Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/demystifying-continued-pharmacologic-therapy-hfref-pivotal-opportunities-improve-patient-outcomes/12902/

Released: 09/28/2021
Valid until: 09/28/2022
Time needed to complete: 1.5 hours

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

Demystifying Continued Pharmacologic Therapy in HFrEF – Pivotal Opportunities to Improve Patient Outcomes

Announcer:
Welcome to CME on ReachMD. This episode is a replay of our HFFA symposium and is part of the Global Heart Failure Academy, and is brought to you by Medtelligence. Prior to beginning the activity, please be sure to review faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Pina:
Good evening everyone, and – and thank you for joining us. I realize this is also dinnertime, and there's some really good food out there, so please, uh, help yourselves. Um, make sure you scan, in all your chairs there, it will have the, um, the bar code to scan it. We're asking you to scan it, so that we can get the data of what we have here in the program, etc. Also want to remind you to put your phones on vibrate, uh, so that, uh, we don't in – interfere with the speakers. Um, so I wanna personally welcome you. Um, we are in a very exciting time in the heart failure world. We – we have, um, a lot of new medications, um, but I think through the years, the patients are getting more complicated, more complex. The comorbidities are raging, and I don't know what's going to exit out of this COVID, uh, pandemic, and we may have to learn new ways of doing things, and now we're facing what will – so we've got all this richness of drugs, what do you do first? So this program really is dedicated to getting sort of an overview and a review, and offers some suggestions. I have some wonderful faculty with me. Uh, Dr. Giuseppe Rosano, who will be on camera, uh, pre-taped. Uh, he is in Italy, and the first author of the European Guidelines, which were just presented at the ESC in August. Um, and in the heart failure world, we work very closely with our European colleagues, and share, um, many programs with them. Um, sitting here to my left is my good friend, Javed Butler, who's the Chair of Medicine at the University of Mississippi in Jackson, uh, and on the editorial board of CERC, uh, and a frequent writer and also one of the principle investigators for the empagliflozin HFpEF trial, which we heard about last week. To my right, my other good friend, uh, Gregg Fonarow, from the Geffen School of Medicine in L.A., at UCLA. Uh, Gregg is well-known for his incredible knowledge of the epidemiology of heart failure. We've been working together – I get with the guidelines for many years, and have produced just an incredible number of papers. When I wanna know a piece of data, I know I can write to Gregg at 11:00 on a Sunday, and he answers me, much to his wife's chagrin (laughs), and no matter what she does, he's still working at 11:00. Uh, and so, this is gonna be a – a – a terrific discussion. And so how we're gonna do it is we're gonna have these short, little vignettes of presentations, and then we're gonna have a very brief discussion back and forth, to really keep it animated.

Um, and then we'll have time for questions and answers, so think of your questions, submit them. We do wanna hear from you, uh, because like I said, this is – this is a complex disease. This is not simple heart failure any more. So, um, without much ado, remember to turn off your phones. Um, we will – and by the way, I want to thank Medintelligence for this work. My good friend, Megan Clem, who has been just very instrung – in – instrumental in putting this together, and to Vifor Pharmaceutical, and I see Fabio sitting there, thanking them for their support of education, which is really – continues to be resound.

So I have a few questions for you. Uh, and here's your first one. This is for the, uh, AR system, or the response system. And the first one is, please identify your profession – cardiology, interventional, nephrology, primary care. And you can see the numbers are changing as we go. 'Kay. So, you're not gonna see the answers to these. These are our pretest. This is an ACGME-approved program, so we have a pretest.

Which of the following statements is true, regarding the use of GDMT – guideline-directed medical therapy – in patients with HFrEF, or heart failure with reduced ejection fraction? More than half of all patients with HFREF receive optimal or close to optimal dosing, of RAAS inhibition or beta blocker; number two, or the second one – the risk of escalating GDMT to optimal dosing in a patient who might tolerate it is higher than the risk of providing subtarget dosing, in terms of heart failure complications and discontinuation of therapy; patients receiving GDMT have a 63% relative reduction in mortality, which increases to 74% when adding an SGLT2 inhibitor; and, according to the Champ registry, greater than 50% of eligible patients receive triple therapy consisting of an ACE, an ARB – ARNI, a beta blocker, and an MRA. So go ahead and choose your number here, and we have a lot of people who are tuning in virtually as well. Uh, we don't see them right here.

'Kay. Next one. Which of the following statements is true, regarding serial or sequential initiation of GDMT versus simultaneous rapid initiation of therapy? Using a serial strategy, GDMT is fully implemented in most patients in 24 weeks; using a simultaneous rapid strategy for GDMT initiation can show a rapid improvement in health status - remember HR-QOL, health status, quality of life – within eight weeks; when employing the simultaneous rapid strategy, the SGLT2 inhibitors introduced one week after the ARNI, beta blocker and MRA have been titrated; and, simultaneous rapid strategy for GDMT initiation can lead to less tolerability, lower adherence and greater adverse effects; and then the final one is, I'm not sure. So, pick your battle there.

What is the relative risk reduction – remember, relative, not absolute – risk reduction observed in patients within 30 days, whose GDMT was initiated with a simultaneous or rapid strategy? Around 15; 75% or greater; around 35%; 90% or greater; around 45%; or you're not sure.

Gosh, you wrote these questions, these are tricky questions. It sounds like you – this one sounds like you. (laughs) I hope you can write.

Having four or more comorbid conditions makes up approximately what percentage of Medicare spending in the U.S.? Because remember, most of our patients are over 65 in most of our studies. 30%; 45; 60; 75; 90; or you're not sure.

In a patient with HFrEF, defined as an LVF of 30% or probably lower, treated with a beta blocker, spiro, enalapril, furosemide, and a serum potassium of 5.7. What is the most appropriate next step, in optimizing therapy? Decrease the ACE; stop the spiro; add SPS; add a novel potassium binder, such as SZC or patiromer; or decrease the beta blocker and ACE doses. I'm giving a minute for our virtual people to catch up.

In what percentage of your patients with HFrEF are you currently initiating the ESC/HFA four main Class 1 therapies, which is a RAS inhibition, a base, or ARNI, beta blocker, MRA, SGLT2, in a rapid simultaneous manner? Read the question – in a rapid simultaneous manner. (Pause) Interesting.

And so, without much ado, I will introduce my good friend, Giuseppe Rosano, from Italy. Uh, they have had some difficulties traveling, uh, and it's – it's not been, uh, readily noticeable, but you don't see any Europeans here in our meeting, at least that I have noted, and, um, we – we do miss them. So, uh, Giuseppe, uh, is in Milano. Uh, he has been working on guidelines and a lot of statements, uh, through the ESC. He holds an office in the European Society of Cardiology, and is an incredibly well-known, uh, speaker. Giuseppe.

Dr. Rosano:
Thank you, Ileana. Uh, the next eight to ten minutes, I will, uh, discuss how the new ESC/HFA guidelines will, uh, impact the treatment of patients with heart failure and reduced ejection fraction. These are my disclosures, and, uh, we have seen with the publication of the, um, ESC/HFA guidelines, that, uh, we have moved away from your concept of a stepwise initiation of, uh, gu – um, medical therapy in patients with heart failure and reduced ejection fraction. So now, instead, we have, uh, suggested to start together, the ACE inhibitors, uh, RAASi, when appropriate, beta blocker, an MRA, and an SGLT2 inhibitor, and more specifically, dapagliflozin or empagliflozin, and a loop diuretic, in cl – case of fluid retention. Then, if, uh, patients, uh, continue to be symptomatic, then we may consider, uh, class 2 recommendations. Now, looking at the, uh, class 11 of, uh, recommendation, we see there is, we have maintained that an ACE inhibitor, beta blocker, MRA's and dapagliflozin and empagliflozin, uh, are all class 1A to reduce the risk of hospitalization and cardiovascular death, and, uh, _(11:37)_ is recommended as a replacement for ACE – an ACE inhibitor in those patients with heart failure and reduced ejection fraction, uh, but continue to be symptomatic despite _(11:45)_ therapy, with, uh, the class 1B recommendation.

The new guidelines have also, um, included and introduced for the first time, a new treatment, which is vericiguat, that can – may be considered with a class 2BB recommendation in patients with, uh, class 224 with worsening heart failure despite treatment with an ACE inhibitor, Enalapril, and a beta blocker, MRA, to reduce the risk of cardiovascular mortality and heart failure hospitalizations. With, uh, the four iso – uh, hydrolyzene and isobi – uh, the nitrate, we have a 2AB recommendation for specific subset of patients, and a 2BB recommendation in, uh, those patients who are symptomatic and cannot tolerate an ACE inhibitor or a NAAB, or an AMI.

