Title: HFA 23: TRANSFORM-HF: Torsemide Vs Furosemide on Quality of Life in Heart Failure
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Dr Stephen Greene

" I'm Dr Stephen Greene from the Duke Clinical Research Institute.

What is the background of this study?

Current guidelines for heart failure give class One recommendations to the use of diuretics for the treatment of congestion and improvement of symptoms. Yet there are no large-scale randomized trials showing which loop diuretic, if any, may best achieve these goals. Now, we presented at the American Heart Association meeting last year the primary results of the Transform HF trial, which showed that a strategy of torsemide versus furosemide had no significant effect on clinical outcomes, including mortality or hospitalization. But at this HFA meeting from the ESC, we will be presenting for the first time the prespecified patient reported secondary outcomes to better understand if a strategy of torsemide versus furosemide might improve quality of life and symptoms for patients with heart failure.

How do torsemide and furosemide differ in terms of their mechanisms of action?

So, there is preclinical data to suggest that torsemide has its potential advantages over furosemide. Things that get talked about a lot are increased bioavailability and more consistent diuretic effect. There are also some studies that suggest maybe antifibrotic or almost aldosterone antagonist like effects with torsemide. Yet we haven't had until TRANSFORM, a large-scale trial designed to test differences in outcomes and patient reported outcomes for those two loop diuretics.

What was the rationale behind this QoL study?

TRANSFORM-HF was a large-scale Pragmatic randomized trial patients hospitalized for heart failure in the United States. We enrolled 2859 patients and prior to hospital discharge they were randomized one to one toa strategy of either torsemide or furosemide. They then were followed up post discharge via routine clinical care with no site study-specific in-person visits. And instead, we had a centralized follow-up procedure where we used the National Death Index as well as had the telephone call centre from the Duke Clinical Research Institute, which we used to gather the patient reported outcome data and other information. Patients were eligible for TRANSFORM regardless of ejection fraction. All patients did need a plan, along term plan for a loop diuretic. And importantly, the other thing to understand with the design of TRANSFORM was that it was an open-label study. So, while the treatment strategy of torsemide versus furosemide was randomized, the dosing actually was not, and it was up to clinician discretion, and they could titrate as they thought needed.

What data are you presenting at HFA 23?

During the follow-up of the trial at the ESC HFA meeting, we presented the effects on the two prespecified patient-reported outcomes in TRANSFORM. That was the change in KCCQ Clinical Summary score and the PHQ two score, which is a screening tool for depression. Overall, when we compared a strategy of torsemide versus furosemide, we found no significant difference in the change from baseline in the KCCQ Clinical Summary score atone month, six month or twelve month follow up. And similarly, we saw no significant difference between the likelihood of having a PHQ twoscore greater than three during follow-up between a strategy of torsemide or furosemide. The results for the KCCQ Clinical Summary score were consistent across several subgroups that we tested, and we also did a responder analysis to say, well, it was our differential odds of clinically meaningful improvement or deterioration in the KCCQ score during follow-up with torsemide versus furosemide but saw no significant difference between the two loop diuretics.

Based on the results, what are the key messages?

So, based on these results from the TRANSFORM Trial and what we saw with no significant difference between torsemide and furosemide for symptoms or quality of life for improving symptoms in quality of life in heart failure, which we all focus on a lot, focusing on which loop diuretic to use should not be a priority for spending in clinical time. Instead, our clinical time is better spent focusing on one, ensuring optimal loop diuretic dosing rather than the agent, but also, most importantly, timely optimization of guideline-directed medical therapy.

What are the remaining unanswered questions regarding the choice of loop diuretic?

Diuretic use in heart failure is really a black box where it gets a lot of emphasis, like I mentioned the Class One guidelines, but not a lot of specifics on how to best use these agents. So, one unanswered question with loop diuretics is, well, what should they be paired with, if anything, in terms of like a second adjunctive diuretic? What is the optimal dosing? That is a ripe question for clinical research. And in Transform, we randomized patients where there was relative equipoise between use of torsemide versus furosemide. But what about the patients that are maybe struggling on one loop diuretic? And in those situations which again were not eligible for TRANSFORM, would it make sense to switch them to a different strategy, a different agent, or what have? So, I think these types of questions are still very unanswered, and we have a lot of work to do with understanding how to best use diuretics for heart failure."