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https://reachmd.com/programs/cme/the-future-of-heart-failure-management-rethinking-approaches-to-care/13089/

Released: 12/16/2021
Valid until: 12/16/2022
Time needed to complete: 30 minutes

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The Future of Heart Failure Management: Rethinking Approaches to Care

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[CHAPTER 1]

Dr. Rosano:
When caring for patients with heart failure, rapid initiation and up-titration of guideline-directed medical therapy [GDMT] is critical to achieve optimal patient outcomes. Specifically, international guidelines recommend a simultaneous or rapid sequencing of the 4 pillars of heart failure treatment. This implementation of guideline-directed medical therapy, however, should be adopted to patient characteristics, taking into account factors like heart rate, blood pressure, and renal function, using a personalized approach to treatment rather than a dose-directed, stepwise up-titration.

This is CME on ReachMD, and I am Dr. Giuseppe Rosano.

As mentioned, all the recent guidelines and guidelines updates suggest implementation of the 4 classes of drugs that have consistently shown a mortality and morbidity benefit in heart failure with reduced ejection fraction. Differences, however, exist in what the different guidelines suggest as foundation therapy, with the ESC/HFA guidelines suggesting the need of an up-titration of ACE [angiotensin-converting enzyme] inhibitors, beta-blockers, and MRAs [mineralocorticoid receptor antagonists] before proceeding to a switch of an ACE inhibitor for an ARNI [angiotensin receptor-neprilysin inhibitor] in those patients who continue to be symptomatic and have a left ventricular ejection fraction less than 35%. Of importance, all the guidelines, however, concur in suggesting a simultaneous initiation and up-titration of the renin–angiotensin–aldosterone inhibitors [RAASi] with MRAs that should be started and up-titrated alongside the ACE inhibitors. This is a big change from the previous stepwise approach and will most probably lead to a greater uptake in the use of MRAs.

So furthermore, after the results of DAPA-HF, EMPEROR-Reduced, and SOLOIST, the SGLT2 inhibitors have now become the 4th pillar of guideline-directed medical therapy in heart failure with reduced ejection fraction. Now given their immediate prognostic and symptomatic benefit, their ease of use, and the lack of any significant effect on heart rate and blood pressure, these drugs should always be implemented alongside RAASi and beta-blockers and/or ARNI. Additionally, the concurrent use may also have to overcome some of the side effects of simultaneous RAASi use like hyperkalemia and decline in renal function.

Despite guideline recommendations and available evidence, the implementation of treatment in heart failure is poor. The majority of patients are not prescribed drugs at target dose that have been proven to be effective in mortality and morbidity trials.

Among other factors, tolerability issues related to low blood pressure, heart rate, impaired renal function, or hyperkalemia are responsible for the low up-titration.

Chronic kidney disease plays an important role in heart failure with reduced ejection fraction, as it affects up to 50% of patients. We

also have to take into account the dynamic changes in the glomerular filtration rate that may occur during the course of heart failure, and this may result in an inappropriate dose reduction or even a discontinuation of neurohormonal modulating therapy in clinical practice.

For this reason, it is important to up-titrate the foundation medications using a personalized approach. This approach suggests a clinically re-entered up-titration of medications according to the spending functions of heart rate, blood pressure, kidney function that may limit the tolerability of the different classes of drugs.

And that's all the time we have for this topic. Stay tuned for Chapter 2, in which Dr. Marco Metra discusses guideline-directed medical therapy. Thank you.

[CHAPTER 2]

Dr. Metra:
Hello, this is CME on ReachMD, and I am Dr. Marco Metra from the University of Brescia, and I'm going to cover a key topic: how to better sequence and optimize medical treatment in the patients with chronic heart failure and reduced ejection fraction.

We know now that there are 4 classes of drugs that are indicated for the reduction in mortality and the reduction in heart failure hospitalizations in all the patients with heart failure and reduced or mildly reduced ejection fraction. ACE inhibitors or ARNI, beta-blockers, mineralocorticoid antagonists, and based on the recent results of DAPA-HF and EMPEROR-Reduced, SGLT2 inhibitors dapagliflozin or empagliflozin. Now the problem is how to implement these drugs that are all lifesaving for our patients. And what has come out, also in the recent guidelines from the ESC, is that we do not have to have a rigid approach based on add-on therapy. The physician is left free to implement and to start these drugs according to the patient's characteristics. The important is that all the 4 classes of drugs, if possible and if tolerated, are administered to all the patients with heart failure in the shortest time as possible, possibly within 1 month.

