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## Worsening renal function precedes and follows worsening heart failure

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Kidney function is of major interest for heart failure (HF) physicians. Kidney function, as assessed by estimated glomerular filtration rate (eGFR), is one of the key prognostic markers in HF, regardless of LVEF<sup>1</sup>. Physician attention to renal function is particularly amplified in patients with worsening HF (WHF) since worsening renal function (WRF) is particularly frequent in this setting, mainly due to renal congestion<sup>2</sup>, but also because WRF is associated with poorer mid-term prognosis<sup>3</sup> and may require some therapeutic adaptation (when WRF is severe)<sup>4</sup>.

In this context, the article first authored by Dr. Chatur<sup>5</sup> and coordinated by Pr. Solomon entitled “Longitudinal Trajectories in Renal Function Before and After Heart Failure Hospitalization Among Patients with HFpEF in the PARAGON-HF Trial” sheds new light on the interplay between WHF and WRF. Owing to the wealth of available data from the PARAGON-HF trial, Chatur and colleagues provide a number of new findings increasing our understanding of renal function changes in HF. First, they show that incident rates of the composite of time to  $\geq 50\%$  decline in eGFR, development of end stage renal disease, or death attributable to renal causes were highest in patients most recently hospitalized and decreased with longer time from last hospitalization. This mid-term association of HFH with declining renal function following HFH was confirmed using repeated measures regression models, and revealed that this decline persisted up to 12 months following HFH. Second, treatment effect of sacubitril/valsartan vs. valsartan on the aforementioned composite renal outcome did not significantly differ between patients with and without prior history of HFH ( $p$  for interaction =0.39) and appeared consistent irrespective of the timing of prior HFH ( $p$  for interaction =0.39). Treatment effect was observed to be numerically more substantial, however, in hospitalized patients (approximately 60% reduction in renal outcome in patients with a prior history of HFH, HR 0.43; 95% CI: 0.26 to 0.75 vs. approximately 40% in patients without prior history, HR 0.63; 95% CI: 0.33 to 1.18).

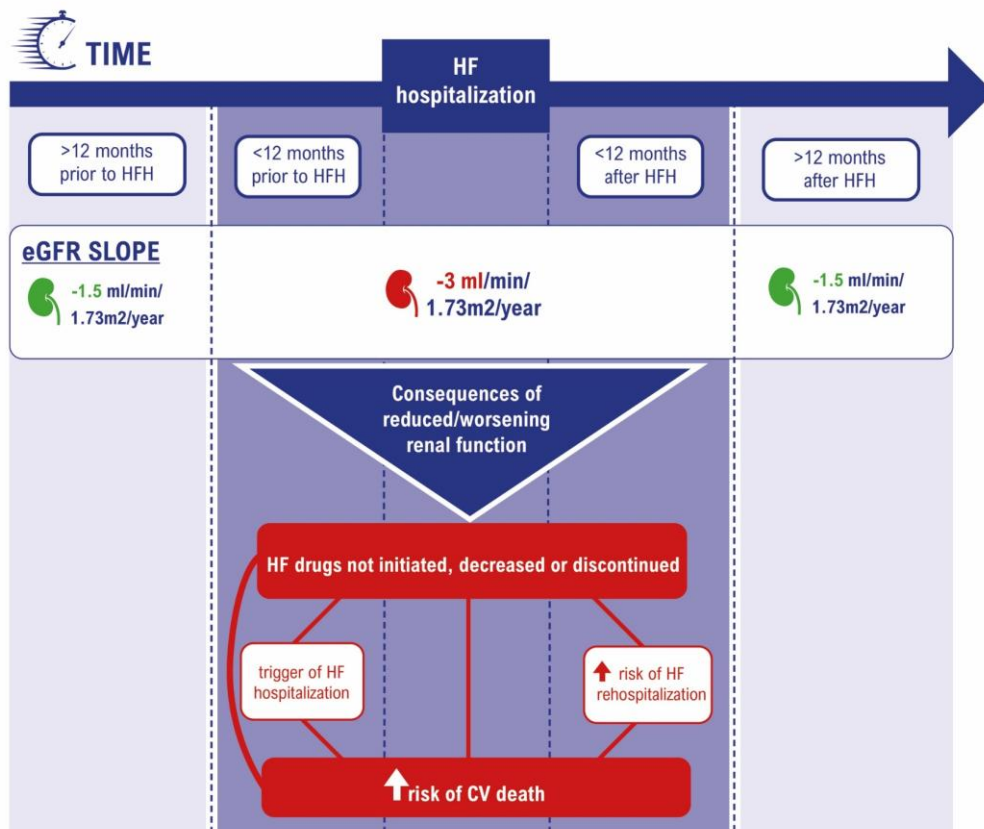
One point that may not necessarily catch readers' attention at first glance could actually be the most intriguing finding. In the trend analysis performed on the PARAGON trial data, patients who experienced an HF hospitalization during follow-up had a **significant decline in eGFR prior to hospitalization** while patients without HF hospitalization displayed a relatively stable eGFR trajectory ( $p < 0.001$ ). What is remarkable is that this faster decline in eGFR (3 ml/min/1.73m<sup>2</sup>/year) began 12 months prior to HF hospitalization and ceased (returning to 1.5 ml/min/1.73 m<sup>2</sup>/year) only 12 months after the HF hospitalization. This pattern is likely to be independent from LVEF, and should therefore also hold in patients with HFrEF, although the latter would need to be ascertained in future studies.

