MACE risk higher in newly diagnosed type 2 diabetes treated with lifestyle alone

Compared to people newly diagnosed with type 2 diabetes who were well controlled on glucose-lowering therapy, those who were not on glucose-lowering therapy were found to have a higher 5-year risk of a first major adverse cardiovascular event (MACE), even if they achieved initial diabetes remission using lifestyle changes, according to this Danish real-world cohort study published in *Diabetologia*. Lower use of statins and RAAS inhibitors for primary prevention were identified in those not on glucose-lowering drugs but with persisting type 2 diabetes or in remission, and this was hypothesised to contribute to the higher MACE rates. Equalising statin and RAAS inhibitor prescribing to levels achieved in people with well-controlled type 2 diabetes taking glucose-lowering drugs was predicted to result in absolute reductions in first MACE risk. Those with poorly controlled type 2 diabetes taking glucose-lowering drug therapy had a similar standardised absolute 5-year cardiovascular risk to those with persisting type 2 diabetes not on glucose-lowering therapy, despite receiving similar levels of statins and RAAS blockade as the well-controlled group. These findings remind us that people newly diagnosed with type 2 diabetes may already be at significant risk of MACE, and we need to consider the need for statins and RAAS inhibitors to reduce this risk, even if glycaemia can be controlled without medication.

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Type 2 diabetes is associated with a significantly increased risk of cardiovascular disease (CVD) and mortality. Despite current guidelines recommending metformin (with or without an SGLT2 inhibitor, depending on comorbidities) immediately at diagnosis, many people are reluctant to start medication for type 2 diabetes straight away, preferring to make diet and lifestyle changes, but it is largely unknown how an initial period without glucose-lowering drug therapy influences cardiovascular risk. There is evidence from the DiRECT and RETUNE studies and the renamed NHS Type 2 Diabetes Path to Remission Programme that remission is achievable, but as yet there is no data from these on how remission impacts the risk of CVD. Observational data from one UK study using the CHIA (Care and Health Information Analytics) database suggested that remission was associated with a reduction in cardiovascular outcomes and microvascular complications, independent of whether participants had CVD at baseline (Hounkpatin et al, 2021).

Amongst those who choose not to immediately start glucose-lowering drug therapy, or those who achieve remission, the optimal management of other cardiovascular risk factors and their impact on CVD risk and events remain unknown.

Method

This Danish cohort study, published in *Diabetologia*, sought to clarify how the risk of a first major adverse cardiovascular event (MACE) differs in people who choose not to immediately initiate glucose-lowering therapy and in those who achieve early remission, compared with those who start drug therapy immediately, using various Danish registers, including the Danish Nationwide Register of Laboratory Results for Research.

Previous Danish guidelines, along with the 2012 ADA/EASD guidelines on glycaemic management in place when this study was initiated (Inzucchi et al, 2012), allowed a 6-month period of lifestyle management alone prior to initiation of medication if the HbA_{1c} at diagnosis was <58 mmol/mol and there was no

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CVD, chronic kidney disease or heart failure. Therefore, this study examined how the delay in initiating drug therapies and/or the achievement of remission in those with a diagnostic HbA_{1c} of 48–57 mmol/mol impacted the risk of first-time MACE. It also sought to examine whether this risk was influenced by the use of statins or renin–angiotensin–aldosterone system (RAAS) inhibitor therapy.

A total of 14 221 individuals diagnosed with type 2 diabetes between January 2014 and December 2020 with an HbA_{1c} of 48–57 mmol/mol and no prior history of CVD or treatment with glucose-lowering drugs, statins or RAAS inhibitors were included in the study. At 180 days after diagnosis (the index date), people were divided into four groups depending on their most recent HbA_{1c} and whether they had received any prescriptions for glucose-lowering medication:

1. Well controlled (HbA_{1c} <48 mmol/mol) on drug therapy (22.3% of participants).
2. Poorly controlled (HbA_{1c} ≥48 mmol/mol) on drug therapy (14.7%).
3. Remission (HbA_{1c} <48 mmol/mol) on no medication (38.3%).
4. Persistent type 2 diabetes (HbA_{1c} ≥48 mmol/mol) not on drug therapy (24.7%).

