DR. GREENE: Good afternoon. I'm Dr. Eddie Greene. Associate professor of medicine at Mayo Clinic. Today, my colleagues and I from cardiology, will be convening a roundtable review on the recently completed Carress trial. joined by Dr. Margaret Redfield and Dr. Horng Chen. Dr. Redfield is Director of our Circulatory Failure program, and Dr. Chen is Professor of Medicine. Welcome, Maggie and Horng. Great to have you with us, today.

DR. CHEN: Thanks.

DR. REDFIELD: Great to be here.

DR. GREENE: We are interested in hearing about the recent results of the trials to look at the response to volume removal in cardiorenal syndrome or in acute decompensated heart failure. As you well know, cardiologists and nephrologists deal with this problem of issues surrounding how much volume to remove in this setting, whether or not it affects renal function, and how much it might actually help cardiac function, as well. And we're looking forward to hearing about your insights from this recently computed trial. Can you start by giving us a brief overview of what the trial was about and what the results implicated for us?

DR. REDFIELD: Great. Maybe, I'll start.

DR. GREENE: OK. Thank you.

DR. REDFIELD: This trial was completed by the Heart Failure Clinical Research network, which a NIH sponsored consortium of leading heart failure sites across the United States. Nine sites and associated institutions, who designed and conducted this trial. So very rigorous NIH funded trial. And the hypothesis was that in patients who have acutely decompensated heart failure, who are still very congested despite outpatient or inpatient diuretic therapy, and who are developing worsen renal function as evidenced by an increase in the creatinine of 0.3 that switching then to ultra filtration based volume removal strategy versus a stepped pharmacologic care strategy using diuretics and escalating doses, and if needed renovasal dilators or systematic based or active compounds, That there would be a difference in that strategy. That ultra filtration would remove more fluid and be gentler on the kidneys. So that was the hypothesis.

DR. GREENE: Correct. OK. And were the outcomes clear from the studies suggesting that this did happen in those patients or did the trial turn out differently? Can you comment on that, please?

DR. CHEN: Yeah. Maybe, I'll take a shot at that. So we had a-- what I would consider a unique end point. It's a bivariate analysis of weight loss and changing creatinine. And I think that is important because we've learned recently that, not only is renal function important, but decongesting patient is equally important, actually. Hence, we have this unique bivariate end point of weight loss, which is surrogate for decongestion versus creatinine. And indeed, our hypothesis was proven to be wrong. We saw in the step care, pharmacological care group. We had an equal weight loss and no change in creatinine. In the ultrafiltration group, we had to associate that with the weight loss was an increase in plasma creatinine, suggesting that slightly worsening renal function with the ultrafiltration group.

DR. GREENE: Right. So this is an interesting point. Do you think this was related to excessive volume loss or did the patient cohort have underlying, unrecognized renal disease as a part of their overall heart failure syndrome?

DR. REDFIELD: Well, certainly, the patients did have some underlying renal dysfunction. The mean creatinine at entry was approximately 2, 2.1. So whether it was from there co-morbidities or their co-morbidities in conjunction with their heart failure, they did have underlying renal dysfunction. I think that the patients actually lost volume, the end point was assessed at 96 hours after entry. So four days. So they had the same weight loss over this four day period. And actually the rate of weight loss was not significantly different between the two groups. So was it too fast in one group versus the other?

This trial doesn't clearly suggest that because they had the same weight loss and yet, the patients treated with ultrafiltration had somewhat worsening of the renal function. I think the question is that important-- is that the fact that the ultrafiltraion patients had more worsening of the renal function, does that mean anything? And so that was addressed in several ways. First of all, they also looked at changes in creatinine at hospital discharge and then, subsequently, at 60 day follow up. And so there was this worsening of renal function at the 96 hour end point but the two groups were equivalent at discharge and follow up. So while the group in terms of that bivariate endpoint did worse, does that mean that, overall, they did worse? And some of the secondary end points of the trial address that sort of clinical question. A previous study with ultrafiltration in a less sick group, just people with decompensated heart failure coming in, had shown that patients treated with ultrafiltration had fewer heart failure re-admissions.

DR. GREENE: Right.

DR. REDFIELD: So we were very interested in that end point, in Carress, to see if it was a small trial, very few endpoints, but very intriguing when we're all trying to deal with this big problem of re-admissions after heart failure. So that was one of the secondary endpoints and, maybe, Horng could enlighten you on--

DR. GREENE: Yeah.

[INTERPOSING VOICES]

DR. GREENE: I'd like to hear about that, Horng.

DR. CHEN: I mean, just to emphasize what Maggie said, the baseline characteristics between the two groups are pretty similar.

DR. GREENE: OK.

DR. CHEN: In terms of another, you know-- 65% of them had diabetes. So I think they do all have underlying renal but they were very similar between the two, actually. But as Maggie said, I think what's important is when we looked at the secondary end points, which is 60 days, death or death and hospitalization. It was actually similar between the two groups. So there was no difference from that aspect. There was a difference in terms of the number adverse effects during the study itself. And this was in the ultrafiltration group, there was an increase in what was classified as serious adverse effects.

DR. GREENE: Sure.

DR. CHEN: Majority of it was due to worsening renal function, and bleeding because they needed to be heparin, and things associated with the line. But once again, I think, one of the important effects, like what Maggie has said, is that at 60 days we didn't see a difference between [INAUDIBLE]

DR. REDFIELD: And I think to me that is really, even though it was a secondary end point and under-powered. We were really hoping we would see a trend or some data to suggest that that other study's observation was real because that was really be a game changer in whether we use the ultrafiltration more.

