Four Pillars of Medications for Heart Failure with Reduced Ejection Fraction (HFrEF) Podcast Transcript

Leslie Davis: Thank you for having me today. I'm honored to join Dr. Midge Bowers to discuss heart failure, a cardiovascular condition affecting many adults worldwide. Despite the remarkable growth and therapeutic options over the past two decades, this condition continues to be associated with high mortality and morbidity. But, nurse practitioners can make a difference in helping reduce both by ensuring patients are offered the latest treatment.

Let's start with what heart failure is and the four main classifications for heart failure. Based on the 2022 American Heart Association, American College of Cardiology, and the Heart Failure Society of America Guideline for the Management of Heart Failure, the universal definition for heart failure is that it's a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling, or ejection of blood. That's a lot. Heart failure can be classified by stages and the left ventricular function.

So, there are four main classifications of heart failure. The first one is heart failure with reduced ejection fraction, or what we will refer to as HFrEF during this podcast. This is where the left ventricular ejection fraction is less than or equal to 40%. Next is heart failure with mildly reduced ejection fraction or EF, 41 to 49%. And then there's what we call HF-PEF, heart failure with preserved ejection fraction, where the EF is greater than 50%. And last, heart failure with improved EF. This is where the left ventricular ejection fraction has a 10% improvement from baseline. So, for today's discussion, we will focus on HFrEF.

Midge, do you want to start the discussion on medications used in treating HFrEF?

Midge Bowers: Sure, thanks, Leslie. Also, both of us want to thank AANP for the opportunity to participate in this NP Pulse podcast on a very significant topic. So, as you noted in the introduction, I see patients in a heart failure access clinic focusing on all facets of heart failure. In this podcast, Leslie and I want to focus on the importance of the four-pillar therapy in treating HFrEF and your opportunities as nurse practitioners in titrating medications across all practice settings. So, the four pillars of therapy for HFrEF are, one, ARNi/ACEi/ARB; two, beta-blockers; three, mineralocorticoid receptor antagonists, or MRAs; and four, SGLT inhibitors. Notice I didn't say SGLT-1 or SGLT-2 because we're all-encompassing in this category. These four medication classes improve morbidity, reduce mortality, most importantly, improve quality of life and contribute to reducing hospitalizations. Leslie, two of these four pillars have been the mainstay HFrEF for as long as you and I have been practicing NPs. Can you please talk about how ARNi, ACEi, and ARB, as well as beta-blockers, benefit patients with HFrEF?

Leslie Davis: Thank you, Midge. Yes, we'll start with talking about patients who need to be on either an ARNI, an ACE inhibitor, or an ARB. The ARNI will go first. That is the one that's newest, but also the one with now the highest level of evidence, Class 1A, for patients with HFrEF and symptoms, specifically New York Heart Association class two to four symptoms. And this class of medicines can reduce morbidity and mortality.

ARNI is a combination agent. It has a neprilysin inhibitor, which is sacubitril, and an ARB, the classic angiotensin receptor blocker, Valsartan in this case. At this current time, this is the only medication in this class of ARNis. Based on the Paradigm HF trial, ARNis has been shown to have a significant clinical benefit. They decrease cardiovascular death and heart failure hospitalization better than enalapril, an ACE inhibitor in that trial. In fact, the number needed to treat to prevent one of those endpoints over about 27 months was 21. That's a lot of numbers for a podcast, Midge. But that's not many when you compare it to other classes of drugs. So, you will see that many patients in your practice and you will have improved their care. The latest guidelines have assigned this class of meds, again, the highest level of evidence higher than ACE inhibitors or ARBs.

