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EDITORIAL COMMENT

Exploiting the Natriuretic Peptide Pathway to Preserve Glomerular Filtration in Heart Failure*

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The intertwining of the heart and the kidneys in regulating salt and water homeostasis is importantly altered in heart failure (1). Clearly, therapies that allow the kidney to sustain its glomerular and tubular function will help to prevent congestion in heart failure. This is of prognostic importance because the presence of congestion determines disease progression, morbidity, and mortality in heart failure. In this issue of *JACC: Heart Failure*, Damman et al. (2) report on an interesting subanalysis of the PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] With ACEI [Angiotensin-Converting-Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial). The use of sacubitril/valsartan, compared with enalapril, resulted in a less steep decline of glomerular filtration rate (GFR) over time. Although the protective effect on GFR was already apparent after 4 months of therapy, sacubitril/valsartan did result in an acute and persistent rise in the urinary albumin/creatinine ratio (UACR) over time. Both a decrease in GFR and an increase in UACR are independent predictors of adverse outcome in heart failure and cardiology in general. Luckily, the large PARADIGM-HF study, with adequate follow-up time, allows us to assess the impact of these 2 divergent prognostic mechanisms (slower GFR decline vs. increased UACR) on renal and cardiovascular endpoints.

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The authors demonstrated that sacubitril/valsartan therapy results in an overall lower risk for the post hoc assembled composite renal endpoint of reaching end-stage renal disease or ≥50% reduction in estimated GFR (eGFR) from baseline. This treatment effect was present in patients with or without baseline chronic kidney disease (eGFR <60 ml/min/1.73 m^2). As expected, patients with more pronounced albuminuria at baseline were at higher risk for developing the post hoc assembled renal endpoint. Interestingly, however, worsening of albuminuria (increase in UACR) was only associated with a higher risk for developing the post hoc assembled renal endpoint in patients undergoing enalapril therapy, not in patients undergoing sacubitril/valsartan therapy, which indicates that the rise in UACR induced by sacubitril/valsartan is mediated by a mechanism that does not result in a progressive loss of glomerular function. Often, increasing albuminuria is associated with the occurrence of glomerular hypertension, which simultaneously results in progressive loss of glomerular function. Clearly, this is not the case when it comes to sacubitril/valsartan therapy. The notion that this therapy-induced increase in UACR is not associated with an adverse effect is also illustrated by the analysis of cardiovascular outcome. Taking the rise of UACR into account, sacubitril/valsartan therapy remained associated with a lower risk for heart failure hospitalization or cardiovascular mortality than with enalapril. Interestingly, following the initiation of

