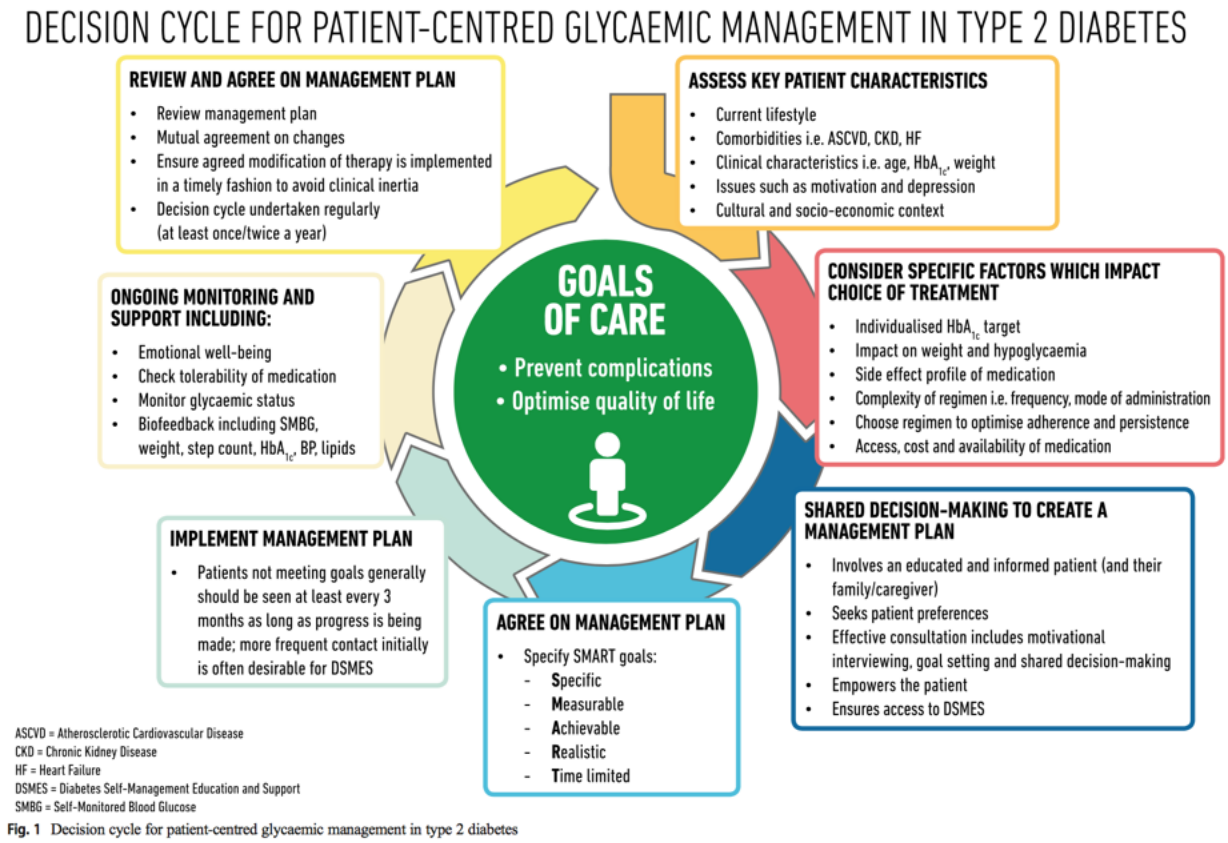

Fig. 1 Decision cycle for patient-centred glycaemic management in type 2 diabetes

Additionally, we find this report to be a truly remarkable example of collaboration. We love that two major organizations put this together very collaboratively, were receptive to review from the entire diabetes community, and received input over multiple months from a multitude of stakeholders. This included invitations to 50 reviewers and 870 comments from the public sent to the ADA alone! As detailed below, some truly meaningful revisions have taken place since presentation of the draft statement at ADA 2018 - it's clear the committee took feedback very seriously.