Then the sequencing is based on the patient's characteristics, and as Dr. Rosano has already pointed out, we have to consider blood pressure, which may be a limitation if low for the start and the up-titration of ACE inhibitors or ARNI, and to a lower extent, beta-blockers. Heart rate, which may be, if too low, a limiting factor for the starting and the up-titration of beta-blockers, which are, however, titrated to a target heart rate of about 60 beats per minute. Then we have mineralocorticoid antagonists which may find a major cause of lack of initiation and lack of administration at target doses in the patients with reduced renal function and in the patients with hyperkalemia. Actually, kidney dysfunction and hyperkalemia may also limit the up-titration and the start of ACE inhibitors or ARNI. And therefore, it is important to consider new potassium-lowering agents as an add-on therapy to facilitate the initiation and the up-titration of the lifesaving therapies. More recently, we have this new class of drugs, the SGLT2 inhibitors, acting through completely different pathways and which do not require up-titration. They have a mild effect or non-effect on systolic blood pressure, and they may improve or protect kidney function in the long term. Although, with all these classes of drugs, kidney dysfunction is a major limitation for treatment and may be a reason to try to add other drugs, like potassium-lowering agents, to improve tolerability of lifesaving therapies.

And now, so with this in mind, unfortunately, that's all the time we have for this topic. And therefore, stay tuned for Chapter 3 with Dr. Javed Butler where he will talk to you about the impact of COVID-19 on heart failure clinical trials. Javed, we are all eagerly waiting to hear your comments. Thank you.

[Chapter 3]

Dr. Butler:
The COVID-19 pandemic has had a tremendous global impact. Not only has it disrupted the clinical care of patients with heart failure, but also clinical trials, leaving some trials shut down permanently, while others are slowly resuming. This has created concerning delays in the research pipeline.

Let's take a closer look at how the COVID-19 pandemic impacted clinical research in heart failure and the clinical implications of the disruption in research.

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

So how has the COVID pandemic impacted trials? Well, the COVID pandemic has impacted trials in all its entire spectrum. So let's start in the beginning, when the COVID pandemic had recently started. There was a lot of concerns. We did not know which direction this pandemic will take. What will be the mortality tolls? What is exactly the infectivity? And at that time, a lot of the hospital centers completely shut down clinical research. The clinical trial staff was repurposed into other areas that were of immediate need for the care of patients with COVID, and even if the research staff were available to do clinical trials, the clinical trials were still shut down because of

the safety concerns for both the staff members as well as the patient safety itself. What did that do to the trials? Well, it significantly delayed trials in its entire spectrum. New trials did not get started up. The trials that were already ongoing had significant delays in terms of the study procedures. The study procedures were not being conducted at the appropriate time or to the appropriate degree. We had to learn a lot of things. A lot of the things were shifted to alternate ways of taking care of clinical trial patients. For example, doing things remotely, having a contract with home healthcare to give investigational drugs, using mail system – all of that had to be engineered. Then what also happened was that a lot of the trials had to just completely shut down, because despite of all of these potential ways of conducting the trial, it was just not feasible to continue some of the trials. So for instance, SOLOIST trial, with sotagliflozin, an SGLT2-1 combined inhibitor, was completely stopped in the middle for all of these COVID-related concerns, and we will never know the answer, whether the SLGT1-2 combined inhibitor has differential effect on outcome than SGLT2 inhibitors alone.

Then let's take a trial like the DIAMOND trial. This was a trial with a potassium binder that was looking at the impact of enablement of RAAS inhibitor therapy in heart failure patients with history of current hyperkalemia. Again, same concerns. All the trials, monitoring is important, but in a trial like this, monitoring is critical, because you are up-titrating RAAS inhibitor therapy on the basis of a potentially efficacious therapy and not following patients closely, not doing the lab tests closely. Slowing in trial enrollment and processes led to also curtailment of that trial, and the trial, the decision was made to change the endpoint and not continue in its entirety, so again, another question for which we don't know the answer.

The evidence generation has become a little bit more difficult to understand, perhaps a little bit more unreliable. The healthcare-seeking behaviors have changed, and that has certainly caused a delay in the research pipeline in trying to address important questions for our patients with heart failure.

