**Operator:**

It is now my pleasure to turn today's program over to Steve Dentel from the American Heart Association. The floor is yours.   
  
**Steve Dentel:**

Thank you so much, and good afternoon and welcome. On behalf with the American Heart Association Get with the Guidelines Heart Failure and our webinar series sponsor, Amgen Cardiovascular, we welcome you to this second event in our webinar series, Heart Science Amplified. Today's presentation is the second in our series of three offerings intended to amplify the conversation around key topics in heart failure. We invite you to join us throughout the series by registering for our next offering on Transitions of Care, with Dr. Nancy Albert. You can also join us at Scientific Sessions in New Orleans on November 13th for our final webinar live event in Heart Quarters. For more information on attending Scientific Sessions, visit professional.heart.org. You can view the archived recordings and slides from this webinar series by visiting heart.org/quality.

On today's session, we have the pleasure to hear from Dr. Clyde Yancy, who will discuss with us current heart failure guidelines and the important of following these guidelines to improve heart failure care. I'd like to introduce our presenter for today. Dr. Yancy is chief of cardiology at Northwestern University, Feinberg School of Medicine, and associate director of the Bloom Cardiovascular Institute at Northwestern Memorial Hospital. He holds the Magerstadt endowed professor of Medicine Chair and also holds an appointment as professor of Medical School Sciences. He is the newly appointed Northwestern University Feinberg School of Medicine vice dean of Diversity and Inclusion. Formerly, he was the medical director of Baylor Heart and Vascular Institute at Baylor University Medical Center in Dallas, Texas, and chief of Cardiothoracic Transplantation at Baylor University Medical Center in Dallas. His research interests are in heart failure, heart transplantation, quality of care, and healthcare disparities. He has published over 300 peer-reviewed papers and has an active web-based CME presence. It is now my pleasure to turn our presentation over to Dr. Yancy. Thank you, Dr. Yancy.   
  
**Clyde Yancy, M.D.:**

Thank you, Steve. And my greetings to everyone that has signed in today. I am absolutely thrilled that 368 of you have already signed on. There are about six pending questions in queue. I would encourage you to continue to populate the queue with those questions. My hope is that we will be able to present what I think happens to be the most relevant content but allow sufficient time to address your questions. So it's very important that we are engaged with you, and for that reason, I look forward to seeing your questions. These webinars have really been one of the important value-adds of the American Heart Association's Get with the Guidelines quality improvement initiative. It gives participants, subscribers, those of you an opportunity to really tap into a real-time ongoing discussion about what we recognize as the leading edge of evidence that allows us to introduce the best practices to generate the best outcomes for our patients. I've had a commitment to the American Heart Association for nearly 30 years and a commitment to heart failure for nearly 25 years, so it brings me much satisfaction to see so many of you engaged with this topic. So I'd like to begin, and I'm happy that now we're up to 375 of you. So I hope that we can all stay engaged throughout the next 30 minutes or so with the information to be presented.

Right now, you should see, present on your screen, a title slide that says "Heart science amplified," and then a subsequent title slide that says "Improving guideline-directed heart failure care, new considerations in heart failure, including an update on the new now jointly-configured American College of Cardiology/American Heart Association/Heart Failure Society of America Heart Failure Guidelines.” You will see the prompt for what's coming up at Scientific Sessions, and you will then see yet another title slide. And then finally, you will see the attribution slide that captures my home institution, Northwestern, and my specific disclosures. This means that you should be through the first six graphical representations for this presentation, and I see that we have more questions coming in, so this is great.

Let me go ahead and get started now with the very first concept. Very straightforward, and all I simply want to do is to let you know what it is we plan to cover over the next half-hour: A new epidemiology of heart failure, new prevention strategies, and new treatment paradigms. So let's begin. Let's start with the new epidemiology. How many times have you listened to a conversation, a lecture about heart failure, and you've heard the recitation of how many millions of people have this condition, how many new people get the disease each year, how many people succumb to the disease each year, and how much money we're spending treating the disease? I will not repeat those numbers. Rather, I wanted to share with you something that I think is the leading edge of our epidemiological understanding of heart failure. These data are approximately a year old, but they reflect a fascinating analysis done by our colleagues at Mayo Clinic, done out of the Olmsted County population. I want you to look very carefully at the screen in front of you. Starting from 2002 through 2010, looking at three data point lines, one that deals with the overall incidence of heart failure, and then one that separates the incidence of heart failure with reduced ejection fraction -- that would be in yellow -- and another line in blue that demonstrates the incidence of heart failure with preserved ejection fraction, here is the news flash. These curves are all diminishing, diminishing, meaning that the incidence of heart failure actually is beginning to turn around and to become less. Yes, the prevalence of heart failure is still elevated because the population at risk is getting older, so that population disproportionately represents more candidates, if you will, in the community. But in truth, the incidence declining, and this is not unexpected. Think about your own hospitals. The care that your hospitals are providing for acute coronary syndromes, the early revascularization strategies, results in the preservation of ventricular function after myocardial injury. That previously was the leading cause of heart failure, particularly HFrEF, or reduced ejection fraction heart failure. That's not happening to the same extent anymore. So you would expect that eventually we would see a decrement in the incidence. Admittedly, this is a homogeneous population, not much ethnic or racial disparity, and a well insured population. But it gives us a hint that the epidemiology is beginning to change from what it was once before. So I want you to embrace this notion that what we're dealing with now is prevalence. What we're dealing with right now is the recurrence of care required by rehospitalization. But importantly, the incidence is declining.