Now, this is how the, uh, algorithm, uh, for the treatment of, uh, for the management of patients with heart failure with reduced ejection

fraction look like. So basically, we start together all the – for the four foundation therapy, and then, according to the different _(13:03) _ - according to whether there are specific conditions that will, uh, suggest the use of ADVICE, CRT, ICD, CRT-P or D, and the presence of, uh, other comorbidities – cardiac or not cardiac comorbidities, like atrial fibrillation, coronary artery disease, iron deficiency or elevated heart rate – then there would be an indication for different therapies or devices.

In, uh, regarding, uh, patients with, uh, uh, an ejection fraction up to 50% - so those patients with heart failure with, uh, uh, uh, morbidly reduced ejection fraction – we see that we have only, uh, class 1C condition for diuretics, whilst all the other, um, classes of drugs have a class 2B-C, uh, given the insufficient data that we have at the present.

Specific, uh, um, algorithm has been researched for those patients with, uh, heart failure and ischemic heart disease who have, uh, still are symptomatic. In these patients, there is a recommendation for a beta blocker, and in case of persistence of symptoms, and – and heart rate greater than 70 beats per minute, the use of _(14:28) _, and in those patients with, uh, a heart rate, uh, lower than 70 beats per minute, anti-anginal therapies, with, as you can see, trimatoziline and ranolazine, uh, uh, to be, uh, um, considered, uh, initially because of the, uh, neutral effect on heart rate and, uh, blood pressure.

However, we have to take into account that implementing medical therapy in clinical practice is difficult. It's difficult because, uh, drugs, uh, side effects can go from hypertension to hypo or, uh, hyperkalemia, caff – cough, or hypertension, and worsening heart failure if implemented too rapidly, or increasing, uh, uh, creatinine and worsening renal function. And also, there can be some, uh, limitations according to the different comorbidities, say, for example, in patients with, uh, asthma, patients with erectile dysfunction, or patients with, uh, cachexia or coronary artery disease, and, uh, angina, where specific drugs are contraindicated.

And for this reason, the Heart Failure Association of ESC has, uh, suggested a different approach to the implementation of medical therapies. So, we've, uh, therefore, maintained the four pillars of treatment for, uh, for heart failure, so the SGLT2 inhibitors, the beta blockers, ACE inhibitors or iron therapies are now meet our MRA, and – but then, there would be a need to adjust the – their implementation, so how to – how titrate the different drugs, according to heart rate, according to blood pressure, presence of an atrial fibrillation, and renal function.

And you can see here, for example, in, uh, these patients with, uh, uh, sinus rhythm with a good blood pressure, and, uh, – and heart rate between 60 and 70 beats per minute, we can see that we can start all the – all medications together, and then we can implement, especially, uh, increase the dose of beta blockers, ACE inhibitors, _(16:52) _, and MRA, as a – um, as appropriate. On the other hand, if we have patients with low blood pressure, or patients with low heart rate, of course the implementation of beta blockers or ACE inhibitors _(17:07) _, becomes more difficult, and, uh, therefore we need to take different approaches. So in conclusion, the heart failure guidelines suggest a fast implementation of the four foundation therapies in patients with heart failure and reduced ejection fraction.

They – however, the recommendations, uh, that we've – we gave on heart failure and, uh, mild and moderately-reduced ejection fraction, and, uh, HFF, already – our data, given that four hours after the presentations of the guidelines, the, uh, EMPEROR-Preserved has been presented. So, there will be a need in the future to revise the _(17:54) _ – uh, um, base, uh, classification of heart failure. We have to think differently. We have to approach them differently. However, the initiation of all life-saving medications is warranted. But then we encounter with patients with heart failure, and their heart titration should be implemented according to the different patient profiles, rather than directed by the target dose of, uh, um, the – the four foundation, uh, therapies that are seldom achieved in clinical practice. Back to you.

Dr. Pina:
Nice is they give us all these tables, that are easy to kind of pull out of the rest of the paper, and – and act on it. But I've noticed now, that they pulled out mrEF as a totally separate indication, so, Gregg, why don't you talk a little bit about that – about the mrEF classification.

Dr. Fonarow:
So it's, you know, certainly been involving. We have – this was reviewed so nicely. This really incredibly compelling data for mortality reduction for patients with symptomatic heart failure where the EF is 40% or below. We have emerging data that has come through in trying to test our same drugs in patients with heart failure that have been globally classified as preserved EF, but often with trials starting off at EF's of 45% or higher, where they're far more attenuated benefits, but certainly in that group between EF of 41-49%, sort of a mixed population, to where we can tease out benefits with Sacubitril/Valsartan, with MRAs, and more recently, and far more robustly with SGLT2 inhibitors. So we always have that problem when we want to categorize and make it very simple, when things are continuous, we know precision for EF is not perfect and down to the single unit, so there's some variability there. But in some ways, that mildly reduced EF population does tell us, look, some of these same medications may work here. Not as robustly, not continuous all-cause mortality reductions, but reduction in hospitalization, CV death, and these drugs should be considered. And then as we get to those EFs – particularly 60% or above, where phenotyping for the research is really gonna be necessary, but still we may selectively consider some of these medications. So, a lot of what this is pointing to, we need more trials and more research in characterizing this

population, and whether we can tease out the subgroups that truly derive large benefit from these drugs.

Dr. Pina:
Well, let's remember that that group has also included the patients that have gotten better. The – the recovered, of which I never stop their drug. Even if they go from 30 to 40 or 45, I keep 'em on the drugs.

Dr. Fonarow:
Well, what I think the universal classification does so well, as does the ESC guidelines, of really distinguishing those patients. Those are no way, heart failure mildly reduced EF or preserved EF. They were heart failure reduced EF that have now improved…

Dr. Pina:
Right.

Dr. Foranow:
Have now in potential remission, but need continuation of the full contingent of medications for heart failure reduced EF…

Dr. Pina:
That improved, though. The drugs had actually improved them.

Dr. Foranow:
Yeah.

Dr. Pina:
Yep. So, Javed, you've been at the forefront here of (21:26), and the, uh, HFpEF population. Have you changed your definition of HFpEF?

Dr. Butler:
Well, I went to the HFSA/ESC/HFA and Japanese Heart Failure Society came up with their release and universal definition of heart failure, and it was, uh, the terminology changed, but the categories pretty much mirrored what, uh, ACCHA and the ESC original guidelines were. Uh, but I think this is really time to – for contemplation, based on the EMPEROR-Preserved results. Uh, let's see what the deliver shows. Uh, but – but I would think that, uh, HFrEF definition – I think probably, uh, mildly reduced or mid-range probably would go away and HFrEF would become something like 50% or 55% and less. Uh, and I think that's the way probably we are heading to, but let's see.

Dr. Pina:
Now, I mean, I went back and I looked up my old Braunwald, from when I was a fellow, and Braunwald clearly said in his heart failure session that heart failure, which was then diastolic, was over 55, and at normal was up to 55. And so I think when we've been dealing with these patients that are just mildly – and then you wonder what the progression is of those patients if you don't treat them, uh, actually. Um, Javed, um, what do you do with your mrEF patients?

Dr. Butler:
Yeah, so, I mean I think the – the – granted it's subgroup analysis, but I think the data are so convincing, with the CHAR, with CANDACE-R10, with TOPGAP, with spironolactone, valsartan, sacubitril, and now, um, empagliflozin, that I think that, uh, the – the European guidelines, the 2BC recommendation, kinda sounds like a soft recommendation, but remember that soft recommendation is largely based, not on whether people believe that should be done or not to it, but based on the secondary analysis of the trial, so it's the evidence…

Dr. Pina:
Exactly.

Dr. Butler:
…base on which it was based. But I would say that at this point, at least up to 50%, and perhaps up to 55% is very reasonable to give quad-therapy.

Dr. Pina:
Ah, I agree. Um, Javed, you can come and convince us of more. Your talk.

Dr. Butler:
'Kay. (Pause) So we're gonna do the…

Dr. Pina:

We may need to go back one more. Yup.

Dr. Butler:
…question. Maybe we'll go back. Yup.

Dr. Pina:
There we go.

Dr. Butler:
So, maybe we can take a few seconds to answer this question. So, "Over the last decade, give or take, uh, the overall use of guideline drive medical therapy in patients with HFrEF – do you think that over time it has gotten considerably worse; uh, it has gotten considerably better; it kinda, sorta, remained about the same; uh, or that we are perfect and the treatment gap has been bridged?" So, some people are optimistic, and some people are pessimistic, and most people are realistic. That's right. Okay. Well, in about, uh, fifth, sixth slide, I – I'll, uh, go over this. Great!

