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This activity has been approved for
1.5 AAPA Category 1 CME credits

Focused Clinical Pathways to Improve Management of Patients with HEART FAILURE

Contents:

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AAPA
American Academy of PAs

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ACTIVITY OVERVIEW

To treat heart failure (HF) effectively, symptoms must first be recognized and followed with an appropriate, timely diagnosis. As well, guideline-directed management must be implemented. The implementation of these recommendations is crucial for maximizing the benefits of HF therapy in clinical practice. Similarly, type 2 diabetes is frequently comorbid with HF, so both conditions require effective co-management. SGLT-2 inhibitors are now indicated for patients with and without diabetes to treat HF, and PAs need to be aware of these new indications. These areas were identified as foundational areas that require additional education. This program is specifically designed to address these gaps and to promote care that will lead to better patient outcomes among patients with HF. Through the tactical combination of online and print formats, this program will appeal to various learning styles and allow participants to reinforce their knowledge and acquire new skills that can immediately be applied to clinical practice.

AAPA TAKES RESPONSIBILITY FOR THE CONTENT, QUALITY, AND SCIENTIFIC INTEGRITY OF THIS CME ACTIVITY.

EDUCATIONAL OBJECTIVES

- Recognize key diagnostic features of HF and use appropriate diagnostic tests to diagnose chronic HF early in the disease course.
- Outline the most up-to-date evidence-based guidelines for the management of chronic HF, including the use of newer pharmacotherapies.
- Use appropriate SGLT-2 inhibitor management strategies when addressing chronic heart failure in patients with and without diabetes.

ACCREDITATION STATEMENT

This activity has been reviewed by the AAPA Review Panel and is compliant with AAPA CME Criteria. The activity is designated for 1.5 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation. Approval is valid through January 31, 2024.

Estimated time to complete this activity: 90 minutes.

HOW TO RECEIVE CREDIT

There are no fees for participating and receiving CME credit for this activity. Participants must: 1) read the educational objectives and faculty disclosures; 2) study the educational materials; 3) complete the post assessments in Learning Central.

In order to receive credit, participants must complete the post-test and evaluation. You will be able to access your certificate of completion in Learning Central as soon as you complete the post-test with a minimum score of 70%. Your certificate will be available under "Transcript" for your records.

DISCLOSURE POLICY STATEMENT

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CLINICAL DIALOGUE

Andy Herber, PA-C: Hello, and welcome to this *Clinical Dialogue* and *eCase Challenge* program, "Focused Clinical Pathways to Improve Management of Patients with Heart Failure." I'm Andy Herber, a physician assistant in hospital internal medicine at Mayo Clinic in Rochester, Minnesota.

Joining me in this conversation are two expert PAs, Shalon Buchs and Dr. Daniel Thibodeau. Shalon is the Director of Continuous Quality Improvement and an Associate Professor at Florida State University's College of Medicine in Tallahassee, Florida.

Dan is Professor and Director for Admissions in Doctor of Medical Science Programs for Eastern Virginia Medical School in Norfolk, Virginia.

My thanks to both of you for your involvement in this important continuing medical education activity.

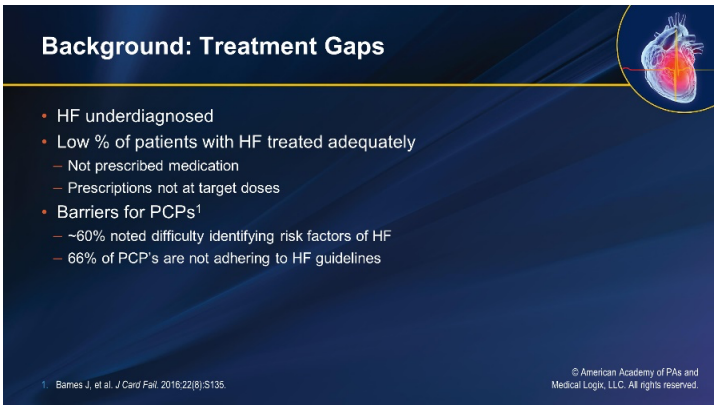
This program follows a previous AAPA CME program titled "A Call to Action: The Role of the PA in Improving Outcomes for Patients with Heart Failure." Key gaps in knowledge and practice in part guided the direction of this program, and we are hopeful that we can close some of those gaps here. So, let's get started.

Well, before we get into the heart of the matter, you guys see what I did there? That one's for free, but the dad jokes are going to keep coming. But anyway, let's discuss a little bit of the background of heart failure. Shalon, can you kind of just go over the nitty-gritty for me?

Shalon Buchs, MHS, PA-C: Sure. I would say that we need to be thinking about heart failure much more frequently in our clinical practice. It's common, and it's thought to be relatively underdiagnosed.

Not only are we underdiagnosing heart failure, but based on the CHAMP Heart Failure study, research has shown that a very low percentage of our patients with a diagnosis of heart failure are adequately treated. So, patients are either not receiving medications at all, so not getting things like ACE inhibitors, beta-blockers, ARBs or ARNIs, or if these are prescribed, only a small percentage of the patients are actually receiving the target dose.

So, in evaluating primary care physicians on their heart failure practices and barriers, research has identified that nearly 60% of primary care providers have difficulty identifying heart failure risk factors in patients with chronic heart failure, and 66% of them are adhering to our guidelines.



Andy Herber: All right, so you bring up a good point. It's one thing when a patient comes in and they've gained a bunch of weight and they're short of breath and they've been eating TV dinners at home and tons of salt, and they have lower extremity swelling. But what about those patients that come in with that, you know, just a little bit of shortness of breath, and you're leaning on history a little bit more? How do you tease that out?

Shalon Buchs: That's a great question. As we know, as PAs and health care providers, we know that history is really a key component to identifying a correct diagnosis for anything. And so that's not any different in heart failure. We really need to stick to the fundamentals and the Sacred Seven, if you will, and really drill down from there.

So, we should start with things like onset, location, duration, severity of whatever symptom the patient's presenting with. Once we have some of that necessary information, a framework can help with our diagnosis or risk stratification and identifying patients who might be at risk for heart failure.

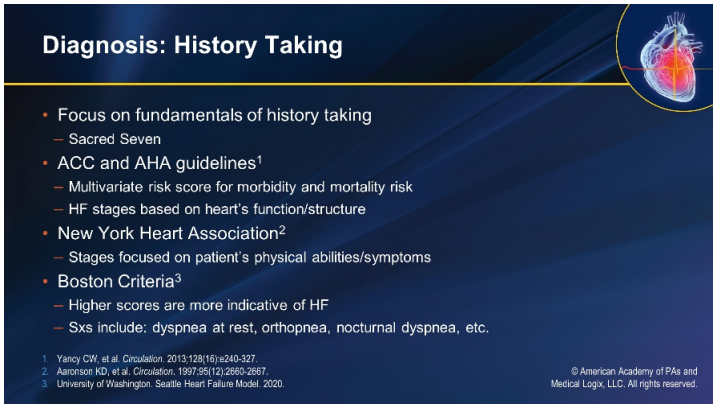
So, the ACC and AHA guidelines recommend using a multivariate risk score to determine a risk of morbidity and mortality in ambulatory and hospitalized patients with heart failure, emphasizing the development, and progression of symptoms.

Most of us are pretty familiar with the New York Heart Association classes of heart failure. These are commonly used, as well.

That particular classification system really looks at what can the patient do versus what's going on with the heart, which is a little better evaluated through the ACC/AHA heart failure stages, which considers the Heart Association class and the structural condition of the heart. These things differentiate patients' reported symptoms and objective assessment of functional class.

So, some questions specific that we might use to tease out the functional capacity while we're taking a history are things like, do you sleep in a recliner because it's more upright, or several months ago, how far do you think you could walk versus now? Are you out of breath even when you're sitting still? And we also want to think about fatiguability and low energy levels over time.

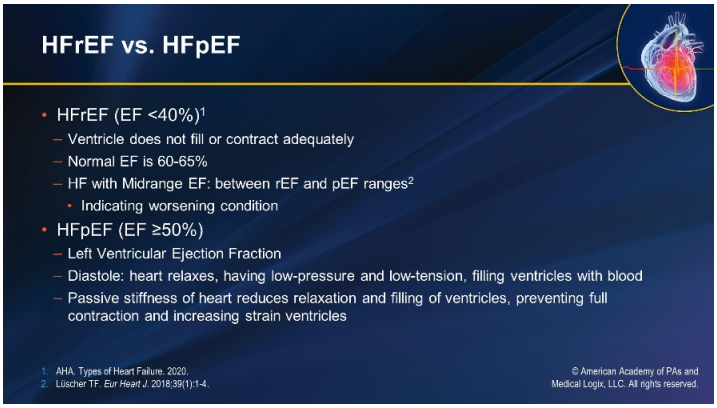
These help us identify some of the Boston criteria, which can be applied to our history and some of our physical exam and diagnostic study findings. The scores are applied to the criteria, and a higher score is more indicative of the presence of heart failure. So, things like dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea or walking on a surface level might get us points in the Boston criteria.



