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EDITORIAL COMMENT

Perils and Pitfalls With Associations in Heart Failure, Particularly in HF-pEF*

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Heart failure (HF) is a major cause of morbidity and mortality worldwide. Diabetes mellitus (DM) and chronic kidney disease (CKD) are also increasing on a worldwide basis. The intersection of HF with DM and CKD contains particular complexity, with both of the latter conditions potentially contributing to the development of HF as well as worsening prognosis. These disease entities are also growing in prevalence in Asia, and this has led to increased interest in understanding disease in this area, leading to the formation of databases such as the Asian-HF registry. In this issue of *JACC: Asia*, Lawson et al[1] uses this registry to examine these important relationships. Previous publications from worldwide clinical trials, as well as registries, have focused on DM and CKD in the HF populations, but these have not usually involved large numbers of Asian patients and have not investigated separately the influence of DM and CKD on outcomes. The current paper does examine prognosis using DM alone, CKD alone, and the combination in individuals with reduced ejection fraction (HF-rEF) and those with preserved ejection fraction (HF-pEF). The data, as analyzed, present a consistent pattern in which clinical outcomes as well as quality of life scores are worse with CKD. However, although DM influences these findings in HF-rEF, provocatively, it does not in HF-pEF. What does this mean? Are we seeing something new and insightful for our understanding of these entities? Or are we looking at spurious results? Furthermore, could the relationship between these entities be different in Asian patients? As this paper does, it would be well to examine DM and CKD in HF separately and in combination as well as within the 2 types of HF.

However, it would be worthwhile to place a particular cautionary note on the interpretation of these diseases in HF-pEF. A particularly well-thought-out schema of the pathophysiology of HF-pEF, by Paulus and Tschöpe,[2] makes the point that the development, and then the subsequent prognosis, are heavily linked to a metabolic pathway that involves elements commonly seen in both DM and CKD. Therefore, that is 1 more challenge in examining the influence of either in isolation or both, particularly in HF-pEF.

DIABETES MELLITUS IN HEART FAILURE

HF has long been known to be 1 of the earliest and most common complications of DM, with pathophysiologic links between type 2 diabetes and HF, such as insulin resistance and activation of neurohormonal systems.[3] In HF-pEF, DM has been known as a precipitant for HF-PEF, and clinical trial data provide convincing evidence for the effect of DM on prognosis. This would align with the concepts by Paulus and Tschöpe,[2] with multiple factors influencing HF-pEF through the metabolic pathway. The findings by Lawson et al[1] do not support an unfavorable effect of DM alone in HF-pEF, unlike in HF-rEF, and the authors point to long-term data from the Get With the Guidelines study.[4] However, the same database has reported unfavorable short-term outcomes, which might make one suspicious that confounding variables may obscure the impact of DM in the long term.[5]

To consider this further, is it possible that DM affects HF-pEF differently from HF-rEF and in a less unfavorable way? Basic science may provide some insight by isolating diabetes in experimental designs. Elegant studies involving structural and calcium handling in cardiomyocytes and also in rat models suggest that diabetes in HF-pEF produces changes

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that resemble those in HF-rEF and, therefore, would add to the pathophysiologic burden of HF-pEF.[6,7] This direction of enhanced risk would also be supported by recent phenogroup data from TOPCAT, in which a group dominated by diabetic subjects was associated with the highest subsequent event rate.[8]

Given that this database is composed of Asian patients, one could also wonder whether DM is different in Asian patients and therefore might have less impact in HF-pEF. There are differences between DM in Asia and DM in other parts of the world, in that DM occurs earlier and with less association with higher body mass index.[9] However, diabetologists also contend that there is an increased incidence of diabetic complications, particularly involving the microvasculature.[10] This would, of course, increase the likelihood of DM for HF and all-cause events.

In terms of treatments that would focus on DM per se, there is a significant history of agents increasing events in patients with HF while focusing on glucose lowering.[3] As will be discussed later, the recent agents developed as diabetic drugs, such as SGLT2 inhibitors, have the capacity to improve control of diabetes and to decrease HF events, including in HF-pEF.