So, uh, appreciate the opportunity to be talking in this seminar. The reason why the answers keep coming because there is a virtual crowd out there that is also answering, and there's a little bit of a delay, in case you all are wondering. You're not answering so, this is – this speaker is manipulating the answers. I'm not. (laughter) Okay, how do I go to the next slide? Ah, here we go. Okay.

So, my, uh, topic of presentation is to talk about the real world data with, uh, GDMTs, so, uh, uh, at the end of the day, uh, practice of medicine is a two-front war. Uh, on one end, uh, is evidence generation, so we need to do research and trials, and figure out from basic science, to clinical science, to population science to figure out how – uh, which are the therapies that can improve patients' outcomes. But that's part of the – the – the deal. The second part is implementation, because we can have as many, uh, good, uh, scientific data points, and, uh, clinical trials, but if you don't in – implement those therapies, then we will not see the benefits. So, how are we doing with all of this positive data, now, uh, going back to early 1990's or late 1980's, with ACE inhibitors and subsequently with beta blockers, MRAs, uh, device-based therapies, ARNIs, SGLT2 inhibitors.

These are my, uh, disclosures. So why worry about it? Why, uh, what is at stake? So what is at stake is that we have a lot of therapies now, in patients with heart failure with reduced ejection fraction, that have changed the trajectory, the actual history of the disease. They make you live longer. They make you feel better. They make your chances of coming to the hospital go down. And they all have cumulative, incremental benefit, so it's not – it's not that if you give one therapy, uh, the – the – the need to give another therapy goes away. They have cumulative benefit, and as you can see here at the bottom, if you were to give the quad therapy with, uh, ARNI, beta blocker, MRA, and SGLT2 inhibitor, you're talking about reducing the relative risk of mortality, uh, by sort of a whopping, 74%. So this is pretty substantial improvement in outcome.

Not only is it important to give the prescribed therapy, the doses, as pr – uh, at which we give the prescribed therapy is also very important. We don't have good dose rangings, really, for everything that we do, but also remember that for certain things, dose ranging is really not that important to begin with. Uh, so for instance, SGLT2 inhibitor – there is just one dose, MRA – sure, 25 to 50, but again, 25, uh, at least with spironolactone is – is – is – is pretty good. Uh, - uh, ARNI, we don't have dose ranging studies, per se, in a randomized patient fashion, but at least with ACE inhibitors and, uh, ARBs, we know that going from low dose to high dose, there's a substantial benefit, in, uh, recurrent hospitalization rates, some benefit in mortality, and with beta blocker there is even a more stronger relationship – the higher the dose, the lower the heart rate, 'cause you can get into the heart rate, into say, mid-60s or something like that. Uh, you're talking about a heart co-mortality benefit as well.

So with all of these data coming out, uh, from, uh, the past, uh, 30, 35 years, where are we? So I really like to, uh, uh, uh, sort of quote these data from CHAMPIONSHIP registry, because this is truly representative, or it's happening in practices in the U.S. So this is about 5,000 patients. The data that I'll show you is about 3,500 patients, cut when we did this analysis. So about 5,000 patients, all across the U.S., and these are academic medical centers, private practices, uh, cardiology, uh, internal medicine – so really a broad group of people, uh, and their practice patterns. But, despite of the fact that we took this broad group of patients, these are still biased data, and the reason why I say "biased data" is because these are the investigators that are interested in heart failure, and they want to participate in a heart failure registry, and they know that their practice patterns are being watched. So despite of all of these things, where you would say that the estimates will be very high use of these therapies, let's figure out what it is. And these are really contemporary data. We're talking about 2017-2018 range. A pretty substantial minority of patients – a quarter of the patients – were not on RAASI therapy. About a third of the patients were not on beta blocker therapy, and a majority – two-thirds of the patients – were not on MRA. These are on all different sorts of combinations, so if you look at all three therapies given – triple therapy – this is just at the edge of, uh, SGLT2 inhibitors data, just coming out soon after this, when we did this analysis, so SGLT2 is not included in it. Uh, but less than a quarter of the patients were on triple therapy. So this is after 30 years of data, going to the practices that are interested in participating in our heart failure registry, and oh, by the way, we asked them if there is any contraindication or if there are intolerances that shake the bog, so that

we know that these patients were not eligible. So even after cleaning and scrubbing that data, and all the eligible patients, you're talking about less than 25% of the patients in the 2017-2018 range.

How are we doing with doses? Well, we are doing even worse with doses. Uh, and if you look at triple therapy in optimal doses, we are talking about single-digit, uh, use, and overall plenty of opportunity to up-titer the doses and people are not on optimal doses. So let's go through some of the concerns and questions that people always raise when we see these data. So one question is, "Well, maybe there's a lot of improvement, uh, maybe right now, 25% of the patients are in triple therapy, and maybe it used to be like 2% ten years ago, so we have gotten a lot better. Just hold on, in the next ten years, we'll get even better." Unfortunately, the answer is not – uh, not so. So these are the data from a decade ago – 2009 versus 2017. Uh, again, Dr. Fonarow played a pretty, uh, intrumental – uh, uh, uh, critical role in all of these data generation, but you can see some improvement in beta blocker use, really not anything going on with RAASI and MRA use. So, give or take, really not a lot to show for, uh, in the eight, nine year period, uh, that we can see.

So then, the next criticism is, "Well, you're showing us cross-sectional data. How do you know that over time, you just took this snapshot when people were just about to up-titrate, and if you'd just followed the data one year later, all of this would have been fixed." So we've kinda, sorta, looked at the data over the next 12 months, and seen what happened to these original patients over the next 12 months, and the bottom line is that nothing happened in the next 12 months. So what happened in the past ten years was the same thing that happened in the next one year – plenty of gaps, no changes. So now, if you want to have a theoretical argument, you can say, well, this is an average change in 12 months, so maybe what happened was that a lot of people had doses go up, and a lot of people had doses go down, and now you're seeing, sort of some sort of an average. Well, the bottom line is, nothing changed. If you look at the category of doses of people who are in suboptimal, optimal, low-dose and no-dose, it is basically, uh, set it and forget it sort of a thing. You just start on sort of low dose, and if you don't start, you don't start, and nothing is changing over time.

In the interest of time, I won't be able to show you some data, but there are some data that this is the same pattern we see, even after somebody comes into the hospital with decompensated heart failure, so even with worsening heart failure that we know, that whatever you were doing in the outpatient is not enough. The body is asking for some more therapy. The biology is getting worse. The prognosis is much worse, and yet, post-discharge, nothing changes and the therapy doesn't, uh, change, per se.

Then, the question is, "Well, the tolerability may be different, because all these clinical trials have really, really select group of patients, and that is really not applicable to the clinical practice, and the clinical practice patients who are much more sick." So again, we looked at it, that in paradigm HF, what were the patient characteristics, and matched them with the CHAMP-HF, uh, patient characteristics, and the bottom line is that the patient characteristics for the greatest part is just matched.

If you take a multi uh, uh, variable risk prediction model, like MAGGIC score – the MAGGIC score, for the risk of overall proportional was very similar. Blood pressure, age, renal function – all of these things, uh, match pretty well. But despite of that, in the clinical trial, the tolerability of the drug was very good, but in the real life, only about 13% of the patients were getting Valsartan/Sacubitril. We did this, uh, experiment again, and sort of looked at the – Get With The Guidelines, the DAPA-HF characteristics, so again, the vast majority of the patients – 80+ percent of the patients in the Get With The Guideline registry met the criteria of the DAPA-HF trial. But the same patients in DAPA-HF were able to get on 90+ percent of, uh, RAASI use, 90+ percent beta blocker use, and 70+ percent MRA use. And here, if anything, beta blocker maybe comes a little bit closed, but RAASI use and MRI use is substantially less.

So then, this question comes up, "You know, but because the blood pressure is the issue, it's that patients just don't tolerate and this is because of the blood pressure." And I do vividly remember a very, uh, uh, uh, a, you know, active discussion with Dr. Spertus. Uh, Dr. Tonner was in on that phone call, and also. So we said, "Well, let's look at this blood pressure issue and what is the cutoff of blood pressure." So both Gregg and I were on the favor that "Let's cut it off at 100." You know, is there a medication change at less than 100 or more than 100? And Dr. Spertus said, "No, no, no. You know, we should use a higher blood pressure, at 110." And we said, "You know, 110 is like, you know, hypertensive crisis for patients with, you know, low ejection fraction. We should use 100." At any rate, we went with his criteria of 110, and looked at that. Even those people with a blood pressure of 110 – 110, the use of less than 110, and more than 110 is basically, uh, interchangeable. Again, the therapies are not given. So there's clearly, uh, uh, this inertia that in – uh, that there occurs in – in heart failure therapy that we don't see in other places. If you look at various centers, I mean it's difficult to believe that some centers have all easy patients and some centers have all difficult patients, but some centers have figured out how to give good medical therapy, and other centers sort of lag behind, and you see this wide variation in the use of these therapies.