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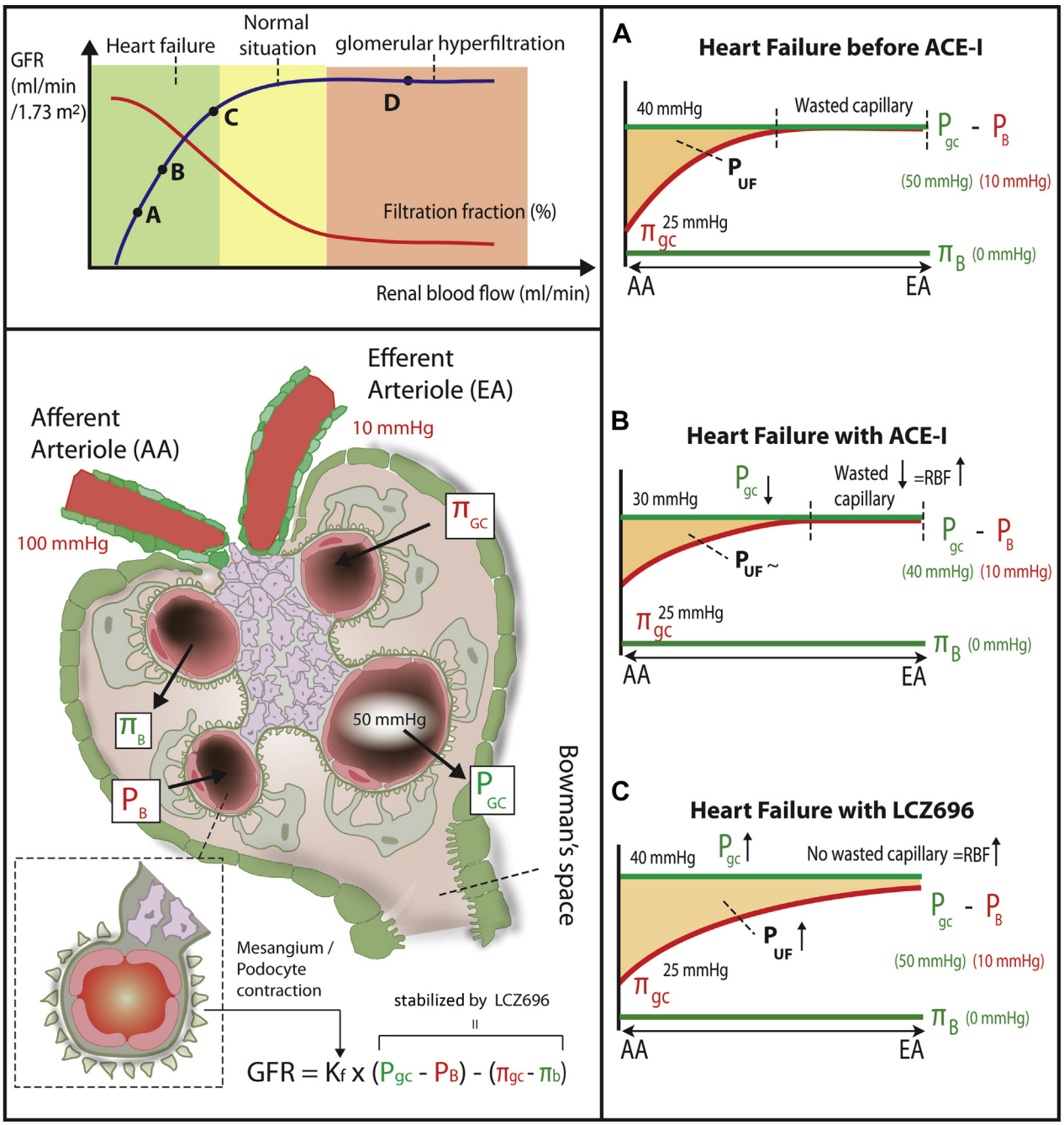
sacubitril/valsartan in the PARAMOUNT (Prospective Comparison of ARNI With ACEI on Management of Heart Failure With Preserved Ejection Fraction Trial), a similar increase in UACR and slower deterioration of eGFR was noted in patients with heart failure with preserved ejection fraction (3). The current analysis adds reassurance to this previous finding, compared with the smaller PARAMOUNT study, because this analysis enables the study of the implications on clinical outcome.

Given the similar finding for sacubitril/valsartan in slowing eGFR deterioration but slightly increasing UACR in both the PARAMOUNT and PARADIGM-HF studies, it begs the question of what effect sacubitril/valsartan has on glomerular function. This is important because protection of glomerular function should be considered an important target in heart failure. To appreciate the potential effects of sacubitril/valsartan therapy on glomerular function, it is important to first recapitulate the effect of a failing heart on glomerular function. More than 7 decades ago, it was shown by direct measurement of GFR by inulin clearance and renal blood flow (RBF) by para-aminohippurate that RBF is reduced to one-fifth of normal in edematous patients with heart failure (4). Despite this profound drop in RBF, GFR is only slightly reduced in untreated patients with heart failure because of angiotensin II-mediated vasoconstriction of the efferent arteriole with a coinciding increase in glomerular hydrostatic pressure (**Figure 1**). This decrease in RBF leads to an increased filtration fraction (GFR/RBF), which is a process that is virtually independent of neurohormonal interference (**Figure 1A**). Importantly, the filtration fraction determines the composition of renal blood reaching the renal tubules (1). The increased filtration fraction in heart failure results in increased proximal nephron sodium avidity, thereby decreasing the amount of sodium presented to the macula densa. This results in renin release, with further activation of the renin-angiotensin-aldosterone system, which contributes to the heart failure syndrome. The use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) results in a predominant vasodilation of the efferent arteriole of the glomerulus (**Figure 1B**). Although vasodilation of the efferent arteriole causes an increase in RBF (and a slight decrease in filtration fraction), the net effect on GFR is determined by the drop in intraglomerular hydrostatic pressures (P_{gc} drop in **Figure 1B**). Therefore, after initiation of an ACE inhibitor or ARB, GFR will drop. However, in patients with glomerular hypertension (e.g., patients with diabetes mellitus), a chronic reduction in intraglomerular hydrostatic pressures often translates to a slower decline of GFR over time (point D on graph in **Figure 1**). In contrast, the effect of sacubitril/valsartan on glomerular hemodynamics can best be explained by the additive effect of increased natriuretic peptides caused by neprilysin inhibition (**Figure 1C**).

