Comparing and contrasting recent guidance for cardiovascular and renal risk reduction in diabetes: can we reach consensus?

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Tables 1

Since the early 2000s, the number of diabetes drugs has more than doubled and over 20 cardiovascular or renal outcome trials have completed. This new evidence has accrued at such a rapid rate that many health care professionals are struggling to keep up. Guideline and consensus committees are tasked with summarising the evidence in a manner that is balanced, easily digestible and practical.

The 2018 American Diabetes Association (ADA) / European Association for the Study of Diabetes (EASD) consensus report emphasized patient-centred care along with recommendations to select specific antihyperglycemic therapy, *after metformin*, based on the cardiovascular / renal status of patients.[1] In individuals with existing atherosclerotic cardiovascular disease (ASCVD), the ADA/EASD supported the use of either a sodium glucose cotransporter-2 inhibitor (SGLT2i) or glucagon-like-peptide-1 receptor agonist (GLP-1RA) to lessen the risk of major adverse cardiovascular event (MACE), whereas in those with heart failure (HF) or chronic kidney disease (CKD), a SGLT2i was recommended.. Metformin remained first-line therapy and the addition of other therapy was recommended only if the HbA1c target was not achieved.

In September 2019, the European Society of Cardiology (ESC) published guidelines on diabetes, prediabetes and cardiovascular disease in collaboration with the EASD.[2] This document included two fundamental differences. First, it recommended that either a SGLT2i or a GLP-1RA be prescribed in treatment-naïve patients with T2D and ASCVD, *without* having to start metformin first. Secondly, the recommendation that a SGLT2i or a GLP-1RA should be prescribed, *regardless* of HbA1c level, as the cardiovascular benefits of these drugs are independent of HbA1c. The guideline further challenged orthodoxy in recommending these therapies be preferentially used not just in those with ASCVD but also in those deemed to be at ‘very high’ or ‘high’ risk of CV disease, using broad definitions that encompass a sizeable proportion of patients with T2D.

The ADA/EASD 2018 consensus report has just been updated with some notable changes.[3] Firstly, in patients with ASCVD, HF or CKD, the use of diabetes therapies proven to reduce risk should *not* be contingent on HbA1c levels, in recognition of the glucose-independent CV and renal benefits of these therapies, bringing consistency with the ESC-led guidelines. However, the ADA/EASD report continues to maintain the primacy of metformin. A further change in the ADA/EASD update is the recommendation that a SGLT2i or a GLP-1RA

should also be prescribed in patients with “indicators of high CV risk”; defined as age over 55 years with “coronary, carotid, or lower extremity artery stenosis exceeding 50%, left ventricular hypertrophy, estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1.73 m², or albuminuria”, based on previous trials. Another important change is the favouring of GLP-1RA for those with ASCVD or with “indicators of high CV risk”, on the basis that the trial evidence was interpreted as showing GLP-1RA reduce MACE in these patients, considered by the authors to be the ‘gravest threat’. SGLT2i reduced MACE only in those with ASCVD, although reduced hospitalization for heart failure and renal outcomes in patients with either ASCVD or “indicators of high CV risk”.[4] Finally, this new update provides more detailed criteria for the type of HF (reduced ejection fraction) and definitions of CKD where a SGLT2i is believed to be better targeted.

The agreement and disagreement between these two new guidance documents is summarised in **Table 1**, as well as potential ways forward.

A key area of agreement between the two is the recommendation that antihyperglycemic therapies that reduce CV and renal events should be offered to appropriate patients, *regardless* of the HbA1c level. SGLT2i and GLP-1RA both lower CV and renal outcomes independently of baseline HbA1c and of the extent of reduction in HbA1c, even if the mechanisms remain unclear. Although this may be misinterpreted as a “demotion” of the importance of glycaemic control, it is not as epidemiological, genetic and trial evidence supports glucose-lowering to lessen microvascular and macrovascular outcomes. The ADA/EASD and ESC documents continue to promote the achievement of an individualized glycaemic target, but not at the expense of delaying initiation of therapies that reduce clinical events (often in a very short time frame) in the appropriate patient. Thus, a comprehensive approach emerges of adding cardioprotective medications *and* achieving HbA1c (as well as cholesterol and blood pressure) targets to maximally protect patients..

A key area of disagreement is the primacy of metformin. Metformin is inexpensive, effective in lowering glucose, helpful in weight control and generally well tolerated. Metformin was background therapy in over 70% of the participants in the aforementioned CVOTs, but the benefits of the new therapies did not differ whether patients were on metformin or not.[5,6] Insisting all patients should be on metformin when there is minimal trial evidence to support any cardiovascular benefit in those with established ASCVD means that such patients have either to start two antihyperglycemic therapies simultaneously, or start metformin first then

add a GLP-1RA or SGLT2i later. The former approach increases pill burden and the latter could delay the provision of medicines proven to reduce CV events. The primacy of metformin remains an ongoing debate that will require self-reflection to recognize how much the reluctance to let go of metformin is based on evidence versus sentimental loyalty. Its low cost and long-term safety might argue for its continued use as first line primary prevention therapy patients without evidence of end organ damage, although it does not have the same strength of evidence in showing reduction in ASCVD in these individuals as GLP-1 RAs (or reduction in heart failure as SGLT2 inhibitors do).