Now hospitalization is a really critical point to provide good medical therapy. You know, there's a lot of things going on. It's not a 15-minute, rushed visit. The patient, the family member is there, they're kinda worried about it. You have pharmacists, and nurses, and some people who supported you. And over and over, we have seen that the start of therapy in the hospital is one of the best predictors of long-term management. There were papers that came out about ACE inhibitors and beta blockers about 15 years ago, now this is with MRA therapy. Again, of all eligible patients, only about 27% were given MRA, but if they were given MRA in the hospital, 80%

continued post-discharge. But the vast majority of the patients that were eligible and were not started in the hospital setting, only about, uh, a small minority, like 30% of those people got the therapy.

Valsartan/Sacubitril, again, you start the therapy in the hospital, you knock out the readmission rate within the next eight weeks, uh, to about, you know, 44% or so, in a clinical trial setting, but if you look at the same data in the, uh, uh, practice setting, substantial improvement in outcomes with Valsartan/Sacubitril, but again, I showed the data that the use is, uh, uh, sort of woefully low in this patient population. So the bottom line is that, you know, we have this mindset only in heart failure, where we have made it a symptom disease, but symptom is only part of it. You know, you will never have a patient with blood pressure of 180, diabetes with hemoglobin of 10, uh, uh, dyslipidemia with, uh, LDL of 160, and you leave them alone and you say, "I will treat them when they get worse." Right? The whole idea is to treat them now, so that you prevent worse. And whereas in heart failure, we all the time say, "You know, my patient is doing okay. Let's just leave them." The problem with leaving them is that a lot of them will die before getting worse. They will have sudden cardiac death, or if they get worse, they're – they might get into the spiral that it's not easy to reverse. Not that means that you don't try it at that point, but the best time is to give optimal medical therapy as soon as possible, in the outpatient setting, so you can fur – uh, prevent worsening, uh, uh or death. Thank you very much.

(Applause)

Dr. Pina:
… I turn on my microphone, here. Here we go. So, I have a question for you, Javed. It's kind of depressing that we've been trying for years to get people on the right therapies, but we're not the people who are seeing these patients. How do we turn this tide around? You know, I – I'm – I'm tired of seeing these numbers. Who do we have to approach? Is it the hospitalists? Is it the primary care? Is it the general cardiologists? I don't think we have to convince the heart failure community, even though the heart failure community doesn't always do it right either. So, what should we do?

Dr. Butler:
Yeah, I mean, I would love to, sort of, hear Gregg's opinion on this also. I mean, I think that first of all, a very strong emphasis in the guidelines, for not only giving these therapies, but giving these therapies early and quickly is really important. So it's turning those guidelines into really measurable, uh, quality metrics, because people are driven not by only doing the right thing, but if the right thing is being checked and it has some consequences, having some accountability for the health care system, right? So if a person comes into any given hospital or any given health care system, uh, it should not be the doctor of the day or the nurse of the day that decides what treatment that person should get. I think the is – institution should be held accountable, and if you enter that institution, that you're getting the best possible care. But on the flipside, if you can also do things like, you know, best, uh, practice advisories, uh, real-time through electronic health record, pathway management, having some extra, uh, uh, nursing support.

Uh, you know, all of those things can – can work, and I mean, there is no way that we can not get this done. This is really not rocket science, it's just really a matter of priority, and – and I think we have just, you know, de-prioritized it. This would not be the mindset in cancer. If we keep saying that…

Dr. Pina:
We know it's…

Dr. Butler:
…you know, heart failure has the same mortality as cancer, but the urgency…

Dr. Pina:
It's not fee for service. You know, it's not the fee for service, and – and I agree with you. If you have a patient with cancer, aren't you gonna send 'em to the oncologist? Don't you want the latest? The oncology treatment for that patient? So Gregg, we – we've been working on Get With The Guidelines for so long, and you think about those hospitals that are interested in quality, and they're, you know, they're competing with each other for awards that went on, and yet we still see – I think Javed showed it, that we're still not there in some. We've done very well with beta blockers. So now, you added the SGLT2's?

Dr. Fonarow:
So, you know, the – the challenge and the opportunities are there. We've certainly seen, with certain quality improvement systems that are truly multi-disciplinary, that measure data – that is not just, oh, here it goes off into a corner, nobody looks at it – but it's actionable data, that the clinicians directly involved in care act on. And so, with Get With The Guidelines were a remarkable improvement, and where, you know, 30% of patients being discharged on beta blockers, now up to, by some measures, up to 98%, in routine use of RAAS inhibitors. Then, much more challenging with the MRAs, because there is this perception of potential harm and risk of hyperkalemia, that in the U.S.…

Dr. Pina:
Whether real or not.

Dr. Fonarow:
…has – has scared people off, but we see in Europe very high treatment rates. And then, there have been cost issues around the newer drugs, that we have to overcome. So I think we need, as Javed was saying, this systematic approach, multidisciplinary, and you can't just be on the heart failure cardiologist, general cardiologist, hospitalist, primary care, anybody involved in the care of the patient. And we need, and have seen examples, where a pharm D's (40:06), or advanced practice nurses, can actually take ownership on the initiation of titration in these meds, and do as good or in many cases, a far superior job to even the heart failure cardiologist. So, making this more systematic _(40:22)_, but what's so critical is that sense of urgency. It's so critical.

Dr. Pina:
And I really think you need the, you know, the upper levels in your health system – your administrators – to really go along with, uh, with the program. Um, but if they back out, then it makes it much harder.

Dr. Butler:
But I think it's – but I think it's the – the illness also is a little bit on us, that to make the upper level feel, sort of the heat, if you may, right? So I mean, if a person comes in with cancer, it is just not acceptable that there is no appointment for CT scan, there is no appointment – I mean, we'll just make it work, because you know that delaying therapy will have bad consequences, but we just don't have that urgency in our field.

Dr. Pina:
But fortunately, money speaks.

Dr. Butler:
Yup. Oh, yeah.

Dr. Pina:
And – and if they have to send back – I mean, that's the only way when I was in New York that we got them to listen to us. If you could say we're sending back to Medicare three percent, and that wasn't acceptable to the hospital, so they allowed us to have some systematic improvement in – in medical therapy. But it was – it was a battle. It was an absolute battle. Well, let's go on, because I – I do want to leave some time for questions. Um, and so, here's your next question: What is the effect of adding one GDMT to another one, in HFrEF? Is it subtractive – one plus one equals 0.5? Is it redundant – one plus one still equals one? Is it partially additive – one plus one equals two. Is it subtractive again, or synergistic? So you have all these choices here, and they keep shifting around (laughter) as I'm reading them, they're going shifting around. So, uh, vote your conscience here, and let's give a minute to our, uh, to our, uh, virtual, uh, groups to – to do this. And you'll see the numbers keep changing. I mean, this is – this is really a challenge. We – we gotta do something, we can't, you know, we just can't keep accepting these numbers. It – it's just the patients are – they deserve to have the – the top of the line of everything.

Alright. So, Gregg, you're up, and you're gonna talk to us about a pivotal situation – how to do it.

Dr. Fonarow:
So, I really appreciate the opportunity to be part of this, uh, symposium, and the stage has been set, uh, so very nicely. We've heard the evidence and guidelines, but we've seen what is taking place in clinical practice. So we – can we take a more focused and expeditious approach, to really make a meaningful difference, and really found the audience response interesting because if we look in practice, in the data that Javed showed us, it looks like clinicians are believing that somehow therapy is partially overlapping. If you're on one or two medications, you're pretty good. You don't need to think about that third or fourth heart failure drug. So what does the data actually show us in this regard? Please keep in mind my disclosures, and let me just center us, and this is such a common case scenario. Uh, the patient presenting, risk factor for a heart failure, but now getting symptomatic, coming to the hospital and being diagnosed with heart failure with reduced ejection fraction, and then we need to think about how are we gonna initiate therapy? What sequences, what drugs to prioritize? How do we actually get this done, now that we've made the diagnosis, to improve clinical outcomes in this patient? And how much time do we have and what our sequencing should be. So fortunately, we're blessed. In heart failure with reduced ejection fraction, a number of evidence-based therapies – proven in randomized clinical trials – have such potent effect. They can reduce all-cause mortality, equal to mer – arbitrary – of benefit and risk being reduced. And relative risk reductions, of significant magnitude. Absolute risk reductions of significant magnitude, with very respectable numbers needed to treat. And these therapies also greatly reducing the risk of heart failure hospitalization, and rehospitalization. But as we look at these therapies, that question becomes, "Are they additive or are they somewhat redundant? Is there truly incremental benefit of using these therapies in combination?" And so, we have the initial data for ACE inhibitor ARBs, giving us approximately 20% relative risk reduction in all-cause mortality.