Andy Herber: All right, so we're talking about heart failure. Dan, you're like one of the gurus out there. So, we have HFpEF with preserved ejection fraction. We have HFrEF, with reduced ejection fraction. Can you just help us all out, kind of figure this out for us?

Dr. Daniel Thibodeau: Well, Andy, thanks for moderating this. Real short, HFrEF, or heart failure with a reduced ejection fraction, we're talking about failure of the ventricle to adequately fill, but more importantly, contract adequate enough to pump what we would consider a normal ejection fraction, which is normally between 60 and 65%. So, we're talking anything less than that would be considered HFrEF, with that reduced ejection fraction. It's what we used to call systolic failure in the past.

And then we have HFpEF, which is a preserved ejection fraction, or LVEF, left ventricular ejection fraction. But what we have is passive stiffness. So, during end diastole, where the heart normally is supposed to fully relax under low-pressure and low-tension conditions, the heart has passive stiffness, and that doesn't allow the ventricle to fully relax and fully be able to fill, but more importantly, be able to give a full contraction without having any strain or stress to the ventricle while it does that.



Now, there is also heart failure with a midrange ejection fraction, which is not quite full-blown HFrEF, but you have just a little bit of a drop of your ejection fraction. But it is a sign that things may be getting worse.

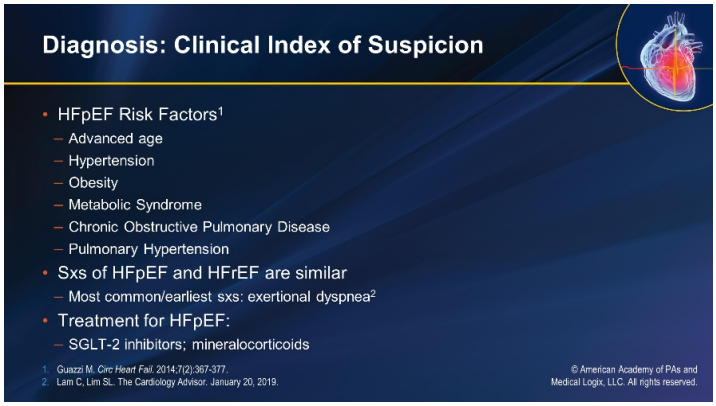
Andy Herber: Great. Thanks. That's super-helpful. So now that we have the clinical context kind of covered, when do we start thinking about this? Obviously, when an 18-year-old comes into our office or a 25-year-old, are we thinking about heart failure then? Or when do we actually have to start thinking about heart failure as a potential diagnosis?

Shalon Buchs: Yes, so I think that's another great question, Andy. The causes of these two types of heart failure really differ, as well. So HFpEF, so the preserved ejection fraction heart failure, is often associated in patients with advanced age. So, the elderly population, those with hypertension, obesity, and metabolic syndrome.

Other things to think about when it comes to HFpEF include things like chronic obstructive pulmonary disease. It's definitely more associated with preserved ejection heart failure, so we need to think about that. And also, when patients have pulmonary hypertension, we may see HFpEF. We should keep in mind that the right side of the heart is more impacted in these two scenarios than the left, particularly if they're the sole contributor to the heart failure.

The symptoms are similar between the two categories, the preserved ejection fraction and the reduced ejection fraction. So unfortunately, symptoms alone are not really going to help us too much. The most common presenting symptom is going to be exertional dyspnea, and it's most often also the earliest symptom. Some patients also will present with that fatiguability I talked about earlier.

Treatments also differ. So historically, there's not a whole lot of data-driven treatment options for the HFpEF. But now we have some new therapies available that are indicated in this scenario, and those are the SGLT-2 inhibitors and a few other agents like mineralocorticoids that have been approved for HFpEF, and similarly for the midrange ejection fraction heart failure, as well. So, this is good news.

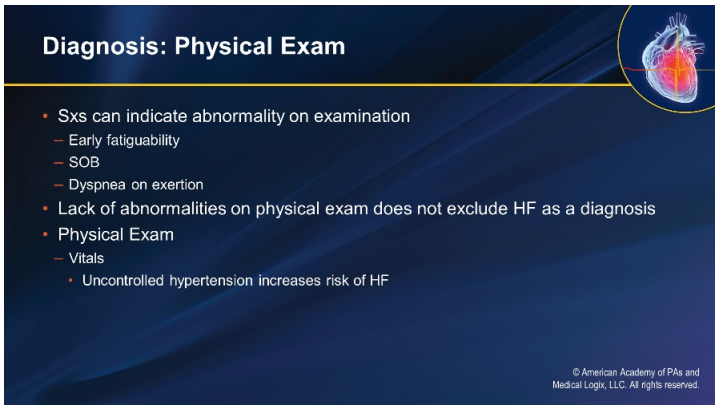


Andy Herber: So, we've talked about the clinical context of heart failure. So somebody shows up in your clinic. Are you guys, I mean, physical exam, I feel like it's kind of, you know, losing some zest. It feels like most people just are ordering echocardiograms and the fancy things like chest X-rays proBNPs. But are you actually doing a physical exam in the office? And then what things are you looking for on physical exam? What has the highest yield for you?

Daniel Thibodeau: So, it's a great question. And as Shalon alluded to earlier, there are symptoms that the patient is giving, and we all know the famous quote of "Listen to the patient. They will give you the diagnosis." Early fatiguability, the shortness of breath or dyspnea on exertion, those types of symptoms sometimes can really help you to at least look for any evidence on exam that you might have an abnormality.

Now, the whole caveat to this is that you may have a completely normal exam, and you may not find any abnormal findings. But that doesn't mean the patient doesn't have heart failure.

Now, in the classic sense, though, what we do look for is, first of all, we want to look at vital signs. We want to see if the patient is hypertensive. Are they not well controlled? Hypertension plays a pivotal role in being able to manage heart failure well, and uncontrolled hypertension over the years places a patient certainly at risk for heart failure to develop.



And I'm sure Shalon could also talk about some of the exams that she sees, as well.

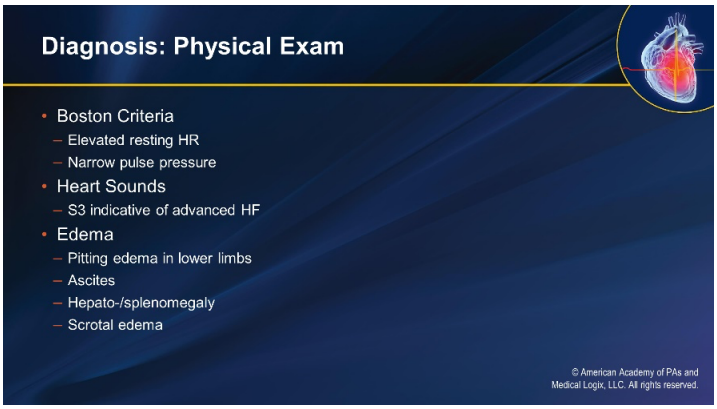
Shalon Buchs: Yes, thank you, Dan. And by the way, I love that Sir William Osler quote, so thanks for bringing that one up. Yes, so I would just add a little bit to what Dan has already offered, just

remembering that the Boston criteria also includes some of our physical exam findings.

And one of those, as Dan kind of mentioned, comes from the vital signs. So, an elevated resting heart rate is indicative of an additional score on the Boston criteria. So that's important, even if it's in the high normal range, so maybe 91 or higher could give you points on the Boston criteria score. Also, a narrow pulse pressure. And that's getting back to that uncontrolled hypertension that Dan was alluding to.

A little bit more about heart sounds. S3 is usually really indicative of heart failure, but they're usually pretty far along at that point, because that would indicate the volume overload that we usually see in our more advanced stages of heart failure rather than the earlier stages.

And then, of course, all the edema signs. So, whether it's pitting edema in the lower extremities, ascites, hepato- or splenomegaly and scrotal edema in our male population.



Andy Herber: That's fantastic. Thanks, guys. So, I work in the hospital. I'm a hospitalist. A patient comes in with heart failure. We like labs and fancy tests, and what I use the most is proBNP. So, they come in, they're short of breath, maybe we don't have the chest X-ray back, but we're looking at that proBNP, and if it's low, we're thinking it's probably not heart failure, and if it's high, we're thinking heart failure. Am I right in this thought process, or am I missing something, guys?

Daniel Thibodeau: No, you're correct. I think the BNP is a very important tool that we can use for heart failure. I think we also have to remind ourselves that it is one tool in the toolbox. It doesn't discount the idea that we need to listen to the patient. The examination also helps us a lot.

