Editor's Page

Noise Pollution is the Heart Failure Community's Biggest Threat

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A numbers of years ago, during the annual meeting of the Heart Failure Society of America, one of us (PJH) argued during a Hyde Park session that "noise" was a threat to our clinical trials enterprise. The main contention was that competing risks were making it difficult to prove that a drug or device intervention favorably impacted a targeted HF-specific endpoint or endpoints. Why would that be so and does the same situation exist today? The answers to these questions provide a perspective on the future of heart failure research and care.

To begin with, patients with heart failure often have problematic comorbidities, two of which (renal failure and chronic obstructive lung disease) not only frequently co-exist but may contribute to the pathophysiology of heart failure, or at the very least, make it more difficult to manage. These and other comorbid conditions can and often do lead to overt symptoms and exacerbations requiring hospitalization. In the VA data base, the triad of HF, renal failure and COPD accounts for a considerable proportion of overall spending within this relatively well circumscribed health care delivery system.[1] It is often difficult to distinguish the cause of dyspnea (is it COPD exacerbation or HF?) but adjudication rules often attribute these hospitalizations to HF if there is demonstrated use of intravenous loop diuretic therapy. The decision to use diuretics in this way is often made by providers in the emergency department or hospitalists who may look at surrogates (e.g. BNP, NT-proBNP levels) to inform the decision. For this reason, hospitalizations labeled as primary HF events may not provide a valid measure of the efficacy of an intervention. In addition, many trials may incorporate a "HF equivalent" so that an ED visit or clinic visit during which a dose of intravenous diuretic is administered is given equal status to a true episode such as pulmonary edema requiring hospitalization. But are these events equivalent? To the extent that administration of a diuretic in a clinic alleviates symptoms much more quickly and at vastly lower cost than an ED visit or hospitalization, it could be argued that such an approach is used in patients with only mild exacerbations. Alternatively, while unproven, in some cases it may represent high quality patient-centric care designed to avoid unnecessary and costly admissions. In other words, they may not be equivalent at all.

Patients with HF are also living longer, at times exceeding our expectations. In an older cohort, other diseases develop or progress, which means that the favorable effect a HF medication or device can impart may be muted because of competing risks, even in patients with relatively advanced symptomatic HF. Further, the mandate to enroll a representative patient population has a price: as the mean age of patients in clinical trials increases, so do competing risks, which leads to the well-established conundrum that a therapy can be efficacious in a trial with selective enrollment criteria, but not very effective when applied to a broader, "real world" population. Not a news flash[2] but a much needed reminder.

Conversely, expansive inclusion criteria are also potentially problematic, best demonstrated in trials of HF with preserved EF. Although the results of such trials may be more generalizable to a broader HF population, the apparent effect of the intervention may be diminished by the occurrence of events, such as hospitalizations and deaths, that are unrelated to HF (and therefore unlikely to be impacted by the intervention), and by the inclusion of patients who may not have HF at all! These challenges could be addressed in part by increasing the sample size in order to have adequate statistical power but this presents an obvious problem from the perspective of trial design and financing. Thankfully, we no longer accept studies that define HFpEF by relatively simplistic standards of dyspnea, a history of a HF hospitalization and a normal ejection fraction. Criteria have become more rigorous but we are almost certainly continuing to include patients with multifactorial contributions to dyspnea.

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At any given time, there are a number of high visibility clinical trials underway in HF. This is a testament to the importance of HF from the societal perspective, as well as to the fact HF science continues to identify promising new therapeutic targets worthy of further evaluation. Let us hope that we can quiet the noise in order to ensure that we do not slow the momentum of innovation in HF therapeutics.

References

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