Let's move on from that perspective on new epidemiology, which is different from what you were expecting, and talk about new prevention strategies. This is incredibly important, and I hope that you are attuned to what I'm going to share with you over the next several minutes. Look at the stages of heart failure as previously articulated in several iterations now of the Heart Failure Guidelines, 2005, 2009, 2013. These stages remain intact for the 2016 version of the Heart Failure Guidelines, and they show the progression from A to stage D, A being at risk only, B being those with established ventricular disease but never having had symptoms, while C is the line of demarcation. These are the patients that have ever had symptoms or currently have symptoms, and D would be those that are refractory. I don't want to dwell on this point, but what I want to do is to highlight the very next graphic.

If you're keeping count, this should be number 11. Again, these data come from our colleagues at the Mayo Clinic, and they demonstrate something phenomenally striking. When evaluating the natural history of an unselected patient cohort under their observational dataset, we recognize that patients with either no risk factors, risk factors only, or asymptomatic LV dysfunction without ever having symptoms have a strikingly different survival over eight years compared to those that have had symptoms in the past or actively have symptoms, persistent symptoms, as in C2, or refractory symptoms, as in D. The message could not be more clear. There would appear to be a very high imperative to halt the progression from stages A and B to stages C1, C2, or D. Is that possible? I'm going to make the argument that it is by focusing on hypertension. These landmark data from a large cohort study known as CARDIA demonstrated that in adults who were followed in this cohort study – the follow-up now is up to 30 years -- those were hypertension of baseline over 10 years were already at significant risk and, in fact, had developed subsequent heart failure, the argument being that hypertension may be a sufficient risk factor to lead to the development of heart failure. These data published in 2014 in the Lancet from the Hypertension Collaborist Group demonstrate something very striking. I want you to pay attention to the arrow highlight. This arrow shows that in the group of individuals with the highest likelihood of having cardiovascular disease based on other risk factors that when blood pressure was successfully reduced with antihypertensive therapy, there was a striking reduction in the incidence of heart failure that favored active treatment. If you're keeping up with me, this messaging would say hypertension leads to or sets the stage for heart failure. And in those at greatest risk, the treatment of that hypertension might reduce the likelihood of having disease. Enter the SPRINT trial.

For those of you keeping up by numbers, this should be graphic number 14. This is less a study of hypertension and more a study of those that have risk factors for heart disease, including hypertension. In this study, where the primary outcome measure was first occurrence of an MI, acute coronary syndrome, stroke, heart failure, or cardiovascular death, in the nearly 10,000 patients in this study who were recruited because of increased cardiovascular risk -- this is articulated on the 15th graphic -- that increased risk is defined by chronic kidney disease, by having a calculated risk of disease of 15 percent or greater based on the Framingham risk score, 7.5 percent or greater based on the ACBD risk calculator, being age 75 years or older, these are people with high risk. In that cohort, the SPRINT investigators demonstrated first the ability to profoundly reduce blood pressure to target levels of 120 milligrams of mercury systolic, compared to standard treatment which is at 140, and in so doing, as notable here on the 17th graphic, there was evidence of a profound survival advantage on the primary outcome, a reduction of death with the initiation of antihypertensive therapy to intensive treatment goals, but uniquely in those at high risk. If you now take a look at the 18th graphic -- and once again, I'm using an arrow to highlight the most important thing -- the primary end point for SPRINT was driven by the benefit on heart failure and the benefit on cardiovascular death from any cause. This would make a very, very strong argument that in those at highest risk, treating hypertension, per se, is sufficient to reduce the incidence of heart failure. For everything else I'm going to share with you about the treatment of heart failure, it is still preferential to not get the disease to begin with.