In the past, many nurse practitioners and other providers would focus on starting their patients on an ACE inhibitor or ARB and then later switch to the quote better class of meds, the ARNis. Now, based on the current guidelines, you can start patients directly on this medication from the beginning. So let's talk about if you have a patient on an ACE inhibitor or an ARB, how you would convert them over. If they're on an ARB, you just stop one day and convert to the other. However, an ACE inhibitor is a special case. It's required to have a 36-hour washout period to reduce the risk of angioedema. If you are switching the patient from an ACE to an ARNi, make sure the patient has adequate blood pressure and that they're not symptomatic with hypotension or decompensated. What you do is stop the medication one day, the ACE, if it's an ACE inhibitor, that's once a day in the morning, or it's twice a day, stop it that last evening, and then make sure there's 36 hours or more washout. So, if the 36 hours was like three in the morning, wait and take that ARNi the next day, but wait at least 36 hours. Now I'm just going to touch on the others.

As a reminder – ACE inhibitors are medications that end in “-pril,” such as lisinopril, ramipril, enalapril, and captopril, to name a few. One thing we keep in mind is if a patient is on an ACE inhibitor for their HFrEF and they develop a cough, consider switching the patient to an ARNi or an ARB. Keep in mind, though, that some coughs are from fluid overload, and it might not necessarily be an ACE inhibitor cough. Also, the ARBs are one of those three options. These are angiotensin receptor blockers, medications that end with “-sartan” - losartan, candesartan, valsartan, and others. For all these classes of meds, be it ARNi, ACE inhibitors, or ARBs, monitor your patients for hypotension. Again, it would need to be symptomatic hypotension to be a concern, or changes in kidney function, in particular hyperkalemia. One of the things Midge and I like to do is to give you a pearl during these podcasts.

And my pearl comes from a nephrologist I work with. They say to expect a bump in BUN and creatinine when you start or maybe up-titrate these ARNis, ACE inhibitors, or ARBs. If that bump is less than 30% and the potassium is controlled, it will level off. Next, I'll switch to the second category, beta-blockers. Beyond the three- ARNis, ACE inhibitor, ARB, you choose one, you also have your patients on beta blockers. Now for HFrEF, it needs to be one of three very specific beta blockers that are FDA-approved for heart failure with reduced EF. Those include metoprolol succinate or XL, (Toprol XL) or Carvedilol, (Coreg), or the last one, bisoprolol. These beta blockers save lives. They have the highest level of evidence, we've known that for 20 years. Class 1A for current or previous heart failure symptoms to reduce mortality and hospitalization. They also reduce angina in patients who have coronary artery disease and ventricular arrhythmias. Before I continue, Midge, can you share the benefits of the other two pillars of therapy for HFrEF? That is the MRAs and the SGLT inhibitors.

Midge Bowers: Thanks, Leslie. There's two MRAs (mineralocorticoid receptor antagonists), and that's really nice because it's easy to remember, either spironolactone or eplerenone. Those two now have a

level of evidence A, the highest level for patients who have NYHA classes 2 through 4. So basically, it's everybody but class 1.

And these are supportive because they benefit by reducing morbidity and mortality. Now, there are a couple of caveats. Obviously, patients must have a potassium of less than 5.0 milli-equivalents per liter, and that's because these are potassium-sparing diuretics, and their estimated glomerular filtration rate, hence further known as GFR, should be greater than 30 milliliters/min/1.73 m^2.

Here's my pearl for this: you're looking at a patient, and they're starting this medication. You need to monitor one week after initiation, four weeks after initiation, and after any titration. And we'll talk more about titration in a few minutes. But concerning also are patients who stop using salt and use a salt substitute. Those salt substitutes are potassium-based. So make sure you are monitoring their potassium, making sure their GFR is greater than 30, and talking to patients about salt substitutes. The other pearl is that patients sometimes think MRAs are a diuretic, and you can let them know it's a very weak diuretic, but mostly it's helping keep your heart stronger.

Some patients develop gynecomastia when they take spironolactone. They may also develop impotence or menstrual irregularities. Consider switching them to eplerenone, which has slightly different pharmacokinetic properties. Sacubitril valsartan has a lower risk of hyperkalemia when used with those MRAs as compared to the ACEs and ARBs that Leslie mentioned previously.

Now we will switch gears to SGLT inhibitors or sodium glucose co-transport inhibitors. These includes dapagliflozin, empagliflozin, and the newest kid on the block, sotagliflozin (Inpefa), all approved for use in patients with HFrEF. Again, the level of evidence is “A” for patients with chronic heart failure to reduce their heart failure hospitalizations and cardiovascular mortality. The question is, why wouldn't we want to use this, right?