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Treatment Algorithms

- **This new guidance report provides detailed algorithms for choosing therapy**, based on a patient's primary area of concern. Specific roadmaps exist for choosing treatment based on ASCVD/ CKD status, hypoglycemia minimization, weight loss concern, and cost issues. These are designed to

reflect health history, weight, costs of care, and individual preferences. This primary emphasis on determining the right choice of diabetes medications is in turn supplemented by lifestyle management, self-management education, and external support. We are absolutely thrilled to see so much focus on so many respects of patient care.

    - **The manuscript discusses cost as a major barrier in developing countries "and increasingly the United States,"** although not in Canada nor Europe to the same degree. Our sense is certainly that cost is an issue for patients and provers across the globe, and we appreciate that the committee took a practical stance and accounted for real-world circumstances.

- **The report recommends GLP-1 agonist as the first injectable medication for most adults with type 2, while SGLT-2 inhibitors are suggested for those with chronic kidney disease.** Both of these represent groundbreaking recommendations in diabetes, and we continue to see this as a big step forward given (i) increasingly strong evidence of cardio- and renal-protection and (ii) better long-term safety and efficacy. As noted, these medicines do not promote hypoglycemia as long as they are not taken with insulin. This prominent position for GLP-1s and SGLT-2s is very important - and we hope it will drive changes in HCP behavior.

    - **The authors discuss how to initiate GLP-1 -** "you'll have to read everything," said Dr. Chantal Mathieu, who emphasized that titration to the maximum dose is very important. Notably, speaking on basal insulin initiation, she also said, "please do not just initiate - also titrate." She also stressed the importance of intensive glucose monitoring as an absolute requirement with mealtime insulin. Adding some clinical wisdom, she also emphasized that basal insulin can be intensified with a GLP-1 agonist, rather than the traditional mealtime insulin.

- **Notably, a patient's adherence is now considered a factor that health care providers should consider** in devising and refining treatment plans. Generally speaking, it's noted that an A1c below 7% is the primary target for most adults. Metabolic surgery is recommended for adults with type 2 and either a BMI of 40 kg/m² or greater (≥37.5 for people of Asian ancestry), or a BMI between 35 and 40 (between 32.5 and 37.5 for people of Asian ancestry) provided that other, non-surgical methods don't result in durable weight loss or comorbidity improvements.

- **We were pleased to note a focus on obesity and acknowledgement that there are not enough treatment options for weight loss.** Dr. Buse sighed in saying that the unmet need for obesity treatment was massive, but that there were not enough options (and for the strongest available option, Saxenda, not enough affordability). He also said further study was needed on lifestyle support; one big question for us is how technology can combine with lifestyle interventions and even pharmacotherapy to promote healthier behavior. We hope more explicit evidence-based recommendations can be made on this front by the next update.

