Prevention of CV outcomes in antihyperglycemic drug-naïve patients with type 2 diabetes with, or at elevated risk of, atherosclerotic cardiovascular disease: to start or not to start with metformin

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This editorial refers to 'Similar cardiovascular outcomes in patients with diabetes and established or high risk for coronary vascular disease treated with dulaglutide with and without baseline metformin. A subgroup analysis of the REWIND Trial', by G. Ferrannini *et al.*, EURHEARTJ-D-20-02626R2

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As well documented,[1,2] a remarkable series of cardiovascular outcome trials have now convincingly shown sodium glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like-peptide-1 receptor agonists (GLP-1RA) lessen risk for major ASCVD-related adverse cardiovascular event (MACE) in patients with type 2 diabetes (T2D). The SGLT2i have also been shown to lower risks of HF or chronic kidney disease (CKD),[2] and benefit those with pre-existing HF with reduced ejection fraction[3] or CKD, whether they have T2D or not. The arsenal with which to lessen adverse cardiovascular / cardiorenal complications in T2D has thereby been meaningfully expanded.

Relevant professional societies have since revised their recommended treatment algorithms and Guidelines, including the European Society of Cardiology (ESC)[4] and American Diabetes Association (ADA) in conjunction with the European Association for the Study of Diabetes (EASD)[5], These societies and others now endorse the use of these two classes of drugs in patients with T2D and existing ASCVD or at high ASCVD risk, as well as to reduce risk for the incidence and progression of diabetic kidney disease and incident HF. These algorithms from diabetes and cardiology societies have aligned by stating the use of these two classes of medications should not be contingent on glycaemia levels, since the CVOTs did not target glucose control per se and the observed outcome benefits were consistent across glycaemia thresholds and similar regardless of the glucose reduction.

So far so good. Nevertheless, as we recently reviewed,[1] important differences remain between the ESC-led and the ADA/EASD consensus algorithms. Chief amongst these is whether all patients with newly diagnosed T2D (or those who are drug-naïve) but now recommended for SGLT2i or GLP-1RA for cardiovascular or kidney protection should first be commenced on metformin, whether metformin should be simultaneously started, or whether SGLT2i and/or GLP1-RA be used first with metformin (and other antihyperglycaemic medications) reserved for those patients who need additional blood glucose control. The ADA/EASD document continues to emphasise the primacy of metformin in all patients with T2D, but the ESC-led guideline, in sharp contrast, does not.

To help further address this thorny question, Ferrannini and colleagues conducted post hoc analyses of the REWIND trial.[6] This CVOT examined the CV effects of the once weekly GLP-1RA, dulaglutide, in patients with established or high risk for ASCVD. In this trial, more than 80% were on metformin at baseline, but a generous number (n=1864, 19% of total population) were not-a subset sample size approaching 50% the size of the entire cohort of the landmark UKPDS trial.[7] The latter group, not surprisingly, included more with lower baseline eGFR and HF, conditions where metformin has historically either been contraindicated or used with caution. The top line results showed no significant difference in the effect of dulaglutide on the primary outcome in patients with vs. without metformin at baseline (HR 0.92 [CI 0.8–1.05] vs. 0.78 [CI 0.61–0.99]; interaction P=0.18). The authors also reported similar results for key secondary outcomes in patients with and without baseline metformin use. In doing so, the authors argued that their findings suggest that the "benefit of the GLP-1 RA dulaglutide is unaffected by the use of baseline metformin in a population of patients with T2D with or at high risk for ASCVD."

Whilst these results are important, they are not without support from other CVOTs using GLP-1RAs. In results from *post hoc* analyses of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial,[8] which tested once daily liraglutide versus placebo, the benefits of liraglutide, as in the present study with dulaglutide, were greater in those not receiving baseline metformin, being significant only in non-metformin users, although there was no formal interaction in either case. And this relationship remained after extensive statistical adjustments for differences in patient mix and propensity for metformin use. Similarly, analyses of the REWIND data adjusting for differences in baseline characteristics yielded similar results. A third GLP-1RA trial,[9] Harmony Outcomes, also reported no difference in treatment effects in analyses stratified by baseline metformin treatment, although in this case, the unadjusted point estimates were near identical whether patients were on baseline metformin or not. Finally, a post-hoc analysis of data from the EMPA REG OUTCOME trial of empagliflozin versus placebo[10] that also adjusted for baseline differences found that empagliflozin was also associated with CV benefits irrespective of baseline metformin use.