This is for patients with HFrEF and an ejection fraction of less than or equal to 40% with or without diabetes, and again, NYHA class 2 to 4. It was originally developed for patients with type 2 diabetes and showed remarkable benefits in patients with HFrEF. Believe it or not, these benefits are seen within days of initiation. This is a game-changer. Start it as soon as you can.

The good news for these SGLT inhibitors is that it's a fixed dose and there's really no titration. Compared to other pillars, they are less likely to cause hypotension and often prevent the need for diuretics and makes hyperkalemia less likely for those who were on the MRAs we just discussed. However, SGLT inhibitors work by causing glycosuria. You should consider reducing the diuretic dose to prevent potential dehydration. Be cautious in initiating this class of medication in patients who are at risk for developing a genital mycotic infection. I stress personal hygiene with patients when I start this.

Now that we've reviewed the four pillars, let's move on to how to initiate and titrate these medications. Leslie, a recent clinical trial supports the benefits of initiating and rapidly titrating these medications. Can you share some of this clinical trial data with our audience?

Leslie Davis: Yes, Midge. So, I think about this as the why for rapid guideline-directed medical therapy titration. For the past 20 years, we initiated and titrated these medicines we're talking about. Now granted, the SGLT inhibitors weren't traditionally on the market, but we started these meds one at a time. We would up-titrate every two to four weeks, and it would take several months to get patients in a stepwise pattern up to the target doses. We have not mentioned that yet, but we get them up to the

target doses shown in the clinical trials to have the most benefit. And the patient needs to be able to tolerate those target doses. One clinical trial called STRONG-HF was a landmark study in the last year or so. It came out in 2022 comparing rapid titration of guideline-directed medical therapy with close follow-up, with a goal to reach target doses by six weeks versus usual care. Wow, six weeks.

But you know, Midge, you just mentioned that the last class of meds can have benefits very quickly. Based on this study, initiating all four therapies and rapid titration of these meds in six weeks can prevent heart failure decompensation, reduce the risk of hospitalization, and decrease all-cause mortality at 180 days. So, these precious months after diagnosis or hospitalization matter. The study was stopped early by the Data Safety Monitoring Board because the benefit was so remarkable. The number needed to treat was six patients to prevent one death or heart failure hospitalization in six months. Just six of your patients that you would have had on rapid titration with close follow-up compared to the traditional method, you would have prevented a death or hospital hospitalization in the next six months. That's an absolute risk reduction of 8.1%. These results of STRONG-HF indicate the benefit of early up-titration of the four pillars was evident even at 30 to 60 days. This makes the case for the four pillars and for rapid titration. But how do we do that? Some of our listeners, Midge, may practice in the hospital setting. Can you talk about how nurse practitioners would use the four pillars of therapy in the hospital setting?

Midge Bowers: Thanks, Leslie. I think it is essential to know that most often, patients are hospitalized with symptoms and need to be decongested. But once they're clinically stable, all four medication classes can be started at low doses simultaneously. Now, for those of us in practice for a while, we're thinking, oh my, I only started one medication, titrated it up, then started the next medication. But your discussion of the STRONG-HF trial debunks that we need to start at least two classes at the same time and then start the other two. Optimizing guideline-directed medical therapy in the hospital setting is associated with a lower risk of readmission and post-discharge death.

So, let's discuss two potential strategies to initiate the four-pillar medications in a six-week period rather than over several months. (discussed below charts)

Strategy 1- Starting all 4 medications at once

Medication	Day 1	Day 7-14	Day 14-28	Day 21-42
ARNi	Initiate low dose	Continue	Titrate as tolerated	Titrate as tolerated
Beta blocker	Initiate low dose	Titrate as tolerated	Titrate as tolerated	Titrate as tolerated
MRA	Initiate low dose	Continue	Titrate as tolerated	Continue
SGLTi	Initiate	Continue	Continue	Continue

Strategy 2- Starting two medications at a time.

