Interactions between the heart and kidney are important for the maintenance of blood volume, vascular tone, and hemodynamic stability. As is well-known, cardiovascular diseases (CVD) are a major cause of death in patients with chronic kidney disease (CKD). Indeed, the frequency of cardiovascular death, mainly derived from coronary artery disease, is approximately 10-20 times higher in dialysis patients. Furthermore, the estimated glomerular filtration rate (eGFR) correlates inversely with the development of cardiovascular diseases and mortality in patients with mild-to-moderate chronic CKD. However, the pathophysiological interactions between these organ systems have not been fully elucidated.

Growing evidence suggests that uremic retention compounds, i.e. uremic toxins, play a critical role in the development and progression of CVD. These compounds are classified into 3 groups: small water-soluble molecules, middle molecules, and protein-bound molecules. Indoxyl sulfate (IS), a protein-bound molecule, is at least 90% bound to plasma proteins, predominantly to albumin. IS is derived from tryptophan, a dietary protein. Colonic microbes metabolize the amino acid tryptophan to indole, which is then oxidized and conjugated with sulfate in the liver. The resulting IS is excreted in the urine via the kidney; therefore, serum levels of IS increase with kidney dysfunction. Several clinical studies have shown an association between serum levels of IS and CVD, such as in cases with heart failure, peripheral arterial disease, prolonged QT interval, and coronary artery disease. In addition, IS levels are also associated with coronary artery calcification and restenosis after percutaneous coronary intervention.

In this issue of the International Heart Journal, Watanabe, et al. demonstrated that higher levels of IS combined with lower levels of albumin were a good predictor of mortality in 351 patients who underwent percutaneous revascularization for coronary artery or peripheral artery diseases. Although the level of IS alone has been shown to be a useful predictor of cardiovascular mortality in CKD patients, this study demonstrated the clinical significance of free IS, unbound to plasma proteins, in combination with albumin.

Albumin is the most abundant serum protein and has a role in ligand transport. Therefore, as serum levels of albumin decrease, free IS levels conversely increase, as hypothesized by the authors. Hence, the reverse relationship of free IS and albumin levels should be evaluated in the process of predicting the prognosis of CVD patients. Albumin is considered to have several other important physiological functions in the progression of CVD. Serum albumin has been shown to have antioxidant activity, and inhibitory effects on human endothelial apoptosis and platelet activation and aggregation. Hypoalbuminemia is also an index of malnutrition, which has been reported to be closely linked with inflammation. These factors form a vicious cycle, leading to the development of vascular calcification and a subsequent increase in cardiovascular mortality. In fact, the association between malnutrition, inflammation, and atherosclerosis has negative effects in patients with end-stage renal disease, leading to the malnutrition, inflammation, and atherosclerosis (MIA) syndrome. Wada, et al. demonstrated that even in non-CKD patients, a decreased serum albumin concentration independently predicted a worse long-term prognosis in patients after percutaneous coronary intervention. Thus, albumin by itself has prognostic value in patients with or without CKD. These harmful effects of low levels of albumin may have had an additional impact on mortality in the CVD patients in the present study. This suggests that IS and albumin are important factors involved in the interaction between the gut, kidney, and cardiovascular system on the progression of CVD (Figure).

The present study may have some limitations in terms of its clinical application, namely, the timing of blood sampling, especially in patients on dialysis, whether the cut-off value of albumin (3.9 g/dL) is appropriate, and whether the results of this study can be applied to all CVD patients in both the acute and chronic phases. Furthermore, the management strategy to be adopted in pa-
Figure. Roles of indoxyl sulfate and albumin in the gut-kidney-cardiovascular interaction. Dietary proteins are digested in the gut and their digestive end-products are used in the synthesis of indoxyl sulfate (IS) and albumin in the liver. Higher levels of free IS and lower levels of albumin are frequently found in the sera of patients with severe chronic kidney disease. These may contribute to the progression of cardiovascular diseases (CVD), resulting in a poor prognosis. On the other hand, IS causes gut dysbiosis and renal dysfunction, and CVD induces IS production. Therefore, the uremic toxin IS may play an important role in the interaction between the gut, kidney, and cardiovascular system.

Diabetic patients with higher IS and lower albumin levels is also an important issue. Three main interventions are used to decrease uremic toxins: dietary protein restriction, maintenance of gut symbiosis, and oral sorbents. Since restriction of protein intake might cause hypoalbuminemia, the latter two interventions could be useful in these patients. We hope that further prospective studies involving a larger cohort will help to establish the clinical significance of the combined biomarkers in predicting the prognosis of CVD patients, and to determine appropriate interventions in patients identified by these markers as having a poor prognosis.

Disclosures
Conflicts of interest: None.

References