Angiotensin-converting enzyme and type 2 diabetes risk: a Mendelian randomisation study

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Background and aims: Three large randomized control trials (HOPE, PEACE, SOLVD) have suggested that angiotensin-converting enzyme (ACE) inhibitors may prevent type 2 diabetes compared to placebo in people at high risk for cardiovascular outcomes. In the DREAM trial, which was the only dedicated trial studying the effect of ACE inhibitor allocation versus placebo on new-onset diabetes, ramipril did not reduce the incidence of diabetes in participants having prior impaired fasting glucose or impaired glucose tolerance. Thus, the causal relationship between ACE inhibition and prevention from type 2 diabetes remains questionable. We hypothesized that ACE concentration-lowering genetic variants could be used to infer the pharmacological effect of ACE inhibitors on type 2 diabetes risk using a Mendelian Randomization (MR) approach.

Materials and methods: We first assessed the association between type 2 diabetes prevalence and ACE serum concentration in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial (N=8,197). We next investigated whether genetically lowered ACE concentration was causally linked to the risk of type 2 diabetes using a two-sample MR analysis. This analysis included 17 independent genetic variants associated with ACE concentration in ORIGIN (N=4,147) and their effects on type 2 diabetes risk estimated in the DIAbetes Genetics Replication And Meta-analysis consortium (n=26,676 cases; 132,532 controls). We then designed an ACE concentration-lowering genetic risk score (GRS) and tested it for association with type 2 diabetes prevalence in the UK Biobank cohort (N=341,872). Finally, we compared the genetically determined effect of lower ACE concentration on type 2 diabetes risk to the pharmacological inhibition of ACE versus placebo, which was evaluated through a meta-analysis of randomized clinical trials (RCT) (N=31,200).

Results: Lower ACE serum concentration was associated with reduced type 2 diabetes prevalence (OR, 0.89; 95%CI, 0.82-0.96; P=3.50x10-3) in the ORIGIN trial. The MR analysis showed that a 1 SD lower genetically determined ACE serum concentration predicted a lower risk of type 2 diabetes (OR, 0.92; 95%CI, 0.89-0.95; P=1.79x10^-7). This result was replicated in the UK Biobank (OR, 0.97; 95%CI, 0.96-0.99; P=8.73x10^-6). Our meta-analysis including six RCTs estimated that ACE inhibitors reduced type 2 diabetes risk by 24% compared to placebo (OR, 0.76; 95%CI, 0.60-0.97; P=2.59x10^-5), while reducing the mean arterial pressure (MAP) of 2.4 mmHg on average. When standardizing the OR estimated from MR for an equivalent 2.4 mmHg lower MAP, we obtained a consistent estimate of the genetically determined effect of ACE inhibition on type 2 diabetes risk (ORstandardized, 0.75; 95%CI, 0.64-0.89) compared to that one derived from RCT meta-analysis (P for comparison=0.95).

Conclusion: These results support the potential protective effect of long-term ACE inhibition on type 2 diabetes risk. Although future research is needed to better delineate the metabolic actions of ACE inhibitors, current evidence supports that targeting ACE may protect from
type 2 diabetes, as well as considering a patient’s risk of developing type 2 diabetes may be recommended when prescribing blood-pressure lowering drugs.

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