Extracting Meaning of Tubular Injury Molecules: Implications for Cardiorenal Health

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Chronic kidney disease (CKD) is a major cardiovascular (CV) health determinant. Both CV and all-cause mortality increase linearly when the estimated glomerular filtration rate (eGFR) is below 60 mL/min/1.73 m² [1]. Beyond eGFR, tubular damage (ascertained tubular atrophy and fibrosis on kidney biopsy) is a strong predictor of CKD progression and CV events [2]. Tubular damage is obviously not well captured by creatinine or albuminuria (which essentially estimate glomerular function and glomerular damage, respectively) [3]. Several urinary proteins have been proposed as biomarkers of tubular injury, including interleukin-18 (IL-18), kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, monocyte chemoattractant protein-1, and chitinase-3-like protein-1 (YKL-40), studied herein, all of which have been associated with both tubular injury/inflammation and CV events [3, 4]. In this context, Jotwani et al. [5] examined the associations of these urinary biomarkers with CV events and mortality among participants of the Systolic Blood Pressure Intervention Trial (SPRINT) who had CKD at baseline.

The SPRINT trial significantly contributed to enhanced knowledge regarding blood pressure targets for the CKD population, having enrolled the largest proportion of patients with CKD (28%) of any blood pressure target trial [6]. Two outcomes were studied: (1) a composite of first nonfatal myocardial infarction/acute coronary syndrome, stroke, heart failure hospitalization, or CV death (SPRINT's primary outcome) and (2) all-cause death. In SPRINT, patients assigned to intensive antihypertensive therapy had lower event rates compared to patients with standard therapy. The treatment effect was consistent across subgroups (including CKD) as well as across patient risk profiles [6]. Furthermore, there was no evidence of a differential treatment effect on CV outcomes between patients with and those without CKD, and there was no difference in the composite of the $\geq 50\%$ decrease in baseline eGFR or end-stage kidney disease between the intensive and standard treatment groups.

Nevertheless, the number of renal events by this definition was very small; thus, this endpoint was mark-

edly underpowered. In parallel, intensive blood pressure lowering was associated with an increase in serious events of acute kidney injury and acute renal failure over 86% of which resolved with continued treatment [7]. In this Journal issue, Jotwani et al. [5] report on a SPRINT trial biomarker of tubular injury, inflammation, and repair in a substudy of 2,377 hypertensive participants with CKD at baseline. They concluded that higher urinary IL-18 and YKL-40 were associated with higher mortality risk, independent of eGFR and albuminuria, regardless of treatment arm assignment (interaction $p > 0.1$).

Of the studied urinary biomarkers, none were independently associated with the primary outcome. The association of these biomarkers with CV death alone was not reported, nor were the associations with kidney events. These features are of particular relevance since if these biomarkers are associated with all-cause death but not CV events, they raise the following key questions: do they solely represent tubular injury or do they potentially underlie other mechanisms associated with non-CV diseases (e.g., cancer or inflammatory diseases, which were not considered as specific exclusion criteria in the SPRINT trial, since the latter only excluded “a medical condition likely to limit survival to less than 3 years”)? Moreover, do these biomarkers “predict” CKD progression, and if so, could they help identify relevant biological pathways and potential therapeutic targets? While these questions may be left unanswered, some “hints” may nevertheless be suggested by the reported data.

Increased risk for all-cause death (but not CV events), patients with higher YKL-40 and IL-18 levels were more often women, non-Hispanic black, obese with higher LDL cholesterol, urine creatinine and albuminuria, with a lower prevalence of CVD or heart failure. The correlation between YKL-40 and IL-18 was quite good ($= 0.48$, $p < 0.05$). These findings suggest that these biomarkers may assist in identifying a “high-risk subgroup” with potential sex-race and metabolic specificities, which may be at higher risk for non-CV events and thus worth exploring.

It would be of interest to assess whether intensive antihypertensive treatment could lower (or increase) these “tubular” biomarkers, which were only studied at baseline in the current study. One would expect that some of these acute kidney injury biomarkers are likely to increase with intensive treatment, given that these CKD patients had more worsening of renal function. Nevertheless, the treatment effect (on the primary outcome and death) fa-

Fig. 1. Insights and questions stemming from the SPRINT trial. YKL-40, chitinase-3-like protein-1; IL-18, interleukin-18; CV, cardiovascular.

vored intensive therapy even in the presence of a worsening renal function episode [6]. This may contribute to the absence of a significant association observed between these biomarkers measured at baseline and the study’s primary outcome Figure 1.

Taking advantage of the landmark SPRINT trial, this well-designed and provocative biomarker ancillary study certainly opens the door for future investigations. More broadly, the true meaning of these biomarkers remains largely unknown, and whether they “only” represent “acute tubular injury” and/or biomarkers of other disease mechanisms including, but not exclusively CV disease is worth exploring. As rightly acknowledged by the authors, “further studies are needed to understand whether the associations with mortality represent a causal link or shared pathogenesis”.

Disclosure Statement

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