Collectively, therefore, the cardiovascular benefits GLP-1RA's and SGLT2i's seem to be independent of background metformin use.

Of course, metformin protagonists would argue that showing a lack of significant interaction by baseline metformin use in the above-mentioned trials use does not negate the possibility that metformin is helping reduce CV risk in patients recruited into these trials. Whilst placebo event rates were lower in those on metformin, the lower CKD and HF prevalence in metformin recipients means that such rates cannot be compared. They would also point out that metformin has clinical trial evidence, the UKPDS,[11] to support its cardiovascular benefit, and that metformin is known to lower some notable cardiovascular risk factors such as glucose (by definition), weight, LDL-cholesterol and CRP levels. They would also point out metformin's long track record of safety, its cheap cost and its avoidance of hypoglycaemia, means that, unless contraindicated, it is an excellent agent to start early in T2D management in most patients.

On the other side of the argument, critics would argue that the metformin-CV benefit result observed in UKPDS, whilst hugely influential for decades, does not stand up to modern clinical trial standards, particularly in terms of limited number of events, lack of central adjudication, and limitations of multiple comparisons increasing chance for type 1 error.[11] All of these concerns are supported by meta-analyses of randomized trial evidence for metformin, with most outcomes lacking statistically significant effects and those with nominally significant differences, the absolute treatment benefits are small.[12] They would also argue that whilst metformin is a good glucose lowering drug, its effects on lipids are at best trivial, and that its weight effects are too modest to lead to CV benefits in the short term, and even though CRP declines, this is a non-causal CV risk factor. Some would additionally argue that metformin is not without issues, with its deleterious effect on vitamin B_{12} levels,[13] and potential early risk of anaemia, as we recently showed in analyses using two RCTs and one real-world study.[14] Given these uncertainties, and the fact many patients being considered for SGLT2i or GLP-1RA are often already on several other drugs due to their high cardiovascular risk status, many would suggest it better to immediately start only drugs robustly proven to lessen cardiovascular risks in

patients at high risk, and to avoid additional therapies with lesser evidence. That metformin must be taken more than once per day with meals, and can cause gastrointestinal upset in a minority, also lessens its appeal. By contrast, once weekly GLP-1RA are now common and SGLT2i's are once daily tablets able to be taken first thing in the morning simultaneously with many other cardioprotective therapies.

We previously suggested many in the diabetes field may have a "sentimental loyalty" to metformin.[1,15] Certainly, it remains a good first-line choice for patients with early T2D without any evidence of end-organ damage and at lower CV risk, as its low cost and global availability, weight benefits, low risk for hypoglycaemia, and excellent glycaemic effects, makes it a good choice for many. This is especially the case in many low- or middle-income countries, where access to the newer therapies will be limited by cost. However, the new evidence from the REWIND trial added to other CVOT findings – that GLP-1RA and SGLT2i outcomes benefits are not dependent on patients already being on metformin – adds more reason to challenge the primacy of "metformin first" mentality. We believe such new evidence, together with the other arguments presented above and in Figure 1, tips the balance away from considering metformin as the primary drug to use in all patients with T2D who are drug naïve. In those at or at high risk for ASCVD, it seems reasonable to consider commencing therapy with drugs proven to lessen risk for hard outcomes, adding metformin or other antihyperglycemic therapies thereafter for those requiring more glucose control.[15]

With all new medicines, higher costs are in play and so formal cost-effective analyses would help determine levels of CV risk beyond which such drugs should be recommended. This latter point is far from trivial and was, as we previously discussed,[1] the key difference between ESC and ADA/EASD T2D algorithms, with the former being far more liberal in its recommending expansion of the use of GLP-1RA's and/or SGLT2i's. Indeed, if the ESC guidelines were to be followed as stated, a substantially higher percentage of patients in high-income countries would be commenced on such medications, leading to large hikes in drug expenditure.[16] What is not known, however, is to what extent such extra costs would be offset by better disease outcomes. One imagines, further trials

directly challenging metformin's primacy in a wider group of patients will likely emerge and, if so, more profound changes in T2D pathways may yet emerge.

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