# Plasma angiotensin-converting enzyme 2 (ACE2) is a marker for renal outcome of diabetic kidney disease (DKD) (U-CARE Study 3)

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#### 1 Abstract

Objective: Angiotensin-converting enzyme (ACE) cleaves angiotensin I (Ang I) to Ang II
inducing vasoconstriction via Ang II type 1 (AT1) receptor, while ACE2 cleaves Ang II to Ang
(1-7) causing vasodilatation by acting on the Mas receptor. In diabetic kidney disease (DKD),
it is still unclear whether plasma or urine ACE2 levels predict renal outcomes or not.

6 **Research Design and Methods:** Among 777 participants with diabetes enrolled into U-7 CARE study, the 296 patients followed up for 9 years were investigated. Plasma and urinary 8 ACE2 levels were measured by the ELISA. The primary endpoint was a composite of a 9 decrease of eGFR by at least 30% from baseline or initiation of hemodialysis or peritoneal 10 dialysis. The secondary end points were a 30% increase or a 30% decrease in UACR from 11 baseline to one year.

12**Results:** The cumulative incidence of the renal composite outcome was significantly higher13in group 1 with lowest tertile of plasma ACE2 (P = 0.040). Group 2 with middle and highest14tertile was associated with better renal outcomes in the crude Cox regression model adjusted15by age and sex (HR: 0.56, 95% CI: 0.31-0.99, P = 0.047). Plasma ACE2 levels demonstrated16a significant association with 30% decrease in ACR (OR: 1.46, 95% CI: 1.044 - 2.035,17P = 0.027) after adjusting for age, sex, SBP, HbA1c and eGFR.18Conclusions: Higher baseline plasma ACE2 levels in DKD were protective for development

and progression of albuminuria and associated with fewer renal endpoints, suggesting
 plasma ACE2 may be used as a prognosis marker of DKD.

### 21 What is already known on this topic

Urinary albumin creatinine ratio (UACR) is known biomarkers to predict the prognosis of
 diabetic kidney disease (DKD).

## 24 What this study adds

Plasma ACE2 may be used as a prognosis marker of DKD and higher baseline plasma ACE2
 levels in DKD are protective for development and progression of UACR and renal function

27 decline.

# 28 How this study might affect research, practice or policy

- 29 In renin-angiotensin system (RAS), ACE2 cleaves Ang II into the heptapeptide angiotensin
- 30 1–7 [Ang (1-7)] and this study sheds light on the importance of ACE2 in pathobiology of DKD.