Medication	Day 1	Day 7-14	Day 14-28	Day 21-42
ARNi	Initiate at low dose	Continue	Titrate as tolerated	Continue
Beta blocker	X	Initiate at low dose	Titrate as tolerated	Titrate as tolerated
MRA	X	Initiate at low dose	Continue	Titrate as tolerated
SGLTi	Initiate	Continue	Continue	Continue

Strategy #1: day one, you start the ARNi, beta blocker, MRA, and SGLT inhibitor, all at low doses. Day seven to 14, this might be for you in primary care or cardiology practice, seeing a patient at a hospital follow-up visit. You'll continue that ARNi at the same dose, but you'll titrate up the beta blocker. Continue the MRA and the SGLT. Days 14 to 28, so that's that two to four weeks mark, you're going to titrate up your ARNi, as well as the beta blocker, maybe the MRA, and continue. Remember, we talked about the SGLT inhibitors being a fixed dose.

During these six weeks, you are also monitoring kidney function, potassium levels and the EGFR because there are specific parameters for all of these medications that you really need to adhere to. So, looking for that EGFR to stay above 30. In that three-week to six-week window, you may have options to continue to titrate up that ARNi, titrate up that beta blocker and you will be continuing your target doses of your MRA and your SGLT. This is the four medications at once strategy.

Strategy #2: starting two medications at once. On day one, you will start the ARNi and SGLT. Remember, we said the SGLT inhibitor has a rapid onset of effectiveness. And then in that 7–14-day period, you will initiate a beta blocker and MRA. In that two-to-four-week window, you are titrating up the ARNi and the beta blocker and continuing the MRA and SGLT. Again, finally, as you wrap up that three-week to six-week window, you continue up to the target dose of ARNi, titrate up the beta blocker and MRA, and continue with the SGLT inhibitor.

Both strategies require a team approach to care. You may want to consider developing protocols or standing orders for medication titration that can be implemented by nursing staff between visits. That is how you keep the patient on track for titration. What about the potential adverse effects of either of these strategies? Well, tolerability is enhanced by starting at those low doses, so you want to make sure you start at a low dose. SGLT inhibitors and MRAs rarely cause symptomatic side effects and are very well tolerated. HFrEF disease progression may be misinterpreted as a medications-related adverse event. I'll give you an example of this. A patient comes in with fatigue and you've just titrated their metoprolol from 25 to 50 milligrams once daily. If they have tolerated the 25 milligrams and you are going up to 50 mg, then fatigue is less likely to be related to the meds. More than likely, it is related to heart failure. So, rapid medication titration will help improve those symptoms. The disease state worsens, and worsening is more likely if you delay the initiation. Think about starting all four at low doses because worsening is more likely if you delay the initiation.

Now that we have discussed all four pillars of therapy in the real world, we want to discuss challenges associated with getting the patients on these needed therapies. What strategies can NPs use to help tackle these challenges?

Leslie Davis: There are many barriers to why patients with HFrEF may not be on the optimal therapy we described. Optimal therapy is defined as guideline-directed medical therapy provided at the target or highest tolerated doses for a given patient, as we've discussed. Target doses, recall, are targeted for in the clinical trials, but many patients aren't on either. One reason is that the landscape is confusing for providers. Provider-facing tools are available, however, to help you with decision-making for the treatment plan. One tool from the American College of Cardiology that is free in the public domain is the Treat HF mobile app. Nurse practitioners and other clinicians can use this to guide decision-making on which class of medication to add based on patient-specific criteria. We will list this in your resources for

this podcast. This is updated every time the guidelines or expert consensus decision pathways are updated. These are patients who have symptomatic heart failure with reduced ejection fraction. And so you enter the patient indications, you review individualized next steps for the medical therapy, and you can email or print a summary of the next steps to yourself or the patient. You don't put in any HIPAA-protected identifiable information; you just put in the details. They reference detailed information on what to start, available options, and how to titrate and monitor each medication. This guidance helps you optimize the overall medication strategy. Also, the second most helpful thing I recommend is these expert consensus decision pathways. These are shorter documents than the more extended clinical guidelines. They are user-friendly, and the tables are invaluable. So this is what the Treat HF app is made from, and in fact, there's one coming out hopefully in February 2024 on HFrEF. There was one on HF-PEF, the preserved EF we're not discussing today, published in May of 2023. And there's one coming out in 2024 for hospitalized patients.