But when we talk about biomarkers, we have been using BNPs more extensively for greater than a decade now, and our guidelines have been consistent in showing that, starting back in 2013, and then reiterating it in 2017, the usefulness of the BNP and the NT-proBNP are very helpful in diagnosing and actually being able to gauge where an individual is with heart failure.

One of the things that we can glean off of this is that most patients have low BNPs when they are asymptomatic, and there's no evidence of volume overload. So, when we see those BNPs rise or elevate along with symptoms, it gives us more reassurance that it's likely heart failure that's causing the patient's problems.

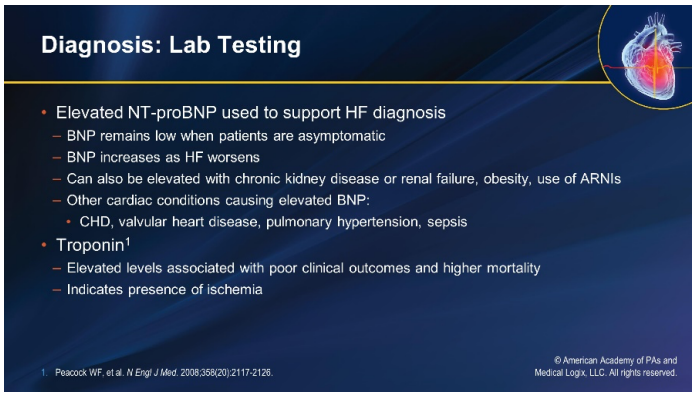
When we have patients who present with heart failure-like symptoms, but we have low or normal BNPs, then we have to look for other reasons why the patient's short of breath. So, the BNP can be very helpful in that regard.

Now, with patients who have acute decompensated, or they have chronic heart failure, one of the other biomarkers that can be elevated is the troponin. And a lot of times this is associated with worse clinical outcomes and higher mortality, while declining levels indicate a more promising prognosis. So, we also follow troponins to look for a possible ischemic component that could be causing an exacerbation of heart failure.

So, it's not necessarily foolproof, though. There are other factors that can cause an abnormal BNP to occur.

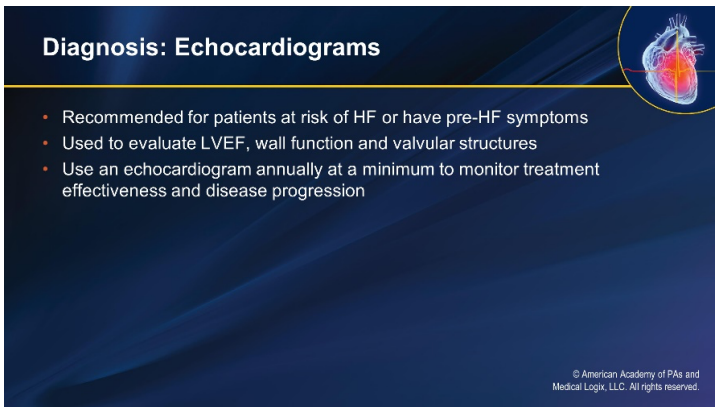
The most common is chronic kidney disease or renal failure. That will hold onto those BNPs within the serum, and then they'll be abnormally elevated, and sometimes that can take a couple of weeks for it to clear. Obesity can do it. And then there are some other drugs that can be used, especially our ARNIs, that can cause abnormalities to the BNP.

There are other cardiac conditions, though, that can be elevated in some patients with non-heart failure conditions. So certainly, coronary heart disease, valvular heart disease, pulmonary hypertension, and then sepsis, which we see a lot of, can cause our BNP levels to be elevated erroneously, and that doesn't necessarily always imply that the patient is in a full heart failure exacerbation. So, we have to keep that in mind.



Andy Herber: All right. So that's a lot about labs. So, the other thing I feel like always that goes hand in hand with heart failure is echocardiograms. So, when do we order these? You know, is there a sweet spot as to the opportune time to get this echocardiogram for you guys?

Daniel Thibodeau: That's a great question. I and many of us are early proponents of getting early echocardiograms. And these are the individuals that we talked about a little earlier that are at risk or have pre-heart failure-type symptoms.



So, when you start having individuals that fall under that at-risk or pre-heart failure stages of potential heart failure, an echocardiogram

is an excellent tool to use to look at that overall left ventricular ejection fraction, wall function, valvular structures, just to get a baseline of where they are during that time that you're seeing them.

And so we need to follow a patient's heart failure over time, so when we have individuals that do have heart failure, usually at a minimum, an annual echocardiogram to look at how you are doing with the patient's medical management, guideline-directed medical therapy we call it, and looking at the echo to make sure that you're maintaining things and you're not showing any signs of progression of disease.

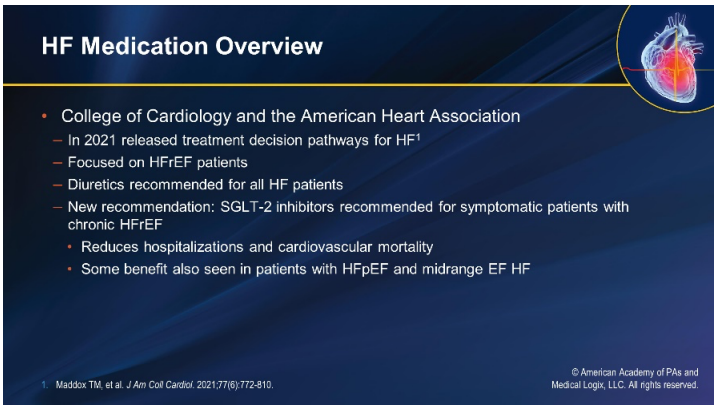
We also need to think about detecting pulmonary hypertension, which occurs in a lot of our individuals who have COPD, and that's a really important factor, because that type of shortness of breath is fixed, and it's difficult to improve. And so, you know that when you have pulmonary hypertension, your goal in managing those patients is to try to slow down the progression or prevent it from occurring in the first place.

Andy Herber: So, we've talked a ton about heart failure. We've talked about HFpEF and HFrEF but Shalon, can you comment on, I feel like there's new heart failure medications like every week. And can you kind of go over some of the heart failure medications for us quick?

Shalon Buchs: Sure, I'd be happy to. So, I think there's some confusion out there sometimes, particularly from providers around selecting their appropriate therapy. And in 2021, so just last year, the American College of Cardiology and the American Heart Association came together and released a set of treatment decision pathways to help us all in our selection.

This is most specifically geared towards the heart HFrEF patients. But, you know, there's still a little bit of hope out there for the HFpEF patients. There's still a need to use diuretics in all of these patients. It's one of the mainstays of therapy. But as you mentioned, there are newer recommendations that are coming out all the time, and one of those is specifically for the SGLT-2 inhibitors in heart failure patients.

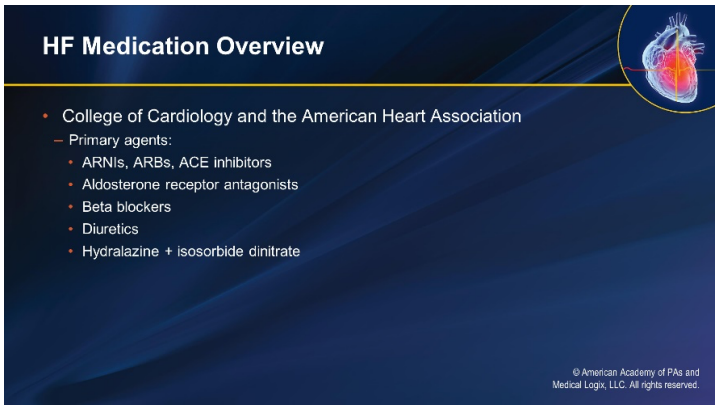
The guidelines now really recommend that any symptomatic patient with chronic HFrEF, again, specifically, should have an SGLT-2 inhibitor in their therapeutic plan. This can reduce hospitalizations and cardiovascular mortality regardless of the presence of type 2 diabetes. And as I said earlier, SGLT-2s have shown some promise in those patients with HFpEF and the midrange ejection fraction heart failure patients that we're seeing.



So, it's important to remember that we should be focusing on treating the underlying cause of our heart failure patients, as well. As Dan alluded to earlier, the most common is going to be ischemic cardiovascular disease. And hypertension's another big one that we need to think about.

So, some primary agents that we'll be using in our heart failure patients, just a quick summary, are going to be the angiotensin system inhibitors, so ARNIs, ARBs, ACE inhibitors, any of those; aldosterone receptor antagonists; beta- blockers, and of course the diuretics.

