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**ReachMD**
www.reachmd.com
info@reachmd.com
(866) 423-7849

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# A New Normal? COVID-19 and HF in Clinical Trials

Announcer:
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Dr. Butler:
The COVID-19 pandemic has had an unprecedented impact on the entire global population. Not only has it disrupted the regular care of patients with heart failure, but COVID-19 fears have impacted clinical trials and their participation rates. These studies are a critical way of proving the safety and effectiveness of new drugs and innovative treatments. And yet, when the pandemic started, some clinical trials shut down permanently, while others are slowly resuming. This has created a delay in the research pipeline that may hinder how quickly new heart failure medications come to market in the next few years. So these concerns beg the question: Where do we go from here?

This is CME on ReachMD, and I'm Dr. Javed Butler.

Dr. Rosano:
And I'm Giuseppe Rosano.

Dr. Bhatt:
And I'm Dr. Deepak Bhatt.

Dr. Butler:
So, Giuseppe, let's start by addressing the current challenges being faced in clinical practice. So let me ask you, how has COVID-19 impacted the management of patients with heart failure?

Dr. Rosano:
Thank you, Javed. The COVID-19 pandemic has had many effects on patients with heart failure. And I think we have to differentiate the different waves. During the first wave, we had less patients coming to hospital, even for heart failure. But that was not because there were less heart failure patients. Because as we've seen, there's been an increase of sudden deaths out of hospital. And these have increased by 30% to 40%. And most of these deaths were due to acute coronary syndromes but also of heart failure patients dying at home. Then we had an impact of patients coming late into hospital. And we have seen around November, December of last year, patients coming with worse heart failure. Some of them were heart failures that have not been treated or didn't come into hospital. Others were patients who had an acute MI and they came late into hospital, and therefore they developed heart failure.

And telemedicine has played a very important role in helping us to catch up with our patients. And we have been very fortunate in the UK for example, where we have the electronic patient records that cover the whole population and, therefore, it's easier to conduct remote consultations with the help of the pharmacist and with the help of the nurses.

Now, I think that we're in the third phase, where we are seeing patients who have been treated late, and therefore we have a different shift in the number of patients with more severe heart failure compared to those with moderate heart failure coming into hospital. But

also we are starting to see some of patients come in with long COVID, with myocarditis due to COVID, and also with now myocarditis, although these are less severe due to the Pfizer and Moderna vaccinations.

Dr. Butler:
So Deepak, it's clear that COVID has had repercussions beyond regular care. But the question now is, what impact have you seen on clinical trials in patients who have heart failure with this COVID pandemic?

Dr. Bhatt:
It's really a great question. It's unbelievable the impact COVID has had on all our lives. You were just discussing clinical impact, but also an impact in the world of research. And I don't think I've ever seen anything quite as disruptive. I've certainly had trials where there have been patients and sites affected with hurricanes or wars or all sorts of bad events. But those are typically localized to a few sites or maybe one country in a global trial. Here, basically everyone was being affected in some way, at the same time, or overlapping times. So very disruptive to clinical research. And I don't think we've recovered yet.

Now, to answer your question, what was the direct impact on trials, the impact was really quite substantial. A number of trials had to halt enrollment of patients; some had to stop altogether. Ongoing trials had disruption of data collection where the patients were enrolled, but it wasn't always possible to get follow-up data. For example, if the patient had to come back to the hospital to get an echo or a cardiac MRI, and that hospital was in the middle of the pandemic, a COVID surge, you can't just ask a patient to come in for research purposes in that condition. You know, they've got to do the right thing, got to do what's right for the patient, but that will hurt the trial. There will be missing data; the trial is tarnished by that. But I don't think we should hold that against trials that have had to respond to the COVID pandemic. I think we have to use more common sense in terms of how we interpret trials.