The closing statement, when the data were released about a year ago now, reads thusly, and this is on graphic number 19. “Treating high-risk hypertensive adults 50 years of age and older to a target of 120 millimeters of mercury systolic significantly reduced cardiovascular events by 30 percent and reduced all-cause mortality by nearly 25 percent compared to treatment to a goal of 140 millimeters of mercury, which previously was the threshold we respected.” It is important at this moment to pause. Think about shared with you, a meaningful and important way to prevent death overall and to prevent heart failure by focusing on hypertension. That should be one of the big three messages you take home with you from today's webinar. The first one should be the changing epidemiology, which I've already presented to you, and the second one should be this ability to prevent heart failure by targeting hypertension. I think that is profound.

Let's keep going. We should be on graphic 20 now. The data in front of you, if you don't recognize them, are the data from the STOP HF trial. Why am I sharing this with you? These are patients with stage B heart failure. If you will, SPRINT addressed stage A heart failure with additional cardiovascular risk. This is now a study of stage B heart failure, and guess what? Another way to prevent heart failure. In these patients with stage B heart failure, never having had symptoms, routine follow-up versus interventional follow-up, which in this case was being seen by a cardiologist or heart specialist, having an imaging study done, an echocardiogram, and if the BNP was greater than 50 picograms per ML -- not greater than 100, but greater than 50 -- the early introduction of RAS inhibition, a striking reduction in the development of heart failure. So for everyone engaged now -- we have nearly 400 people listening -- I want to be very clear. The epidemiology is changing, in part because we've done a better job of treating acute coronary syndromes. Now we can arguably talk about prevention in a way that we could never talk about it before. By targeting hypertension and by identifying those with stage B who have a modest increase in the BNP not greater than 100, just greater than 50, we can, again, prevent heart failure. These are fundamental statements because previously we have all been engaged in treating the disease once it developed. Now we can have the important conversations about preventing the disease. Another pause moment.

So we've dealt with the first two issues, new epidemiology and new prevention strategies. For the rest of the time, I want to focus on the new treatment paradigms, which necessarily means I want to present to you the new guidelines as we've configured them, and everybody should be on graphic number 21. Graphic 22 is what we published in circulation in 2013, which was the flow diagram, the treatment algorithm for our best understanding of HFrEF in 2013. The evidence-based therapies appear. We made very clear that for all classes of heart failure, the highest order of magnitude for treatment was an ACE inhibitor or ARB – the preference is an ACE inhibitor -- plus an evidence-based beta-blocker. And then, one of three variables needed to be explored. All three may have been pertinent, but either explore whether or not the patient is volume overloaded, and/or explore whether or not the patient is African-American with persistent symptoms, and/or explore whether or not the patient has intact renal function that will qualify for candidacy for an MRA. The end result is a regiment that is uniquely configured, if you will, the beginning of personalized medicine with an ACE inhibitor or ARB plus evidence-based beta-blocker and diuretics as needed and the combination if hydralazine isosorbide dinitrates, if indicated in a very unique cohort, and mineralocorticoid antagonist if renal function is intact, understanding that there are additional other provisos for device therapy. This should be the floor of our understanding about the treatment of heart failure with reduced ejection fraction, remembering that heart failure with preserved ejection fraction is treatment by the comorbidities, because we don't yet have a specific intervention that changes the natural history of HFpEF, but we know that, by treating the comorbidities, we can lessen the burden and reduce the symptoms, particularly controlling hypertension and using diuretics judiciously.

So why can I speak with such conviction about the importance of this 2013 algorithm? This is why. If you look at the data that Dr. Fonarow and I presented in the American Heart Journal in 2012, and have repurposed and updated in 2016 in JAMA Cardiology, we make evident that the number needed to treat to save a life, standardized over 36 months, is truly in the single-digit range. And the relative reduction heart failure hospitalizations is between 30 and 45 percent. The reduction in mortality is between 15 and 45 percent. These therapies work, and they work incredibly well. And I'm making that point of emphasis now because it's important to realize that as we move forward and talk about introducing yet again brand new therapies for heart failure, we should not retreat from these tried and true therapies that really are the difference maker.