Well, unfortunately, that's all the time we have for this topic right now. Please do stay tuned for Chapter 4 in which Dr. Ileana Piña takes a closer look at clinical trials of heart failure with preserved ejection fraction. Thank you so much, and over to Dr. Piña.

[Chapter 4]

Dr. Piña:
Traditionally, heart failure has been divided into distinct phenotypes based on the measurement of left ventricular ejection fraction. The evidence behind this relates to the original treatment trials in heart failure that demonstrated significantly improved outcomes in those who had an ejection fraction of 40% or greater and a worse outcome for those who had it less. Heart failure, however, really spans the entire range, and measurement by echocardiography is always subject to substantial variability.

The recent ESC/HFA guideline updates, we have now seen that patients with ejection fractions between 41 and 49, what we would call mildly reduced LV systolic function, or mrEF, has become now a definition that we use. This is based on retrospective analyses of randomized, controlled trials with reduced ejection fraction, or HFrEF, or those who have preserved ejection fraction, or HFpEF. These trials have included patients with ejection fractions in the 40-50 range, suggesting that they may benefit from the same therapies as those with HFrEF, or less than 40.

In light of these recent characterizations of heart failure in these aforementioned phenotypes, this really deserves a discussion. How can we rethink our approach to these clinical trials?

This is CME on ReachMD, and I'm Dr. Ileana Piña.

So, HFpEF. We used to call it diastolic dysfunction years ago. A colleague of mine actually, in 1983, while at the University of Miami where we were both fellows, was sitting in the ECHO lab, watching some of these ECHOs coming through of patients who were admitted with decompensated heart failure, but nonetheless had ejection fractions of over 40. And he realized that the primary presentation – these were women, older women, with the same exact symptoms, with lots of comorbidities. We then moved through time and we started calling it heart failure with preserved ejection fraction, a lot of it based on the CHARM trial, CHARM-Preserved, which was a whole big trial of over 2,000 patients. Who were they? Primarily women and primarily older women. The drug was candesartan. But a recent analysis of that trial showed that beyond about 50, the benefits of candesartan was diminished. Then we go through I-PRESERVE. Same thing. We go to TOPCAT. TOPCAT – spironolactone. All of us had tremendous hopes for spironolactone in this HFpEF population, and overall, yes, a reduction in hospitalizations, with lots of problems about where the venues were that the trial was done. But that same type of analysis shows that the effects of spironolactone lessen as the ejection fractions go up.

So I asked myself, and I'm asking all of you, have we really been studying HFpEF? Or have we been studying a milder form of HFrEF, what we call this mrEF? So I think newer definitions are very worthwhile, because the patients have similar symptoms. You can't tell them apart. They come in with diabetes, hypertension, renal dysfunction, and the drugs that we love to use, that we have been using now for over 30 years, do have their side effects – hyperkalemia is one of them – and now we have potassium binders that we can work

with those to lower the potassium and do it completely safely. We have two of those on the market in the United States, not all over the world yet.

So I'm asking all of us to really rethink, does HFpEF really exist as a separate entity, or is the heart an innocent bystander in the midst of all these comorbidities? In addition, we often don't talk about the aging of the heart, and these are, in fact, older patients. What is the effect of the aging of the heart? Is there more fibrosis making those hearts thicker and stiffer? Should we be looking at left ventricular volumes instead?

Unfortunately, that's all the time we have today, so I want to thank you, our audience, for listening. It was great speaking to you, and now we are going to move into our panel with my colleagues. Stay tuned.

[CHAPTER 5: PANEL DISCUSSION]

Dr. Piña:
Hello, I'm Dr. Ileana Piña, and I'm joined today by my colleagues, Dr. Javed Butler, Dr. Giuseppe Rosano, and Dr. Marco Metra. We will be recapping our views and the data that we presented in the previous chapters of this program. We'll also look at ways that we can all adopt the changes to the ESC/HFA guidelines into our own clinical practices.

This is CME on ReachMD. Drs. Butler, Rosano, and Metra, welcome again, and thank you for joining me today.

Dr. Butler:
Absolutely a pleasure to be here with you, Ileana.

Dr. Rosano:
Thank you for having me.

Dr. Piña:
So Giuseppe, let's just start with you. And let's start by discussing the key points from your presentation in Chapter 1.