Daniel Thibodeau: There are some other circumstances where other medications can be used, and that's especially true in the African American population, where we use the combination of hydralazine and isosorbide dinitrate.



And so, it's really important to add that as patient symptoms persist. Even though African Americans may already be on ACE inhibitors, beta- blockers and aldosterone antagonists, that hydralazine-nitrate combination can be very helpful.

Andy Herber: So, it's a difficult balancing act, because the creatinine and the blood pressure and, do you guys have like an order, or which one's more important, or when do you scale back on some of the ACE or, when you have somebody with low blood pressure, or their creatinine is a little bit up, any tricks on that?

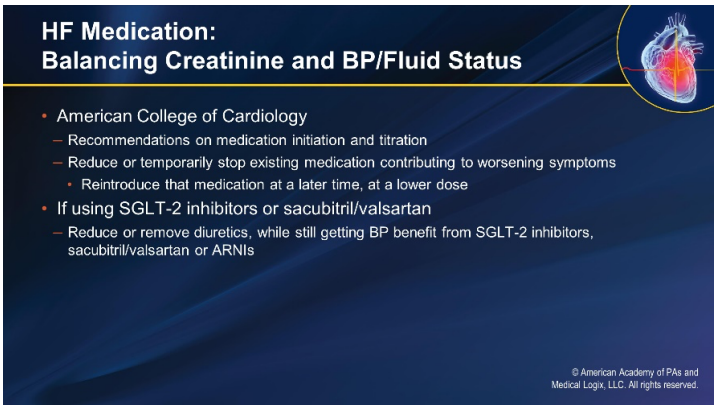
Daniel Thibodeau: So, my approach on this is, you have an algorithm that, the American College of Cardiology has a beautiful diagram and description of how you can start and titrate up on medications. And so, what I normally do is that, if we start having individuals that are having more symptoms related to certain medications, I may start reducing some of the doses of the medicines that they're already on.

If we have enough hypotension that occurs, and a lot of times this will happen more in the hospital setting, like what you're seeing Andy, is that you may just stop a drug temporarily and then reintroduce it at a lower dose later on in the phase of the hospitalization or when they leave as an outpatient. And so, I normally progress it up as the guidelines allow based on the stage of heart failure, and then I bring it back down based on the last thing I might have added.

Now, I will say, and Shalon may speak to this, as well, with the SGLT-2 inhibitors, one of the really nice things about that class of medications, as well as sacubitril/valsartan, is because their mechanism of action is drawing fluid out of the patient, you may get lower blood pressure as a result.

But what I would recommend people doing is thinking about it this way, is that this is a perfect time, that if you have individuals who are on daily use or some type of use of a diuretic like furosemide or bumetanide, that's a perfect time to pull away from those diuretics, because those diuretics tend to be more harmful to the kidneys, and

you still get a negative effect with the use of SGLT-2 inhibitors, as well as sacubitril/valsartan, or the ARNIs.

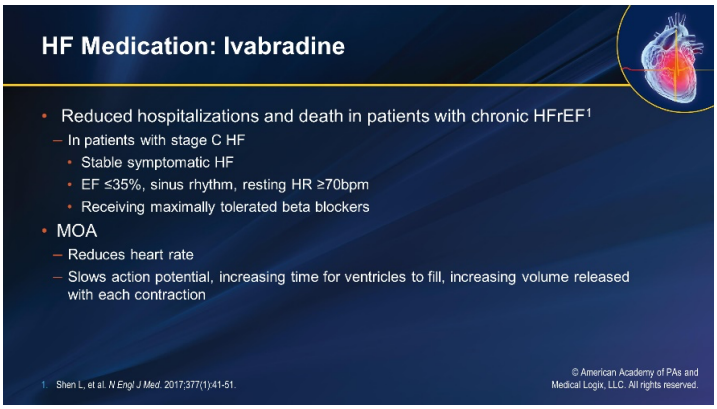


That can be a great benefit. But if you have that balance where you have to draw off some of the medication, I would draw off the diuretics if you're using those other two agents at that time.

Andy Herber: So, Dan, in 2015, ivabradine and sacubitril/valsartan were approved to treat chronic heart failure. Can you tell us a little bit more about these medications? How do they fit into your practice? And can we start with maybe ivabradine first?

Daniel Thibodeau: Certainly. So, these are two drugs that were approved back in 2015, and gaining more and more traction as the years go on. Ivabradine and sacubitril/valsartan both showed a reduction of hospitalization and death with patients who have chronic heart failure and reduced ejection fraction, so these are our HFrEF patients.

The way ivabradine works is it affects heart rate alone, and so it works for individuals that you may see who have heart failure who tend to have higher heart rates than other individuals. It has no effect on heart contractility or blood pressure, and the way it works is that, if we think back on our action potential, where we have that little blip after each recurring beat, the action potential is just slowed down a very small amount.



But you do that for every beat throughout the day, it gives a little bit more time for filling. It takes a little bit more time to allow the ventricle to fill and actually increase your overall volume that you can pump out. So that's how ivabradine works.

And so, it's indicated for lowering hospitalization rates in patients who are stable, with stable symptomatic heart failure with a reduced left ventricular ejection fraction that is either less than or equal to 35%, who are in sinus rhythm and have a resting heart rate of at least 70 bpm or more, and they're taking all the maximally tolerated beta- blocker doses, and there's no contraindications to that.

So, we use that, and it's supported by the 2017 guidelines, primarily to reduce heart rate in those patients who have stage C heart failure with a left ventricular ejection fraction less than 35%.

Andy Herber: That's great, Dan. Thanks a lot. So, do you have to maximize the metoprolol dosing or the beta -blocker dosing before you add ivabradine or any of the other rate-limiting medications? Or when is the opportune time to add ivabradine?

Daniel Thibodeau: So, the idea is that you want to maximize your beta- blocker therapy first before starting ivabradine. So, yes, you want to use that first tool in the toolbox with beta- blockers first, maximize that dose. And then if you still have an individual who has low EF who has a heart rate greater than 70, you can initiate ivabradine as part of that regimen.

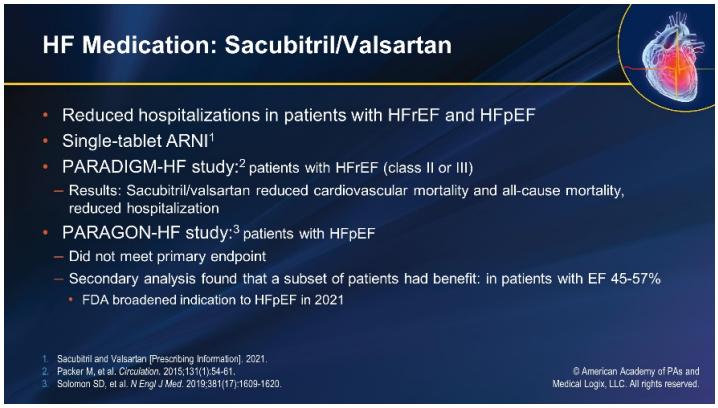
Andy Herber: Awesome. So, Shalon, can you talk a little bit about sacubitril/valsartan?

Shalon Buchs: Sure. So sacubitril/valsartan is one of our single-tablet newer angiotensin receptor neprilysin inhibitors, so an ARNI for short. And it's now indicated for the reduction of cardiovascular death and hospitalization in patients broadly with heart failure. This is both actually useful in patients with HFpEF and HFrEF, so we can use these ARNIs in both categories.

The PARADIGM-Heart Failure study was a randomized double-blinded trial in patients with HFrEF. Most of these patients had class II or III stage heart failure. And the study found that sacubitril/valsartan reduced not only the cardiovascular mortality, but all-cause mortality. The drug also reduced hospitalizations, as I stated earlier, for heart failure compared to the recommended dose of the ACE inhibitor enalapril. This trial was actually stopped a little bit early because the prespecified boundary had been crossed.

And then further, the drug's indication was expanded to include those with HFpEF in 2001 based on the results of the PARAGON-Heart Failure trial. And this trial didn't meet its primary endpoint, but further analysis found some secondary outcomes in patients, with ejection fractions between 45 and 57% seeing benefit from use of this drug.

So, because we really don't have a lot of treatments, which we talked about earlier, approved for HFpEF, the FDA approved this broadened indication just in 2021.



