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Clinical Implications of Updated Heart Failure Nomenclature

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Dr. Goldberg:
Hello, and welcome to Medical Minute One: Clinical Implications of Updated Heart Failure Nomenclature. This is the first in a 3-part series called Expert Insights on Navigating and Implementing the 2022 Heart Failure Guidelines. I'm Dr. Lee Goldberg, Section Chief of Advanced Heart Failure and Cardiac Transplant and Vice Chair of Medicine for Informatics at the University of Pennsylvania in Philadelphia.

Here are my disclosures.

Our learning objective for today is to discuss the clinical implications of the updated heart failure staging and classification recommendations.

So now let's talk about how the approach to heart failure has evolved over time. The traditional paradigm, which was really developed starting in the 1960s and through the late 1990s, really focused on heart failure as a hemodynamic disorder. The key thing here was volume control. This was diuresing patients to control their symptoms, and this was the cornerstone of therapy. The concept here is that patients would go into heart failure, perhaps come into the hospital, get diuresed, their symptoms would improve, and then they'd be out of heart failure, kind of a series of exacerbations over time. And they were typically classified by New York Heart Association classification, or their functional capacity alone.

Now, the challenge to this tradition was really based on a series of, first, clinical observations and then laboratory observations. The first is that the NYHA class changed over time. And that thought, NYHA class could change even over a matter of days with someone being very symptomatic, and then being diuresed and being much better. We started to learn that heart failure was a cellular disease, and that despite symptomatic improvement, the neurohormonal changes, cytokine and cellular changes continue to occur and allowed heart failure to progress with patients getting sicker over time. And we also learned an important lesson, that ejection fraction really did not correlate well with functional capacity; someone could have an ejection fraction of say 15, or 20%, and be NYHA Class I, while someone with an ejection fraction of 35% can be NYHA Class III.

So this led to a shift to more of a chronic disease model when we started to think about heart failure, and led to the development of a staging system in the late 1990s. The heart failure staging system emphasized that heart failure or the concept of ventricular dysfunction was a chronic disease. And even in the absence of symptoms, the activation of neurohormones and negative remodeling of the ventricle can occur, and this can lead to progression. So, if we begin to focus on prevention of disease or disease progression, this will have the biggest impact on our patients.

We also know that there are specific risk factors that can be identified and managed to actually prevent heart failure in the first place.

And that our current medical and device therapies have literally changed the natural history of heart failure, but are most effective when we initiate the therapies early.

So, the newest guidelines were published in May of 2022. And this was a collaboration between the American Heart Association, American College of Cardiology, and the Heart Failure Society of America. Now, here are the stages of heart failure. And they've been recently updated, at least in terms of their nomenclature. Stage A are patients at risk of getting heart failure. This was very controversial initially, because how could you have a patient that doesn't have the disease be in the guidelines? Well, the thought was that there are specific risk factors that can lead to heart failure, and therefore, treating those risk factors can really prevent the development of heart failure in the first place, much like controlling risk factors can prevent the development of coronary artery disease and myocardial infarction. Now, Stage B is now named pre heart failure. These are patients who have some form of structural heart disease, either stiffened heart or thickened heart or a weakened heart muscle, but these patients have never had any symptoms of heart failure whatsoever. Now, Stage C are the symptomatic heart failure patients. These are individuals who have structural heart disease, but have had symptoms of heart failure either in the past or currently, but can include patients that are currently asymptomatic. And we're going to spend a lot of time focusing on those for the remainder of the talk. And then in Stage D, these are the advanced heart failure patients that, despite our best efforts, all of the guideline-directed medical therapy and devices continue to have significant symptoms.

So if we focus on the Stage C patients, we can see the correlation between NYHA classification. A Stage C patient can be NYHA Class I if they're asymptomatic, currently, all the way to New York Heart Association Class IV, if they have shortness of breath, even at rest. Now, if you look at Stage A, they don't even have an NYHA class because they don't have heart failure or any structural heart disease. The Stage B patients, the pre heart failure patients, by definition have to be NYHA Class I. If they're anything else, then by definition, they'd be Stage C. And lastly, the stage D are the advanced heart failure patients.

So how does NYHA classification fit into this? Well, we know that NYHA class can change quickly. The example I gave, a 64-year-old man with a left ventricular ejection fraction of 35%, comes into the emergency department, very short of breath, can't even speak in full sentences, and therefore he's New York Heart Association Class IV. But he's admitted to the hospital, is diuresed, has his medications optimized, and is discharged NYHA Class II. And so, you can see that over a matter of days, he's moved from one classification to another. And so, it became difficult to figure out what therapy should this patient get? The staging system makes it very clear that anyone that had symptomatic heart failure is ACCHA Stage C, and therefore should be treated with the 4 core medications.

So the heart failure classifications provide information about disease progression, the NYHA functional classification tells you something about symptoms at the time and functional capacity. Now let's talk a little bit about whether those stages of heart failure actually correlate to survival. This is a paper from a number of years ago and broke patients down by stage of heart failure, A being at risk, B asymptomatic left ventricular dysfunction, Stage C were patients who had had heart failure in the past but currently were NYHA Class I or II, CII, Class III, and IV, and then D all Class IV. And you can see that the stages actually really do correlate to survival, giving us some prognostic information.

