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Ejection Fraction in Heart Failure: Does It Matter?

Dr. Butler:
You are listening to *Heart Matters* on ReachMD. I am Dr. Javed Butler, and joining me to talk about ejection fraction in heart failure is Dr. Faiez Zannad, Emeritus Professor of Cardiology at Université of Lorraine in Nancy, France. Faiez, thank you for joining me today.

Dr. Zannad:
My pleasure.

Dr. Butler:
So, Dr. Zannad, let's start with some background here. 0What can you tell us about the relationship between heart failure and ejection fraction?

Dr. Zannad:
Yeah, well, that's a very good and timely question, but traditionally, we have been very much obsessed about systole and diastole, and we have been very much dividing heart failure in two different conditions, which are systolic heart failure and diastolic heart failure. But these were the old time, right? And ejection fraction is not the ideal way to distinguish between systolic and diastolic dysfunction because even in systolic dysfunction and low ejection fraction, you have some sort of diastolic dysfunction, vice versa, so it's very important that we distinguish the systolic and diastolic from ejection fraction, which is not a depiction of systolic and diastolic dysfunction.

And ejection fraction actually came into play early in the development of heart failure medication. And actually, if any, it was an invention of trialists because basically, ejection fraction is a risk condition, a risk marker, and thereby low ejection fraction patients have the higher risk, and this was really granted and great idea for trialists. You know, they decreased the sample size and increased the event rate, and therefore, we started doing much of the heart failure drug research—and by the way, devices as well—in patients with low ejection fraction, so if any, initially, we have been using ejection fraction just as a risk marker and more so in the trials in order to increase the risk and event rate.

But then from there, because we had so many successes in heart failure with low ejection fraction, it has become really very fashionable to have HFrEF and HFpEF—heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. And really, the divide was even more emphasized by this discrepancy between a very large body of evidence of medication which were very effective in HFrEF and almost nothing in HFpEF, so we perpetuated this divide, but heart failure is a continuum, and you may progressively go from one to another. You may have heart failure with preserved ejection fraction short after myocardial infarction, and if the heart remodels in a bad way, you may end up by heart failure with reduced ejection fraction. The contrary may also occur in patients with reduced ejection fraction. They may recover.

Dr. Butler:
So, that's a really good sort of historical background of you how we got to where we are today.

Can you give us a little bit of a guidance at what ejection fraction do you define heart failure with reduced versus preserved ejection fraction and what proportion of heart failure is each?

Dr. Zannad:
Yeah, well, this is a very challenging question because as mentioned, ejection fraction is a continuum, and if you screen heart failure patients and you log their ejection fraction on a graph, you will end up by normal distribution, and therefore, there is no cutoff, whereby you are HFrEF or HFpEF patients, and therefore, the definition came actually from the trials. Most of the trials of HFrEF-enrolled patients with ejection fraction below 35 percent, and some of them had enrolled patients at 40 percent and therefore, HFrEF usually is defined by an ejection fraction below 35 to 40.

Now, when it comes to HFpEF, this is much more complex because no trial was published so far, and the diastologists and HFpEF specialists agreed to disagree and there is no single cutoff, and because of this and because of the gap of evidence and some evidence in patients with ejection fraction between 35, 40 and 50, people have created a new category, which is called HFmrEF, mildly reduced ejection fraction.

But again, this is a continuum and the frequency of HFrEF appeared to be declining as a result of better treatment of acute coronary syndromes, and indeed, there are many more ischemic heart disease in HFrEF than in HFpEF. Now usually, the distribution is 50/50, but it is largely that there will be more than 50 percent of HFpEF in the future because of the failure to prevent HFpEF post-acute coronary syndrome as efficiently as preventing HFrEF on the one side and on the other hand the aging of the population which produces for frequent HFpEF.

Dr. Butler:
Can you give us a brief overview of what medical therapies are available today for the management of patients with heart failure? And how does that relate to ejection fraction?

Dr. Zannad:
Most of the evidence and certainly positive trials were in the HFrEF space, and we have RAS inhibitors and valsartan, beta blockers, mineralocorticoid receptor antagonists, and more recently SGLT2 inhibitors. And by the way, the guidelines in HFrEF are almost all of them for these four categories of medication—1A, meaning the strength of evidence A and the strength of recommendation 1. This is to be contracted to the HFpEF situation where the evidence is at best circumstantial so far with some sort of evidence with mineralocorticoid receptor antagonists and potentially with secondary to valsartan because the trials were not 100 percent convincing, and the magnitude of benefit was 7 or 8 percent improvement in outcomes. But what is most striking in the recent building evidence from SGLT2 inhibitors and this is where the future is because we have got now medication which may be actually effective across all the spectrum of ejection fraction.