Dr. Rosano:
So basically, the new guidelines moved away from the stepwise approach that we had in the previous guidelines, where we had to start with an ACE inhibitor and beta-blocker, then going to an MRA, and then if patient's still symptomatic, to an ARNI or ivabradine.

Now, there is a clear suggestion to start the 4 foundation therapies all together, all from the start. All at any encounter with patients with heart failure and reduced ejection fraction. Also, there is a very important point on the SGLT2 inhibitors that have a Class 1A recommendation after the tremendous results of the clinical trials in patients with and without diabetes. The problem is that sometimes it's difficult to implement medical therapies, and so we have to do that, profiling our patients according to heart rate, blood pressure, kidney function, and the Heart Failure Association of the ESC has proposed a new algorithm to implement medical therapy according to what's suggested by the guidelines.

Dr. Piña:
Thank you, Giuseppe. Dr. Butler, do you want to add anything to that?

Dr. Butler:
The only other thing that I would highlight is that the guidelines also specifically mentioned to try to achieve the GDMT in the hospital setting if somebody is in the hospital, because we know that starting therapies in the hospital is one of the best predictors of long-term adherence.

Dr. Piña:
Well, I think that all this really requires a very important thing, which is a conversation with the patient, because you're – especially a new patient, you're going to be blasting them with 4 new drugs. If they've had hypertension, maybe they've had one RAAS inhibitor, and now you're going to give them 3 more? So you've got to really have good tools to share with a patient, and a good conversation.

So, Marco, can you take us through the key considerations of your Chapter 2?

Dr. Metra:
Yes. The key considerations are that we have 4 drugs that are indicated for all our patients with heart failure and reduced or mildly reduced ejection fraction. And we must try to administer them as soon as possible, within possibly 1 month from when we make the diagnosis of heart failure in the patient. And of course, the clinical characteristics of the patients are of utmost importance. And drugs, and namely, it's also pointed out in the relatively long section regarding comorbidities, they play a major role. In some cases, it's not really a problem. Hypertension and/or coronary artery disease share similar drugs, some similar drugs, both in patients with heart

failure and with the patients with heart failure. But in some cases, a comorbidity may be a major limitation. And this is, mainly the case of kidney dysfunction and electrolyte abnormalities. We know that kidney dysfunction is a major limitation for the start, if not the up-titration, of ACE inhibitors or ARNI and with respect of hyperkalemia, of mineralocorticoid antagonists. And it is at this level that potassium-lowering agents may have a major role because they favor the concomitant administration of these lifesaving therapies. So it's a synergic treatment, and this may guarantee a better quality of life and a longer life to our patients.

Dr. Piña:
Thank you, Marco. Giuseppe, do you want to add anything to that?

Dr. Rosano:
I think it's that was very complete, and Marco highlighted very, very well the importance of the comorbidities that play a very important role, also, limiting the possibility sometimes of up-titration of medical therapy.

Dr. Piña:
Javed, comments?

Dr. Butler:
Yeah, I mean, Marco covered it very well. The two very quick points that I would emphasize, one is that the whole premise of practice of medicine is to avoid patients getting sicker, so we need to give these therapies as early as possible and not wait for people to get sick. And then the second point is, again, it's 4 foundational therapies. This is synergistic, additive benefit. This is not something that you can just get 2 medications or 3 medications and get by. So we also have to change that mindset. We now have very credible data that these drugs work on completely independent pathways and the benefit is additive, and we add different medications on top of each other. So 2 medications is not as good as 3, and 3 is not as good as 4. We really need to give all 4 foundational therapies.

Dr. Piña:
Let me add a touch of reality to the hospitalized patient, where at least in the United States, you may only have 3 or 4 days to do anything. And so that transition of care to the outpatient setting is going to be absolutely critical, and if you're seeing the patient in the outpatient, you're going to have to see them more frequently.

So, Javed, I've been watching these COVID-19 trials during the COVID-19 period, and what havoc the pandemic has wreaked on a lot of the trials, and I think your comments were right on the money. Can you do a summary of your thoughts on this?

Dr. Butler:
You know, the beginning phase was very concerning. Some trials were basically just shut down. But even as things slowly started opening up, there were a lot of issues, right? I mean, the natural history of the disease changed; the healthcare-seeking behavior changed; the number of heart failure hospitalizations went down; the issues related to power of the trial; the trials, because of slow enrollment, patients' fear, the sites not working.