Now, if we go on to graphic number 24, we're beginning to discuss the mechanisms of action of a brand-new drug. What’s up with this brand-new drug? I'm sharing with you the way we knew the drug in 2014, as LCZ696. We now know it as a combination of Valsartan and Sacubitril -- the proprietary is Entresto -- but the important piece of this is that it brings together a RAS inhibitor and a natriuretic peptide system enhancer. Let me say that again. Graphic 24 shows the schema for bringing together a RAS inhibitor and a natriuretic peptide system enhancer. Why the marriage? By inhibiting RAS, we remove the prototypical burden of an exaggerated neurohormonal system on the natural history of heart failure. But also, by adding a natriuretic peptide system enhancer, we take advantage of endogenous pathways that promote vasodilatation, that retard growth, that reverse fibrosis, and the test that was proposed here was to demonstrate that bringing these two strategies together would, in fact, change the natural history of heart failure. I want to point out one nuance here. Understand that when you enhance the natriuretic peptide system by disrupting the Neprilysin enzyme that breaks down the natriuretic peptides, you discovers that the NP, as we measure it in clinical medicine, is, in fact, a substrate for that enzyme while NT pro BNP is not. So when you utilize this therapy, the NP levels will go up, not down. If you're following BNP to make decisions about your patient's clinical status, you should know this nuance. NT pro BNP, on the other hand, will fall. So that's a little caveat to tuck away.

But let me have you move forward to graphic number 25 because it introduces the important design of the landmark trial PARADIGM-HF. Remember, it was an open-label run-in study that started with a reasonable dose of Enalapril, five milligrams twice a day, then escalated to 10 milligrams twice a day, the recommended dose for an ACE inhibitor in the setting of heart failure. Many of your peers, your colleagues, have argued this is a low dose of an ACE inhibitor. It is not. It is consistent with the dose that was studied in the landmark solved trials, so it is the dose that is targeted in clinical medicine. Then after the exposure to the ACE inhibitor, again, on a progressive dose titration starting at 100 milligrams with the combination of Valsartan and the Neprilysin inhibitor Sacubitril, escalating to 200, those patients that made it through the open-label run-in then entered the double-blind treatment period. The reason patients didn't make it all the way through was because of hypertension. About 20 percent, one in five patients, were unable to enter the double-blind treatment period. So remember the importance of blood pressure when you're anticipating use of the ARNI compound. Remember the necessity to demonstrate tolerability of a reasonable dose of ACE inhibitors before moving forward.

If you now go to 26, I won’t belabor the point. These are the signature findings from the PARADIGM-HF trial which show that death from cardiovascular causes reflected a 20 percent risk reduction -- this is a relative risk reduction -- and heart failure hospitalizations a 21 percent relative risk reduction. If we now go to graphic 27, remarkably, the curves begin to separate within 30 days. We typically don't make a lot out of the separation of curves, but those of us who have begun to use this clinically have begun to talk about a phenomenon in heart failure cure that we never appreciated before, something called substrate stabilization. In the patient that responds to the combination of the ARB and the ARNI, what is recognized pretty early on is that the patient begins to feel better, and the disease appears to become more quiet. That may sound like a colloquialism, but it actually corresponds with the objective data looking at biomarkers where the stimulus that would incite further elaboration of biomarkers appears to be attenuated with this combination of therapies. That becomes important. So what does that mean now?

If we go on to graphic 28 in the presentation, we recognize, when we re-create the 2013 algorithm, that we have to accommodate something that we didn't have to accommodate before. The first is treatment with a combination of Valsartan and Sacubitril. For the purposes of brevity, I didn’t go through the data with Ivabradine. I could have. This is a compound that selectively targets the funny channels, the F channels, has one functionality, which is to decrease heart rate. SHIFT-HF made it very clear that the application of this therapy on top of evidence-based therapies for heart failure with reduced ejection fraction was, in fact, associated at a minimum with a reduction in morbidity. There is some evidence that it’s associated with a reduction in heart failure related mortality, as well. So both of these therapies have to be incorporated as new therapies in this treatment algorithm. But in addition to that, there are other strategies that have to be considered. Disease management, particularly after heart failure hospitalization; genetic counseling in those with a family history; frailty assessments in the older patients, something that's being done for transcutaneous valve replacement that needs to be appreciated in heart failure, particularly with regard to those at risk for rehospitalization; palliative care, a very appropriate step for those patients that have refractory advanced system disease. Comorbidities have to be incorporated. There are new data about anemias, new data about sleep disorder breathing. I’ve introduced you to new data about hypertension. There’s ongoing work with atrial fibrillation, particularly regarding AF ablation and heart failure. And then devices, remote PA monitoring, much promise; wearable vests, we need more data. And quality improvement, process improvement, patient education, all of these are the dynamics that, interestingly enough, have evolved just since the 2013 guidelines were published. So heart failure is a dynamic, exciting field now.