CKD AND HEART FAILURE SUBTYPES

The association of impaired renal function and worse outcomes in HF is very well established, with mechanisms including inflammation, oxidative stress, and apoptosis, which like diabetes overlap between the 2 conditions and HF. However, Lawson et al[1] suggest that the association is less well established with Hf-pEF. The authors include 2 Asian databases in which renal failure was not a strong predictor of subsequent outcome.[11,12] Although it cannot be entirely excluded that renal dysfunction affects prognosis differently in Asian HF-pEF patients, these databases had important limitations: 1 in size (n = 1,604)[11] and the larger only in-hospital outcomes with a mild renal insufficiency cohort.[12] Still, the authors have a reasonable point in considering that the data for renal dysfunction in HF-pEF is less than straightforward, and different from HF-rEF. However, to consider the impact of comorbidities and risk factors on outcomes, particularly in HF-pEF, large numbers of patients are helpful in interpreting findings. The Asian-HF registry is relatively small (n = 5,239, 1,332 HF-pEF), and the signal can be difficult even in larger databases. In the MAGGIC (Metanalysis Global group in chronic heart failure) database (overall, 20,574 subjects with HF, 4,792 with HF-pEF), the association of CKD and mortality was stronger in the HF-rEF group than in the HF-pEF group, at least in part because of the lesser number of patients but also because of fewer events, and the signal for worse outcome was only apparent with more advanced renal insufficiency (CKD -4).[13] Similar findings were seen in the Cardiovascular Research Network PRESERVE study (14,579 subjects with HF-pEF) with only a trend for risk in the subjects with HF-pEFs.[14] Unfortunately, the issue of CKD and HF-pEF may be even more complicated when one considers how the these patients respond to renal-angiotensin-system inhibitors. Multiple reports, including a metanalysis of HFpEF data, demonstrate a worsening of renal function and renal outcomes,[15] in contrast to HF-rEF, where renal function may transiently worsen, but there is generally not an association with worse renal outcomes. Interestingly, there is no clear mechanism; perhaps this may just be an unmasking of vulnerable HF-pEF patients (who are now experiencing a risk that is unbalanced by the clinical benefit seen with renin-angiotensin-aldosterone inhibitors in HF-rEF).[16] This would then argue for care in the application of renin-angiotensin system inhibitors in HF-pEF patients. Interestingly, there is also a difference in response in outcomes with sodium-glucose cotransporter-2 (SGLT2) inhibitors between HF-rEF and HF-pEF patients: improved estimated glomerular filtration rate (EGFR) and renal outcomes in HF-rEF, but whereas EGFR improves in HF-pEF, renal outcomes do not.[17,18]

SUBGROUP INTERPRETATIONS

Although the Lawson et al[1] paper takes its data from a registry in examining the analysis of subgroups of patients with DM and CKD, analyzing association with risk and not treatment effect, one might consider the lessons in considering subgroups from randomized clinical trials. Two particularly important points are relevant to the current analysis: 1) biologic plausibility, as mentioned earlier, for the finding regarding DM in HF-pEF would be lacking; and 2) characteristics of the database in general, particularly size and number of events. The Asia-HF registry is a noble effort but is relatively small, with a minority of patients with HF-pEF. Considerations along with the factors already discussed suggest that the DM finding in HF-pEF is likely chance.

CLINICAL CONSIDERATIONS

The Lawson et al[1] paper illustrates the difficulty of studying and understanding the complex risk factors and comorbidities in HF-pEF in a registry, where even advanced statistical techniques may not be able to

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remove the issues of confounding. In clinical trials, where enrollment criteria moderate the comorbidities, the signals may be clearer. The authors do have the conclusion for clinical considerations correct: with the treatment of HF, there needs to be particular attention to interventions that are neutral on renal function and, hopefully, with favorable effects. The SGLT2 inhibitors, developed as diabetic drugs, at least have favorable effects on EGFR (though not necessarily demonstrable effects on renal outcomes) and provide benefits on HF events in HF-pEF. In the complex world of this kind of HF, further work to define the phenotypes of the population and then selection of appropriate therapy, perhaps by phenogroup, are directions that may help to improve clinical outcomes. Will these turned out to be different in Asia? We do not know currently, but databases like Asian-HF may be valuable steps in finding that answer.

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