When we then look at our beta blocker trials, these were done on high-background use of ACE inhibitor and ARB, and what we see is about a 34-35% incremental, truly additive, reduction in all-cause mortality. As we get to the MRAs, it is true the original RAAS trial, done on high-background ACE inhibitor/ARB use, for relatively low beta blockers at the time this trial was done. But as we go to emphasis, we see on high-background ACE inhibitor and ARB and beta blocker use, this truly additive benefit, of a similar degree. So again, we're not seeing any potential interference or overlap of these medications. Truly additive with regards to their benefit. Now with Sacubitril Valsartan, this was compared to the ACE inhibitor Enalapril, and here we're looking at the incremental benefit of neprilysin inhibition, and we truly see, for the primary composite endpoint for CV death, and even for all-cause mortality an incremental benefit being demonstrated. And then for the SGLT2 inhibitors, in heart failure with reduced ejection fraction – in both DAPA-HF and EMPEROR-Preserved – and when pulled together metanalysis, reduction in all-cause mortality on very high background medical therapy rates, reduction in CV death, and the same benefit whether the patient had Type 2 diabetes or not. So again, this incremental, truly additive benefit.

And as we then look at that magnitude of benefit on two-year mortality of these therapies, this remarkable, almost 75%, reduction in relative risk, and absolute risk reduction – the number of lives being saved of 26 – 26 out of a hundred patients who otherwise would have died, now being saved with these quadruple therapy approach – number needed to treat to save a life of just four.

So now, that key question becomes how should we apply these therapies? And if you think about this historically, and follow this sequential kind of approach of, I will begin with an ACE inhibitor and gradually titrate up and target-dose, at two to four week intervals. And only then, start the beta blocker and follow its up-titration. And only then, add the MRA. And only then, switch to Sacubitril/Valsartan. And only then, add the SGLT2 inhibitor. We get to 28 to 56 weeks before guideline-directed medical therapy is fully implemented, with each of these steps. Some patients may slip through the cracks, and we never ultimately get there.

But another key question is also the timing of benefit. Do we have 28 to 56 weeks before we fully get on these therapies? So the timing is critical, and what the timing in our trials show is absolutely astounding early benefit. As we look at the benefits of beta blockers, within two weeks the survival curves are diverging. Delaying therapy by a few weeks, the patient is much less – more likely to have worsened heart failure. MRAs benefits well – these curves separating in days. And by 30 days, significant benefit. The remarkable data, looking at Sacubitril/Valsartan, not versus placebo, but versus ACE inhibitor for in-hospital initiation. By 30 days, CV death, heart failure hospitalization reduced. At that eight-week mark, this was a 6% absolute risk reduction, 46% relative risk reduction. And the SGLT2 inhibitors – within days, you're already seeing a two-thirds risk reduction. It's highly statistically significant, at either two weeks or four weeks in the various trials. So there is significant benefit of each of these drugs within 30 days. Delaying any one of them by more than a few days, you are having patients have events that otherwise could have been prevented, and these therapies are again, truly additive to each other.

And so, as we think about some of the earlier algorithms, even trying to be more complex, compressed, the ACC expert can panel decision pathways, sort of start with your ACE inhibitor or ARB. No, actually we can go ARNI first, and then the beta blocker and then think about the add-ins. Others began to highlight – maybe we need to be more rapid, but as Javed alluded to, and the data truly supports, it was first proposed, at HFSA last year, and published here in JAMA Cardiology, that in fact, for eligible patients without contraindications, newly diagnosed in the hospital, hemodynamically stable or outpatient hemodynamically stable, the ideal approach, starting low doses of all four of these, simultaneously.

Or in patients where there may be some considerations, delay by a day or two, but rapid-sequence intervention and initiation. Why? Very early benefit – these drugs are complementary to each other, improve the tolerability. Up-titration should focus on the beta blocker, the steepest dose response curve, as Javed showed us, and then focus on the other ones, and actually by day 21, we can, in fact, an accelerated pathway, be on optimal doses, of each of these medications, getting a 75% or greater risk reduction in CV death or heart failure hospitalization. And then can focus on some of the comorbidities, and other conditions – select use of other drugs.

So this very focused, expedited approach – what benefits would it actually have for our patients? So, in fact, the four pillars started as first-line treatment up front, versus a drawn out, historic sequence. The benefits – rapid improvement in health status, rapid improvement and yes, some patients will improve so much, will not need an ICD, rapid reduction of hospitalizations, and rehospitalizations within 30 days. Nothing's really worked to reduce that rehospitalization. Medicare penalties – this works phenomenally well. Rapid reduction mortality, importantly, the clinical inertia completely defeated and overcome. Tolerability, adherence, persistence is dramatically improved with upfront, in-hospital initiation over the long term.

Now what are some other strategies to help facilitate guideline-directed medical therapy initiation performance improvement systems that were alluded to? Multi-disciplinary teams with advanced practice nurses, pharmacists, specific navigators solely focused on guideline-directed medical therapy, clinics just focused on initiation, telehealth, digital health tools, and even engaging patients, explaining to them the key meds and asking them to prop the physician – why don't you have me on this life-saving medication – and

getting it started on that visit.

Now we can ask the question of what does it truly mean to these patients to be on all four of these therapies? Can we just leave 'em – some of 'em on ACE inhibitor or these beta blockers, call it a day? So we looked at it using the trials. (0:52:27) was the first author on this, published in Lancet last year. And looking at the relative risk reductions here, of comprehensive treatment versus that old prior standard. And you can see these remarkable risk reductions. What does it mean to median survival? We can give these patients back more than six years of median survival by the use of comprehensive therapy – not compared to no treatment, but compared to ACE inhibitor or ARB and beta blocker therapy. Remarkable benefits that we can offer patients, if we get the job done, and we need this focused approach.

So the patient benefits are large. What about the population health benefits? This is the number of lives we could save in the U.S. each year, with truly optimal implementation of these guideline-directed medical therapy, and device therapies when indicated.

130,000 additional lives could be saved – I think compelling evidence of why we should all work together to overcome these barriers, take that urgency – time matters in getting these therapies started, and clearly still need further research, additional therapies to add on. But the existing therapies – remarkable benefits.

So the approach to heart failure with reduced ejection fraction meds – benefits are truly additive and incremental. No substantial overlap has been demonstrated with any of the four key evidence-based therapies for heart failure with reduced EF optimal approach – I hope I've convinced you to use those medications demonstrated, reduce all-cause mortality, in combination, up front, so long as not contraindicated or not tolerated. Start each without delay. Serial selective approach leaves our patients vulnerable to events that could have been prevented with earlier use of these therapies. And additional therapies may be beneficial in specific patients, in clinical scenarios, and should be considered. Thank you so much for your attention.

(applause)

Dr. Pina:
Thank you Gregg, that was great. Um, you know, as we sit here and – and reflect on the science, and there's also the art of getting the drugs onboard, and I often recommend that if you can manage around the diuretics, you're probably gonna be able to get them on the drugs. And I think one of the major mistakes that I see out there, in – in chronic care, is that they wanna keep the 40 of furosemide or the 80 of furosemide, and aren't willing to back off a little bit which will give you blood pressure room, for example, to be able to get the RAAS inhibitor on. And so, I have a question for you, Javed. Will the patients feel better when they get the SGLT2? I can tell 'em they're gonna feel better when they get the RAAS. Will they feel better when they get the SGLT2? That's a big question out there.

Dr. Butler:
Yeah, so, both, uh, DAPA-HF and EMPEROR-Reduced have now published papers looking at the KCCQ, in all three domains of KCCQ – uh, uh, clinical summary score, total symptom score, and, uh, uh, overall summary score. Uh, there was about a 20-25% odds of feeling better at five – fif – uh, five, ten and fifteen percent – point improvement, and a five-point deterioration which is clinically meaningful, uh, was higher with placebos. So for both therapies, uh, we have seen this benefit. And EMPEROR-Preserve results are being – being looked at right now.

Dr. Pina:
So one of my criticisms about the approach, starting with the beta blocker and the SGLT2, is that I am not truly comfortable in saying to the patient, "You're gonna feel better in a few days," because actually, with the beta blocker, they may actually feel a little worse…

Dr. Butler:
Yes.

Dr. Pina:
…until we can get them on, you know, on the right dose, and I'm not sure that the SGLT2, in a week or two, they're going to feel better.