The seminal work of Brenner et al. (5) showed that after infusion of natriuretic peptides, a relative vasodilation of the afferent arteriole occurs. This results in an increase in RBF but also a slight increase in intraglomerular hydrostatic pressure, which offsets the ARB-mediated drop in intraglomerular hydrostatic pressures, thereby probably explaining the preserved GFR in PARADIGM-HF. However, at this point in the pathophysiology, the less steep slope of GFR decline observed by Damman et al. (2) is of significant importance. Indeed, in case of a high glomerular filtration pressure, vasodilation of the afferent arteriole would further increase intraglomerular hydrostatic pressures. It has been demonstrated that the higher intraglomerular hydrostatic pressures in people with diabetes mellitus often result in heightened stress on renal podocytes, thereby contributing to the occurrence of albuminuria. However, in contrast to such patients, heart failure is not characterized by hyperfiltration because the renin-angiotensin-aldosterone system-induced vasoconstriction often contributes to reduced RBF. In addition, the immediate increase of UACR observed in PARADIGM-HF after initiation of sacubitril/valsartan, with normalization of UACR to pre-screening values following discontinuation after the run-in phase, suggests that irreversible podocyte damage is not the mechanism of increased UACR. Previous studies have shown that natriuretic peptides can alter hydraulic conductivity by influencing the contractile state of mesangial cells (or potentially podocytes) (**Figure 1B**). It is therefore possible that alterations in the contractile state of mesangial cells, more than hyperfiltration, are responsible for the observed UACR. Despite the reassurance provided by the analysis of Damman et al. (2), which suggests no long-term detrimental effects of sacubitril/valsartan therapy on glomerular function, further studies directly measuring renal hemodynamics (RBF and GFR) and glomerular filter permselectivity/permeability would be valuable. Finally, we should also entertain the possibility that some of the beneficial findings relating to renal function are a reflection of improvement in heart failure status. We and others have found that sacubitril/valsartan induces beneficial left ventricular reverse remodeling (reduction in left ventricular volumes and improvement in ejection fraction) and reduces cardiac filling pressures.

FIGURE 1 Effect of Heart Failure, ACE Inhibition, and LCZ696 on Glomerular Hemodynamics



The single-nephron glomerular filtration rate (GFR) depends on the area and permeability characteristics of the glomerular membrane and Starling forces in the glomerular capillary membrane and Bowman's space favoring **(green)** and opposing **(red)** filtration. Heart failure reduces renal blood flow (RBF) **(A)**, which results in a lower plasma volume being exposed to the ultrafiltration gradient per unit of time, thereby resulting in a quicker rise of π_{gc} (wasted capillary), albeit with a higher filtration fraction. **(B)** Use of an angiotensin-converting enzyme inhibitor (ACE-I) results in a higher RBF with this smaller wasted capillary, but as it reduces P_{gc} (from 40 to 30 mm Hg in this example), it reduces GFR. **(C)** Sacubitril/valsartan (LCZ696), however, improves RBF more by vasodilation of the afferent arteriole (AA), thereby maintaining P_{gc}, which translates to a preserved GFR. Natriuretic peptides modulate hydraulic conductivity (K_f) leading to albuminuria. EA = efferent arteriole; P_b = hydrostatic pressure in Bowman space; P_{gc} = hydrostatic pressure in glomerular capillary; P_{uf} = net ultrafiltration pressure (single-nephron GFR); Π_b = oncotic pressure in Bowman's space; Π_{gc} = oncotic pressure in glomerular capillary.

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Indeed, increased renal outlet venous pressures are associated with reduced RBF. An improvement in filling pressures can therefore have a significant impact on glomerular function over time.

Although cardiologists should already be convinced of the beneficial effect of sacubitril/valsartan based on the PARADIGM-HF study, the current analysis should further support this conviction. Despite a more pronounced drop in blood pressures observed in clinical practice with sacubitril/valsartan, this does not translate to an accelerated decline in eGFR, even in patients with chronic kidney disease. Moreover, the patient population with chronic kidney disease might actually benefit most from sacubitril/valsartan in terms of absolute risk reduction, given their intrinsically higher baseline risk. We hope the current analysis will reduce the inertia observed in clinical practice in initiating and optimizing this Class I lifesaving therapy.

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