Screening and Diagnosis of Heart Failure

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DR. ALANNA MORRIS: Hello, my name is Dr. Alanna Morris. I am an associate professor of medicine and the director of Heart Failure Research at Emory University in Atlanta, Georgia, and I am excited to talk to you all today about heart failure. We know that heart failure is becoming more and more common with the aging of the population, as well as the increasing prevalence of multiple cardiometabolic risk factors. So as clinicians it is extremely important for us to understand both the pathophysiology of heart failure, the appropriate steps to diagnose so that we can institute appropriate treatment for patients.

Let us start by talking about the definition, epidemiology, as well as the pathophysiology of heart failure. Again, the epidemiology is extremely important to understand because heart failure is associated with very high morbidity, mortality, as well as high cost. In the U.S., for example, the prevalence of heart failure is probably somewhere between 6.2 and 6.5 million Americans. We are also seeing an increasing incidence of heart failure diagnosis - almost a million new diagnoses every year.

The mortality of heart failure is worse than any cancer. We see estimates around 42% but in some cases it is as high as 50% at five years. We often quote patients with a mortality of 50% at five years. We know that hospital discharges are extremely common. In fact, heart failure is the most common cause of cardiovascular hospitalization amongst adults over the age of 65, and so because of the high incidence of heart failure hospitalizations, the cost is also extremely high with cost estimates that are at least 30 billion dollars, but if you take into account indirect costs such as lost wages and others, this estimate is probably an underestimate.

We know that the incidence of heart failure differs by race and ethnicity. This is the data from the multiethnic study and atherosclerosis, however, this type of data has been validated and confirmed in multiple other epidemiologic studies where we see that the incidence of heart failure is highest amongst self-reported Black Americans, followed by Hispanic Americans, and then white Americans, and again that type of pattern where we see a higher incidence of heart failure in Black Americans is true whether there is an interim myocardial infarction or not and in fact we know that nonischemic heart failure is actually more common in Black Americans than in white Americans.

We also know that the incidence of heart failure differs by gender. If we look at ejection fraction as sort of the marker of the type of heart failure that we see, we know that heart failure with preserved ejection fraction which we will talk about a little bit more is more common in women particularly amongst older women whereas heart failure with reduced ejection fraction is more common amongst men, in part because of coronary artery disease and the prevalence of antecedent MI which maybe more common amongst men.

As we think about the prevalence of heart failure, again I mentioned that it is going up again in part because of the aging of the population, particularly here in the United States, as well as increasing prevalence of multiple cardiometabolic risk factors. We know that prevalence also differs by race and ethnicity. We can see that Black Americans again have the highest prevalence of heart failure in part due to the burden of traditional cardiovascular risk factors followed by white non-Hispanic Americans with Hispanic and Asian Americans having slightly lower prevalence of heart failure as compared to other groups.

When we talk about hospitalization, we also see that Black Americans have higher rates of heart failure-related hospitalization. This is the data from the National Inpatient Sample looking at hospitalization rates from 2010 to 2013, and there are a couple of things that are relevant when you look

at this slide. If you just look at crude heart failure hospitalization rates, we can see that they are highest for Black men and women who are here in the yellow lines, followed by white men and women, followed by Hispanic men and women, and finally Asian and Pacific Islanders have the lowest rate of heart failure hospitalizations.

When we adjust for age, however, because we know that the onset of heart failure is a younger age of onset in Black Americans, we can actually see that this disparity widens with Black men having the highest risk of heart failure hospitalization followed by Black women. We can also see that over this time period, while there was hospitalization amongst Hispanic men and women in the beginning, we were able to sort of close that disparity by 2013 with Hispanic men and women having only a slightly higher risk of heart failure hospitalization as compared to white men and women. However, the risk of heart failure-related hospitalization between Black men and women versus white men and women really did not change over that entire time period.