So, what should we do with those Stage A patients who are at risk? Well, we know that 1 in 5 Americans will develop heart failure in their lifetime. And there are a series of cardiovascular risk factors that begin to pile up and increase the risk of developing heart failure over time, coronary heart disease, hypertension, hyperlipidemia, diabetes, etc., are all cardiovascular risk factors. And then we know there are a number of non-cardiovascular risk factors that are also very important, including things like toxic exposures to chemotherapy and other drugs.

Now, the lifetime risk of heart failure is high in patients with hypertension. And we know that higher blood pressure and BMI increases the risk across all groups; 1.6 times higher for blood pressures greater than 160/90 versus 120/90, and 2 times higher for BMIs greater than 30. Now, a number of comorbidities can cause heart failure, but also really block a patient's ability to self-manage, may mask symptoms, or may trigger exacerbations.

We think about heart failure and diabetes. Diabetes is a major risk factor for heart failure, and the event rate is greater than an any other cardiac complication with diabetes. About 50% of patients with type 2 diabetes may develop heart failure, and diabetic cardiomyopathy results in structural myocardial abnormalities. And this can occur even in the absence of other risk factors. If we look at the outcomes of patients, including mortality with heart failure and diabetes, you can see that a well-controlled hemoglobin A1c, but not too well controlled, of 7.1 to 7.8, gives the best outcomes with very low hemoglobin A1c's having increased risk, and very high also having increased risk. If you think about hospitalization risk across the clinical trials, those patients that had diabetes were much more likely to be admitted to the hospital.

So how do we prevent heart failure? Well, one is we want to diagnose and treat hypertension and the cardiovascular risk factors aggressively. And the blood pressure target for all patients is a blood pressure systolic of less than 130, diastolic of 80. Other conditions or agents that may lead or contribute to heart failure should be controlled or avoided. And then more frequent screening in these high-

risk patients to make sure that we're identifying patients who may benefit from other therapies.

What about our stage B patients? These are patients with asymptomatic left ventricular dysfunction. This is old data from the Framingham Heart Study that showed that actually about 45% of patients that have asymptomatic left ventricular dysfunction with an ejection fraction of less than 40% will go on to develop Stage C heart failure, or symptomatic heart failure in their lifetime. And if we look at mortality, the same is true. If you have a worsening ejection fraction, your mortality is significantly worse than patients that do not have asymptomatic left ventricular dysfunction. And this is the type of data that made us think about this being pre heart failure.

So how would we manage these folks? Well, an ACE inhibitor we have data for that can improve patient's outcomes, reduce their chance of going on to symptomatic heart failure, and reducing mortality based on the prevention trials. We also know that in patients that have coronary artery disease, that they should be on a statin. And in patients that are intolerant to ACE inhibitor, there's some data to use and angiotensin receptor blocker. And then you can consider the use of beta blockers and you consider the use of an ICD in selected patients based on their symptoms, history, and current ejection fraction.

So if we think about our approach for patients at risk for or having pre heart failure, you can see that several drugs in the blue here are the ones that we start to think about, or several interventions anyway. We want to control blood pressure, consider the use of an SGLT-2 inhibitor, optimal management of cardiovascular disease, including coronary artery disease. I think about genetic counseling and screening for those patients that have a family history, and then use risk scores or biomarkers for screening. For the Stage B patients, the use of an ACE inhibitor or an ARB, consider a beta blocker, and consider an ICD, and again with a family history, consider genetic testing.

Now there's one other layer to think about. What about those patients with varying ejection fractions. Well, with heart failure with reduced ejection fraction, the definition is less than or equal to 40% ejection fraction, mildly reduces 41 to 49%, preserved ejection fraction greater than 50%, and then as we mentioned earlier, heart failure with improved ejection fraction, meaning they had an ejection fraction less than 40% and now it's greater than that with medical therapy.

Now there's some exciting news for heart failure with preserved ejection fraction. Recent clinical trials have led to several new drug approvals and updates in the guidelines. So for SGLT-2 inhibitors, empagliflozin and dapagliflozin, currently have clinical trials data, with empagliflozin a little bit ahead in the regulatory process. Mineralocorticoid antagonists, including spironolactone and eplerenone, and then the angiotensin receptor blocker, neprilysin inhibitor, sacubitril/valsartan.

So we used to think about patients that had an improved ejection fraction as being cured or getting better. But now we've learned that these patients that continue their heart failure with reduced ejection fraction treatment indefinitely. The TRED-HF trial randomized patients who had recovered their ejection fraction to either withdrawing their medications or continuing that. And unfortunately, the trial had to be stopped because those in the withdrawal arm had worsening ejection fraction and the development of symptomatic heart failure. And this validated a lot of the laboratory observations that even in the setting of recovered ejection fraction, there are persistent cellular and extracellular changes in the myocardium. And this is what the outcome of the trial looked like, and based on this, continuing medications indefinitely is what is recommended.

So, in conclusion, heart failure is a chronic disease that requires lifelong treatment. Management of risk factors can prevent or delay the development of heart failure. The ACCHA staging system guides therapy regardless of symptoms, and this correlates to prognosis. Stage B, pre heart failure, should be managed with medical therapy, given the high risk of progression to Stage C heart failure. And even when the ejection fraction recovers to normal, maintaining lifelong medical therapy can prevent heart failure reoccurrence.

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