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Released: 11/23/2022
Valid until: 11/23/2023
Time needed to complete: 1h 08m

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Torsemide Comparison with Furosemide for Management of Heart Failure

Announcer:
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Dr. Mentz:
Hi, I'm Rob Mentz, a heart failure cardiologist at Duke University, and on behalf of the Transform HF investigators and participants, thank you for the opportunity to share the primary trial results for torsemide comparison with furosemide for management of heart failure. By way of background, loop diuretics are routinely used to manage congestion in patients with heart failure. Furosemide is the most commonly used loop diuretic. However, the loop diuretic torsemide may offer advantages over furosemide. It has more consistent oral bioavailability and a longer duration of action. Studies have demonstrated anti-aldosterone and antifibrotic effects that are not seen with furosemide, and prior observational studies have suggested potential outcome benefits with torsemide. However, without a robust randomized clinical trial it is unknown whether torsemide improves clinical outcomes compared with furosemide.

Therefore, we designed and executed the Transform HF Pragmatic Comparative-Effectiveness Trial with the primary objective of comparing the treatment strategy of torsemide versus furosemide on long-term clinical outcomes in patients with heart failure. We focused on the recruitment of patients hospitalized with heart failure and had broad eligibility criteria that included patients regardless of ejection fraction as long as there was a long-term plan for a loop diuretic. We recruited at 60 US sites and included one-to-one randomization to a diuretic strategy of torsemide or furosemide. This was executed in an open label fashion where both the patients and the clinicians knew which diuretic the patient was on. Dosing was per the routine clinician and participants continued with routine clinical follow-up with no in-person study-specific visits and the trial follow-up was centralized by the DCRI Call Center with follow-up at 30 days, 6 months, and 12 months, and further supported by the National Death Index. The primary endpoint was all-cause mortality. With the primary hypothesis that torsemide reduces mortality by 20%. The trial was event-driven, targeting 721 death events for 85% power. Additional secondary endpoints are included here and included a composite with all-cause hospitalizations as well as total hospitalizations.

In total, we began recruitment in 2018 and recruited through the spring of this year, 2022. In total, we recruited 2,859 participants. The two groups were well-balanced. A mean age of 65 years, 37% women, and 34% self-identified Black individuals. With regard to heart failure characteristics, approximately 30% had newly diagnosed heart failure and for ejection fraction, a majority had heart failure with reduced ejection fraction, approximately two-thirds. Baseline NT-proBNP was 4,000 picograms per milliliter, and about 30% had ischemic etiology. Other baseline characteristics are noted here and included a systolic blood pressure of approximately 119 millimeters of mercury, a BMI of 32, and an estimated glomerular filtration rate around 60.
We'll now present the primary endpoint of all-cause mortality over a median follow-up of 17.4 months. There was a very high event rate in the furosemide arm. 374 events, or 26.2%, with 17 per 100 patient years. In the torsemide group, there was a similarly high event rate. 17 per 100 patient years, with 373 events, or 26.1%, giving a hazard ratio of 1.02 that was not significant. Overall, a neutral primary endpoint demonstrating no benefit from torsemide as compared with furosemide. This was consistent across all pre-specified

subgroups. For the secondary endpoint of all-cause mortality or all-cause hospitalization at 12 months, as similarly to the primary endpoint, a very high event rate in the furosemide group, 704 events, 49.3%, 107.6 per 100 patient years. And in the torsemide group, 677 events, 47.3%, 99.2 per 100 patient years, giving a hazard ratio of 0.92. That was not statistically significant.

And for our last clinical endpoint of total hospitalizations in the furosemide group, there were 987 hospitalizations among 577 participants. And in the torsemide group there were 940 hospitalizations among 536 participants, giving a rate ratio of 0.94. That was not statistically significant.

There were a number of important insights that were learned related to the pragmatic trial design features. The broad eligibility criteria and streamlined study protocol embedded within routine care supported the inclusion of diverse participants with 37% women and 34% self-identified Black individuals, much higher than many recent heart failure trials. Pragmatic elements lowered traditional barriers for patient and site participation, and supported robust recruitment even during the COVID pandemic. We identified opportunities to further enhance patient adherence and engagement at follow-up in the setting of a decentralized trial. And in this context, this real-world comparative-effectiveness study provides results that are generalizable to routine clinical practice.

In conclusion, a strategy of torsemide had similar effectiveness compared with the strategy of furosemide for the clinical outcomes of mortality and hospitalization in patients hospitalized with heart failure. Clinical time should, therefore, be spent focusing on appropriate diuretic dosing and prioritizing guideline directed medical therapy, initiation and titration. Importantly, insights from this pragmatic trial design and execution inform future studies aiming to assess real-world comparative-effectiveness. Thank you so much for the opportunity to present these results. And thank you to our investigators, our sponsor, our DSMB and importantly, our participants. Thank you.

Announcer:
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