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## The Crossroad of RAAS Modulation, Inflammation, and Oxidative Stress in Dialysis Patients: Light at the End of the Tunnel?

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After four decades of fully reimbursed chronic dialysis therapy in the United States under the justification of lifesaving treatment, the survival rate of dialysis patients remains worse than many fatal cancers.<sup>1</sup> Most recorded causes of mortality on death certificates are cardiovascular or infectious; however, the true etiology of poor survival is unknown. Some slight improvement in the survival of dialysis patients reported over the past few years may be attributed to increased life expectancy in the background healthy population, although in the interest of fairness, the increased use of cardio-protective and other pharmacologic agents should also be noted as potential contributors.<sup>1</sup> Nevertheless, we have not succeeded in saving lives more significantly than before.

In line with ongoing attempts to uncover the underlying etiology of death in dialysis patients, sporadic attention has been paid to the evil axis of malnutrition, inflammation, and oxidative stress. There are compelling reasons why we cannot afford to ignore this axis: up to two-thirds of long-term dialysis

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patients show evidence of suboptimal protein and energy intake, muscle and fat wasting, and chronic or recurrent inflammation, along with a state of heightened oxidative stress.<sup>2</sup> In fact, high levels of inflammatory markers such as C-reactive protein (CRP) or IL-6 and low levels of nutritional markers such as serum albumin and creatinine are by far the stronger predictors of cardiovascular and infectious events and death and poor quality of life than any traditional risk factor.<sup>3,4</sup> Evidence suggests the strong mortality predictability of serum albumin in dialysis patients may be by virtue of the association between hypoalbuminemic conditions and proinflammatory processes.<sup>2</sup> Additionally, inflammation, which may be a primary culprit or a mediator of other conditions such as protein-energy wasting or oxidative stress, can contribute to relative thrombocytosis and platelet activation, endothelial dysfunction, and adhesion molecule activation, leading to increased risk of thromboembolic and cardiovascular events and death.<sup>5</sup>

Interestingly, the role of inflammation becomes even more evident when one considers how its deleterious impact on vascular pathology can be modulated by genetic constellations or race.<sup>6</sup> The malnutrition–inflammation complex may be the secret behind the greater survival of the African-American dialysis patients, which is in sharp contradistinction to the racial survival disparity in the otherwise healthy population without kidney disease.<sup>7</sup> The lower prevalence of inflammation among dialysis patients in South East Asian countries, whether caused by genes or diet or both, may explain their greater longevity compared with the dialysis patients in North America and Europe.<sup>8</sup> Inflammation may confound bone and mineral disorders and lead to low parathyroid hormone levels in dialysis patients.<sup>9</sup> Inflammation is associated with poor outcome in acute kidney injury<sup>10</sup> and can result in faster progression of CKD and higher death rates in predialysis patients.<sup>11</sup> All in all, the enlarging footprints of inflammation are evident wherever we see major survival differentials within kidney disease populations.

If inflammation is indeed the genesis of all unfavorable outcomes in kidney disease, hypothetically any intervention—be it dietary, pharmacologic, or otherwise—that modulates an inflammatory process leading to a decline in expression of proinflammatory cytokines and/or their circulating level could potentially have a clinically detectable impact on patient outcomes, including better survival. If effective, such an intervention may save thousands of lives.<sup>2</sup> Relevant to this hypothesis are emerging data that corroborate the proinflammatory features of angiotensin II pathway activation; hence, blockade of the renin–angiotensin aldosterone system (RAAS), outside of its BP effects, can be explored as a potential therapy to modulate inflammatory conditions including kidney disease. If this hypothesis is true, RAAS blockade, at least by virtue of its anti-inflammatory properties, might improve survival in these patients.

Consistent with this notion, in nondialysis patient populations, blockade of the RAAS has been shown to reduce cardiovascular morbidity and mortality and to slow the progression of

renal dysfunction.<sup>11</sup> Several previous studies exploring RAAS blockade in maintenance dialysis patients have yielded mixed results. A randomized placebo-controlled trial failed to show a decreased rate of cardiovascular events in chronic hemodialysis patients with the addition of the angiotensin-converting enzyme inhibitor (ACEi), fosinopril, over a 24-month trial period.<sup>12</sup> Conversely, a 3-year randomized double-blind placebo-controlled trial showed that the addition of the angiotensin-receptor blocker (ARB), telmisartan, to conventional therapy reduced all-cause and cardiovascular death in maintenance hemodialysis patients with underlying chronic heart failure.<sup>13</sup> Finally a recent larger retrospective study revealed that cardiovascular death was counterintuitively highest in hemodialysis patients who received a combination ACEi and ARB therapy.<sup>14</sup>

