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### Practice Changing Heart Failure Presentations from ACC 2022

#### Dr. Felker:

Hello, this is Michael Felker from Duke University. I'm pleased to speak to you today about three posters recently presented at the American College of Cardiology Scientific Sessions in Washington, DC focused on new and evolving therapies for patients with chronic heart failure.

First, I'll discuss a poster presented by Javed Butler on the relationship between ejection fraction, biomarkers, and outcomes in patients enrolled in the VICTORIA Trial. Just to refresh everyone, VICTORIA was a randomized trial that enrolled 5,050 patients with chronic heart failure, a recent worsening heart failure episode, and an LV ejection fraction less than 45% to treatment with either vericiguat or placebo. Now this current analysis looks at the relationship between ejection fraction divided into tertiles and a variety of potentially relevant biomarkers and the way those interact with the outcomes and treatment effect of vericiguat in the VICTORIA Trial.

This analysis found that patients in the lowest tertile of ejection fraction had other markers of higher risk including elevated natriuretic peptides, high sensitivity CRP and interleukin-6, and also higher risk of adverse outcomes such as cardiovascular death or heart failure hospitalization. When you look at the treatment effect of vericiguat across these tertiles of ejection fraction, you see that the effect was greatest in patients with the lowest ejection fraction, although this was not statistically significant interaction.

So in inclusion, I think we can see from these data that patients in the VICTORIA Trial who had a lower ejection fraction had a fairly distinctive biomarker profile, reflecting higher risk and indeed they did have greater risk of adverse clinical outcomes. We did not identify a statistically significant interaction for the benefit of vericiguat across these range of left ventricular rejection fraction tertiles, although certainly there was a suggestion that the effect was greatest in patients with lower ejection fraction.

Next, we're going to turn to a paper also from the VICTORIA Trial looking at the way clinical events are categorized in heart failure trials, such as VICTORIA. So we're all familiar that heart failure hospitalization is a major driver of cost and morbidity and is an important endpoint in our clinical trials, but I think we also recognize that there can be wide variation in what people experience during something like a heart failure hospitalization. And this could range from a brief hospitalization lasting only a day or two to a prolonged hospitalization requiring ICU care and more severe forms of treatment. So in this analysis, we wanted to look at the heart failure hospitalizations that occurred in the VICTORIA Trial and split them out based on how severe they were, and we did that based on what degree of therapy was required, whether it was oral diuretics, IV diuretics, vasodilators, inotropes, or inotropic support.

In this analysis, we looked at inpatient events like in-hospital mortality and length of stay. Indeed, we saw a very close relationship between how severe the event was and outcomes, again, something you would probably expect, but we also saw that patients who had a more severe presentation of heart failure during a heart failure hospitalization had worse discharge outcomes whether we looked at cardiovascular death or the composite of cardiovascular death on heart failure hospitalization. In particular, we did note that the outcomes tend to be better in patients treated with IV vasodilators, which may reflect that those patients had elevated blood pressure, which we know is actually a marker for lower risk in patients in the setting of acute heart failure hospitalization.

In this analysis, we did not identify any particular treatment difference across these types of events with vericiguat or placebo, suggesting that the treatment effects of vericiguat seen in the VICTORIA Trial seem to be relatively similar across all these types of

events. And I think these data have implications for how we might be more nuanced in our interpretation of clinical trials moving forward.

Now, the last poster I speak about is from a different study, the GALACTIC Trial, which studied a different agent, omecamtiv mecarbil. This drug has not yet been FDA-approved for heart failure, but this poster looked at data from the GALACTIC Trial, a large outcomes trial with omecamtiv mecarbil, which did show an improvement in the composite of heart failure events or cardiovascular death in that trial. This paper was focused on resource utilization and cost. And to drill down on the patients most likely to benefit, it focused on a subgroup of patients within GALACTIC who seemed to have the greatest benefit. And those are patients with ejection fraction less than equal to 30% and also patients who were not treated with digoxin in the setting of atrial fibrillation. This latter group was one that seemed to have less benefit or perhaps even harm in the GALACTIC Trial, so they were excluded from this analysis.

So when we analyze these data in this way, what we see is that indeed there's a significant evidence of treatment effect in this subpopulation for patients treated with omecamtiv, but also, there's a significant reduction in resource utilization whether that's cost, heart failure hospitalizations, emergency room visit, urgent care use. And all those things added up to an estimated cost reduction in this subpopulation of about \$3,000 per patient, which was about a 19% reduction in cost driven primarily again by avoiding heart failure hospitalization. So I think data like these, as we continue to get more data about the benefits of omecamtiv mecarbil will be extremely helpful as we weigh the role of this new therapy in our armamentarium. So it's been my pleasure to speak to you today about some of these new developments in the heart failure space. And I think there'll be a lot more to come. So thank you very much.