Up until now, WRF has typically been perceived as being a close satellite to WHF, occurring either shortly prior to or shortly after the onset of WHF. Indeed, WRF and WHF

were usually perceived as contemporary features, occurring so simultaneously that it was difficult to determine whether WRF favored WHF or whether WHF actually promoted WRF. The article by Chatur et al. hence sheds valuable new light on this topic, showing that WRF and WHF do not have the same tempo: renal alterations begin way before and end way after WHF.

The fact that renal function decreases both before and after WHF may extend our understanding of cardiorenal interaction in WHF (see figure). Indeed, when renal function becomes altered, physicians often discontinue and/or decrease certain HF medications,<sup>4</sup> which in turn can have a number of harmful consequences. A detailed analysis of the EORP registry showed that renal dysfunction had an association with mortality (HR=1.40) that was nowhere near that of HF drug discontinuation (HR=13.52 for ACE inhibitor discontinuation and HR=7.46 for MRA discontinuation)<sup>6</sup>. In keeping with this notion, the increase in mortality observed in the setting of WHF may be partially related to the decrease in helpful HF drugs. Specifically, prior to HF hospitalization, the decrease in HF medication may actually promote HF hospitalization itself (since the beneficial effects of HF hospitalization are withheld with the discontinuation of HF drugs). During the hospital stay, discontinuation of renin-angiotensin-system blockers has been shown to be associated with nearly doubled mortality.<sup>7</sup> After the hospital stay, having less HF medication could also be partly responsible for the poor prognosis observed as shown for example in the GREAT network data<sup>8</sup>. This is especially true for the withdrawal of renin-angiotensin-system blockers.<sup>9</sup>

The article of Chatur et al., owing to its wealth of data available in the PARAGON-HF trial, showed that renal function speeds up its decrease from 12 months prior to 12 months after an HF hospitalization. We need to confirm that this is not an isolated feature of HFpEF in subsequent analyses, although this is likely a feature of worsening HF unrelated to LVEF. This important finding may suggest that the kidney is actually the *primum movens* of worsening HF, perhaps through increased water and sodium retention occurring before the actual onset of WHF. In addition to being a cardinal prognostic marker in HF, renal function may also actually be the cornerstone of HF aggravation. In addition, on a more practical note, when facing WRF, we need to resist unnecessarily decreasing HF medication (possibly using the practical approach published recently<sup>4</sup> by a multidisciplinary group) to avoid precipitating HF hospitalization, aggravating HF severity during hospital stay, and increasing the risk of morbimortality following HF worsening.



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