So that gets us to this. If you're now with me on graphic 29, you see that part 1 of the new guidelines emerged -- this was May 20, 2016 -- and it was uniquely focused on new pharmacologic therapies. Let me remind you that when we bring forward a guideline statement, we follow a strict algorithm. This is depicted on graphic 30. It really is articulated along a dichotomous pathway. One arm is to look at the class of recommendation, which is the strength of the recommendation. What is our conviction that the benefits outweigh risk -- far outweigh risk, match risk, or there's more risk than benefit? And the second arm of this pathway is, what's the standard of evidence? What’s the level of evidence? Incontrovertible, multiple randomized trials, or opinion? That would be seen by level C, that says expert opinion. So keep that in mind.

So what do we come up with? Look at graphic 31. This is the top line, and this is the reason why I paused and reminded you of the importance of the predicate now legacy therapies for heart failure. As a class of recommendation I, inhibition of the RAS system is the preeminent recommendation, whether it’s with an ACE inhibitor or, for those that don't tolerate it, an ARB. For those that do tolerate an ACE inhibitor and meet the provisos that can be converted to an ARNI, one of these three strategies, we believe, is a must-do, must be in place unless there's an overt absolute contraindication. Now, let me remind you of how we got to this place. I love this portrayal. Look at the data for ACE inhibitors, for mineralocorticoid antagonists, for ARBs, and for the ARNI compound, all represented on this one graphic, number 32. Further, you can see the data for post-MI low ejection fraction heart failure, mild to moderate heart failure with reduced EF, and severe heart failure. And you can even get some hints about preserved heart failure. Once you're completely facile with this graphic alone, you'll begin to develop a unique appreciation for how important it is for us to modify the renin-angiotensin-aldosterone system in virtually every iteration of heart failure. Even for HFpEF, we've uniquely incorporated those trials where at least there is a hint that an ACE inhibitor might be effective in the older patient with HFpEF, an MRA might be effective, particularly in the patient biomarker positive with heart failure and preserved ejection fraction, an ARB might be effective to reduce morbidity, i.e. hospitalization. Those data points emerge from that column that is right most on your screen. But once you digest this information, follow the references that are highlighted, you'll begin to appreciate the importance of targeting the renin-angiotensin-aldosterone system. So that gets us the first one.

But now let's get to graphic 33. I won't go through this with any detail, you have access to these slides, but this one makes clear the importance of the ACE inhibitor and makes clear the importance of the ARB. Level of evidence is A. And on graphic 34, we make clear the benefit of the ARNI compound. Level of evidence is B from a randomized trial of very successful, large, important randomized trial. And all the provisos, vis-a-vis blood pressure, natriuretic peptide levels, the requirement to show tolerability to a reasonable dose of an ACE inhibitor, all of that appears in this graphic. Again, you have access to this graphic, and you can refer to that at your leisure. There also is the importance to discuss harm. We know there's risk of angioedema when a Neprilysin inhibitor is used. There's no reason to dismiss this very important observation. Previously, the combination of an ACE and a Neprilysin inhibitor led to striking cases of angioedema, particularly in African-Americans, so much so that the ACE/ARNI -- that is the ACE/Neprilysin inhibitor combination -- was no longer developed. But the ARB Neprilysin inhibitor, the true ARNI, has been developed and is safe. But one of the important provisos is as you're making the transition from the ACE to the ARNI, a minimum time lapse of 36 hours must be observed to be certain that you fully metabolize the ACE, if you will, three and a half half-lives of the standard ACE inhibitor so that there's no ACE inhibitor on board. So they should not be giving an ACE, even in a miniscule amount, with an ARNI concomitantly.

Now, what about the funny channel inhibitor, or the shift channel inhibitor? And that would be Ivabradine? This compound, based on the data that I just shared with you, has a class recommendation 2A, level of evidence is B, a single randomized trial importance, that demonstrates that the addition of Ivabradine that inhibits these F channels, from the SHIFT-HF data, in patients with a heart rate greater than 70 -- and the data are even more persuasive when the heart rate is greater than 77 -- is associated with a benefit on morbidity, heart failure related hospitalizations. This is on the background of beta-blocker therapy being on board. There were few patients in the SHIFT-HF trial not on beta-blockers, but overwhelmingly, being on a beta-blocker was present in all patients, but only about 25 percent were on the maximal dose as the guidelines might have inferred. But for the average patient not on a maximal dose, but the dose that was maximally tolerated, the addition of Ivabradine was beneficial.