Okay, so moving from the provider-facing tools, let's talk about another reason there are barriers to having patients on these meds. From the patient's perspective, it's confusing, especially when they have other conditions requiring treatment medications. So, what I like to use are shared decision-making aids. For example, we've talked about the patient and clinician's need to make a decision on whether to use an ARNi with the highest level of evidence versus an ACE inhibitor or an ARB. So, decision aids help patients, and their caregivers make informed choices. The American College of Cardiology has various shared decision-making tools that you can show on a computer, or what we do in the clinic is print it out. So these are in different conditions, but if you look for the heart failure ones, we'll make the link available. It's basically a four-page document that's very user-friendly and helpful for those with lower health literacy. It shows the three choices between ACE inhibitor, ARB, and ARNi, and what those are, have the thumbs up or thumbs down. You work through this with the patient. It talks about how often you would take each medication, whether side effects like cough or dizziness and then it shows after two years of, for example, being on an ACE inhibitor, how many patients died and were still living. They show little figures of different colors compared to two years on an ARNi. And so the patient can decide if that's enough of a difference.

And then, let us not forget the cost. The tool shows three scenarios, patient A, B, and C, with different coverage from none, partial to total coverage. It talks about what, for example, would be a copay for each of those classes of meds. Finally, it advises calling the insurance company or the pharmacy to get more information to decide for a patient and a caregiver.

And then at the bottom, it shows the benefits on like a scale, a scale from zero to 10 of what the patient thinks of the benefits, one versus another, and how the benefits and the cost would weigh into their decision. So, it's a very helpful aid that makes decision-making more transparent. And I find it helps in educating patients.

Speaking of cost, it is particularly challenging for some patients with newer meds, like the ARNis and the SGLT inhibitors. What I recommend is to discuss out-of-pocket costs and copays upfront. Use that decision-making aid, consult with social workers, pharmacists, and pharmacy assistant plans to help with prior authorization. Helping with access to copay assistance helps patients when prescribing. Another thing you can do is try and prescribe 90-day refills when available. Also, you can ask the pharmacies to synchronize so you can pick them up all at once because sometimes going back and forth to the pharmacy is a barrier, never mind the gas and parking. Cost comparisons, pharmacists can do that. And

there are many other strategies for cost issues, as well as how to tackle those pre-authorizations, in the resource guide that we provide. Finally, sometimes it's just tricky titrating, starting and titrating these meds.

So, a few pearls. If the patient is “wet,” where their fluid is a little bit above their ideal level, not ideal weight, we get to know what a good weight is for each of our patients. And I'm not talking about what the best BMI is. I'm talking about a good fluid weight. If you find they are a couple of pounds up or they're a little wet, that's the time to start the ARNi, the ACE inhibitor, or the ARB because you've got a little more fluid there, and it's less likely to have a hit to the kidneys. Whereas in the clinic or wherever you're seeing them in the hospital or clinic if they're a little dry, maybe they're a pound or two down from their good dry weight, that's the time to start or go up on a beta blocker.

Another pearl is if the patient is hypotensive, consider prescribing the MRAs or the SGLT inhibitors. They're less likely to drop blood pressure. Kidney dysfunction, as I said, could get in the way. A lot of our patients have chronic kidney disease, so they may need closer monitoring and a little slower titration. But remember the pearls that Midge has shared - low potassium diets and salt substitutes that do not contain potassium. An SGLT inhibitor may be an excellent place to start with those patients with kidney dysfunction because it helps lower potassium. And there are also new potassium binders on the market.