I was personally affected by a trial, actually a few trials that were disrupted. One was the SOLOIST trial, where we just couldn't continue the trial at the height of the onset of the pandemic. And the trial, fortunately, was overall positive, but there were some endpoints such as real endpoints where the hazard ratios are going in the right way consistent with meta-analyses of SGLT-2 inhibitors, but the *P* value was not less than 0.05. Does it mean that that particular drug doesn't work to prevent renal events as every other drug in that class has? Again, I think we have to use common sense. I think the drug works for that endpoint, but if we're going to strictly worship at the altar of the *P* value, then we'll say, “Oh, that endpoint didn't reach statistical significance,” even though from a common sense level and looking at all the data preceding, and in this case also data coming afterwards, there's a consistent story there. So I think it's a real finding.

So that's an example. But there were are a number of trials like that in the heart failure space and other areas of cardiovascular medicine or medicine more broadly, that were affected. In some trials, it just had to be terminated with no information contributed.

And I think we have an ethical mandate as physicians and investigators to those patients who've enrolled in trials and to salvage whatever data we can and not be overly obsessing about the statistical aspects or if there's some amount of missing data. It's a pandemic. We've got to adapt and do what we've got to do to preserve scientific integrity, but to also honor the contribution the patients already enrolled in a trial have made and to salvage what useful information we can.

Dr. Butler:
So, Giuseppe, this is great. Do you have any specific example, for instance, how the pandemic affected a particular trial?

Dr. Rosano:
Yes, Javed, we had several examples. The first example was the AFFIRM-AHF, where the COVID sensitivity analysis basically showed that the trial would have been positive. The second one was the adaptation of the endpoint, as we've heard from Dr. Bhatt, on SOLOIST, that showed very significant results. And more recently, we have heard about the new primary endpoint of the DIAMOND study. The new primary endpoint will allow to investigate the role of patiromer in controlling serum potassium and potentially preventing hyperkalemia in patients with heart failure treated with RAASi [renin-angiotensin aldosterone system inhibitors]. And this is very, very important, given the strong recommendation from guidelines to use RAASi to reduce mortality and morbidity in our heart failure patients. Therefore, the new endpoint from the DIAMOND study will have a greater clinical importance because we'll look at the very important endpoint that affects the daily management of patients with heart failure together with the effect on events.

Dr. Butler:
For those just tuning in, you're listening to CME on ReachMD. I am Javed Butler, and here with me today are Dr. Giuseppe Rosano and Dr. Deepak Bhatt. We are discussing the impact of COVID-19 on the care of patients with heart failure and on current clinical trials.

So, Deepak, help me dissect this issue a little bit more. So what parts of the clinical trial process got affected by pandemic? Is it that the patients were not willing to be enrolled in clinical trials and the sites didn't have the infrastructure to continue with research enrollment? Was it that the study procedures could not be done in terms of endpoint ascertainment, the testing, and anything that was to be done after enrollment? Or is it that it primarily affected the event rate and that because people were not being hospitalized? What part was

affected, or is it all of it?

Dr. Bhatt:
Great points. And the right answer is all of the above. Not necessarily every trial was affected by all the above, but I would say every trial was affected by at least one of those things if enrollment and/or follow-up was occurring during the pandemic.

So it certainly made it tougher to enroll patients. In many cases, research personnel were not allowed to physically come to the hospital. So doing a trial of inpatients wasn't at all possible. In many cases, cardiovascular and even cancer trials were deprioritized because the emphasis was on completing COVID trials. So for a variety of reasons, the infrastructure, even at places with good research infrastructure, just wasn't present for enrolling patients.

As far as data collection in the follow-up phase of trials, that too can be challenging. I mentioned the example of a follow-up echocardiogram or cardiac MRI or a biomarker test that would involve, say, the patient coming back to the hospital or even some other hospital-affiliated office or healthcare facility. Just it wasn't going to be possible in many cases as the pandemic was surging. It would expose the patient to an unnecessary risk of exposure to COVID. And just not the right thing to do. So, of course, not everything could be ascertained in terms of follow-up.

And then you mentioned event rates, which also are affected by a pandemic in both directions. That is, the patient with chest pain that really has an NSTEMI not coming to the hospital because they're afraid. They just saw on the news that it's dangerous to go to the hospital because you might catch COVID. So they're not going to the hospital. Your patients with heart failure exacerbations toughing out at home, short of breath, uncomfortable – normally would have gone to the hospital, but you know, doing poorly. Some of them will decompensate and end up coming to the hospital in extremis. Some will die out of hospital, and it won't necessarily be known what they died from. Was it COVID that killed them? Was it heart failure? Was it an ACS [acute coronary syndrome]? Was it something altogether different?