Finally, when we look at outcomes, particularly with the outcome of death, we can see very, very morbid statistics. So this is an analysis from the AHA Get With The Guidelines Registry looking at five-year outcomes for patients over the age of 65 who had been hospitalized with heart failure. Again, we see a couple of very important statistics on this slide. Number one, this population includes patients who have reduced EF heart failure, preserved EF heart failure, as well as an ejection fraction that we would consider borderline and mildly reduced somewhere between 41% to 49%, and what we can see is that when you look at five year mortality, the mortality is actually equivalent despite the ejection fraction. So we can see the ejection fraction really does not associate with mortality even though we sometimes have a tendency to think that patients with reduced EF heart failure have a worse prognosis. In fact data like this as well as other analysis show us that that is not true.

When you look at the crude mortality rates, again independent of ejection fraction, we can see that there are about 75% in five years, so again this is an elderly population over the age of 65, the 75% mortality in five years is extremely high. When we look at rates of readmission, again extremely high somewhere between 82% to 85%, we can see that cardiovascular or heart failure-specific readmissions are slightly more common amongst those with reduced or borderline ejection fraction, whereas those noncardiovascular readmissions are slightly more common amongst patients with preserved EF heart failure, but when you look at a combined endpoint of mortality or readmission, it is almost 100% at five years, so again emphasizing how both morbid and mortal this condition can be.

So, with the recognition that these patients with heart failure are at extremely high risk for both hospitalizations as well as death, there was an important consensus document that was published just in the early part of 2021 sort of helping us to redefine heart failure and this is the new universal definition of heart failure. It is patients who had symptoms and or signs of heart failure caused by a structural and or functional cardiac abnormality that is corroborated by at least one of the following. The patients seem to have elevated natriuretic peptide levels, and that is in part because we know that most of the recent clinical trials that we have done define heart failure based on the presence of elevated natriuretic peptide levels.

However, in some cases natriuretic peptide levels were not elevated, particularly in those patients who had obesity or other risk factors, so we could also diagnose heart failure by objective evidence of cardiogenic pulmonary or systemic congestion. These are the levels of the natriuretic peptides that

support the definition of heart failure, and in an ambulatory setting such as the clinic, it is the BNP ≥ 35

or an NT-proBNP ≥ 125. In a hospitalized setting or emergency room setting, we use higher levels, so a BNP ≥ 100 or NT-proBNP ≥ 300. It is also important to recognize that this document gave us new stages of heart failure.

So many of us are used to the old ACC/AHA stages where patients were called stage A, stage B, stage C, or stage D depending upon where they were in the continuum of heart failure. We have now adjusted that terminology. Patients who were previously being called stage A are now being called at-risk for heart failure. So these are patients who are without current or prior symptoms or signs of heart failure and also without structural biomarker or genetic markers of heart disease. So these were essentially patients who have risk factors. Risk factors like hypertension, coronary artery disease, diabetes, and obesity. Maybe, perhaps the patient who has a known exposure to a cardiotoxin such as a woman who is getting treated for breast cancer and is going to get anthracyclines or patients who have family history of cardiomyopathy.

Those patients who we used to call stage B are now being called pre-heart failure. So these patients do not have current or prior symptoms or signs but they do have evidence of structural heart disease such as left ventricular hypertrophy, ventricular or atrial chamber enlargement, and other findings. They may have evidence of abnormal cardiac function such as reduced left ventricular or right ventricular systolic function or evidence of increased filling pressures or abnormal diastolic dysfunction. They can also have evidence of elevated natriuretic peptide levels or elevated cardiac troponin. So either of those cardiac biomarker abnormalities or evidence of structural heart disease would put a patient in this pre-heart failure category.

And of course patients with stage C or symptomatic heart failure would be defined by both current or prior symptoms or signs of heart failure as well as a structural or functional cardiac abnormality. And of course these were patients who we want to implement appropriate guideline-directed medical therapy.

It is also important to recognize that we have an increased incidence of patients with advanced heart failure, or stage D. These are patients who have severe symptoms and or signs of heart failure either at rest or based on recurrent hospitalizations, despite guideline-directed medical therapy. And these patients may be refractory or intolerant to guideline-directed medical therapy and may require advanced therapies like heart transplantation, mechanical circulatory support, or palliative care.

