lower optimal cutoff (28 ng/ml) has been reported (2). The 35 ng/ml threshold has never been evaluated in AHF, where higher cutoffs (up to 65 ng/ml) (5) have been identified as the optimal cutoffs (**Table 1**).

Given that sST2 is being increasingly evaluated in HF, we believe that there is a crucial need to establish the best sST2 threshold for outcome prediction in AHF, instead of simply adopting the likely suboptimal 35 ng/ml cutoff.

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REFERENCES

1. Pascual-Figal DA, Bayes-Genis A, Asensio-Lopez MC, et al. The interleukin-1 axis and risk of death in patients with acutely decompensated heart failure. J Am Coll Cardiol 2019;73:1016–25.

2. Emdin M, Aimo A, Vergaro G, et al. sST2 predicts outcome in chronic heart failure beyond NT-proBNP and high-sensitivity troponin T. J Am Coll Cardiol 2018;72:2309–20.

3. Aimo A, Vergaro G, Ripoli A, et al. Meta-analysis of soluble suppression of tumorigenicity-2 and prognosis in acute heart failure. J Am Coll Cardiol HF 2017;5:287–96.

4. Daniels LB, Bayes-Genis A. Using ST2 in cardiovascular patients: a review. Future Cardiol 2014;10:525–39.

5. Pascual-Figal DA, Manzano-Fernández S, Boronat M, et al. Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure. Eur J Heart Fail 2011;13:718–25.

REPLY: Interleukin-1β and sST2

We are thankful to Dr. Baldetti and colleagues and Dr. Aimo and colleagues for their insightful letters in response to our original paper (1) that asked 2 relevant questions in the battlefield of heart failure (HF). The first question: Is there an interplay between HF of ischemic etiology and the interleukin (IL)-1 axis? Dr. Baldetti and colleagues suggest that an interaction between coronary artery disease and IL-1β may be missed in our analysis, as supported by results of the CANTOS trial (Canakinumab Antiinflammatory Thrombosis Outcome Study) (2). As stated by Dr. Baldetti and colleagues, coronary disease was present in 33% of our patients with HF, slightly lower than the rate reported in the European Society of Cardiology Heart Failure Long-Term Registry (3). As shown in Table 1 of our original paper (1), there was no association between IL-1β concentrations and the presence of coronary disease in our cohort. Furthermore, if the predictive value of IL-1β was confined to HF of ischemic origin, it would likely disappear in the whole population after multivariable adjustment. The studies reported in patients with idiopathic dilated myocardiopathy also support a role for the IL-1 axis in the progression of myocardial dysfunction, irrespective of the etiology. Whether the favorable results of inhibiting IL-1β with canakinumab in CANTOS would be observed in nonischemic HF is at present unknown. We concur with Dr. Baldetti and colleagues that further research is necessary to address the role of IL-1 axis-mediated inflammation in both HF and coronary disease.

The second question: What is the role of soluble suppression of tumorigenesis-2 (sST2) in this battle? Dr. Aimo and colleagues argue against the selected threshold for defining high sST2 in our study. Our study was not pursuing a multimarker approach for patient risk stratification in acute HF, where the search for the optimal prognostic cutoff is critical. By contrast, our report sought to provide pathobiological insight into the interplay between IL1β and ST2: close correlation and interaction. Because this was the first report to establish a cut-point threshold for IL-1β concentrations in acute HF, we used the Youden index, as pointed out by Dr. Aimo and associates. For defining high sST2, we used the only Food and Drug Administration–approved prognostic cutoff value in HF, which is higher than the 90th of the reference group percentile in a healthy and general population (4). Furthermore, it is well known that the relationship between sST2 and prognosis is almost linear; in other words, the higher the ST2 value, the higher the risk irrespective of whether a patient is admitted with acute HF or is seen as an outpatient with chronic HF. In our report, we explored the interaction between IL-1β and sST2 and found that low IL-1β and high IL-1β separated those patients with high sST2 values (>35 ng/ml) in patients with low and high risk of death, respectively. As shown in Figure 1 of our article (1), this categorization was not exclusive for patients with very high sST2, but for all patients in the entire range of concentrations >35 ng/ml. Our aim was not to identify a prognostic threshold for sST2; therefore, we selected a meaningful and validated sST2 threshold.

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REFERENCES

1. Pascual-Figal DA, Bayes-Genis A, Asensio-Lopez MC, et al. The interleukin-1 axis and risk of death in patients with acutely decompensated heart failure. J Am Coll Cardiol 2019;73:1016–25.

2. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119–31.

3. Crespo-Leiro MG, Anker SD, Maggioni AP, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail 2016;18:613–25.

4. Lu J, Snider JV, Grenache DG. Establishment of reference intervals for soluble ST2 from a United States population. Clin Chim Acta 2010;411:1825–6.