Let me have you move forward now to graphic 37. This, again, is for your benefit. This is excerpted from an article that we co-authored that was published this month in Nature Review's Cardiology that demonstrates the predicate guidelines from 2013 and how those guidelines change for 2016, showing the inclusion of the ARNI, showing the inclusion of Ivabradine. I'll share with you another reference from that review article that combines the ESC and the North American guidelines, and you can use that for future reference. Let me share with you one candidate algorithm placed in the literature by a colleague of ours that was focusing on a very sophisticated review of Ivabradine demonstrating how best to use that compound in clinical practice. Again, the intent is not to belabor the point but to provide this as a resource or reference that might be of benefit to demonstrate importantly the complexity that we now have with multiple indicated therapies for heart failure, I think this is a good thing that forces all of us to be quite studious but to appreciate we have many more for heart failure than ever before. Let me share with you some opinions generated by our colleagues from the ESC now that highlight an algorithmic approach we can take for heart failure. And if I can get some technical support because the slide will not advance at this moment. I need to bring up – Janine, if you will, I need to bring up number 39.   
  
**Operator:**

Ladies and gentlemen, please stand by. We are experiencing some technical difficulties and will resume momentarily. Thank you for your patience and please stand by.   
  
**Clyde Yancy, M.D.:**

As you're standing by, let me begin to take a look at our questions. Because there are several that have come in that I think are helpful for us to evaluate. I'm trying to get to the top of the question queue. That's not happening right away. So let me suggest some of these are about technical issues. So here's a question that says, “I have read different guidelines regarding treatment of hypertension, all with different blood pressure goals. What blood pressure goal do you have for your patients?” Let me help you with this. There is a guideline being developed as we speak. I've been collaborating with the writers. We recognize that there are many extant guidelines addressing hypertension, and the ACC/AHA are working diligently to clarify the indications for any hypertensive therapy. I will tell you that the SPRINT data will help inform new guidelines. I can't be more definitive than that. I would argue that for those that parallel the SPRINT study, that is those that already have risk factors for cardiovascular disease and a blood pressure greater than 130/80, even in the older persons, the recommendation will likely be to lower blood pressure at least less than 130/80, with a target of 120/80. There was a different way in which blood pressure was surveyed in the SPRINT study, so that may be of some mild importance. But importantly, for those with an increased set of risk factors, targeting the lower blood pressure, likely 130/80, will be important. For those with lesser risk, we might discover that a blood pressure threshold of 140/80 might be okay. So stay tuned for the work that the guideline writing committee is doing. But I think we can be fairly definitive – high risk, low blood pressure.

**Steve Dentel:**   
I think they fixed your slides.

**Clyde Yancy, M.D.:**

Okay. But let me get to some more of these questions since they're up. Another one that I want to deal with very quickly was to expand on new data regarding AF ablation and heart failure. Many you know that there is a very important intersection between atrial fibrillation and heart failure. And we are working hard to understand how we can interrupt the natural history of diseases. There are some smaller studies that have suggested that AF ablation may be safe in the setting of heart failure, and at a minimum, may improve symptoms. How it changes the natural history, we don't know. There has been an effort to do what would be called raft 3, where ablation would be a randomized approach in patients with reduced EF heart failure. We’re waiting to see how those data will come forward. There also have been smaller data points that suggest that when rate control in atrial fibrillation can't be fully achieved, it could be that AV node ablation following by the application of cardiac resynchronization therapy might be a useful way to improve symptoms and increase ejection fraction. We know from the AFCHF study that rate and rhythm control appear to be similar in benefit, and the preference has been in rate control because there is some risk with rhythm control, either because of the [inaudible] rhythm therapies and the repetitive cardioversions, so we hope that those issues will be clarified as we go forward.

One other question that I’ll answer before I go back to the presentation is whether or not I believe, going forward, that the ARNI class -- because recognize there will be more ARNI compounds -- will ever be approved as first-line therapy APR before exposure to ACE inhibitors. It will have to be driven by evidence. In the absence of evidence, we should not extrapolate the data from PARADIGM-HF to those patients never exposed to an ACE inhibitor. And that would be okay because, remember, the ACE inhibitor-based therapy is a very effective strategy. It's only after demonstrating that patients can tolerate those drugs that one should begin to think about the switch, and we should be slow to rush to introducing the ARNI a priori. What's the timing going to be? That's a judgment call. Patients tolerating the ACE inhibitor early on and you make the conversion early, nothing would be wrong with that. But waiting until you've tolerated all evidence-based therapies to optimal doses before switching to the ARNI, nothing would be wrong with that, as well. I, for certain, would have beta-blockers on board before switching to an ARNI, and the Europeans, as I'm about to show you, would advise that the mineralocorticoid receptor antagonist should also be on board before making that switch.

