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Both natural variation in ACE concentrations and lowering BP with ACE inhibitors associated with lower risk of T2D

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New research presented at this year's Annual Meeting of the European Association for the Study of Diabetes (EASD) in Barcelona, Spain (16-20 September) shows that usage of angiotensin-converting enzyme (ACE) inhibitors to lower blood pressure, is associated with a 24% reduced risk of developing type 2 diabetes (T2D) when compared with placebo.

Furthermore, natural genetic variations related to ACE concentrations in the body are also related to T2D risk. The study is by Assistant Professor Marie Pigeyre of the Genetic and Molecular Epidemiology Laboratory, Hamilton Health Sciences and McMaster University, Hamilton, ON, Canada and colleagues.

Although previous research has suggested that ACE inhibitors may prevent T2D, the causal relationship between ACE inhibition and prevention from T2D remains questionable. In this new study, the authors used a 'Mendelian Randomisation' approach. Specifically, they assessed a person's risk of developing T2D based on natural genetic variations that influence the concentration of the ACE enzyme in the blood, and used this to infer the causal effects that ACE inhibitors would have on T2D risk.

First, the authors assessed the association between T2D prevalence and ACE serum concentration in the Outcome Reduction with Initial

Glargine Intervention (ORIGIN) trial (N=8,197). Next, they investigated whether 17 genetic variants linked to lower ACE concentrations in the ORIGIN study (N=4,147) were also linked to lower prevalence of T2D in the DIAbetes Genetics Replication And Meta-analysis consortium (n=26,676 cases; 132,532 controls).

The researchers then constructed an ACE concentration-lowering genetic risk score (GRS) and tested it for association with T2D prevalence in the UK Biobank cohort (N=341,872). Finally, they compared the genetically determined effect of lower ACE concentrations on T2D risk to the pharmacological inhibition of ACE versus placebo, with a meta-analysis of randomised clinical trials (including 31,200 patients).

The MR analysis showed that a lower genetically determined ACE serum concentration predicted a lower risk of type 2 diabetes, and a meta-analysis of six RCTs estimated that ACE inhibitors reduced type 2 diabetes risk by 24% compared with placebo.

The authors say: "These results support the protective effect of long-term ACE inhibition on type 2 diabetes risk. Although future research is needed to more accurately clarify the metabolic actions of ACE inhibitors, current evidence supports that targeting ACE may protect a person from developing type 2 diabetes. Furthermore, considering a patient's risk of developing type 2 diabetes may be recommended when prescribing blood-pressure lowering drugs—if at high risk of type 2 diabetes, an ACE inhibitor could be considered."

They add: "Current guidelines do not take account of the protective effect of ACE inhibitors on T2D risk and this is something that could be considered."

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