DR. GREENE: Correct.

DR. REDFIELD: Now there is an ongoing trial. I believe it's called--

DR. CHEN: Avoid.

DR. REDFIELD: Avoid. Yes. It's going to be a big trial. Almost 900 patients.

DR. GREENE: Similarly structured?

DR. REDFIELD: More like the unload trial. So the patients with just acutely decompensated heart failure, not stipulating that you have to have worsening renal function. So more of a broader heart failure population and the primary endpoint is does an ultrafiltration base strategy reduce re-hospitalization. So I think that will be a key, key trial. One thing worth mentioning that ultrafiltration is very different than what we're used to dealing with in cardiology. Usually, whether it's a drug or a device, there are multiple trials. When there's a body of evidence, the product is labeled.

DR. GREENE: Correct.

DR. REDFIELD: And you get the product, and you use it, and you know what it's supposed to do. Ultrafiltration was approved many-- this particular ultrafiltration device, was approved many years ago just because it could do ultrafiltration with no data, really, to suggest that it was a specific heart failure trial. So we're having to learn as we go with a dearth of really the kind of big randomized clinical trials that we're used to having. So it's been challenging to know where it fits.

DR. GREENE: You bring up a very important point in that ultrafiltration, in of itself, might be different than some of the hemodynamic effects we can see that accompany diuretics. For example, are there effects of the diuretics? From a cardiovascular standpoint, there may be more effective in their short term, with less loss of renal function. Was that considered in the trial, at all, the secondary human anomic effects of diuretic therapy versus the effects of ultrafiltration therapy?

DR. CHEN: Right. I think that's an interesting point. I think the nice thing about the career study, which is unlike the [INAUDIBLE] studies, that we had this very rigorous, standard pharmacological therapy group, which we ensured that the patient had similar decongestional weight loss.

DR. GREENE: Right. OK.

DR. CHEN: And with that, like Maggie said, we didn't see a decrease in re-hospitalization like the [INAUDIBLE] study. But the difference is that the diuretic study in the LASIK group, there was last weight loss. So I think that is one important point. Now, in terms of the hemodynamics, we didn't really look too much at hemodynamics in this study but there was a recent small One Center experience from the Cleveland Clinic [INAUDIBLE]. But they looked at patients that was admitted to the intensive care unit with PA catheters. And they actually showed that the patients who underwent ultrafiltration did have improved hemodynamics. But yet, they didn't see improvement in renal function.

DR. GREENE: May I ask you one other important question. Other drugs may have affected the hemodynamics in the patients, in addition to that caused by the ultrafiltration, were patients also receiving vasodilators and other drugs to unload the cardiovascular afterload and preload in your study?

DR. CHEN: Yes. At 48, I was part of the pharmacological treatment. If they had not seen a good response, they were allowed to use vasodilators or iontubes, according to their blood pressure. I believe about 2% of the patients had inotopes, and maybe, about 10% to 12% received vasodilators.

DR. GREENE: And did this skew the results at all, in any way, in the initial, sort of, outcomes.

DR. REDFIELD: Well, of course, we don't--

DR. GREENE: In 96 hours.

DR. REDFIELD: --we don't really know, for sure, if certain medicines, like vasodilators have specific renal preserving effects. And I'll let Horng tell you about another study the network is doing because he's leading that trial to try and get some more insight.

DR. GREENE: Can you, briefly, tell us about that?

DR. CHEN: So we are doing this study called, the role study, where we are, specifically, looking at the role of low dose of dopamine or low dose [INAUDIBLE] which is a vasodilator, in patients with acute decompensates heart failure. And chronic renos insufficiency is defined by [INAUDIBLE] less than 16.

DR. GREENE: OK.

DR. CHEN: And in that study, we hope to define if these, what we consider [INAUDIBLE] therapies, would help to preserve renal function with this group of patients.

DR. GREENE: Let me close the session by asking for the practitioner, and his or her colleagues, what are they to take away from this, in terms of ultra filtration versus the standard, sort of, approach with diuretic therapy? Especially, as it relates to prolong hospitalization and their re-admissions. If you could summarize that for us.

DR. REDFIELD: Well, I can summarize what our approach will be, is that important to remember these were patients who were, to some degree, diuretic resistant, and getting worsening renal function. And certainly, there was nothing in this trial to suggest to us that ultrafiltration approach is inherently better than step pharmacological care. So our initial approach will be step pharmacological care.

However, the conclusion of the paper, which I very much agree with, is that these can be incredibly challenging patients. And this was probably a spectrum, and there are patients who are both, getting worsening renal function and who are incredibly diuretic refractory, despite high dose diuretics, multi-diuretics, and it's those patients that we continue to be challenged by. And I think that ultrafiltration still has a role there but it needs to be in partnership with our nephrologist because some of those patients may end up needing renal replacement therapy.

DR. GREENE: Sure. Well, we're clearly-- there will have to be ongoing studies, it appears. And we look forward to seeing your study, Dr. Chen, and additional studies that may give us some more insight into how we can best treat these patients. Thanks for your lively insights, today. And thank you to our viewers. We hope you can continue to follow our roundtable reviews on the heart that orbit. Thank you very much.

DR. CHEN: Thanks--

DR. REDFIELD: Thanks, Eddie.

DR. GREENE: It's our pleasure. Thank you.