We mentioned classifications of heart failure according to ejection fraction a few slides ago. A normal ejection fraction is typically above 55%. We defined those patients with reduced EF heart failure or HFrEF based on an ejection fraction ≤ 40%. And these were the patients who at this time get the bulk of the guideline-directed medical therapy because we have many, many clinical trials that have shown the impact of guideline-directed medical therapy in this patient population. Those patients who had a mildly reduced ejection fraction between 41% to 49% - usually referred to as borderline EF - and we also know that patients who have an ejection fraction ≥ 50% are those who we refer to as preserved EF heart failure or HFpEF.

There is also a new category based on this universal definition of heart failure document and that is heart failure with improved ejection fraction. Those are patients who had a baseline EF ≤ 20%, but based on either some reversible etiology or the institution of appropriate guideline-directed medical therapy, they have been able to achieve ≥ 10-point increase from that baseline ejection fraction with the second

measurement of ejection fraction above 40%. And so those were patients who had again improved

ejection fraction or left ventricular recovery and it is important to recognize that because we do not want to withdraw guideline-directed medical therapy from those patients. We now have randomized controlled trial data, the ELEGANT study that shows that in patients where we withdraw medical therapy when they had improvement in their ejection fraction, that over half of those patients will go back to having reduced EF heart failure, and we really want to avoid that sort of outcome.

The pathophysiology of these different ejection fractions HFrEF versus HFpEF can be different. We have significant data looking at the pathophysiology of HFrEF and most commonly HFrEF is centered on the reactive model where an initial insult leads to reduced cardiac output further triggering a cascade of maladaptive processes. That insults can be related to predisposing factors that induce myocardial injury of any cause, particularly the antecedent myocardial infarction but can also be chronically abnormal loading due to hypertension, valvular disease, or tachyarrhythmias. We get systemic neurohormonal activation that is characterized by activations of the sympathetic nervous system and the renin–angiotensin-aldosterone system that leads to pathophysiologic processes behind peripheral vascular effects, as well as localized changes affecting the cardiac substrate which leads to chronic adverse remodeling and heart failure. As such, medical therapy in HFrEF is traditionally aimed at neurohormonal modulation, and we have seen significant successes with this approach.

The pathophysiology of HFpEF may be more complex, and I say that because our understanding of HFpEF pathophysiology continues to evolve. If we look at the pathophysiology of HFpEF from a molecular perspective, we know that comorbidities are not just passive bystanders in HFpEF. Comorbidities including overweight and obesity, hypertension, diabetes, and others actually induce a systemic proinflammatory state with elevated plasma levels and inflammatory cytokines and biomarkers and reaction coronary microvascular endothelial cells produce reactive oxygen species and other molecules that result in reduced nitric oxide availability and lower levels of soluble guanylate cyclase activity in adjacent cardiomyocytes. These changes not only increase the resting tension of cardiomyocytes but also induce migration of monocytes into the subendothelium where they release TGF-β stimulating conversion of fibroblasts to myofibroblasts which deposit collagen in the interstitial space.

From a hemodynamic perspective, even although chamber volumes and ejection fraction are similar at rest in patients with HFpEF depicted here in red or controls depicted here in blue would exercise patients with HFpEF have evidence of impaired contractile reserve related to both diastolic as well as systolic dysfunction and vasodilator reserve dysfunction. Also with exercise, we see an increase in left ventricular filling pressures as well as pulmonary capillary wedge pressure which really relate that dyspnea that we have seen in patients with HFpEF that oftentimes is only evident with exertion. We also see the chronotropic response is impaired in patients with HFpEF impaired with controls, and the extent of chronotropic impairment is associated with more severely depressed aerobic capacity. Finally, we see that peripheral vascular function is also impaired in HFpEF which may be related to impaired endothelium-dependent vasodilation.

Let us spend some time talking about the cardiometabolic risk connections in patients with HFpEF. Again, we reviewed the newer universal definition of heart failure as it pertains to the stages of heart failure. This new document published in early 2021 gave us new terminology for the stages of heart failure, and there needs to be a recognition that although many of our resources for disease management are concentrated among those with manifest symptomatic heart failure who would either

be classified under stages C and D or advanced heart failure. If the heart failure process is defined as the continuum

for stage A through stage D, the highest number of patients would actually be in stage A or B due to the prevalence of hypertension, diabetes, coronary disease, or obesity and metabolic syndrome. The risk factors with significant relative risk as well as population attributable risk for the development of heart failure.