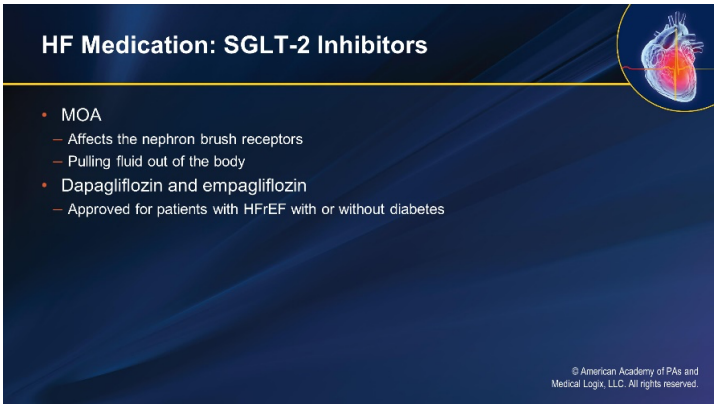
And as we talked about earlier, both ivabradine and sacubitril/valsartan were recommended in the 2017 ACC/AHA guideline update, stating specifically that in patients with chronic symptomatic heart failure with reduced ejection fraction at classification II or III who tolerate an ACE inhibitor or an ARB, replacement with an ARNI is recommended to further reduce morbidity and mortality. So

basically, the ARNIs or the sacubitril/valsartan is now preferred over our classic ACE inhibitors.

Andy Herber: Awesome. Man, you guys know this stuff really well. It's fantastic to listen and learn from you guys. So, Dan, SGLT-2 inhibitors, I mean, these are diabetic meds, so why are you guys using them in heart failure? Teach me.

Daniel Thibodeau: So, it's a great question. And just a little bit about how the SGLT-2 inhibitors work is that they work on the brush receptors of the nephrons. And what they found was that, while it was geared towards diabetes and glucose control, they started noticing that during the interaction with the brush receptors, it was pulling fluid off of individuals. And then they started realizing, "Gosh, this will work great with heart failure."

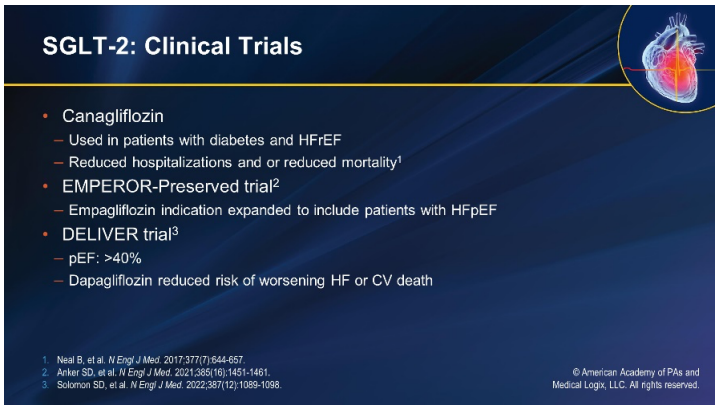
And so, the current guidelines are now that we use SGLT-2 inhibitors for patients with heart failure, even if they don't have diabetes. And so, when we look at heart failure with reduced ejection fraction, specifically two drugs within that, dapagliflozin and empagliflozin, those are both approved for patients who have heart failure with a reduced ejection fraction regardless of if they have diabetes or not.



One is canagliflozin if they do have diabetes and HFrEF, and all of these are based on several clinical trials that all demonstrated reduced rates of hospitalization and/or reduced deaths of individuals that are receiving these agents.

Now, with respect to heart failure with a preserved ejection fraction, the unfortunate thing is that there's not as many pharmacotherapies for managing individuals of this class. This year, though, in an exciting outcome based on the EMPEROR-Preserved trial, empagliflozin had an expanded indication to be approved for those individuals who have HFpEF.

In August of this year, results from the DELIVER trial released showing that patients who had a preserved EF, that was EF greater than 40% in this particular study, treatment with dapagliflozin reduced the combination risk of worsening heart failure or CV death. So, there's a lot more data that's coming out with the use of SGLT-2 inhibitors. I think there's a lot more exciting information to come as we continue to use them.

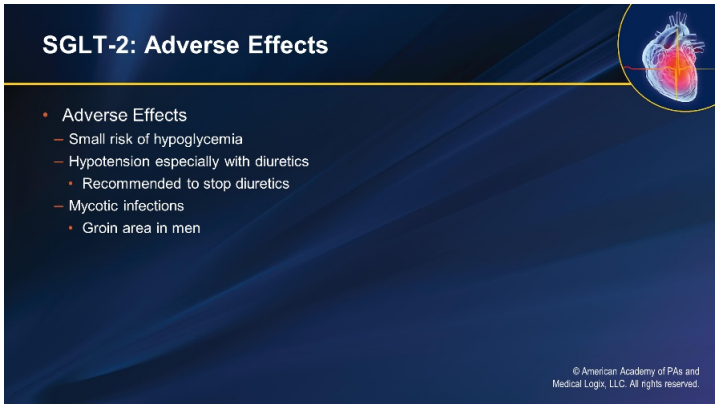


Andy Herber: So, Dan, what about hypoglycemia? Any of the flozins, are they going to be associated with hypoglycemia, where if a patient's fasting, or do they not take it at night when they haven't been eating? Or is that not an issue?

Daniel Thibodeau: So, the adverse effects related to SGLT-2s are that there's always the potential it could cause a little hypoglycemia. The numbers are actually relatively small. Hypotension can happen for these individuals with SGLT-2s, so we have to watch, because we're changing amount of volume, and so we have to watch how much volume comes out.

And that's where the adjustment of medications related to the diuretics, so if we have individuals who are already on a diuretic, and we put them on an SGLT-2, pulling off the diuretics because they are not renal-friendly but keeping them on the SGLT-2s can be a strategy to use.

Some of the other possible adverse effects that occur with SGLT-2s are mycotic infections, especially in men around the groin area. We just have to be mindful of that. The numbers are small, but it's something that could potentially happen.



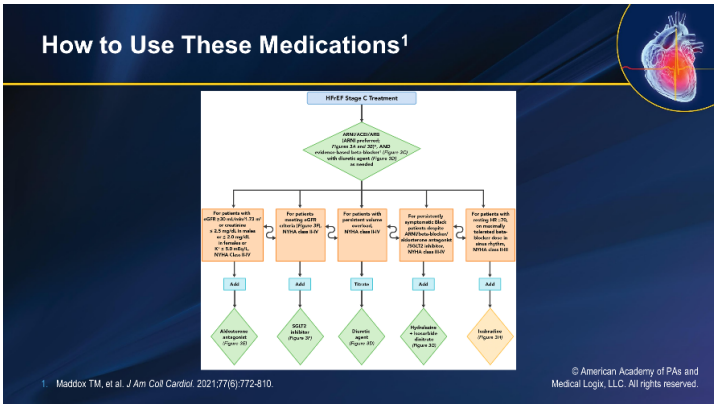
Andy Herber: Thanks. Again, I mean, there are so many new meds, and there's new guidelines out there. Shalon, how do you put this all together using the 2021 guidelines, ARNIs and ARBs and beta blockers and the flozins, and you have a heart failure patient, and you have all these new meds at your disposal. What's your process on when you start them and stop them and titrate them?

Shalon Buchs: Yes, that's a great question. And we spoke before about the confusion about what to start and when to start it. I do think that this pathway is intended to make it simpler for us as we start to treat our patients. So, as we are likely aware, treatment really starts specifically for heart failure when a patient has entered into stage C heart failure.

So usually, we're going to start with a beta- blocker and one of the RAAS-inhibiting agents. So that could be an ACE inhibitor, an

ARB or an ARNI. And as I mentioned before, ARNIs are really preferred at this point over the other two, so beta- blockers and a RAAS system inhibitor. And then each of those agents should really be titrated up to maximally tolerated or target doses.

Initiating the beta- blocker is best tolerated when patients are dry, if you will, and ACE inhibitors when they're wet. So, just thinking about the level of congestion the patient might have can help us decide when we should initiate those two specific drugs. And we need to be sure we're only initiating the guideline-recommended beta- blocker, so things like carvedilol or bisoprolol, things like that, those should be used in the patients with HFrEF.



When we talk about the RAAS system inhibition, ARNIs, again, are the preferred agents. Renal function and potassium should be checked for sure within 1 to 2 weeks of initiation of any of the RAAS inhibitors, or when we titrate those up, we need to check our renal function and our potassium.

And then, of course, diuretics, which Dan appropriately stated, they're not going to decrease morbidity and mortality in our patients, but they certainly help with symptom management. These should be added as needed, and the dose needs to be titrated to achieve appropriate decongestion.

If doses of furosemide or other loop diuretics are exceeding 80 mg twice daily, then we need to look at another loop diuretic. We shouldn't be going over that. And then, if we need to, we can add a thiazide if we're not getting the diuresis level that we need. But as Dan mentioned, we are seeing some level of volume control with our ARNI and our SGLT-2 inhibitors, so that's something to keep in mind, as well.

After initiating a beta- blocker and an angiotensin antagonist, adding an aldosterone antagonist, which should be considered if the patient is still not maximized, if they're not well controlled. When we do this, we need to make sure that we're looking at their electrolytes.