Dr. Butler:
But with ARNI, it's the next trip. They will tell you they feel better…

Dr. Pina:
Right. We wrote the paper – you're right, in fourteen days, you see the – the difference, and it's – it's in – incredible. It's actually quite remarkable. Uh, so I think that the RAAS inhibition for improvement in symptoms – the patients come in, they don't feel well. They feel terrible. They want – they want something done for their shortness of breath, beyond just a diuretic. Gregg, what – what are your…

Dr. Fonarow:

There is not any – any shred of evidence that is compelling or that would guide us to want to delay any one of these four therapies…

Dr. Pina:
I agree.

Dr. Fonarow:
…and that's why these arguments really kind of get off-base, because what we find, the earlier we start the therapies, the earlier patients improve. We need less of the loop diuretics…

Dr. Pina:
Exactly.

Dr. Fonarow:
…and less likely to get into trouble…

Dr. Pina:
Exactly.

Dr. Fonarow:
… these drugs enhance their – their own tolerability and so much of what we've attributed, uh, when a patient, due to their underlying condition getting worse because of inadequate treatment, to potentially be in medication side effect, when it's the underlying disease progression.

Dr. Pina:
Absolutely.

Dr. Fonarow:
So, the adherence that is started, and by getting these therapies up front, plays out over that longer term in a very, um, synergistic way.

Dr. Pina:
So I think it's really also important to have that conversation with the patient on day one. Day one. You're not gonna be on one drug alone. We're gonna have you on several. They all work for different pathways. They're complementary, and I'm gonna be changing those doses, off and on. Uh, and so, if you have that conversation the first day, then you – you're not gonna see the eyes rolling back in the head when you say, "And I have one more pill for you." Or, "I have one more medication for you." They hate that. So a good conversation with patients, and maybe we need to have some scripts of what the conversation should be, with those early, uh, visits with the patients. And in the hospital, the same thing. We're gon – because they're gonna come out with medications that they haven't been on, so, uh, adherence is an issue. It's a big issue.

Dr. Butler:
Yeah, but – but again, I mean, you know, uh – I'm – I'm – I don't wanna make light of it, and absolutely first, do no harm, is important, and absolutely make sure that we do the – give the therapies in a safe way, but again, if you look at the – sort of the cancer, uh, model…

Dr. Pina:
Oh, yeah.

Dr. Butler:
You know, you give all therapies that are life-saving and then deal with side effects.

Dr. Pina:
Yup, yeah.

Dr. Butler:
And the mindset is so different in heart failure, it's amazing.

Dr. Pina:
Totally different. And then you give – you're right, the side effect treatments to enable the chemotherapy…

Dr. Butler:
Absolutely.

Dr. Pina:
…that they need, and so the word "enabler," you know, starts to come in. Do you wanna say anything else?

Dr. Fonarow:
Yeah, I – you know, the oncology analogy, if we had a chemotherapeutic agent that extended median survival by six months, despite disastrous side effects, we would hail it as the greatest breakthrough, and it would be three or four hundred thousand a year, and that's what many of them cost. Yet here, we have, you know four medications in combination that can extend survival, not over natural history, but of what used to be prior standard of care by six years, and, you know, somehow …

Dr. Piina:
Yeah. How trivial.

Dr. Fonarow:
…we can take a leisurely approach with it, and we shouldn't and we can't.

Dr. Pina:
And pricewise, you know, spironolactone is what – ten cents a tablet, fifteen cents a tablet? Wal-Mart has specials on ACE inhibitors and beta blockers, so you can really medicate the patients with very little money. We really – it – it's really startling, and I – I agree, I think it's time that we really do something about this.

Alright. Let's, uh, let's go on, and here's your next question: What concerns you the most regarding the presence of multiple comorbidities in patients with heart failure? Comorbidities may affect how I select and use the various heart failure-related treatments; therapies used to treat comorbidities may cause worsening of heart failure; therapies used to treat heart failure and comorbidities may interact and reduce patient adherence; comorbidities are associated with worse clinical status. So vote your conscience there. I'll give you a second or two here.

This is really interesting to see how the – the, uh, responses change, and go back and forth. (laughs) Who knows…

And while we're waiting for this, we're gonna have Dr. Rosano again, who is going to talk about Pivotal Situation Number Two: Maintaining Optimal Dosing. 'Cause it's not just getting there, but it's maintaining it, and addressing polypharmacy, which is really what we're dealing with. 'Cause we keep focusing on the heart failure drugs, but the patients are on a lot of other stuff. Right? And when they leave the hospital, I counted it – 13 drugs. It's what they leave the hospital with, and how – how can you take 13 drugs in a day? I – our transplant patients do it, but I don't know how. So, Giuseppe, take it away.

Dr. Rosano:
Thank you again, um, Ileana. With this case, I will, uh, uh, discuss on how to manage the optimum dosing of, uh, um, uh, RAASi, uh, therapy and how to address the problems of polypharmacy in a patient with, uh, heart failure with reduced ejection fraction. These are my disclosures, and this is our patient. He's a 67-year-old male, with, um, heart failure with reduced ejection fraction, uh, 30%. Still in your heart association class 2, but with a dilated left ventricle, a primary prevention ICD seated because of a history of ischemic heart disease and previous _(1:02:25)_. On physical examination, we see there is a, uh, blood pressure still, uh, adequate, and, uh, and heart rate on target – 54 beats per minute – plus the same size of injections raise an increased LHAVP and presence of a beating edema. Looking at this laboratory data, we clearly see that he is, uh, hyperkalemic, and, uh, is, uh, um, severe, um, uh, CKD with, uh, with an EGFR of 36 mm/minute. There is also a raised, uh, B&P. His cardiac medications are bisoprolol, 75, or, uh, 7.5 mg once daily, uh, enalapril 5 mg, b.d., furosemide 40 mg b.d., spironolactone 12.5 mg, once daily, and _(1:03:19)_.

And if we look at the, uh, at his, uh, medical therapy, we can see that, uh, uh, the beta blocker is not for your target, but is more than 50%, but the RAASi therapy, so the enalapril and spironolactone are clearly underdosed. Now the _(1:03:43)_ factor, that will, uh, limits the up-titration for the beta blockers is the heart rate. For ACE inhibitors, the EGFR and the hyperkalemia. And for the MR, uh, MRA, the hyperkalemia. So, we have to think, um, how we can implement medical therapy in this patient that is starting to decompensate.

So, what I showed you before, the algorithm for the implementation of, uh, the medical therapy according to patient profiles. So, if we have a – the easy patient, with a good heart rate and good, uh, um, blood pressure, and preserved EGFR, there's no problem. We can, uh, uh, up-titrate all medications. But in those patients where, say, the blood pressure is low, heart rate is low – we don't have a possibility of room for improving – for increase the beta blockers or the ACE inhibitors, and if anything, we need to reduce the beta blockers or the ACE inhibitors _(1:04:48)_. And, uh, in those patients that have, uh, hyperkalemia, we have to think of potassium binders, in order to, uh, enable the use of, uh, RAASi that otherwise should be reduced. And if the blood pressure is adequate, then we can use _(1:05:09)_. But in this case, with the bottom line low blood pressure, low heart rate, then we need to use potassium binders in order to, uh, enable RAASi therapy. So what are the therapeutic options? Uh, for RAASi therapy, we can either decide to discontinue therapy, but this will, uh, uh, mean stopping, uh, or suboptimalization of a guideline-directed medical therapy. Of course we can add an SGLT2 inhibitor, because in this patient, will, uh, improve, uh, uh, clinical outcomes, would reduce mortality and morbidity. Also – will also have a, uh, uh, a beneficial effect on hyperkalemia and, uh, on, uh, on the progressive decline of renal function.

Then we'll need to treat the hyperkalemia. We can use the traditional potassium binders, but for patient on potassium binders, can be used only acutely, not chronically. Poorly tolerated, and are used chronically only in France. And I think someone has to taste the SBF's before prescribing, to uh, the patient because an – is an art creating texture, very unpleasant and very _(1:06:30)_. Instead, with a noble poto – potassium binders, that are supported by clinical trials – that is very important – are effective in reducing, uh, chronically, the hyperkalemia in patients receiving RAASi therapy. Uh, well-tolerated, and an excellent safety profile.

We see that both the ESC/HFA guidelines and the ACC, uh, AHA guidelines will suggest the use of sodium zirconium cyclosilicate, or patiromer in patients with, uh, hyperkalemia, in order to either treat the hyperkalemia or enable the use of, uh, RAASi, uh, therapy.

So what is next for our patient? So, we can up-titrate, uh, macr – uh, the RAASi therapy to the maximum tolerated doses, alongside the use of patiromer, and we can optimize guideline directed medical therapy in four weeks.