Many of the trials were stopped prematurely, earlier than what they were supposed to do. New trial initiation was delayed. So if you put sort of all of these things together, it has really impacted on being able to answer novel important questions how to manage our patients with heart failure, and we are sort of living now in a sort of pandemic, COVID, you know, go through the cycles. Every time we sort of think that we are beyond pandemic and then some part of the world, the cases will start rising up again. So we actually don't know which direction things are going. But, there's a little bit of a silver lining here is that now we are thinking a little bit more in terms of pragmatic clinical trials and how if we just assume that this pandemic is going to be with us for a little while, in the future we can still generate evidence by employing some different ways of conducting clinical trials. But so far, it has really impacted clinical trials in a significant way.

Dr. Piña:
Giuseppe, Europe has been just as impacted as the United States, and in some areas, even more. Any comments on Javed's points?

Dr. Rosano:
I think he covered all the problems related with the COVID pandemic, but I think we now, here, have an opportunity, an opportunity to learn from what has happened and what we have done. We have learned to use more remote systems. So this is something we should more implement in future clinical trials, and that will probably streamline the clinical trials of the future.

Dr. Piña:
Marco, what are you seeing in Italy that was really hit very, very hard early on?

Dr. Metra:
Now the situation is different, but we still have patients with COVID, despite higher than 85% of the patients who are – or subjects who

are vaccinated in Italy. But we still have COVID patients, and I think we are learning – we have learned and we are starting to live with this deadly disease, and we have to deal with it, and this will not stop science in the end.

Dr. Piña:
Yeah, I fully agree with all your comments. We've been sort of stunned by the drop in hospitalizations for acute heart failure, and we've tried to think about this, and Dr. Butler and I have had this conversation before. I think the patients were taking their medications like they should because they were absolutely terrified of getting sick and having to come into the hospital and be around COVID patients and get sick. So how we emerge out of this, it's not going to be the same. I think we're going to be quite different.

So that leaves us with my presentation and, Javed, you will be presenting the EMPA-REG Preserved, and it was presented at the ESC and you're going to be presenting the health status. And I think those drugs are going to be a game changer in HFpEF. We cannot forget that we still need to control blood pressure. That, you know, diabetics need to be cared for, and now the SGLT2s, initially used for diabetes, can now be used for all the patients. But that these patients have a lot of comorbidities. They also tend to be older and frail, and we're going to have to find ways to get these patients moving more within their own environment. This is going to be very hard to put them into cardiac rehab, and yet we know that cardiac rehab works on these patients. So we're learning a lot, and to me, it's opened just a brand-new chapter in the HFpEF patients that will probably be sitting in the primary care offices. They're the very last to get to us with their symptoms.

So those are my key takeaways. Javed, do you want to comment on what I've just said?

Dr. Butler:
Yeah, no, I mean, I completely agree with you. We finally have a drug which is unequivocally positive in patients with heart failure and preserved ejection fraction. The second thing is that we know that these drugs prevent heart failure in type 2 diabetic patients, prevent heart failure in CKD patients, with or without diabetes, and we have data for improved outcomes in HFrEF and HFpEF.

Dr. Piña:
Marco, I'm going to go to you next.

Dr. Metra:
I think we have dealt with an important topic which is implementation of evidence-based medical treatment for the patients with heart failure and how to better titrate the drugs to have the most favorable effect as possible and a better tolerance by the patient.

Dr. Piña:
Giuseppe, any comments on the HFpEF population?

Dr. Rosano:
So we have to think of the devices, therapies, that may also be complementary to the SGLT2 inhibitors, and all other interventions – metabolic interventions or other type of interventions that will come in the future that will complement. But what is good is that now, we have at least the first type of drugs. It's like 20 years ago when we started with the beta-blockers and then we had the ACE inhibitors.

Dr. Piña:
So unfortunately, that's all the time that we have today, but I want to thank our audience for listening, and thank you, Giuseppe, Marco, and Javed, for joining me and sharing all these great insights. We hope they are helpful to the audience, and it was great speaking to you today.

Dr. Butler:
Absolutely a pleasure to be with you, Ileana.

Dr. Rosano:
Thank you for having me. It's a pleasure.

Dr. Metra:
My pleasure, too.

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