Thus, patients who are at risk for heart failure - otherwise called stage A - are those who do not yet again have current prior symptoms or signs or structural or biomarker evidence of heart disease but they do have risk factors. Those patients who are pre-heart failure otherwise old stage B are those again who do not yet have current or prior symptoms or signs, but do have structural or biomarker evidence of heart disease. And of course those patients with symptoms and the presence of a structural or functional cardiac abnormality would be called symptomatic heart failure or advanced heart failure.

Again, part of the rationale for this new classification of the stages of heart failure is to put more emphasis on prevention. This is some data that we put together from various epidemiologic cohorts including residents of Olmsted County, participants in the cardiac cohort as well as Black participants enrolled at the Jackson Mississippi site and the ARIC cohort. We can see that the majority of patients would be classified as either at-risk (or stage A) in the orange bars, or pre-heart failure (or stage B) in the grey bars. And there was a much higher prevalence of those at-risk or pre-heart failure than those who would otherwise be classified as symptomatic heart failure (stage C or D) and the yellow bars.

We can also see that the prevalence of risk factors varies by gender and race ethnicity, with Black patients having a much higher prevalence or risk factors and in fact when we look at the cohort that was enrolled in the Jackson, Mississippi, site of ARIC, many of those patients were classified as pre-heart failure (or stage B) solely based on evidence of left ventricular hypertrophy which was actually present in 98% of those participants.

It is also important to recognize that these cardiometabolic risk factors put patients at risk for heart failure even if there is no antecedent myocardial infarction or obstructive coronary artery disease. Each of these factors has both a mechanistic and prognostic association for the development of heart failure, again emphasizing that if we appropriately manage these risk factors in our patients, we can actually prevent the onset of heart failure.

So let us look at some of the screening and diagnostic approaches for patients with heart failure or who were at risk for heart failure. Many of us are accustomed to using risk scores such as the pooled cohort equation for incident atherosclerotic cardiovascular disease to counsel patients about their 10-year risk for heart attack or stroke. In a clinical setting we can put in risk factors like age, gender, race, lipids, or blood pressure to again give our patients a firm calculation for their 10-year risk for ASCVD.

It is important to realize that similar risk equations exist to counsel patients on their 10-year risk of heart failure. This is one such equation the PCP-heart failure tool that actually gives race and sex-specific 10-year risk equations for heart failure that were derived and validated for individual level data from 77 mini-based cohorts with at least 12 years of followup. And again, we can see familiar risk factors like age, gender, race, current smoking, BMI, vascular lipids, treatment for diabetes or hypertension, as well as QRS duration, and we can put these factors into this risk score which is available online and give our

patients estimates of their 10-year risk for developing heart failure.

There has also been increasing emphasis on the use of biomarkers to further risk-stratify patients who were at high risk for incident heart failure. For example, in patients with diabetes who were at very high risk for incident heart failure algorithms such as this one have been published and suggest that clinicians check an NT-proBNP which if elevated will move the patient from an at-risk stage of heart failure to the pre-heart failure stage. As such, appropriate therapy might include initiation of an SGLT2 inhibitor, which we know from multiple cardiovascular outcome trials can actually prevent the onset of heart failure in this population.

What about the diagnosis of heart failure? The diagnosis of heart failure really does require the presence of symptoms and/or signs of heart failure as well as objective evidence of cardiac dysfunction. This figure was taken from the recent ESC Heart Failure Guidelines and sort of gives us an approach to take patients from symptoms to the actual diagnosis of heart failure. We should always start with a history to elicit the presence of traditional risk factors as well as the three generation family history which may clue us into patients who may have familial cardiomyopathy and could benefit from genetic testing as part of their workup.

