Title: AHA 22: Late-Breaker Discussion: The TRANSFORM-HF Trial

Participants: Dr Harriette Van Spall & Dr Robert Mentz

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Please note that the text below has been copyedited.

Dr Van Spall:
I'm Harriette Van Spall, Associate Professor of Medicine from McMaster University and I am here at AHA 2022 with Dr. Rob Mentz, who is well known as an Associate Professor of Medicine, Chief of Heart Failure at Duke and a clinical trialist who has published several pragmatic clinical trials.
We are here to discuss his late-breaking clinical trial presentation of the TRANSFORM-HF trial. Welcome, Rob.

Dr Mentz:
Harriette, thank you so much. We're delighted to be able to share the results of TRANSFORM-HF at AHA this year, and I'm really looking forward to this discussion with you today.

Dr Van Spall:
Rob, I'm going to ask you to put your trial in the context of the problem of decongestion among patients hospitalised for heart failure. Why does it matter? And what question were you hoping to answer with your trial?

Dr Mentz:
Great, thanks so much Harriette. So really a foundational question is what we set out to explore. This idea that's the primary reason that many patients with heart failure come into the hospital is fluid build-up, is congestion. What we know is that during this hospitalised period we helped to decongest them with IV diuretics and then transition back to an oral regimen. And what we were interested in exploring was, is there a difference between these two commonly used loop diuretics, with furosemide being the most common loop diuretic in the US and worldwide.
Torsemide has some data to suggest that has advantages over furosemide. We are really interested in looking at these two diuretics head-to-head to better understand, not just how effective are they in terms of congestion, but are there clinical outcome differences?
I would summarise by saying very commonly what we see is that patients are initially started on furosemide, but when they're not absorbing the diuretic as well, or they're still building up fluid, sometimes those individuals are then transitioned to torsemide. The data suggests potential advantages, but we need to compare them head-to-head to better understand which diuretic is best for our patients.

Dr Van Spall:
Why might torsemide offer advantages to people who are congested?

Dr Mentz:

I would highlight some of the earlier preclinical data that shows that torsemide has a longer half-life and it has increased bioavailability compared to furosemide. There are also some earlier studies that suggested that torsemide may have anti-aldosterone and anti-fibrotic effects that are not seen with furosemide. Some smaller observational studies suggested a potential improvement in clinical outcomes with torsemide as compared with furosemide. But really without a robust, randomised trial, we do not know whether torsemide definitively improves clinical outcomes.

Dr Van Spall:
Tell us how you established dosing for the patients who were randomised in your trial.

Dr Mentz:
A very important question. TRANSFORM-HF was a pragmatic comparative effectiveness study and the randomization was to the diuretic strategy. So, it was either a strategy of torsemide or a strategy of furosemide, but we left the dosing up to the routine clinician. We provided guidance that, on average, it's a two to one ratio. Meaning torsemide is twice as strong as furosemide. But we appreciate that there's some variability, and in some practises, it's perceived as even four times as strong. In that context, we gave guidance of a two to one, or in some cases even up to a four to one, but left that up to the routine clinician both at baseline as well as follow up.

Dr Van Spall:
Sure. I love that your primary endpoint was a clinical endpoint. This was an event driven trial. Tell us about your primary endpoint.

Dr Mentz:
The primary endpoint was looking at all-cause mortality over long term follow up. In our trial, patients had a follow up at 30 days, which was centralised by the DCRI Call Center, 6 months and 12 months. And then the first 1500 patients had additional follow up at 6 months interval.
Our median follow up was just over 17 months, and the rationale for mortality was several fold: One, this was an unblinded trial: Meaning both the practising clinicians, as well as the patients, knew which therapy we they were on. So, we felt it was important to minimise bias and have an endpoint that that would do that. So that was some of the rationale for all-cause mortality combined with these earlier observational studies that did suggest that there might be not only a reduction in hospitalizations, but also the hard endpoint of mortality. So, we felt that that will be an important primary endpoint. But equally important, we wanted to capture the full journey for patients, so we looked at all-cause hospitalizations. In additionally we'll report out in the future around quality of life and depression measures as well.

Dr Van Spall:
So really an ambitious selection of endpoint for pragmatic trial. We know the needle is so hard to move for this kind of endpoint. I commend your team for selecting something that is robust, not prone to bias, and that really has stood the test of time in terms of endpoints for interventions. Did you have any protocol changes?

Dr Mentz:

We really did not. There were just some administrative changes with transitions of PI from institution and some clarification of language. But really, I think some of the strengths of this pragmatic trial were not only that the protocol was just tens of pages rather than the usual 200 plus pages that we see. And then similarly, at a site level, we had a consistent database throughout that had a case report form or the document that the clinical teams were filling out. There was only 15 pages.
So really trying to reduce the burden in terms of the protocol characteristics as well as the case report form for both patients and for the clinical teams to really support broad inclusion and efficient execution of this study.

