

Does weight loss come at a cost in type 2 diabetes?

In this large, population-based study from Korea, Park and colleagues explored the relationship between body weight variability and major cardiovascular outcomes in 1 522 241 people living with type 2 diabetes but without a history of cardiovascular disease. Over a median follow-up of 7 years, a U-shaped association was observed between weight change and adverse outcomes; that is, both weight loss and weight gain of >5% within a 2-year interval were associated with an increased risk of major cardiovascular events and all-cause mortality. These findings suggest that there remains significant residual cardiovascular risk in those living with type 2 diabetes who lose significant weight. Is it perhaps premature to stop cardioprotective medications, including statins but also SGLT2 inhibitors and GLP-1 receptor agonists, in those people who achieve type 2 diabetes remission?

Obesity is a major risk factor for type 2 diabetes, and it is well established that weight loss has a beneficial impact on metabolic parameters including blood glucose, blood pressure and triglyceride levels. However, it remains unclear what impact these metabolic improvements have on the risk of future major cardiovascular events. We also lack high-quality evidence about the future cardiovascular risk of normal-weight or low-weight individuals living with type 2 diabetes. Moreover, previous evidence actually suggests that “weight cycling” or weight variability is independently associated with increased risks of myocardial infarction, stroke and all-cause mortality in people living with type 2 diabetes (Nam et al, 2020).

Over the last 7 years, seminal cardiovascular outcome studies for type 2 diabetes therapies, specifically the SGLT2 inhibitor and GLP-1 receptor agonist classes of medications, have demonstrated significant improvements in the risk of major adverse cardiovascular events. These classes are now recommended for their cardiovascular benefits independent of their glucose-lowering effects in multiple international guidelines and consensus reports, such as the ADA/EASD consensus report (Buse et al, 2020).

Separately, there is growing international interest and consensus regarding the definition of diabetes remission. Whilst the specifics

of diabetes remission differ between current definitions, all recently published consensus reports, including the joint report from the ADA, EASD and Diabetes UK (Riddle et al, 2021; [reviewed previously in *Diabetes Distilled*](#)), agree that diabetes remission can only be established if it is off all usual glucose-lowering medications. And indeed, from my own clinical experience, a major driver for my patients living with type 2 diabetes who are striving for diabetes remission is the cessation of all diabetes medications.

This presents a quandary to us as healthcare professionals with our patients who do lose significant weight and normalise their HbA_{1c} levels: how do we reconcile the benefits of significant weight reduction (from both physical and mental health perspectives) and the positive diagnosis of diabetes remission versus the organ protection benefits of type 2 diabetes therapies such as SGLT2 inhibitors and GLP-1 receptor agonists?

In the present large, well-conducted, population-based cohort study from Korea, Park and colleagues explored the relationship between body weight variability and major cardiovascular outcomes (including myocardial infarction, ischaemic stroke, atrial fibrillation, heart failure and all-cause mortality) in 1 522 241 people living with type 2 diabetes but without a history of cardiovascular disease. The study



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was undertaken during 2009 and 2012; that is, before SGLT2 inhibitors and GLP-1 receptor agonists were in widespread use. Individuals were categorised into five groups according to body weight change between health checks every 2 years: $\geq 10\%$ loss, 10–5% loss, 5% loss to $\leq 5\%$ gain, 5–10% gain and $\geq 10\%$ gain).

Around one quarter of participants experienced weight loss or weight gain of $>5\%$ at 2 years of follow-up. The weight-gain groups tended to be younger individuals with higher BMIs and lower use of oral hypoglycaemic medications. Unsurprisingly, the weight-loss groups demonstrated better metabolic profile changes, including blood pressure and lipid profiles.

Overall, after a median follow-up of 7 years, a U-shaped association was observed between weight change and major cardiovascular events and all-cause mortality; that is, both weight loss and gain of $>5\%$ within a 2-year interval were associated with an increased risk of major cardiovascular events and all-cause mortality in people with type 2 diabetes.

This U-shaped association was consistent in all exploratory subgroups, including age, gender, baseline BMI, duration of type 2 diabetes and type 2 diabetes medication.

These findings suggest to me that there remains significant residual cardiovascular risk in those living with type 2 diabetes who lose significant weight, and it may be premature to stop their cardioprotective medications: not just SGLT2 inhibitors and GLP-1 receptor agonists, but also statins. However, the authors do discuss the cardioprotective effects and substantial weight loss benefits of SGLT2 inhibitors and



GLP-1 receptor agonists, and they specifically advise against extrapolating these study results to individuals taking these classes of medications.

Managing obesity is about more than just reducing weight; obesity is a complex multisystem condition. We await hard clinical endpoints to guide treatment decisions surrounding cardioprotective medications.

Buse JB, Wexler DJ, Tsapas A et al (2020) 2019 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* **43**: 487–93

Nam GE, Kim W, Han K et al (2020) Body weight variability and the risk of cardiovascular outcomes and mortality in patients with type 2 diabetes: a nationwide cohort study. *Diabetes Care* **43**: 2234–41

Riddle MC, Cefalu WT, Evans PH et al (2021) Consensus report: definition and interpretation of remission in type 2 diabetes. *Diabetologia* **64**: 2359–66