Recent hospitalizations or emergency room visits for dyspnea or chest pain may also be a clue. On physical - or on history, I should say - patients may complain of dyspnea, orthopnea, PND, fatigue or exercise intolerance, unexplained weight gain due to peripheral edema or abdominal distention as well as early satiety. Symptoms and signs, however, may lack sufficient accuracy to be used alone to make the diagnosis of heart failure. So we will need to attain appropriate diagnostic tests including a 12-lead electrocardiogram, laboratories that may also help point to the etiology of the heart failure, as well as biomarkers including the natriuretic peptides or cardiac troponins. Other tests that may be specific to the suspected heart failure etiology include a cardiac catheterization or ischemic functional testing, genetic testing in those who have a suspicious family history or advanced imaging such as cardiac MRI or technetium pyrophosphate scanning to rule out cardiac amyloidosis, for example.

It is worth noting that the diagnosis of HFpEF may be more challenging than the diagnosis of HFrEF. With HFrEF usually when we see a reduced ejection fraction echocardiogram, particularly in the presence of symptoms, the diagnosis is fairly straightforward; however, with HFpEF, the ejection fraction echocardiogram is often normal and certain laboratory parameters such as BNP or the electrocardiogram can be normal for some patients with HFpEF thus making the diagnosis more challenging.

Currently, there are actually two scoring systems in existence that are validated and available to diagnose HFpEF. Both systems are based on the combination of clinical characteristics and diagnostic data which helps increase the sensitivity of detection of HFpEF. So let us talk about these, because currently in clinical practice they may not be commonly used. The H2FPEF scoring system is a validated scoring system with high sensitivity. It relies on simple clinical characteristics and echocardiography, and enables the discrimination of HFpEF from noncardiac causes of dyspnea.

You can see the clinical variables that make up the score which are easily ascertained in any clinical setting. The presence of obesity or heavy the presence of hypertension, atrial fibrillation, pulmonary hypertension based on echo measures, a patient who is elderly based on age, or again Doppler evidence

of elevated filling pressures and in patients who have score of ≥ 6 they have more than a 90% probability of having HFpEF. This can also help determine the need for further diagnostic testing in patients who have sort of an intermediate score and unexplained exertional dyspnea.

Another scoring system from the European Society of Cardiology is the -- the European Society of Cardiology has also proposed another algorithm, the HFA-PEFF score. It includes a four-step diagnostic approach from initial clinical assessment to more specialized tests. Step one would be a pretest assessment that includes symptoms and or signs of heart failure, comorbidities and risk factors, EKG, standard echo, as well as natriuretic peptides. Step two would be a further diagnostic workup including an echocardiogram or natriuretic peptides if those were not measured for some reason in step one. Step three might include an advanced workup with functional testing like exercise echocardiogram or invasive hemodynamic measurements (in cases of uncertainty) and step four would include a final etiological workup such as cardiac magnetic resistance imaging, biopsies or other genetic testing to get at the specific etiology.

In step two, detailed echocardiographic measurements are recommended with the addition of natriuretic peptides. We can assign points based on both major and minor criteria that can help with the diagnosis of HFpEF. This diagram summarizes what we have discussed so far from the HFA-PEFF algorithm. Again, it is very important to start with clinical assessment, diagnostic tests, and then we move onto the other more advanced tests for those patients who have an intermediate score to confirm the diagnosis of HFpEF.

Let us try to apply all of what we learned so far to a case presentation. So our patient is patient AM. She is a 48-year-old female with a history of hypertension, prediabetes, and class 2 obesity. Her EKG shows some left ventricular hypertrophy. Her only current medication is lisinopril 20 mg daily, and on exam, we see a blood pressure of 142/85 a heart rate of 70 beats per minute, and a BMI of 38 kg/m2. You order an echo which is notable for grade I diastolic dysfunction as well as a left ventricular posterior wall diameter of 1.2 cm putting her in the category of mild left ventricular hypertrophy. Her laboratories are notable for NT-proBNP of 100 as well as a GFR of 65, and she reports compliance with all of her medications and attends all of her scheduled office visits.

