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Rethinking Risk in Heart Failure with Preserved Ejection Fraction

Announcer:
You're listening to *Heart Matters* on ReachMD. Here's your host, Dr. Alexandria May.

Dr. May:
Welcome to *Heart Matters* on ReachMD. I'm Dr. Alexandria May, and today I'm joined by Dr. Javed Butler to better understand the risk of heart failure with preserved ejection fraction, also known as HFpEF. Dr. Butler is the Maxwell A. and Gayle H. Clampitt Endowed Chair and the President of the Baylor Scott and White Research Institute in Dallas, Texas.

Dr. Butler, it's great to have you with us today.

Dr. Butler:
Absolutely. Great to be with you, Dr. May.

Dr. May:
To begin, Dr. Butler, what do you think drives the misconception that preserved ejection fraction equals lower risk of heart failure?

Dr. Butler:
Yeah, partly, it's a logical way of thinking, and partly it's because of history. So for the longest time—30 years or so—we were only focusing on heart failure with reduced ejection fraction. And our mindset was that HFrEF is a high-risk disease, and we didn't really think about HFpEF.

But again, if you think about any other disease, we know that the worse the number, the worse the prognosis. So the lower the GFR, the worse the prognosis. The higher the cholesterol, the worse the prognosis. The higher the blood pressure... So there is this linearity in disease progression and outcome.

And here, there's a little bit of a different situation, in that your ejection fraction is normal. So it's not even like it's abnormal, but not that abnormal. The ejection fraction is just simply normal, and now, you're equating normality with really bad outcomes.

And I think there's a conceptual logical folly, if you will, in the way clinicians are designed to think in their medical training. Having said that, the outcomes of these patients are so poor that we need to continue to just fight against that misperception that patients with heart failure and preserved ejection fraction absolutely do not have a better or good prognosis—that these patients are at a very high risk.

Dr. May:
Now, in reality, how do outcomes in HFpEF actually compare with those in HFrEF, particularly when it comes to hospitalization and mortality?

Dr. Butler:
So if you look at the epidemiologic data, large observational data—whether from Medicare, other sources, guidelines—and even if you just look at international data, the outcome for these patients are almost indistinguishable. So the mortality risk, the risk of hospitalization, and recurrent hospitalizations are almost the same.

So with the nuance of heart failure, we're looking at 40 or 50-percent five-year mortality. Once you have worsening heart failure and you get readmitted, then the mortality rates are even higher. Post hospitalization, you have, give or take, about a 20 percent risk of hospitalization within one month, and then 50 percent at about six months or so. And then one-year mortality gets to the north of 15 or 20 percent.

So this is a pretty high-risk condition, and then, on top of that, it's not only the mortality and morbidity, which we as clinicians obviously worry about quite a lot, but from patient's perspective, it's quality of life, symptoms, functional capacity—all of those things are also pretty important.

And, if anything, those parameters in patients with HFpEF are actually even worse than heart failure with reduced ejection fraction. Now, whether it's because, on average, heart failure with preserved ejection fraction patients are old or because, on average, these patients have one extra comorbidity—HFrEF patients have plenty of comorbidities, but HFpEF have, on average, even one more comorbidity— whatever it is, the bottom line is that the quality of life and health status is even poorer.

So again, we need to fight this perception that just because your ejection fraction is normal, that—if you have the syndrome of heart failure—you don't have any better outcomes than HFrEF.

Dr. May:
For those just tuning in, you're listening to *Heart Matters* on ReachMD. I'm Dr. Alexandria May, I'm speaking with Dr. Javed Butler about our evolving understanding of HFpEF and its true clinical impact.

Dr. Butler, let's focus now on how we can better identify and manage HFpEF. From your perspective, what are the most important clinical clues that should prompt clinicians to suspect it earlier?

Dr. Butler:
Yeah, so this is a really interesting question. So now, we have published data both from the US and from the UK that shows that the number one place where HFpEF is diagnosed is in the emergency room. Now, what's interesting is that if you look at the medical records of those patients, they have complained about something that should have alerted the clinician to heart failure, and in a majority of the patients in the preceding year, it's documented in their medical record.

The problem is that their signs and symptoms are relatively non-specific: shortness of breath, tiredness, and fatigue. And what ends up happening in the clinical setting is that we do all sorts of right things, right? We rule out COPD, we rule out asthma, we rule out hypothyroidism, we rule out anemia. But after those common things, for whatever reason, heart failure doesn't come in the differential diagnosis. And then we say, well, you're deconditioned, you're overweight, you're obese, you're aging, not realizing that three months ago, when the patient did not have that symptom, the person was equally overweight or equally old.

And these are nuanced symptoms. So I think, first and foremost, is to keep new onset heart failure in the differential diagnosis of patients presenting with these non-specific symptoms. But then, there are certain characteristics that really put patients at high risk—so anybody who has new onset shortness of breath over the age of 50 or 55, if somebody has family history, if somebody, has history of hypertension, if somebody has history of diabetes, past coronary artery disease, or has arrhythmias— all of those things then incrementally increase the risk even further, and a more detailed evaluation to rule out the diagnosis of HFpEF is really indicated.

Dr. May:
Building on that, how are newer diagnostic frameworks helping clinicians move beyond ejection fraction to help better identify HFpEF?

Dr. Butler:
Yeah, so with the ejection fraction being normal, life does get a little bit more complicated. Because if you have somebody short of breath and you just do an echocardiogram and their EF is 20 percent, boom: you get your diagnosis and you're done. But with HFpEF, you're going to get a normal, ejection fraction.

So how do you diagnose? The definition of heart failure is that you need to have three things. You need to have symptoms: shortness of breath, tiredness, fatigue, and what have you. You need to have some cardiac abnormality, so even if the EF is normal, you have left atrial enlargement, left ventricular hypertrophy, fibrosis, diastolic dysfunction, or some cardiac dysfunction.