So, his medications for three months, were enalapril 10 mg, b.d., bisoprolol 5 mg, once daily. Reduce those in order to give room for the, um, uh, up-titration of, uh, enalapril and spironolactone, but still 50% of the dose. Spironolactone 25 mg, uh, once daily, dapagliflozin, furosemide, and, uh, reduced to once daily, and aspirin - _(1:08:09)_. And if we look at three months, his potassium is quite controlled, his, uh, HFR is sta – stable, and, uh, uh, he's, uh, clearly better, because his, uh, NT-proBNP is half of the one that we've seen before, after the up-titration. So, we can see that with the use of, uh, uh, drugs like, uh, patiromer, we can, uh, implement guideline-directed medical therapy. Of course, uh, uh, targeting patients according to the patient profile – of course, we will have a problem about the – uh, about adherence. Pro-adherence, uh, the – is multi-faceted, and, uh, can be due to, uh, different factors, but one factor that is, uh, uh, very effective is the – uh, is in bringing together the medications in the blister packs. This is what we give in, uh, uh, the U.K. So where, uh, when, uh, all the tablets are given together and that will facilitate the use and the administration of medical therapy.

And, uh, I look forward to hearing the next case.

(applause)

Dr. Pina:
Thank you, Guiseppe. So, we're gonna keep this one briefer, so that we can get to, uh, to the questions. I just have one – one observation here, and that is that keeping patients on the drugs is so difficult. So during the pandemic, when readmissions went down, and admissions went down, do you think they were taking their drugs at home? No? That – that's a good question for the audience. Why do you think that readmissions and admissions went down during the pandemic?

One – one of my – my opinions is that they were taking their drugs at home, because they were terrified to come in and get sick.

Dr: Butler:
Yeah, and I mean, I haven't seen any published, credible data that, uh, outpatient heart failure mortality went up, so if the hospitalizations did – went down, and outpatient mortality didn't go up, then this rapid transition to telemedicine, of all sorts, from telephone, Facetime, to whatever needed to get things done, and patients taking their medicines, uh…

Dr. Pina:
And eating at home, and not going out to, uh, I'll use McDonald's because they have the highest sodium content of food. It was pretty scary. I – so, um, one more question here for you guys, and then it's my turn. So for the management of hyperkalemia, you heard in this case that we just saw, to enable MRA and to enable RAASi use in patients with heart failure, with or without CKD, which of the following management approaches do you prefer to use: low potassium diets; sodium polystyrene sulfinate; calcium polystyrene sulfinate; calcium polyfi - which is CK again, they keep changing (laughter); SPS; OCC; or patiromer?

Oops, I lost – there we go. So vote your conscience there. And we do have some questions coming in about, uh, diets, etc. They're in there.

So my talk is gonna be about comorbidities, because when we started tonight, I said heart failure patients are very complex, and they're getting more complex, and there are more things that we have to pay attention to besides the four pillars of care. Um, so how are we gonna manage those?

And so, I'm gonna give you another case scenario, and I'll go through this one pretty quickly. So this is a patient that was referred to our heart failure team, because they had been hospitalized recently for acute decompensated heart failure, and they had hyperkalemia documented in the EMR, and they called it an allergy to ACE inhibitors. Patient had history of hypertension, HFrEF, EF-25, class 3, already had an ICB in, CKD, stage 3A, diabetic so there's another comorbidity besides hypertension, and then things like osteoarthritis and obesity. Creatinine – 1.7, GFR – somewhere in that range between 45 and – and 60, serum potassium was 4.9, even though he had been taken off the ACE inhibitor and was actually on the basodilator combination hydrolosene and a nitrate. He was taking naproxen for his, um, arthritis. Blood pressure was still 144/96, so remember the U.S. guidelines talk about parallel treatments, that we need to – in

the heart failure guidelines – to stick to the hypertension levels that are in the hypertension guidelines, so that we need to get that pressure down. Heart rate in the 70s, and he was on dig, and torsemide, which I think has become one of our favorite loop diurectics, uh, chronically. Also on metformin and insulin.

So, why are comorbidities so relevant in heart failure? Because there are a lot of 'em. And – and there is a confluence of comorbidities in this population – things like, you know, COPD, and then things like gout, and hyperlipidemia, and we're gonna talk a little bit about iron. Plus hypertension in the background – if patients have coronary disease, they may have angina. Renal dysfunction – rare for us to see a creatinine that's perfectly, 100% normal, even though I think we've learned from the SGLT2 inhibitors that the kidneys are actually being protected all along, and that, to me, is one of the most impressive items about them. And then, a growing amount of diabetes, and I fear that out of this COVID pandemic, we are seeing a lot of obesity in cities and in towns, and it's family obesity. Uh, and you wonder what's gonna happen to diabetes in the next five years, uh, and heart failure.

So, Medicare has identified this for a long time. They know that this – the patients are not simple, and that if you look at the number of comorbidities in each of these beneficiary groups, it's really substantial. So they know that when they're paying, they're paying not just for the underlying disease, but they're paying for all the additional comorbidities. And the reason I have this up – this is Rob Mensa's slide, and I really like it, because he looks at HFpEF through the comorbidities, and if you think about what we think about as the HFpEF population, which maybe Javed can tell us who they are – if he should know who they are. What do they have? They have COPD, they're obese, they may be inactive – inactivity should be a risk factor. It is, in fact, a comorbidity. They may have a low hemoglobin, or they may have iron deficiency, even though the hemoglobin may not show it. Sleep disordered breathing, particularly with obesity and obstructive sleep apnea. And obesity in itself is a comorbidity. So the – this is what we're dealing with today, folks. And – and these patients are tough to handle.

How have we been doing – and this is from JAMA – just looking at temporal traits, and notice that these end in 2016. And by 2017-18, we started to see the mortality of heart disease actually turn the wrong way, and most of it – it was based in the African American population. So we were doing okay with the incidence rate overall, and women always a little bit lower than the men, and blacks usually worse than the men – than the, uh, Caucasians, even though it doesn't really show it here. But when we look at the difference between the patients who have the comorbidity, and those who don't, there's a huge gap. And the gap is there, even for things like atrial fibrillation. And every time we do an analysis for prognosis, AFib keeps coming out as one of the negative prognostic indicators. So, lots of comorbidities to deal with.

And what impresses us, I think, about the fact of the SGLT2's is that there is an element of some osmotic diuresis, even though it's very – very limited, very mild, particularly in the non-diabetic. Um, but are they anti-inflammatory? Are they reducing oxidative stress? I don't think we really know, but we do know that the change in hospitalizations happens very, very fast. Is there some reverse remodeling in there? Is there some attenuation of fibrosis?

But those things take time, and these changes happen awfully fast, and I figure that Gregg's gonna tell us the mechanism of all these things, 'cause I sure as heck don't know it. What we do know is that they are renal-protective, and I think that's a very important function of – of these drugs. And it's different than other diuretics. There are – so there is some literature out there, showing that the SGLT2's will decrease the incidence of hyperkalemia. And again, mechanistically, we don't know.

So, we need to think of these drugs like we did the beta blockers, because they reduce a lot of the things that we worry about. And rather than saying, is it this SGLT2 or this other one, let's think of it as a class and let's get patients on the drugs. And whichever one you use may depend upon your own system, and your own health care system and what's available on the formulary.

I borrowed this nice slide from Beham Balskurd (1:18:13), who makes some of the best slides I know, and she puts in here the HFrEF population that we've just been talking about, with the pillars of care – hydralazine nitrate for the patients who may be African Americans and still symptomatic; ivabradine for that population that you can't get the heart rate down; and then the role here of vericiguat – we saw Dr. Rosano added to his, uh, circle of medications; and omecamtiv – still not approved, but it may get to the FDA for approval as well.

So those are like really basic, and then we still have to think of ICB and CRTB, because these are proven therapies. And I think Gregg showed that, when you listed all the proven therapies, but what else should we be talking about? How to get the blood pressure down, folks. I mean, that's one of the biggest, uh, imperatives right now across the – across the world. Actually the World Health Organization has it as an imperative to get the blood pressure down – not just to give the drugs, but actually have them work, and if they don't work, adjust 'em. Change them.

Iron deficiency – we've ignored this for a long time, and I can tell you, I've started really doing iron studies on these patients, and in the Bronx, when I was in New York, a lot of the patients were anemic, and I kept saying, "Why – why is this patient anemic? Well, it's chronic disease." We're not so sure. Chronic disease, because it appeared in the chart the last time they were in here. It became

chronic. So we worked 'em up, and if, in fact, they were iron deficient, we've gone to IV iron. Uh, done very nicely, and it is amazing how much better the patients feel when they get the IV iron.

Um, we also have to think of valvular heart disease. You know, TAVR's, we have the mitraclip, and soon to come, the tricuspid clips, which are now being looked at. And then, all these other things, like management of AFib, and we haven't even mentioned the NT-proBNP's, which to me, help guide those physicians in the hospital to get the NT-proBNP down.