And on the note of inclusion, you included patients with heart failure across the spectrum of EF. Tell us about any pertinent eligibility criteria.

Dr Mentz:
So we really had aimed to have broad eligibility criteria so that the results would be applicable to the patient sitting in front of you in clinic. So we focus on patients in the hospital with heart failure, regardless of ejection fraction, as you noted. As long as there was a long-term plan for a loop diuretic. So we excluded those transplants or LVAD or with end stage renal disease where a loop diuretic would not be consistently used. But otherwise it was pretty much all-comers in the hospital with heart failure.

Dr Van Spall:
What were the baseline characteristics of your trial population?

Dr Mentz:
We recruited 2859 participants and they were very well-balanced between the two groups. The mean age was 65 years. 37% were women, much higher than in many of our earlier heart failure studies. And 34% were self-identified black individuals.
In terms of some of the key characteristics for for heart failure, it tended to be a majority of heart failure with reduced ejection fraction. About two-thirds. There were about 30% new heart failure, or de nova heart failure. So, this was their first time coming into the hospital and really a number of important comorbidities as well, with I would highlight the baseline NT-proBNP, just under 4,000 pg/mL, and importantly also non-ischemic etiology.
Lower than in some of the ear, the earlier programmes at about 30%, likely related in part to the more diverse patient population that we included as well as some of the younger characteristics.

Dr Van Spall:
So, tell us about the results. I'm hearing them before the AHA audience hears them, so I'm pretty excited.

Dr Mentz:
That's right. So, we've certainly kept all of our embargoes and we're eager to now share these results. So, the primary endpoint of all-cause mortality over a median follow up of 17.4 months. We observed a very high event rate in the furosemide arm.
17.0 per 100 pt-yr, with more than 26% of the patients experiencing a death event during follow up. And when we compared that to the torsemide group we observed a similarly high event rate. So again, just over 26% with no between group difference. We did not

demonstrate a benefit with torsemide as compared to furosemide, a hazard ratio of 1.02. And these were really consistent across all of our pre-specified subgroups.
So, while neutral overall, I think demonstrates how high-risk this patient population is and it'll be a number of important clinical implications of these data.

Dr Van Spall:
Sure. Do you have any secondary endpoint results to share with us?

Dr Mentz:
Great. So, we we would like to share the hospitalisation endpoints as well. So, the secondary endpoints of all-cause mortality and all-cause hospitalisation. Demonstrated similarly high event rates between the two groups: 49.3% with a hospitalisation or death during 12 months in the furosemide arm, and 47.3% in the torsemide arm, with no statistical difference.
And then for the total hospitalizations, again we saw very high event counts, but no difference in total hospitalizations at 12 months between the two groups. And then I would highlight that we did perform a pre-specified sensitivity analysis that looked at an on-treatment population at both discharge and 30 days, and they were overall consistent with the primary results for both all-cause mortality, and the composite with all-cause hospitalisation.

Dr Van Spall:
Did you look at length of hospital stay at all?

Dr Mentz:
Great question. So certainly, a very important measure for systems of care as well as for our patients. And we do not have those data yet available and we'll plan to share in future work. Not only data such as that, but also quality of life measures as I noted earlier.

Dr Van Spall:
Sure. Really important findings demonstrating both the high risk that our patients who are hospitalised for heart failure face, and that, despite what we might have expected, a strategy of upfront torsemide use doesn't improve the primary endpoint of all-cause mortality relative to furosemide among patients hospitalised for heart failure.
Any implications that you think will change care or transform care?

Dr Mentz:
I would emphasise a couple key points. One is practising clinicians. We so commonly are spending our time thinking about switching from one diuretic to another. And we've now taken this foundational clinical question and answered it definitively, that there's no difference for clinical outcomes.
We really should be focusing our efforts on making sure patients are on the right dose of their diuretic, and then we can use that clinical time best spent now to make sure we're getting on those guideline-directed medical therapies, proven to improve outcomes for our patients.
So, getting on those therapies and titrating those and let's spend less time focusing on switching from one diuretic to another, more broadly speaking.

And realising that further insights will be gleaned from secondary analyses of this important database and a diverse population. To better understand, are there populations that may benefit from one diuretic more versus the other.
And then two, I would say that there were a number of important insights that we learned related to the pragmatic trial design, that reduced the burden on participants and sites helped support a diverse population. And this can serve as a model for future clinical trials to answer meaningful questions looking at the comparative effectiveness of different therapies. At the end of the day as practising clinicians, we all want these data to help inform our decision making, and we're delighted to now be able to share that in this case of a diuretic choice, in this diuretic strategy in patients with heart failure.

Dr Van Spall:
Well, Rob, let me congratulate you and your team for another well executed trial that answered a clinically important question and had the courage to choose a clinically relevant endpoint. I can't wait to hear your presentation at the hotline session at AHA. Congratulations.

Dr Mentz:
Thank you so much Harriette, and I'm looking forward to further discussion around TRANSFORM at AHA.