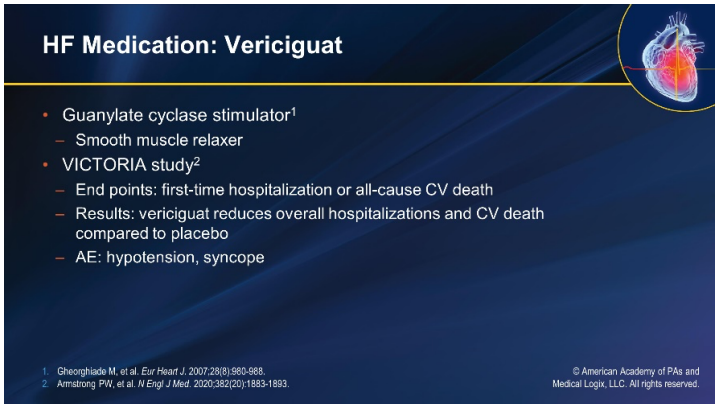
Andy Herber: So, Dan, can you tell us a little bit about vericiguat and how it plays into heart failure management?

Daniel Thibodeau: Sure, Andy. So vericiguat is yet another tool in the toolbox for heart failure. It is for individuals who have chronic heart failure. It is a guanylate cyclase stimulator, so it's a smooth muscle relaxer. And the trial that we point to is called the VICTORIA trial that looked at this drug compared to placebo.

And the end goal was first-time hospitalizations or all-cause CV death. And it was shown that it reduced overall hospitalizations and CV death, whichever came first, compared to placebo.

We have to worry about symptomatic hypotension and syncope. They were not necessarily significantly increased during this with the active treatment group in the overall study, and so it was proven to be useful in individuals in reducing overall CV death and heart failure hospitalization following a hospitalization for heart failure or the need for outpatient IV diuretics.

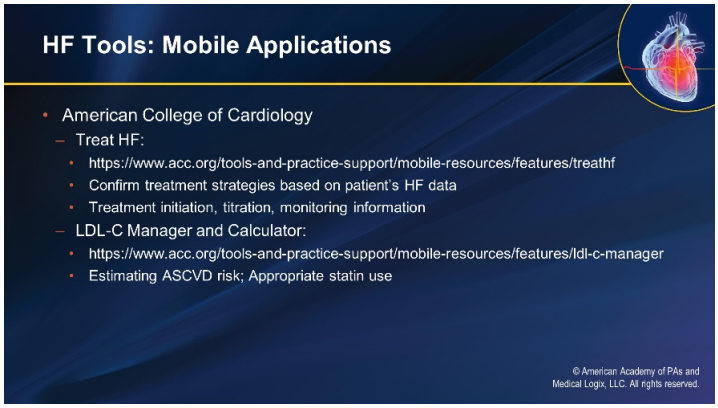
So, you took these individuals who had been in the hospital for heart failure as a hospitalization, you got them as an outpatient, you started them on the vericiguat, and by starting them on this medication, it was shown that they reduced their overall hospitalization or rehospitalization and overall CV mortality. So, it's yet another tool in the toolbox that we can use for the management of heart failure.



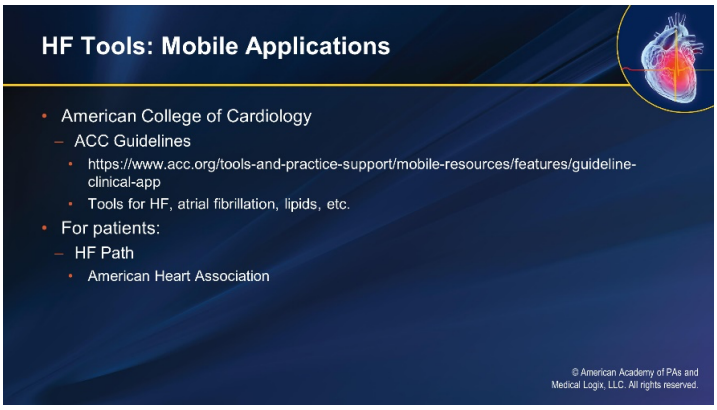
Andy Herber: That's fantastic. Thanks a lot. So, I mean, you guys know this stuff really, really well. And my fear is that I'm going to forget some of it after talking with you guys. But there's got to be apps on your cell phone or guidelines you can go to on the Internet that can help kind of keep this fresh, and things that you can maybe plug in the patient's data. Are there things that you guys use maybe to help?

Daniel Thibodeau: Well, Andy, it's a great question. The American College of Cardiology has several. And they're all free by the way.

One is called Treat HF, for heart failure, and we'll have a link that helps support this. This really helps clinicians confirm the therapies based on data that you can put in, individualized to your patient, and it'll pull up the strategy based on where that patient is with their heart failure. So, there's a lot of information on initiation, titration of meds and monitoring of them.



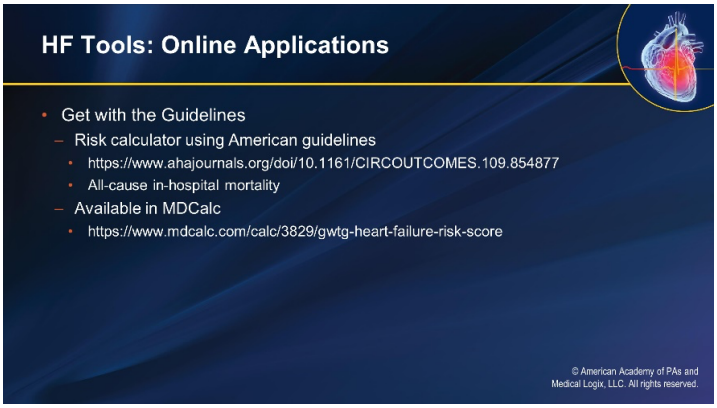
Another one is the LDL-C Manager and Calculator, which talks about estimating patients' overall ASCVD risk and the appropriate intensity of statins that you could be on. And then there's the ACC Guideline app that goes through all of these tools, as far as heart failure, atrial fibrillation, lipids, and a variety of other very useful tools.



And for the patient side there is the HF Path that the American Heart Association has for patients, along with heart failure health storylines that can be used for the patient side, all very helpful. And I know, Shalon, you probably have another app or two that you could potentially recommend, as well.

Shalon Buchs: Yes, Dan. All the apps that you've already talked about are great. The only thing I would really add is specifically for providers. So, there's a Get with the Guidelines app, it's a risk calculator, actually. And that is directly looking at all the guidelines we've talked about.

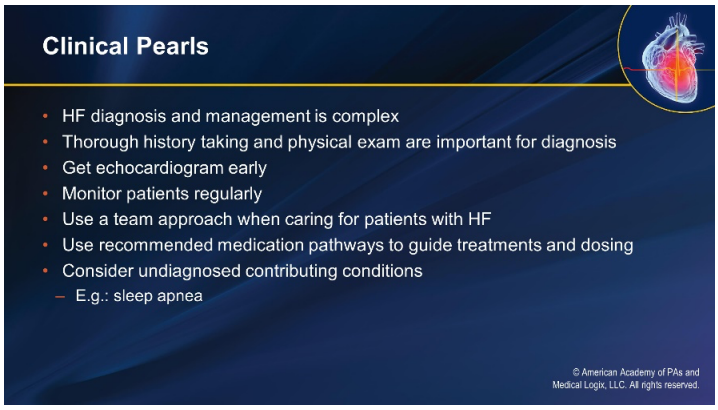
And it's available in MDCalc, which many of us already have anyway. What this particular calculator does is it estimates the all-cause in-hospital mortality for patients who are admitted with heart failure. So, it's really helpful in that regard, Andy. I know, as a hospitalist, that might be something you want to look at. And there's also a calculator for the Seattle Heart Failure Model, but I'm not completely sure if it's available in an app. It's definitely available online.



Andy Herber: What would be some of your take-home points, some of your need-to-know when you're managing heart failure patients from the experts? Give me your need-to-knows, if you don't mind.

Shalon Buchs: So, one thing I want to reiterate is that heart failure is a complex condition. It's not easy to diagnose or manage. So don't beat yourself up. Just continue to do better for your patients.

Keep in mind that thoughtful history-taking. As Dan said, the patient's going to tell you the diagnosis. A good physical exam also can lend insight. Get those echocardiograms early, for sure. That's important. And then regular check-ins with you as the primary provider. And don't forget the team approach. It takes all of us to take care of heart failure, regardless of our specialty, and it takes those outside of our comfort area to do this.



And then I guess I'll end with making sure that our patients are on the right medications. We have that nice pathway to help us, and we can always refer back to it, make sure that they're on the right meds and at their target doses if they're able.

And then finally, think about undiagnosed problems that might be contributing. So, things like sleep apnea can contribute to hypertension and then exacerbate heart failure. And I think that's a lot, but that's all I have. Dan?