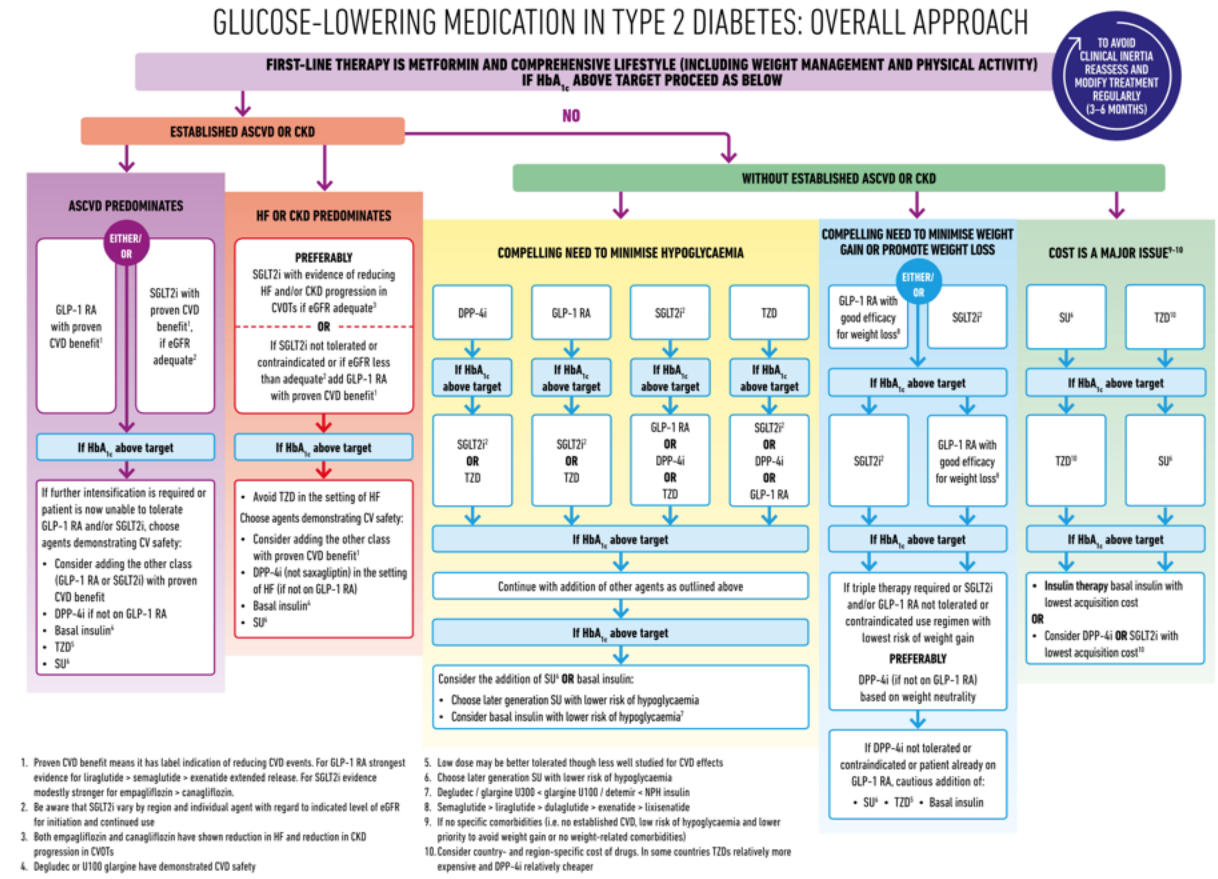

Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach

Cardiovascular and Renal Recommendations

- **The statement explicitly recommends prescribing an SGLT-2 inhibitor or GLP-1 agonist for patients with ASCVD.** If a patient is not meeting A1c goals, consideration should be given to adding an SGLT-2 or GLP-1 with proven CV benefit; if a patient is at target A1c, consideration should be given to switching to or adding one of these (as per the algorithm below). The algorithm recommends either an SGLT-2 or GLP-1 with proven CV benefit for those with predominant ASCVD, but prefers an SGLT-2 over a GLP-1 if heart failure or CKD predominates (SGLT-2s should only be used if eGFR is adequate). If A1c remains above target after this addition, or if the patient cannot tolerate the therapy, adding the other class should be considered; subsequently, any class with CV safety can be considered.
    - **This section has seen notable revision since the draft statement was presented at ADA 2018.** First, the equal recommendation of SGLT-2s vs. GLP-1s on predominating ASCVD was revised from a recommendation of GLP-1s over SGLT-2s. Additionally, chronic kidney disease (CKD) was added as a consideration in this algorithm, with a preference for SGLT-2 use in the case that CKD (or heart failure) predominates. At ADA 2018, Dr. Silvo Inzucchi commented that the evidence for renal benefit with SGLT-2 inhibitors was as strong as the evidence for heart failure, leading him to question why the committee had - at that point - chosen to make a recommendation on heart failure but not CKD. We imagine this is the logic that led to this specific revision, and we're thrilled to see the renal benefits SGLT-2s have now demonstrated making their way into recommendations.

    - **The committee stuck with its drafted "ranking" of SGLT-2 inhibitors and GLP-1 agonists.** Within the GLP-1 agonist class, liraglutide is preferred over semaglutide, which is preferred over exenatide; we continue to be somewhat surprised by this ranking given semaglutide's (Ozempic's) stunning efficacy, but we also understand the CVOT data from SUSTAIN 6 (for Ozempic/semaglutide) isn't as strong as from LEADER (for Victoza/liraglutide). For SGLT-2s, empagliflozin is preferred over canagliflozin, presumably for reasons of safety (i.e. amputation risk for Inovkana/canagliflozin). We wonder how, once the DECLARE CVOT fully reads out, dapagliflozin might factor into this equation.

