SIGNIFICANCE STATEMENT

Inhibition of the renin-angiotensin-aldosterone system by angiotensin-converting enzyme (ACE) inhibitors is one of the best established strategies to reduce the decline of kidney function in CKD. This study, which uses a novel Mendelian randomization–based approach, identifies human EGF receptor 2 (HER2) and uromodulin (UMOD) as potential causal mediators of CKD, and ACE as a potential regulator of HER2 levels. These findings implicate HER2 as a mediator of ACE inhibitors' protective effect on CKD and as a marker which may help reveal patients likely to benefit from ACE inhibition. Both UMOD and HER2 inhibition represent potential novel targets for interventions to slow progression of CKD.