Daniel Thibodeau: All excellent points. And I'll echo what, Shalon, you just said, two things. Be patient with yourself as a practitioner. This is a very complex disease. There are a lot of tools in the toolbox, and methodical, start first by thinking about risk assessment of all your patients.

Really try to just think about heart failure even early on, when patients have had hypertension for 10 years, and you've been managing hypertension for 10 years, and you can't quite get it under control. You think about things like heart failure as a potential risk that they may be developing, and they're just not showing it right away. So be patient with yourself.

Use the guidelines to your advantage. And the apps are extremely helpful to kind of guide you through how to first initiate meds and then titrate up, adding additional agents, and then when to switch and when to think about other alternative therapies, and things as we get into the later stages of stage C, as well as the refractory part of stage D.

When we get to stage D, of course, and we're starting to get into the refractory part, that's where that team approach really comes into play, as well, when you've exhausted therapies, you've maximized everything on board, and you have to know when to say when on some individuals who are sort of at that end stage of their heart failure, which I know we don't really talk a lot about here.

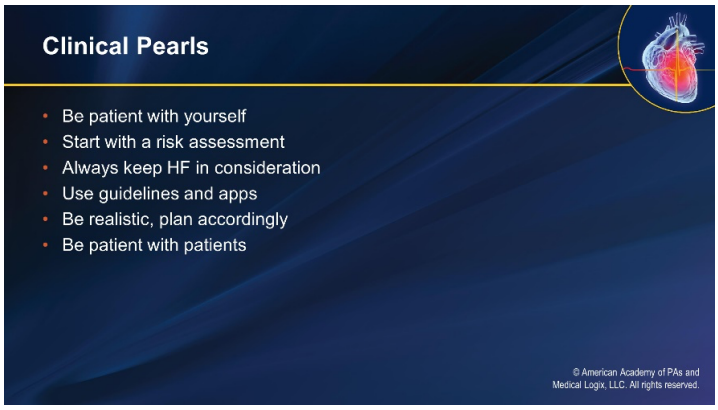
But we have individuals who have been on maximal therapy, and they're just not progressing along, and they're getting worse, you have to think about those end-stage discussions with the patient and family members, to be realistic about what to expect and to plan accordingly.

On the patient side, you have to be patient with the patient. This is a complex disease for us. You can only imagine what it is for the patient. And so, I use the question back to the patient, "Tell me what you know about your heart failure, or tell me what you've been told, what you think is going on with your heart." That's a good starting point so you have an understanding of what level of education they have related to their heart failure.

And then you really have to work with them and be very patient, because it gets very frustrating for them at many different stages of

their heart failure, and you just have to realize that they're going to have times when they struggle, and you just really have to work with them.

And I think that's where I reinforce Shalon's point, is that it's a team approach, and you really have to have solid team members around you to manage these patients, because it just gets quite complicated for both of you, but also the patient and the family members.



Andy Herber: I would like to thank both our expert faculty, Shalon Buchs and Daniel Thibodeau, for their great insights and discussion. And I would like to thank you, our audience, for participating in this *Clinical Dialogue*.

References

Aaronson KD, Schwartz JS, Chen TM, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation*. 1997;95(12):2660-2667. doi:10.1161/01.cir.95.12.2660

American Heart Association (AHA). Types of Heart Failure. www.heart.org. Accessed July 23, 2020. https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/types-of-heart-failure

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021;385(16):1451-1461. doi:10.1056/NEJMoa2107038

Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *New England Journal of Medicine*. 2020;382(20):1883-1893. doi:10.1056/NEJMoa1915928

Barnes J, Ellis ML, Gilliam T, et al. Identification of Educational Gaps Amongst Physicians Who Manage Patients with Chronic Heart Failure. *Journal of Cardiac Failure*. 2016;22(8):S135. doi:10.1016/j.cardfail.2016.06.418

Gheorghiade M, Abraham WT, Albert NM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J*. 2007;28(8):980-988. doi:10.1093/eurheartj/ehl542

Guazzi M. Pulmonary hypertension in heart failure preserved ejection fraction: prevalence, pathophysiology, and clinical perspectives. *Circ Heart Fail*. 2014;7(2):367-377. doi:10.1161/CIRCHEARTFAILURE.113.000823

Lam C, Lim SL. Treating Heart Failure with Preserved Ejection Fraction. The Cardiology Advisor. Published January 20, 2019. Accessed July 23, 2020. https://www.thecardiologyadvisor.com/home/decision-support-in-medicine/cardiology/treating-heart-failure-with-preserved-ejection-fraction/

Lüscher TF. Heart failure subgroups: HFrEF, HFmrEF, and HFpEF with or without mitral regurgitation. *Eur Heart J*. 2018;39(1):1-4. doi:10.1093/eurheartj/ehx750

McIlfatrick S, Doherty LC, Murphy M, et al. "The importance of planning for the future": Burden and unmet needs of caregivers' in advanced heart failure: A mixed methods study. *Palliat Med*. 2018;32(4):881-890. doi:10.1177/0269216317743958

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644-657. doi:10.1056/NEJMoa1611925

Packer M, McMurray JJV, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. 2015;131(1):54-61. doi:10.1161/CIRCULATIONAHA.114.013748

Peacock WF, De Marco T, Fonarow GC, et al. Cardiac troponin and outcome in acute heart failure. *N Engl J Med*. 2008;358(20):2117-2126. doi:10.1056/NEJMoa0706824

Sacubitril and Valsartan [Prescribing Information].; 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207620s018lbl.pdf

Shen L, Jhund PS, Petrie MC, et al. Declining Risk of Sudden Death in Heart Failure. *N Engl J Med*. 2017;377(1):41-51. doi:10.1056/NEJMoa1609758

Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2019;381(17):1609-1620. doi:10.1056/NEJMoa1908655

Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2022;387(12):1089-1098. doi:10.1056/NEJMoa2206286

Streng KW, Nauta JF, Hillege HL, et al. Non-cardiac comorbidities in heart failure with reduced, mid-range and preserved ejection fraction. *Int J Cardiol*. 2018;271:132-139. doi:10.1016/j.ijcard.2018.04.001

University of Washington. Seattle Heart Failure Model. Accessed July 23, 2020. https://depts.washington.edu/shfm/index.php?width=2048&height=1152

Writing Committee, Maddox TM, Januzzi JL, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;77(6):772-810. doi:10.1016/j.jacc.2020.11.022

Yancy CW, Bozkurt B, Butler J, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):e240-327. doi:10.1161/CIR.0b013e31829e8776

CASE CHALLENGE

Case Presentation

Chantal is a 69-year-old woman who presents to the hospital with shortness of breath and leg swelling. She was diagnosed with chronic heart failure 4 years ago, with her most recent echocardiogram (2 years ago) showing an ejection fraction (EF) of 45%.

She describes worsening fatigue over the last couple of months and more shortness of breath while climbing the stairs in her house.

She also has a history of coronary artery disease (myocardial infarction 5 years ago, with one stent to the right coronary artery), hypertension (5 years) and hyperlipidemia (9 years). She does not have a personal history of diabetes. Previously, she reported no limitations in her functioning. She is currently maintained on furosemide 40 mg PO once daily, valsartan 160 mg PO BID, carvedilol 25 mg PO BID, and atorvastatin 40 mg PO once daily.

On physical examination, the patient's current height is 5 feet 4 inches and her weight is 179 pounds (last year 172 pounds), with a body mass index of 30.7 kg/m^2, considered obese by most national standards. Her heart rate is 72 beats per minute. Her blood pressure is 123/79. Her oxygen saturation is 90% on room air, which increased to 96% on 4L of oxygen via nasal prongs. On lung auscultation, there are faint bibasilar crackles with no wheeze. Examination of her lower limbs reveals pitting edema up to the mid-tibial region that disappears within 5 seconds. Other physical examination findings are normal.

Other laboratory results show that liver function tests, electrolytes, serum urea nitrogen/creatinine ratio, and microalbumin levels were normal. Chantal's lipid profile shows total cholesterol of 151 mg/dL, low-density lipoprotein cholesterol of 79 mg/dL, high-density lipoprotein cholesterol of 52 mg/dL, and triglycerides of 101 mg/dL.