- **Dr. John Buse said outright that there were not nearly enough patients taking cardioprotective diabetes therapies,** given the strong evidence some of these have for conferring cardiovascular risk reduction. It is terrific for HCPs in particular to see cardiovascular and renal risk factors discussed in depth.

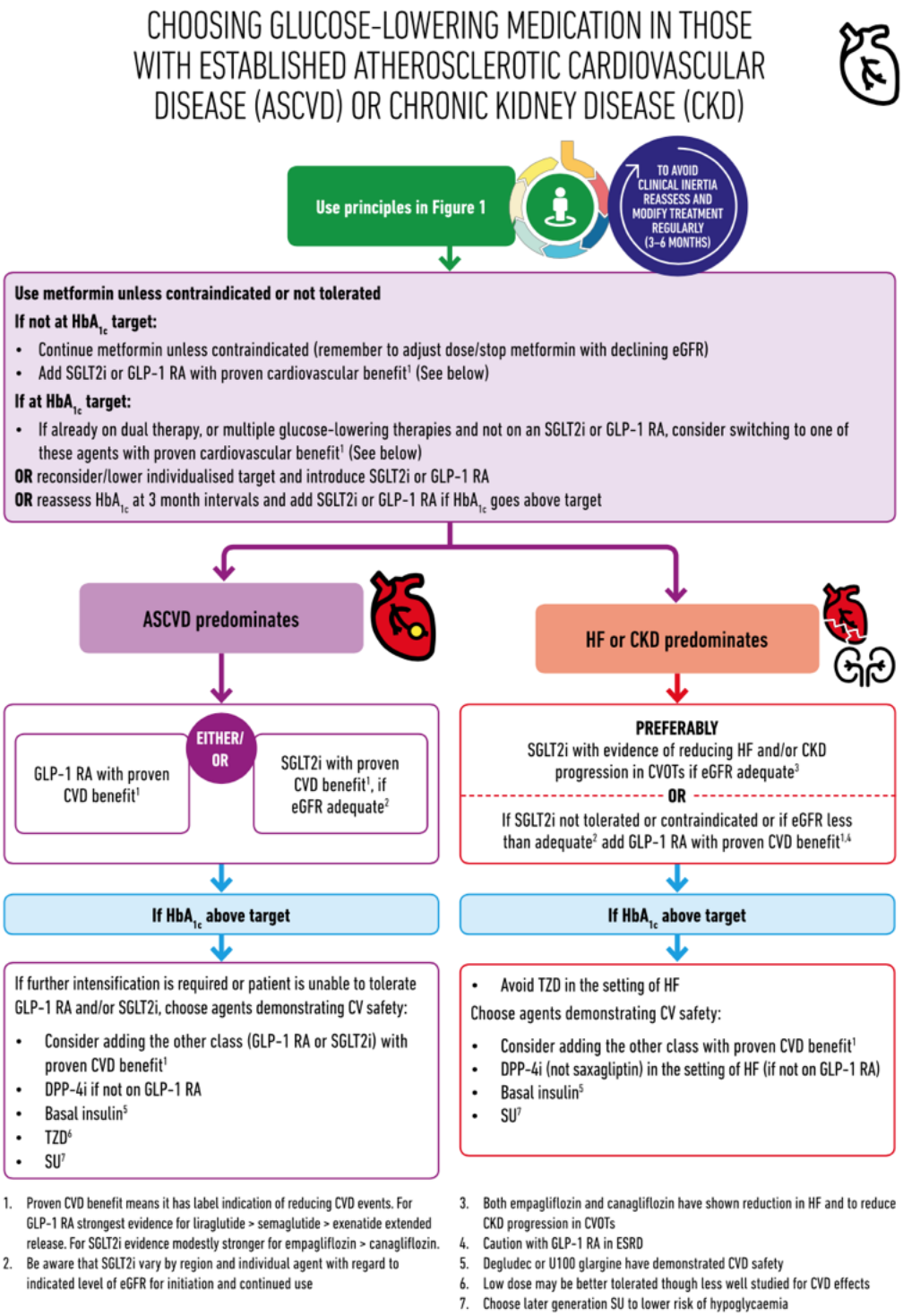

Fig. 3 Choosing glucose-lowering medication in those with established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD)