Dr. Butler:
So, can you expand that a little bit more about this whole SGLT2 inhibitor? Are you saying that you would recommend this therapy across the range of ejection fraction if you have the syndrome of heart failure?

Dr. Zannad:
Yes, I really would like to emphasize this very much because it's a very important recent development in this space because we have EMPEROR-reduced and DAPA-HF which has demonstrated very strong benefit, cardiac and renal by the way, down to an EGFR of 20 so that we have now very strong evidence which has prompted this class of drug becoming grade 1A recommendation in HFrEF. But recently, we have EMPEROR-preserved, which actually exactly mimicked the result of EMPEROR-reduced with the same kind of benefit on cardiovascular outcomes and renal outcomes. So, one wonders why are we considering patients in categories of HFrEF and HFpEF because EMPEROR-reduced and EMPEROR-preserved elected to enroll patients with adjacent ejection fraction, so this is covering the whole spectrum of ejection fraction without any gap, and it happens that this drug is effective across all the spectrum of ejection fraction.

Dr. Butler:

For those just joining in, you are listening to *Heart Matters* on ReachMD. I am Dr. Javed Butler, and I'm speaking with Dr. Faiez Zannad about ejection fraction in heart failure.

Can you briefly tell us about the safety and tolerability of these therapies across the range of ejection fraction? You mentioned that for some therapies the benefit seems to be more with lower ejection fraction. With SGLT2 inhibitors there were comparable primary endpoint results in both heart failure with reduced and preserved ejection fraction. Now, what about safety and tolerability across the range of ejection fraction?

Dr. Zannad:
Thank you for asking this question because this is also another important breakthrough with the class of SGLT2 inhibitors because these are a drug which are used at one single dose once a day and with almost very little safety concern as compared to the other categories of drug, whether it is RAS inhibitors, valsartan, MRA or beta blockers whereby you need to start low and go slow with uptitration, and you know much the hurdles related to the use of these medications, which actually is the main reason of their underuse and under-prescription and suboptimal titration with all this medication.

Now, we have got a class of drug, SGLT2 inhibitors, where the safety is really very favorable, and there is hardly any need to monitor ejection fraction, or eGFR or potassium. If any, there are hints that actually there are fewer hyperkalemia when using this drug together, with MRAs, for example, and also renal function because these drugs are also renal protective. So indeed we have got a drug, which is effective across all spectrum of eGFR of ejection fraction but also for eGFR, by the way, because in both trials patients were enrolled with an eGFR down to 20, and therefore, the subgroup analysis across all the spectrum of CKD showed that the benefit was consistent and safety was not an issue at all. So we really expect that with implementation of this class of drug should be very straightforward.

Dr. Butler:
So, the safety and tolerability is comparable across the range of ejection fractions in HFrEF and HFpEF?

Dr. Zannad:
Absolutely. There is no specific side effects in HFrEF and HFpEF from this class of drug. The only persistent signal, and it's not only in heart failure but also in diabetes trial, is genital infection. The numbers are very small, but there was a persistent excess of the genital infection with this class of drug in all types of patients.

Dr. Butler:
So, Faiez, we are almost out of time, so I will give you the last word. Do you have any final thoughts to share? And what do you think is the role of ejection fraction in 2021 then?

Dr. Zannad:
Well, I really would like that what we've monitored over the last few years would put less emphasis of the ejection fraction-centric view of cardiology, and this will liberate the creativity of heart failure specialists as to look at heart failure in different ways. And I am sure that there are many more interesting phenotyping and stratification of heart failure than simply on ejection fraction, and this would potentially prompt more interesting research in better understanding this disease.

Dr. Butler:
Well, that was both informative and provocative. And with those thoughts in mind, I want to thank you, Dr. Zannad, for sharing your insights on ejection fraction in heart failure. It's been a pleasure speaking with you today.

Dr. Zannad:
Thank you so much.

Dr. Butler:
And for ReachMD, I am Dr. Javed Butler. To access this and other episodes in our series, visit ReachMD-dot-com-slash-HeartMatters where you can Be Part of the Knowledge. Thanks for listening.