I think we're back up with our presentation, so let me get you to the algorithm as it appears in the European literature. That would be graphic 40. And I'm delighted that 376 of you have remained engaged. I want to share this with you because it demonstrates, first of all, the complexity of treating heart failure in today's world, but it also has some nuances that are incredibly important. As we originally suggested, it highlights the importance of beginning the ACE inhibitor and evidence-based beta-blocker as a first step. The Europeans will suggest you then add the MR antagonist, MRA, provided renal function is intact. And after surveying symptoms, then you would consider adding the ARNI to replace the ACE inhibitor. This is a strategy, not the strategy. The view of the guideline writing committee from the US is that the MRA does not have to be a prerequisite therapy before the ARNI, does not have to be a prerequisite therapy before Ivabradine. Beta-blockers, however, do need to be on board before Ivabradine, as does the ACE or ARB. So again, this gives you a sense of the evolving complexity of treatment that I hope everyone can appreciate.

If we now move forward, I want to introduce the last topic of importance here, which is the introduction of a new vernacular in the treatment of heart failure. In the European guidelines published in May, those guideline writers endorsed the presence of something called heart failure with mid-range ejection fraction, identifying it as ejection fractions between 40 and 49 percent, suggesting that this was a different phenotype characterized by elevated natriuretic peptides, by symptomatic disease, and by structural heart disease. I want to remind you that in the 2013 guidelines published by the ACC and the AHA, we articulate it, as shown here in graphic 43, a subdivision of heart failure with preserved ejection fraction that captured this 40 to 49 percent range either as borderline ejection fraction or as an ejection fraction that was improved, having previously been reduced. Is all of this just vocabulary, or is there something to say that there's something here? We think there's something here. If you now look at graphic 44, in these data published earlier this year, July, in JAMA Cardiology, an observational dataset from the Emory experience demonstrated compellingly that for that 15 percent of their cohort in whom the ejection fraction had improved, whether the outcome was death, death or all-cause hospitalization, death or cardiovascular hospitalization, death or heart failure hospitalization, that group fared decidedly better and have rEF or HFpEF, the two curves in blue and yellow above the lowest most curve, which reflects those patients with what we are now calling heart failure with improved ejection fraction. So this has opened up a brand-new direction for us to consider. So now, this article published this month showed the merger of the ESC and the ACC/AHA/HFSA guideline update. I share this with you -- Volume 13 – it’s published monthly and allows you to pull this reference and really have a crisp viewpoint of what's different in this guideline writing process.

And I'll close with the final graphic published in JAMA Cardiology, again, by Dr. Fonarow and I, demonstrating an update of the number needed to treat to save a life, the relative risk reduction in all-cause mortality, and the number needed to treat for all-cause mortality, all compelling data, compelling data that there is decided evidence that we can fundamentally change the natural history of heart failure. And I would ask you to take a more careful look at this graphic for the important information that is portrayed here. So I want to thank you for your attention. We still have 373 of you that are engaged with us. I've opened up the question queue, and with the permission of Janine and Liz and Steve, I’d like to immediately get to the question queue. But I'll pause for a moment to be certain that everyone is on the same page.   
  
**Operator:**

Thank you. At this time we would like to take any questions you might have for us. As a reminder, to ask a question via the web, click the “Q&A” button in the lower left corner of your screen, type your question in the open area, and click "Submit." and I'll turn it back for the Q&A session.