How would you optimize her medical management at this time? Would you increase her lisinopril to 40 mg? Would you increase her lisinopril to 40 mg and add semaglutide 2.4 mg? Would you add empagliflozin 10 mg daily? Or add isosorbide mononitrate 30 mg daily? Technically, all of these could be reasonable maybe, except for choice D, but I actually feel like D is the most aggressive approach in this patient. Her blood pressure was not controlled with lisinopril 20 mg daily. So she definitely needs intensification of her blood pressure regimen. She also had evidence of grade 1 diastolic dysfunction and left ventricular posterior wall diameter of 1.2, indicating structural cardiac abnormalities. So you might consider the addition of an SGLT2 inhibitor as a preventive strategy; however, she is not actually diabetic at this point.

Here, I will also consider adding semaglutide as a therapy for her obesity with the idea that treating obesity as a comorbidity is just as important as treatment of diabetes and hypertension particularly in obese women. In this patient's case, she has prediabetes and her NT-proBNP was somewhat elevated, which we could argue would put her into the pre-heart failure stage. In addition to that we saw that on her echocardiogram she had evidence of left ventricular hypertrophy as well as some diastolic

dysfunction. So she is someone who we really want to place aggressive emphasis on prevention of heart failure.

And, fortunately, we are in an important space where the treatment landscape for both risk factors for heart failure as well as the treatment of manifest heart failure has changed so dramatically. Again, for

risk factors like diabetes, we have medications that we know can prevent the onset of heart failure; however, we also are in a space right now where we have medications that we can use to treat risk factors like obesity as well as diabetes such as the GLP-I receptor agonist. As I mentioned, this patient has obesity and we know that obesity increases the risk for the development of heart failure. A recent meta-analysis of over 23 prospective studies with over 6,47,000 participants confirms these findings where again we know that obesity increases the risk for incident heart failure in women and men. It is important to separate heart failure subtypes since we know the bulk of medical and device therapy is to treat heart failure used in HFrEF, but what is more daunting about the relationship between obesity and incident heart failure is the association seems to be more tightly correlated to incident HFpEF and that relationship actually maybe more prominent in obese women as I mentioned than in obese men.

Obesity also harbors a greater risk for HFpEF in women from race-ethnic minority groups. This is data from over 42,000 postmenopausal women who had a new followup of 13 years looking at an outcome of incident hospitalized heart failure and what we can see is that the risk for incident HFpEF is present for Hispanic women. Certainly, once you got to a BMI above 35 is also there for African American women but that risk is present at really all stages of obesity with a much higher relative risk as compared to Hispanic women or white women at a BMI of 25 to 30, 30 to 35 and certainly at a BMI above 35, almost an eightfold increased risk for incident hospitalized heart failure in Black women.

When we look at those data in aggregate, we can see that over 90% actually of the population-attributable risk in this study in Black women for HFpEF was due to the presence of hypertension and obesity. In Hispanic women about 70% of the population-attributable risk was due to the presence of hypertension and obesity. So again aggressive treatment of obesity in patients who were at risk is extremely important particularly in women from underrepresented race and ethnic minority groups and as I mentioned the opportunity for prevention, I think, is present more so than it has ever been because of the GLP-1, and as I mentioned the opportunities for prevention are present perhaps more so than they have ever been in the past because of the availability of the GLP-1 receptor agonist. Drugs like semaglutide and liraglutide have been shown to be very effective in the treatment of obesity in appropriate patients, and so we should use these drugs in patients in addition to therapeutic lifestyle changes again to help treat obesity and to perhaps prevent the onset of heart failure.

So in conclusion, patients at risk for heart failure were those at stage A or pre-heart failure; those who used to be referred to a stage B really do constitute the largest group of patients with heart failure. Patients at risk should be treated with medical therapy that could prevent the onset of heart failure, and those pre-heart failure patients such as those asymptomatic patients with elevated natriuretic peptide levels or who have evidence of cardiac structural or functional abnormalities may require referral to a cardiologist for further diagnostic and treatment strategies to prevent the progression of heart failure. Patients who have symptomatic heart failure who would otherwise be referred to as stage C or even stage D can receive a timely diagnosis using a combination of elevated natriuretic peptide levels or recognition of evidence of systemic or pulmonary congestion and elevated filling pressures, and I think in one of your subsequent lectures you will hear more about appropriate treatment of those patients who

are stage C from Dr. Ileana Pina. Thank you.