In this issue of *JASN*, a study by Gamboa *et al.*<sup>15</sup> explores the anti-inflammatory effects of both ramipril, an ACEi, and valsartan, an ARB, on a relatively small cohort of hemodialysis patients. In a well-designed, randomized, double-blind, placebo controlled 3×3 crossover study, 15 hemodialysis patients were treated with placebo, ramipril, or valsartan. After 7 days of treatments, the patients underwent serial blood draws during their hemodialysis treatment to examine biomarkers of oxidative stress and inflammation, along with markers of coagulation, fibrinolysis, and endothelial injury. The investigators report that, although both ACEi and ARB treatment resulted in a decrease in two proinflammatory cytokines (IL-6 and IL-8), ACEi treatment showed some proinflammatory effects, with an increase in IL-1 $\beta$  and a decrease in the anti-inflammatory cytokine IL-10. Additionally, whereas both lowered a marker of thrombosis, D-dimers, only ramipril prevented an increase in plasma von Willebrand factor, a marker of endothelial injury.

The difference between ACEi and ARB treatment is one of the more provocative and interesting findings of the study. In theory, the use of an ACEi would prevent the breakdown of bradykinin, known to increase during hemodialysis, whereas ARBs would have no effect. Although in the present study bradykinin levels are higher in the ramipril group, levels are only reported during the first hour of hemodialysis and appear to decrease or remain unchanged from baseline in all groups at the 1-hour time point. Complicating the matter further, bradykinin is noted to be both proinflammatory and protective of the endothelium.<sup>16,17</sup>

Thus, the authors' suggestion that increased inflammatory markers seen in the ramipril group can be ascribed to increased bradykinin levels may be an oversimplification. Regardless, it does suggest that the different mechanisms of actions will prevent extrapolating the results of ACEi treatment to those of ARBs and *vice versa*. Future trials will have to consider each agent separately and potentially explore whether these differences could be exploited to target subpopulations of hemodialysis patients with specific inflammatory and endothelial/coagulation profiles.

Despite the study's clean design, there were a few limitations. The cohort of patients was relatively small and as such cannot adequately address any potential demographic differences,

especially given that the impact of key inflammatory biomarkers on mortality appear to differ based on race (*vide infra*).<sup>18</sup> Additionally, the short-term treatment (7 days) handicaps the applicability of the results. Most, if not all, studies attempting to address cardiovascular outcomes of ACEi/ARB therapy focus on the long-term effects of these drugs. As therapy time is extended, it may be progressively more difficult to tease out whether potential outcome differences are due to changes in inflammatory or endothelial/coagulation status versus better control of BP.

Finally, and most significantly, there still remains a large void between the measurement of biomarkers of oxidative stress, inflammation, coagulation, fibrinolysis, and endothelial injury and hard cardiovascular outcomes in the chronic dialysis population. As mentioned above, elevated levels of inflammatory markers, including IL-1, IL-6, and TNF $\alpha$ , have been associated with increased mortality in this population. However, given that inflammation is a rapidly evolving field, with new markers being introduced at a high rate, the general nephrologist is often left wondering which one is truly relevant to the care of their patients. Additionally, these markers often do not take into account the permissive effect of genotype on the lethality of inflammation.<sup>6</sup> For example, two recent studies<sup>3,18</sup> suggested that, in African Americans, the mortality predictability of IL-6 is significantly less than Caucasians, implying that the impact of key inflammatory biomarkers on mortality is mitigated in African Americans. Clearly, additional studies including randomized controlled trials and/or long-term pharmacologic interventions are needed to solidify the link between markers and outcome.

Notwithstanding these limitations, the results of the study contribute substantially to advancing the field. Importantly, they point toward a future where anti-inflammatory treatments are more aggressively pursued, because decades of treating such conventional risk factors as hypercholesterolemia and hypertension have not improved survival in dialysis patients. Even the old soldiers of RAAS blockade, who have long been allies on the cardiovascular battlefield, may still have an important role in the ongoing war against inflammation.

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## DISCLOSURES

None.

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See related article, "Comparative Effects of Angiotensin-Converting Enzyme Inhibition and Angiotensin-Receptor Blockade on Inflammation during Hemodialysis," on pages 334–342.