That doesn't mean you're gonna draw it every day, but you would like to see a nice decrement during the hospitalization – to me, at least 30%, which is what I think we all want to think about.

Sleep apnea, CKD, and then mental health. 35% of heart failure patients are clinically depressed. I mean, a – it's tested. We tested them in – in our heart failure exercise trial, and they were mark – and some of them were markedly depressed, that may need medications. So getting a mental health expert to work with you, I think is equally important. So let's promote the drugs. Let's promote the drugs that work. Let's educate our colleagues. We talked a little bit today about education. I think it's still considerably needed. How do we do it, is maybe a little bit different than we've been doing. The small, you know, clips of information rather than the 45-minute lectures that we've been so used to, uh, and we're still fighting pricing. Uh, our pharmacists in the hospital are wonderful at getting prior approval. We have to get prior approval, they – they know what – what – what we do, and maybe every drug isn't going to be generic. We have a lot of new drugs that are not gonna be generic, and you want to do something good for your patients? Get on the P&T committee. Volunteer to get on the P&T committee, because you will have a lot of power to get the drugs that you want to use, and get them on the formulary. And precision medicine is what I think we're all trying to get to – the right drugs, for the right patient, at the right time, and for the right reason. So I will stop here, and Gregg? You were gonna do a question for us.

Dr. Fonarow:
So, uh, this question – which of the following statements is true regarding the use of guideline-directed medical therapy in patients with heart failure with reduced ejection fraction? So answers are, uh, shown here. With regards to, uh, having seen this question before, so please respond now. So, audience, so we see initial ones answering, uh, we're paying attention (laughter) to slides shown, that's really good. As we see a few more coming in…

Dr. Pina:
I like that 74.

Dr. Fonarow:
A little more, uh, time, so, you know, certainly, um, the data that we've seen from the puri – purists and across the key randomized trials, and a network-type analysis, and really, um, looking directly at the trials really showed this, uh, impressive, uh, reduction that occurs, uh, with, uh, all four therapies, compared to the natural history that, you know, gets us really close to a 75% relative risk reduction. It looks like, uh, almost all our answers are there, so that's really, uh, terrific in that regard.

Think we're, uh, getting closer, to, uh, getting through these, so the next one: Which of the following statements is true regarding a serial and sequential initiation of GDMT versus simultaneous rapid initiation of therapy? So, you saw this question before. Let's see where you're at now. So, the initial, uh, respondents coming in really, uh, seem to believe there is that rapid improvement, with a little, uh, question that, uh, delaying the SGLT2 inhibitor, that Ileana pointed out didn't make a whole lot of sense. So, looks like the, uh, majority are really going with, uh, this rapid benefit and certainly we saw, you know, remarkable improvements in that eight-week mark, uh, for – for each of these therapies, so it really is impressive in that regard, and our audience really seems to agree with that.

So let's go to our next, uh, question. What's the relative risk reduction occurring within 30 days in GDMT therapy being initiated with the simultaneous rapid sequence strategy? So, around 15%, 75 or greater, those other answers, and – wow. So far, we've been…

Dr. Pina:
(Inaudible)

Dr. Fonarow:
…It's, uh, right in line with that 75% or greater, and that's, uh, certainly what we've seen with the, uh, early, uh, benefits in the trials that have looked in that first 30 days, to, uh, first eight weeks. So, it's really remarkable that magnitude of relative risk reduction that can be achieved. Give it a few more seconds for answers to come in. It looks like our, uh, audience online and in person, uh, agree with that.

Next question – having four or more comorbid condition makes up approximately what percentage of Medicare spending in the United States? So, uh, Ile showed that, uh, slide, and we've got, uh, kind of a mix so far, between 75% and 90%, so, really, uh, the audience is agreeing, uh, that there's a substantial component here, how much of it is. But, it's really remarkable, if you think about it, that – how little spending is occurring in those with, uh, few comorbid conditions, but it also reflects how much of the U.S. population…

Dr. Pina:
Is comorbid. (laughs)

Dr. Fonarow:
… actually has three or more comorbid conditions. So, looks like the majority went with, uh, 75%.

And then, uh, patient heart failure reduced EF, with an EF 30%, treating with beta blockers, spironolactone and now pro furosemide, potassium at 5.7 – what is the most appropriate next step in optimizing therapy?

So, you know, pre-test, we had a lot of, uh, various answers with most, uh, kinda favoring, uh, you know, some version of decreasing or stopping the spironolactone, but now we actually – so far, 100% having a novel potassium, uh, binder, so impressive, uh, learning going on there, at least agreement with the, uh, speakers, uh, so that's great.

So, uh, I think, uh…

Dr. Pina:
Got a couple of questions.

Dr. Fonarow:
…we're at the top of the hour, but we'll try and get a few questions in.

Dr. Pina:
Yep. We have lunch…

Dr. Fonarow:
So, Ile, take it away.

Dr. Pina:
We have a couple of questions here from the audience. So, should we be considering our mRF patients – so, this is the middle road patients – the same as our HFrEF, in terms of GDMT? Should we be initiating RAASi or SGLT2 in these patients? Javed, why don't you handle that.

Dr. Butler:
That – definitely, yes. And that's where at least the European Society guideline deliberations were, and their recommendation was given to consider that, yes.

Dr. Pina:
So Dr. Butler, there's a question here directly for you. What does your facility do for improving GDMT dosages? Do you have a nurse or a pharmacist-like team that focuses on titration-based protocols?

Dr. Butler:
Yeah, so we have inpatient nurses that will do on – uh, consults on all patients that are admitted to the hospital, hospital service or whatever service. And they will help set the GDMT at the time of discharge, and then any person that requires, we sort of have this, uh, open, uh, uh, spot in the outpatient clinic that they can refer the patient to the outpatient clinic, and we'll see in the heart failure clinic. Anybody that is found to be challenging.

Dr. Pina:
So here's one for you, Gregg. When someone goes out of the hospital on all four drugs, and the patient bounces back in renal failure in our institution, how can we avoid this?

Dr. Fonarow:
Yeah, so, it's a great question. Uh, actually if the drugs have been started, and there is appropriate monitoring, you are rarely going to see that. These drugs are actually renally protective. Most often now, will reflect over-diuresis or improper dosing. Key to safety is starting those guideline-recommended doses, certainly for patients where there is chronic kidney disease, thinking about lower doses of the MRA to start with, the low dose of the Sacubitril/Valsartan, and so what you'll see is a dramatic reduction in all hospitalizations with regards to the use of these therapies. But, there will be patients, if you indiscriminately dose and don't have follow-up monitoring or testing, where there can be hyperkalemia, where there can be worsening renal function. There needs to be dynamic adjustments of their diuretics, so we don't at all mean to imply, oh you start these four meds, send the patient out, and you never need to see them again. Close early follow-up is, you know, a critical component of care, but that's true regardless of whether you're using the meds or not, but you'll be far less likely to have a patient rehospitalized or having adverse effects, or having their heart failure worsen with these drugs than without. And again, you know, at least for three of them, they are actually renally protective, lowering the risk of progression of renal

disease or going on to dialysis or renal death.

Dr. Pina:
You know, and – and, uh, just one – one more point, there. Let's not forget to check urine protein, as I think we have not been routinely doing that, and, you know, the urine proteins, especially the micro albuminuria is highly, highly predictive of worsening renal function, and it's something that if you start the patients on the RAAS inhibitors, it should go down, and that's in the drugs were approved exactly for that. We actually have a flexible diuretic regimen that I use on patients, if I'm gonna send them out with a relatively low dose. I think we use diuretics terribly, and everybody talks about all the other drugs, and not what to do with the diuretics, and you can do a lot, if you manage the diuretics around – we call it the three – three in three. Three pounds in three days. That's the day you take your extra diuretic. Write it down. Put it in your booklet, whatever, and then tell us about it. And some of the patients are very proud when they say to you, "I only needed my extra diuretic two or three times." And, or, "I haven't needed it at all." Um, with – with sodium restriction, otherwise the diuretics don't work either. So we – we – the – that's where the art comes in.

I want to thank everybody for being here with us. I – again, I want to thank our team that has been on top of things, uh, and on top of all the, uh, video , and the questions, and before for all their, uh, support with our education. Hope we've helped you. We'll hang around a little bit out here, uh, Javed and – and Gregg and I, to answer others of your questions. So I hope you have a wonderful rest of your meeting. Good night.

(applause)

(music)

Announcer:
You've been listening to CME on ReachMD. This activity is provided by Medtelligence. To receive your free CME credit, or to download this activity, go to reachmd.com/heartfailure. Thank you for listening.