Potential Areas for Improvement

- **We'd like to see CGM more strongly encouraged when patients have a meaningful risk of hypoglycemia.** While we understand the fundamental need to be evidence-based, CGM is pretty heavily downplayed. In our view, given that CGM is still very underutilized in people with both type 1 and type 2 diabetes, it would be great to see guidelines promote its use where its value

can be reasonably assumed. There are so many patients on basal-bolus insulin therapy or taking insulins that carry hypoglycemia risk (not to mention SUs) who are at major risk of severe hypoglycemia - to say nothing of the tens of millions of patients who experience far too much hyperglycemia each day.

- **We felt the negative features of the sulfonylurea class should be highlighted.** In our view based on multiple KOL interactions, SUs should feature much less prominently in treatment algorithms. We appreciate that the treatment characteristics table notes uncertain CV safety, high rate of secondary failure, hypoglycemia, and weight gain associated with SUs. But given that so many far superior therapies are now available, we think writing committees could make a more aggressive push to promote the use of better drugs over a class with questionable safety and side effect profile.
- **We'd like to see more prediabetes** focus given that hyperglycemia is such a concern in this phase of diabetes. As well, we'd like to see far more discussion of prevention of complications - prevention of cardiovascular disease, prevention of renal disease.
- **Metformin: Is its role as foundational therapy warranted or is it a "historical quirk?"** Dr. Buse highlighted that the writing committee seriously debated this topic - one that's garnered significant attention lately - and we'd like to see this debated more.
- **Questions on language:** We do wonder about some of the language used. For example, saying that GLP-1s should be the "first injectable" may imply to many people with type 2 that GLP-1 is exclusively a "later stage experience." On the contrary, many experts point out that GLP-1 has shown to be of great use early in disease progression, particularly for preservation of beta cell function. We very strongly agree with the recommendation that GLP-1 is an option preferable to basal insulin for most patients, but we also think GLP-1s could be preferable to many other therapies for many patients - and this will only become truer with the advent of oral GLP-1. Moreover, for some patients, GLP-1/basal combinations may be a better therapy. Our other concern on language is around "clinical inertia" - although we know it's used widely (and we're not certain what a good alternative would be), we don't think it is appropriately respectful of all doctors and nurses.
- **Sequential therapy vs combination therapy:** The speakers today said there are potential downsides to potential multiple agents at baseline; we'd like to see this further examined, since so many patients experience so many delays in moving to combo therapy when it is clearly warranted.
- **Youth and the Elderly:** As Dr. Buse noted, the writing group felt very constrained by the lack of evidence on how to treat type 2 diabetes in youth; so far, there's little evidence on how to successfully treat this population. He also stressed that the field needs more focus on the elderly and individualization of treatment targets. In terms of other individualization, we are particularly pleased to see different guildelines for Asian people given recent learning on this front.
- **From Professor Miles Fisher (Glasgow Royal Infirmary, UK):** "I would comment that this is a very detailed document and that it requires detailed reading alongside looking at the presentation that was given. The suggestion of GLP-1 RAs first after tablets for the majority fits with current routine practice in the UK and is welcome. The figures are complex and will be difficult for primary care doctors to use so some form of simplification would help. The insulin figure in particular is hard to follow. There was an error when it was presented in that Peter Rossing said the HFH (heart failure hospitilization) was not adjudicated. He means that CHF (congestive heart failure) at baseline was not adjudicated. In all of the CVOTs, HFH was blindly adjudicated by a CV endpoints committee and the criteria applied were the same as those use in CV studies of heart failure treatments. As a broader comment I think that there should have been a cardiologist on the committee!"

This report was published October 4th and expanded October 5th.

-- Ann Carracher, Sarah Kolk, and Kelly Close