**Clyde Yancy, M.D.:**

So let me go to question 30. “Are these treatment options cost neutral?” The better way to pose this question is whether or not these treatment options are cost-effective. I will tell you now that there are two independent publications in the literature, one in JAMA Cardiology, one in JAG Heart Failure, demonstrating that, in fact, the use of the ARNI compound is cost-effective, with conservative estimates on the prolongation of life. These are conversations that are very complicated because there's enough front costs for the cost of acquisition. There have been some programs introduced to make it easier for patients to access these medicines. But with regards to the costs to the healthcare system, these compounds are cost-effective. There's another question that I think is very important about whether or not there's a need to wash out when you’re switching from the ARB to the ARNI compound. The answer is no. You’re going from ARB to ARB. You simply stop the ARB you're prescribing, be it Losartan or Candesartan, and begin the combination of Valsartan and Sacubitril. If the ARB was Valsartan, you’d simply stop the Valsartan given singularly and start with the combination therapy. I really enjoy this question that Silvi submitted regarding the risk for diabetes in this presentation. Silvi, you may be aware of data in the trial known as the PONTIAC-HF trial, which took diabetic patients and, again, screening those patients with a biomarker, in this case, an NT pro BNP. For those patients that had a positive screen, that is an elevated NT pro BNP, not only the early introduction of evidence-based therapy, RAS inhibitors, and beta-blockers, but titrating those therapies to an optimal strategy was, in fact, once again, associated with the reduction and the eventual development of heart failure. And then we can change the frame and look at the data from the SGL T2 inhibitors used as hypoglycemic agents, where, remarkably the first hypoglycemic agents yet that we've seen that are not only free of cardiovascular risk but appeared to exert a favorable profile on heart failure. The mechanisms are under intense discovery. I do not believe it's simply because they're glucose urea, ureic drugs, but certainly the signals cannot be ignored. The datings from the initial studies are robust. We're waiting for additional studies to come out.

There is a different set of questions here, if I can get my screen to move. Here we are, with regards to the costs, per se, for the ARNI compound. So again, I would request that you work carefully with your hospital. We have incorporated a specialty pharmacist in our heart failure clinic. I realize this is a resource that may be only available in larger facilities, but I think listening to the story of our experience may encourage you to approach your hospital leadership. By bringing on a specialty pharmacist, we've been able to triage patients who need compounds for which the upfront costs are significant and having those pharmacists work with the patients, explore all the available options. And I've been really impressed that very few patients, if any as of late, have been unable to access not only the ARNI compound, but other more costly interventions, like PCSK9 inhibitors, for example. So there is a real advantage to having a team management approach, with the pharmacist deeply embedded in the team and the care of your patients with heart failure. There is another question here from Shany that says, “If we have to admit the patient who is on an ARNI and Ivabradine, should we stop the medication? And what will be the dose for discharge?” Very good question. There's no overt indication to stop either therapy unless the patient presents with compelling bradycardia. The incidence of bradycardia was real in the SHIFT-HF study, and if you believe that the symptomatic heart failure presentation is driven in part by bradycardia, it would be reasonable to hold Ivabradine and, when it's resumed, resume at a lower dose. And the same thing for the ARNI compound. We have learned in a very real way that if we abruptly stop RAS inhibition at the time patients are decompensated, they do less well. That's especially the case with beta-blockers. So the advice that we give practitioners is to reduce the dose of the beta-blocker in half, if necessary. The same can be said for RAS inhibition. We would advise the same thing with the ARNI. We would refrain from the abrupt cessation of these compounds unless the patient is in abject shock, where you have to stop all oral agents and agents that may impact blood pressure.

To the extent that my screen can navigate the questions that have been submitted, I've dealt with many of those questions. I'd be delighted to deal with any other questions that you may have. I think some of the earlier questions were referable to technical issues, and hopefully everyone has had their issues resolved. Shany, thank you for your kind words. The question from Beth, the last reference, the article by Fonarow and Yancy, that's in JAMA Cardiology, June of 2016. We publish that journal on a monthly basis, so it should be relatively easy. If you go to the JAMA Cardiology website and search on Yancy or Fonarow, it should come up. So thank you for wanting clarification there. Are there additional questions? We have about two minutes left. Well, in the absence of additional questions, I want to thank everyone. We've lost some of our group, but remarkably, over 300 of you are still engaged. I hope this has been helpful, meaningful, that it helps you orchestrate care for patients that you're likely to see. Remember the three big takeaways. The first is the epidemiology of heart failure is changing. The second, in a very robust way, the opportunity to prevent heart failure is very real by focusing on hypertension, by looking at natriuretic peptide levels, perhaps, in patients with stage B disease, and even in the diabetic patient, an exciting time. And then these new therapies give us great enthusiasm that the success we've had to date with evidence-based drug and device therapy for heart failure will only be enhanced now that we have more therapies, more strategies, more opportunities to provide care. Thank you for your time and attention. It's been a joy to speak with you today.

**Steve Dentel:**   
So on behalf of the American Heart Association, our webinar series sponsor, Amgen Cardiovascular, we'd like to thank you, Dr. Yancy, and our attendees for your valuable time and participation on today's webinar. A recording of today's webinar will be available in the next few weeks on heart.org/quality, and all attendees on this webinar will receive a notification when the recording is available for download. Thank you again for your participation in today's webinar, and have a great day.   
  
**Operator:**

Ladies and gentlemen, we hope you found this webcast presentation informative. This concludes the program, and you may now disconnect.