The people were then followed until a first MACE occurred or until the end of the study.

Results

During 52 006 person-years of follow-up, 1351 people had a first MACE (947 deaths from any cause, 161 myocardial infarctions and 243 strokes). Over the 5 years from the index date, those with well-controlled HbA_{1c} on glucose-lowering therapies had the lowest standardised 5-year risk of MACE, at 10.3%, and this was taken as the comparator for the other groups.

The absolute 5-year risk of a first MACE event was 3.3% higher in those with persisting type 2 diabetes and not on any glucose-lowering therapy at 6 months post-diagnosis, 2.0% higher in those who achieved remission and 3.5% higher in those with persisting type 2 diabetes and poor glycaemic control despite being on pharmacotherapy.

In both of the groups not receiving glucose-lowering drugs, fewer people were receiving statins or RAAS inhibitors at 6 months, and these differences persisted at 18 months post-diagnosis. As a result of lower statin prescribing, the proportion of people achieving the LDL-cholesterol target of <1.8 mmol/L at 18 months was 26% in both groups on glucose-lowering medication but only 11–12% amongst those not on glucose-lowering therapy.

Extrapolation of the data and modelling demonstrated that, hypothetically, if those not on glucose-lowering drugs had achieved the same level of statin and RAAS inhibitor treatment as those who were well controlled on glucose-lowering drugs, their estimated absolute risk of MACE would have been 2.1% lower in those with persistent type 2 diabetes and 1.1% lower in those in remission. Increased prescribing of statins alone would have changed the risk in both groups not on glucose-lowering therapy, whereas increased prescribing of RAAS inhibitors alone would have improved risk only in those with persisting type 2 diabetes, not those who achieved remission. Levels of statin and RAAS blocker prescribing to those with persisting type 2 diabetes poorly controlled on glucose-lowering therapy were similar to levels in those who were well controlled.

In sensitivity analyses, defining the four groups at 1 year instead of 6 months post-diagnosis did not change the main findings.

The study had strengths and limitations. It was an observational study, so the findings only demonstrate associations and can only be hypothesis-generating. Confounding cannot be ruled out. The study focused on differences in initial treatment with statins or RAAS inhibitors, but these differences persisted. Initiating drugs early may be a surrogate for a person's more proactive health management, including healthy lifestyle. It is also not clear whether the lower numbers taking these two classes of drugs were caused by decisions not to prescribe or simply due to people not redeeming their prescriptions.

Comment

This study identified a lower rate of statin and RAAS inhibitor treatment in those using only

lifestyle to control glycaemia early after type 2 diabetes diagnosis, compared with those who were on glucose-lowering drug therapy. The authors propose that this contributed to the higher 5-year risk of a first MACE seen in the former group, even if remission was achieved.

This is a salutary reminder that people newly diagnosed with type 2 diabetes may already be at significant MACE risk, and that we must not be lulled into a false sense of security that lifestyle changes effective for glucose-lowering are all that are required to optimise cardiovascular risk, even if they successfully lead to early remission. Even if people choose to have a trial of lifestyle change alone after diagnosis, we need to consider the need for statins and RAAS inhibitors to reduce MACE risk.

Although the early glucose-lowering treatment in this study was mainly metformin, many people at diagnosis today will have a QRISK of >10%, so early treatment with both metformin and an SGLT2 inhibitor should be considered to further reduce the elevated MACE risk.

Lifestyle combined with medication offers significant benefit over lifestyle alone, and for most people this must now be our recommendation. Selling the benefits of drug therapy whilst supporting long-term lifestyle change should be our goal and is likely to lead to fewer cardiovascular events. ■

Hounkpatin H, Stuart B, Farmer A, Dambha-Miller H (2021) Association of type 2 diabetes remission and risk of cardiovascular disease in pre-defined subgroups. *Endocrinol Diabetes Metab* **4**: e00280

Inzucchi SE, Bergenstal RM, Buse JB et al (2012). Management of hyperglycemia in type 2 diabetes: A patient-centered approach: Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **35**: 1364–79

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