Leslie Davis: I'll wrap up with special populations. I know we don't have time to go into all of them, but special populations include older patients and frail patients, and they're not necessarily the same group as those with polypharmacy. We know that more than 50% of patients with heart failure on Medicare have four or more non-cardiovascular comorbidities. And more than 25% are on six or more medicines, which makes adding more meds for heart failures challenging. Therefore, despite our best efforts to start or up-titrate the four pillars of drugs we've discussed today, nurse practitioners and other clinicians sometimes need help from experts. Midge, how do you know when a referral should be made to a heart failure specialist?

Midge Bowers: Leslie, thank you for that in-depth focus and for helping us narrow our perspective on why patients don't get titrated. I think I will add only one thing to this – pharmacists. Whether you have them available in your clinic space or your local pharmacy, pharmacists find out who delivers. As Leslie mentioned, when picking up and getting the prescriptions on the same cycle, it may be better if a pharmacy can deliver them because we know that sometimes transportation is a medication barrier. The other is once that six-week window has passed, and you have rapidly titrated up their meds, if patients have literacy issues, cognitive impairment, or challenges, get them in pill packs so that they're all together. The patient won't miss any doses. But when should you refer to a heart failure specialist?

Well, there's an excellent mnemonic that was published several years ago, and it's called **I Need Help**. I still have to refer to “I Need Help.” The **I** stands for patients who are on inotropes. Sometimes, they're discharged from the hospital, or sometimes, they recently needed to be treated on inotropes, and maybe they're discharged off it. So, remember that inotropes like dopamine, dobutamine, and milrinone. The “**N**” is for NYHA class 3b or 4 OR persistently elevated BNP and pro-BNP levels. Always compare pro-BNP to pro-BNP and BNP to BNP because they have different scales. The first **E** is for end-organ dysfunction. If you start seeing worsening kidney function or worsening liver function, consider a decline in the heart failure condition for patients with HFrEF. The **D** is for defibrillator shocks. Patients who have an ICD, which is part of the guidelines, start having defibrillator shocks. That's a sign you need to refer to a specialist. **H** is for hospitalization more than once in the past 12 months. So Leslie, if I asked

you right now how many patients you saw who are not on optimal GDMT have been hospitalized in the past year, you might say, oh, three or four times, right? So, really pay attention to the frequency of hospitalizations. **E** is for edema despite your escalation of those diuretic doses or worsening heart failure symptoms of shortness of breath and reduction in exercise tolerance. **L** is for low systolic blood pressure, less than 90. Along with that, there is an elevated heart rate. So maybe they have maximally tolerated their beta-blocker dose. They're on metoprolol 200 once daily, but their heart rate is increasing. That's a time to call for help and then **P** - progressive intolerance or down titration of that GDMT. Maybe they're becoming more hypotensive or more lightheaded or symptomatic.

So these are a lot of pearls I've just shared around when you need to think about referring to a heart failure specialist. They don't need to meet all these criteria for help, but think about "I need help." Leslie, would you like to summarize key points and wrap up this podcast?

Leslie Davis: Thank you, Midge. I'll remind our listeners that we will have the resources and that the I Need Help list key. I like to remember that the top reasons I refer to a heart failure specialist are that EF is less than or equal to 35% or if I'm either not able to titrate the meds up or have to decrease doses due to kidney dysfunction. To summarize my three key points when treating patients with HFrEF.

1. Patients benefit most when all four med classes are on board. So that's why we call them the four pillars to hold up that great care.
2. Prompt initiation and rapid titration of those four pillars over several weeks. Six weeks based on the trial data, rather than months, significantly impact mortality and morbidity in this patient population. That's a game changer, as we've discussed. So, we should have a sense of urgency in treating these patients.
3. Lastly, don't hesitate to refer patients to a heart failure specialist if you need help. And you notice I said a heart failure specialist, you can refer them to a nurse practitioner in a heart failure clinic. I didn't necessarily specify a heart failure cardiologist. We all work as teams. So, Midge, any final remarks as we wrap up today?

Midge Bowers: Leslie, I think both of us shared not only pearls but the real significance of not only heart failure as an illness but the impact we can make with our patients with rapid titration of the guideline-directed four pillar therapy.