So there's lots of different ways that the COVID pandemic has confounded trials and the interpretation of trials. And I think the only way around it is using a lot of wisdom that we've gained through the years in terms of how to interpret clinical trials. And also realizing that no trial lives in isolation. There's other trials, there's related basic science, there's observational data, and it's a matter of integrating all that and making sure whatever data we can get out of these trials that were disrupted by COVID, that we don't just throw out that valuable data.

Dr. Butler:
So that's actually really very insightful perspective that the natural history of the disease was affected in more than one way.

So, Giuseppe, let me come back to you now. Given that the disruption of both patient care and clinical trials in heart failure, this brings us to the question that I asked earlier. Where do we go from here?

Dr. Rosano:
Thank you, Javed. I don't think we're going to face the extraordinary events that we've seen during the first wave of the pandemic in the foreseeable future. Of course, we will be seeing the long wave of the COVID-19, but we will have to adapt to a new normal. Now a new normal that will involve using a different way of recruiting patients, in following patients, but also to adjudicate events. We have evidence from clinical trials that have been completed during the pandemic that the adjudication is very important. And Dr. Bhatt said earlier that we need to be sure that when a patient will have an event, that event is really a cardiovascular event and is not a COVID-19 event and vice versa. Because in the first and second wave, and even now, many patients that die with COVID, they are labeled as dying for COVID. And therefore, that raises the issue of adjudicating events in a proper way.

Also, I think we'll need to use different ways of recruiting patients and in this way, probably the randomized registry studies can be useful. We probably have to limit the in-person appointments. And also because patients are liking the use of the new technology, and we can use that telemedicine to limit the in-person appointments.

So I think we will have to readjust our way of working. We also need to work with the regulatory agencies in order to understand whether if we see patients remotely, then we can count that as a visit, and whether our assessment of endpoints can be done remotely. So there will be a lot to be to be organized. But I think that the technology and the big adaptation to technologies that we've seen in the past year and a half will prove very important to adapt to these new changes.

Dr. Butler:
Well, this has certainly been a fascinating conversation. But before we wrap up, can you each share a take-home message with our audience? Giuseppe, let me begin with you.

Dr. Rosano:

Yeah, we probably have to say that the COVID-19 pandemic has performed what we call a crash test on our national health services. And many of the national health services have proven to be very resilient and very effective. We have a great NHS in the UK, and that demonstrated a very, very good response.

But also, we had a crash test on the way we conduct clinical trials, and we have to learn from the COVID-19 pandemic in order to adapt and use new ways of conducting clinical trials – limiting the in-person appointments and using technology in order to simplify clinical trial procedures, and of course, with a continuous dialogue with the regulatory agencies.

Dr. Butler:
Thank you. Deepak, what about you?

Dr. Bhatt:
Again, those were really great comments; I agree with all of them. I think whenever there's a crisis, of course, we can just lament the crisis; that's understandable. But we can also learn from it, and that's what we need to do. We need to figure out ways to adapt our healthcare system so that they're more patient centric, patient friendly. But that also, they're geared to make sure that healthcare workers, physicians, nurses, researchers, et cetera, are operating in an environment that's good for their own mental and physical health. I think there's a lot of room for improvement on those fronts, too. So a lot that we are learning that we have learned that we'll continue to learn from the pandemic.

Dr. Butler:
So very well put by both of you. And I completely agree that the biggest thing is that this is not going to go away anytime soon and that we have to be flexible, and we have to adapt and change to the challenges in front of us.

Well, unfortunately, that's all the time we have today. So I want to thank our audience for listening in. And thank you both, Dr. Giuseppe Rosano and Dr. Deepak Bhatt, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Bhatt:
Terrific being with both of you.

Dr. Rosano:
Thank you very much. Has been great having been with you both. Goodbye.

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