A third point of note is placement of GLP-1RA as the preferred option for patients with established ASCVD in the ADA/EASD update, on the basis that MACE is a more common outcome and the perception that GLP-1RA reduce MACE more consistently than SGLT2i do. This differs from the ESC guidelines. Direct comparison of GLP-1RA and SGLT2i is not possible as there have been no head-to-head outcome trials. Whilst the individual components for MACE appear more consistently reduced with the positive GLP-1RA studies, SGLT2i's also reduced overall MACE, as well as hospitalization for heart failure and hard renal outcomes[4] – the GLP-1RA's do not do the latter convincingly.[7] Yet heart failure and renal failure are clearly important and some patients may prefer an oral medication. Therefore, even though oral GLP-1RA is now available, the decision to choose one class over the other in any patient with diabetes and ASCVD is complex. Perhaps, a risk calculator that estimates the likelihood of each of these key outcomes (MI, stroke, CVD death, heart failure, CKD) could be developed to help guide choice of therapy. For the time being, both drugs appear viable options in patients with existing ASCVD and shared decision-making with the patient should determine the selection on a case-by-case basis.

Fourth, the largest and arguably the most contentious discrepancy between the updated ADA/EASD consensus report and the ESC guidelines, are the different definitions of high/very high CV risk patients. As noted above the ADA/EASD consensus report criteria are quite specific, whereas those advocated by the ESC are far less so, encompassing a substantially larger proportion of patients with T2D, many with a low absolute risk of MACE. The ESC criteria seem to be adapted from those originally developed to identify patients for treatment with LDL and blood pressure lowering therapy and include individuals with ≥3 risk factors (from age, hypertension, dyslipidaemia, smoking or obesity). Strict adoption of the ESC guidelines would mean a substantial widening in use of these newer classes, leading to considerable increases in drug expenditure that may not be feasible in many healthcare

systems. We believe this substantial broadening of use needs more discussion. The potential use of risk scores to better target treatment needs investigation, coupled with formal cost effectiveness analyses.

Finally, the ADA/EASD update recommends SGLT2i specifically for those patients with reduced ejection fraction HF (HFrEF) and patients with eGFR 30-60 ml/min/1.73m^2 or UACR > 30mg/g. The renal criteria seem sensible on the basis of CREDENCE[8] and health authorities should now amend such criteria to allow wider use of SGLT2i's. The recommendation for HFrEF is appropriate on the basis of DAPA-HF,[9] which showed that SGLT2i are effective in treating as well as preventing HF. Prospective trials will soon report whether SGLT2i's also reduce risk in patients with heart failure and preserved ejection fraction (HFpEF).

In summary, interest in the cardiology community in these new classes of drugs is increasing, brought about by the consistency of outcome benefits in recent trials. Yet, two algorithms, one led by the diabetes community, ADA/EASD, and the other by the cardiology community, ESC, are in the public domain and differ in important respects, even if they agree on others. This situation will lead to confusion on key points for primary care and between-specialty debates. Such discordance may promote the perception that even the experts cannot agree on the evidence which can lead to suboptimal care. We believe that diabetes, cardiology and nephrology experts need to come together to create a unified approach, something that would benefit both health care professionals and their patients.

Table 1. Comparing and contrasting key elements between the new ADA/EASD consensus iteration and the ESC-led guideline

	ADA/EASD guidelines	ESC guidelines	Comment and potential ways forward
Independence of HbA1c concept	New position Explicitly stated	Implied but not explicitly stated	Future recommendations should clearly state that there is strong evidence that benefit of SGLT2i and GLP-1RA are independent of HbA1c
Metformin recommended as first line except when contraindicated	Yes	For most but not necessarily in drug naïve patients with ASCVD or high or very high risk	Given lack of evidence that metformin reduces CV events, first-line treatment with a SGLT2i or GLP-1RA in drug naïve patients, or add-on SGLT2i or GLP-1RA therapy in those already treated with metformin, should be recommended in patients with established ASCVD (and SGLT2i in those with CKD or HFrEF). Also in selected individuals at very high risk of ASCVD events, HF and CKD.
First choice in patients with *established* ASCVD	GLP-1RA preferred but SGLT2i also an option	SGLT2i or GLP-1RA	SGLT2i or GLP-1RA: both lessen overall MACE to broadly similar extents. SGLT2i also reduced hHF and renal outcomes. Only head-to-head trials can provide the robust evidence needed to recommend a preference for one over the other. In the meantime, new risk scores estimating absolute risks of individual outcomes in this population could aid clinical decisions as SGLT2i protect more against cardiorenal outcomes, whereas GLP-1RA protect more against atherothrombotic outcomes. GLP-1RA may be favoured in those with prior stroke.
Defining high risk primary prevention patients recommended for SGLT2i or GLP-1RA	Very specific (Age ≥ 55 yr + LVH or coronary, carotid, lower extremity artery stenosis > 50%)	Less specific, including patients with evidence of microvascular end-organ damage, long duration of disease or multiple risk factors, based on DECLARE and CANVAS	The ADA/EASD criteria are MACE centric and conservative; the ESC-led criteria would substantially expand number of eligible patients and costs. As drug costs decline, such issues will become less important but for now, targeting therapies to those at higher absolute risks/ end organ damage would seem sensible. Risk scores and cost effectiveness analyses may help in targeting therapies to those most likely to get a worthwhile benefit.
First choice of drug for patients at elevated ASCVD risk (dependent on definition)	GLP-1RA	SGLT2i or GLP-1RA	GLP-1RA may be better for those with coronary, carotid, lower extremity artery stenosis > 50% to prevent MACE but as LVH is stronger risk factor for HF, SGLT2i may be better. Future risk scores in diabetes patients calculating absolute risk for each of MACE, HF and CKD might help in choice of therapy. Potential value of NT-pro BNP testing also worth investigating further.
SGLT2i in HFrEF versus HFpEF	Suggest prioritise to HFrEF	No specification made	Treat HFrEF. HFpEF trials to report in next 1-2 years

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Declarations of interest:

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