And then you have some evidence of congestion, whether it is frank congestion and edema in the legs or whether it is something that is concealed and not available on physical examination, for which you may need to do invasive testing. But in this day and age, with the wide availability of natriuretic peptides, that becomes a really good screening tool to rule out or rule in heart failure just by doing natriuretic peptides— testing BNP or NT-proBNP.

Now, there are standardized risk prediction models. So there's the H2FPEF that was developed by our colleagues at Mayo Clinic. I really like that score, because it gives you, directionally, the higher the score, the higher the risk. And I would encourage people toto look into it.

The problem is that it’s not a particularly good tool to look at in the primary care setting, because you already need an imaging study to actually use the H2FPEF score, because it requires an echocardiographic-based pulmonary pressure estimation.

So you are coming in a little bit late. What you want is something early for somebody just coming in with symptoms. So they came up with a follow-up score, also called ABA, which is aging body composition and atrial fibrillation. So if you have these non-specific symptoms and a person is older, has atrial fibrillation, or is obese, then the risk of HFpEF goes pretty significantly higher up. So you can do those things. But my biggest recommendation would be that if somebody has these symptoms, just to check natriuretic peptides, and if the natriuretic peptide levels are high, then you can be pretty much certain that somebody has this syndrome of heart failure.

You still need echocardiography to see whether it is HFrEF, HFpEF, valvular disease, or pericardial disease. So it's not that you don't need an echo, but at least for the screening, if somebody's BNP is greater than 35 or NT-proBNP is greater than 125, then you're closer to your diagnosis.

Now, here is the problem, and the problem is that there are patients who are overweight, and obese patients have lower NT-proBNP. Now I'm going to do a little fine tuning here, and that is that lower is not necessarily normal. So yes, a patient who's not overweight who has heart failure, their NT-proBNP may be 600, and the overweight patient may have 300, but then there is a distinct minority of patients whose NT-proBNP is going to be completely normal, and they still have the syndrome of heart failure.

If you do a right heart cap, their wet pressures will be elevated up. I would say, in the primary care setting, the easiest thing is to do natriuretic peptide, and the vast majority of the patients you will cover.

But now, if you have somebody with shortness of breath and you have ruled out other things, other comorbidities, the natriuretic peptide is okay, and their symptoms are not resolving, I would refer them to a cardiologist for invasive evaluation. And invasive testing can assess that. But again, sometimes in these technical details, we miss the big picture. And the big picture here is that most of the time, the majority of the time, natriuretic peptide will get you home.

Dr. May:
And as our understanding of HFpEF risk evolves, how has our treatment approach shifted in recent years?

Dr. Butler:
There was a long period almost of 20 years of nihilism that nothing will improve HFpEF outcomes. So, while in the 1990s and 200s, we had a ton of positive trials in HFrEF, every time we tried a drug or therapy in HFpEF, the trial was negative.

So that dynamic broke in about mid-2010, I think—2015 or 16, something like that--when we started doing SGLT2 inhibitor trials in HFpEF. And then we had two successful trials with empagliflozin and dapagliflozin. Both trials were positive in heart failure with preserved ejection fraction.

So up until then, which is less than a decade ago, the treatment of HFpEF was basically diuretics for symptoms and congestion, and comorbidity management: treat blood pressure, treat diabetes, that sort of thing. But now, we have a specific HFpEF therapy, regardless of the ejection fraction—whether it's 45, 55, or 65, it doesn't matter—to treat these patients withSGLT2 inhibitors.

And then we had another trial with the non-steroidal MRA finerenone that came out, FINEARTS, and that was also positive. And that was positive regardless of whether you were on baseline SGLT2 inhibitors or not. So now we have at least two therapies that have been shown to improve outcomes for these patients.

So diagnosis of these patients early, early screening for these non-specific symptoms, and treating these patients can change the trajectory of the disease in two ways. One is that these patients unnecessarily suffer from debilitating symptoms, and you can change them and make them feel better. But two, the earlier you give therapy, you improve the outcome for these patients in terms of mortality and hospitalization risk.

If you look at the data for when the curves were statistically significantly different in the active arm or the placebo arm in these trials, both with non-steroidal MRA finerenone and with a SGLT2 inhibitor, it was less than a month. So the benefit occurs relatively early, and therefore it makes it imperative on us to give the therapies early as well.

And then, not in all patients with HFpEF, but in obese patients with HFpEF, there are two trials with the GLP-1 receptor agonists semaglutide and tirzepatide that have also shown improvement in symptoms, but not clinical outcomes. We need larger outcome trials, and those are ongoing, so we have a whole bunch of options.

Then, the last thing I will mention is that we have made a ton of progress in amyloidosis and hypertrophic cardiomyopathy. So when you get diagnosed with HFpEF, consider the clinical history and don't forget to rule those conditions out as well.

Dr. May:
Dr. Butler, as we come to the end of our program, what's one takeaway you want our audience to remember about HFpEF Risk?

Dr. Butler:
The biggest thing that I would say is to realize that ejection fraction being normal does not mean they have a better or a good prognosis. Their prognosis is equally bad as HFrEF.

And just think about heart failure with preserved ejection fraction, or for that matter, heart failure, in your differential diagnosis when people come up with completely non-specific symptoms. As you are ruling out other common diseases, think about heart failure and check natriuretic peptides or an echocardiogram.

Dr. May:
With that closing comment in mind, I want to thank my guest, Dr. Javed Butler, for joining me to discuss how we can better recognize and manage HFpEF in clinical practice. Dr. Butler, thanks for being here today.

Dr. Butler:
Great to be with you, Dr. May.

Announcer:
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