Biometrics:

- Height: 5 feet 4 inches
- Weight: 179 lbs.
- Current BMI: 30.7 kg/m^2

Vital Signs:

- Heart rate: 72 bpm, irregularly irregular
- BP: 123/79 mmHg
- Respirations: 16/minute

Past Medical History:

- Hypertension for 15 years
- Dyslipidemia for 9 years
- Chronic heart failure for 4 years (Preserved ejection fraction)

Family History:

- Father with T2DM managed with oral agents
- Older brother with previous MI and history of hypertension

Social History:

- Non-smoker
- Alcohol use: non-drinker
- Occupation: office manager
- Spouse: married, 1 child

Current Medications:

- Furosemide 40 mg PO QD (see above)
- Valsartan 160 mg PO BID
- Carvedilol 25 mg PO BID (see above)
- Atorvastatin 40 mg PO once daily
- Potassium 20 mEq PO once daily

Known Allergies:

- None

Recent Laboratory Findings:

- A1C, 1 year ago – 5.9%
- Liver function tests, normal
- Electrolytes, normal
- BUN/Creatinine 24/1.1
- Total cholesterol, 151 mg/dL
- LDL-C, 79 mg/dL
- HDL-C, 52 mg/dL
- Triglycerides, 101 mg/dL

Question #1

During her admission, her N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels are followed. Other than heart failure, which of the following factors may cause elevated NT-proBNP levels?

A. Diabetes mellitus
B. Obesity
C. Renal failure/chronic renal disease
D. Atrial fibrillation

The 2013 guidelines[1] identified two biomarkers to help diagnose HF: brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). The updated 2017 guidelines[2] and 2022 guidelines[3] underscored the usefulness of these biomarkers, not only for diagnosing and evaluating acute and chronic heart failure, but also for differentiating pulmonary and cardiac causes of shortness of breath.

In patients with acute decompensated or chronic ambulatory heart failure, higher troponin levels are associated with worse clinical outcomes and higher mortality, while declining levels indicate a more promising prognosis.[4] When assessing heart failure, consider demand ischemia, NSTEMI, and MI with non-obstructive coronary arteries (MINOCA).

However, there are some confounding factors in natriuretic peptide testing:

- Renal failure/chronic kidney disease: plasma BNP and NT-proBNP concentrations are elevated in patients with renal failure and chronic kidney disease.[5]
- Obesity: Obese patients tend to have lower plasma BNP and NT-proBNP concentrations than nonobese patients.[6,7]
- Drugs: During treatment with the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril-valsartan, plasma NT-proBNP levels but not plasma BNP levels can be used to guide therapy.[8]
- Other cardiac conditions: Natriuretic peptide levels are elevated in some patients with non-heart failure conditions such as coronary heart disease, valvular heart disease, pulmonary hypertension, and sepsis.

As such, when using BNP and NT-proBNP, one should clinically correct for lower than expected levels in obese patients, and correct for higher than expected in patients with renal disease.

Of all the listed options in our question, renal disease/chronic renal failure falsely elevates BNP/NT-proBNP levels, thus making the correct answer C. As described above, obesity falsely lowers these levels. The remaining choices do not affect BNP/NT-proBNP levels.

This brings us to our next clinical question.

Question #2

Which of the following agents is recommended by the 2022 ACC/AHA guideline update for lowering risk of hospitalization and death in patients with chronic heart failure, in sinus rhythm with a heart rate ≥70 beats per minute, and already on maximally tolerated doses of beta-blockers?

A. Candesartan
B. Carvedilol
C. Ivabradine
D. Sacubitril/valsartan

In the most recent 2022 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) heart failure guideline update, both ivabradine and sacubitril/valsartan are recommended for use in patients with HF though with slightly different specific indications.[3]

Ivabradine affects heart rate alone, while having no effect on heart contractility or blood pressure. Specifically, it works by inhibiting the I_f ion current in the sinoatrial (SA) node. It is indicated for lowering hospitalization rates in worsening HF in patients[9]:

(1) with stable, symptomatic chronic HF with a left ventricular ejection fraction (LVEF) ≤35%,

(2) who are in sinus rhythm with a heart rate of ≥70 beats per minute, and

(3) who are taking maximally tolerated doses of beta-blockers or have contraindications to them.

Use of ivabradine is supported in the 2022 ACC/AHA/HFSA guideline update, primarily to reduce heart rate in patients with stage C HF and an LVEF ≤35% or less,[3] thus making the correct answer C.

In the SHIFT trial, patients' enrollment criteria reflect the above indication regarding reduced EF, sinus rhythm, elevated heart rate, and on maximally tolerated doses of beta- blockers. A total of 6558 patients were randomly assigned to ivabradine or placebo groups.[10] Patients were followed for a median of 22.9 months.

The primary endpoint (a composite of CV death or hospital admission for worsening HF) was significantly lower in the ivabradine group compared with the placebo group: 24% vs. 29% (HR 0.82, 95% CI 0.75–0.00, p<0.0001). This effect was largely driven by the reduction of hospital admissions for worsening heart failure. The authors concluded that this trial showed the importance of heart rate reduction, specifically with ivabradine, in the improvement of clinical outcomes in heart failure.

Overall, there were fewer serious adverse events in the ivabradine group compared with the placebo group. Though more patients in the ivabradine group had symptomatic bradycardia (5% vs. 1%; p<0.0001). Visual side-effects (phosphenes) were reported by 89 (3%) of patients on ivabradine and 17 (1%) on placebo (p<0.0001).

Of note, ivabradine is not indicated in acute decompensated heart failure.[11]

The other additional recommendation in the 2022 ACC/AHA guideline update surrounded the use of the new agent sacubitril/valsartan. This brings us to our next clinical question.

Question #3

For what indication and in which population is sacubitril/valsartan recommended in the 2022 ACC/AHA guideline update?

A. To reduce composite of CV death or hospitalization for worsening heart failure vs. placebo (in patients with reduced ejection fraction (EF)
B. To reduce mortality (in patients with diabetes mellitus)
C. To reduce composite of CV death or hospitalization for worsening heart failure vs. placebo (in patients with preserved EF)
D. To reduce all-cause mortality (in patients with preserved and reduced EF)

Sacubitril/valsartan is a new single tablet angiotensin receptor-neprilysin inhibitor (ARNI) indicated for lowering cardiovascular death and hospitalization in patients with NYHA class II-IV HF with low ejection fraction.[12] Within the 2022 guideline update, the authors note, "In patients with [heart failure with reduced ejection fraction (HFrEF)] and NYHA class II to III symptoms, the use of ARNI is recommended to reduce morbidity and mortality."[2]

Importantly, they prioritize ARNI over ARBs and ACE inhibitors in many cases.

If patients have chronic symptomatic HFrEF with NYHA class II or III symptoms and they tolerate an ACEi or ARB, they should be switched to an ARNI because of improvement in morbidity and mortality. An ARNI is recommended as de novo treatment in hospitalized patients with acute HF before discharge given improvement in health status, reduction in the prognostic biomarker NT-proBNP and improvement of LV remodeling parameters compared with ACE inhibitors/ARB.

Given this recommendation, the correct answer to this question is A. To monitor the efficacy of sacubitril/valsartan, decompensation of HF should be evaluated with NT-proBNP levels, with higher levels indicating increased HF.[13]

In the PARADIGM-HF trial, 8,442 patients with NYHA functional class II-IV HF with reduced EF (≤40%) were studied.[14] Researchers randomized patients to receive either sacubitril/valsartan or enalapril. Patients were followed for a median of 27 months. The trial was stopped early due to benefit, as the researchers found that the primary endpoint of cardiovascular (CV) death or HF hospitalization was significantly improved for the sacubitril/valsartan group compared with the enalapril group: 21.8% vs. 26.5%, respectively (HR, 0.80; 95% CI, 0.73 to 0.87; P<0.001).

Regarding the frequency of specific selected outcomes, when comparing sacubitril/valsartan to enalapril, the mortality was 17.0% vs. 19.8% (HR for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001). Of these patients, 13.3% vs. 16.5%, respectively, died from CV causes (HR, 0.80; 95% CI, 0.71 to 0.89; P<0.001). Similarly, sacubitril/valsartan reduced the risk of HF hospitalizations by 21% and decreased the symptoms and physical limitations of HF (P=0.001).

Adverse events within this trial showed that the sacubitril/valsartan group had higher proportions of patients with hypotension and nonserious angioedema. Interestingly, however, this agent was associated with lower proportions of renal impairment, hyperkalemia and cough than the enalapril group.

Of note, in 2021, the indication of sacubitril/valsartan was expanded to include those with preserved EF, based on the results of the PARAGON-HF trial. While this trial did not meet its primary endpoint, a secondary analysis found that a subset of patients with EF between 45% and 57% saw benefit.[15] Given the lack of treatment options in HF with preserved EF (HFpEF), the FDA approved this broadened indication.

Sacubitril/valsartan is associated with fetal toxicity, which is a class effect of medications affecting the renin-angiotensin system.[12] The most common adverse events associated with this agent are hypotension, hyperkalemia, cough, dizziness, and renal failure. Thus, these potential adverse events should be monitored for.

Other classes of medications have new evidence for their use in heart failure as well, including SGLT-2 inhibitors. Most recently, the EMPEROR-Preserved trial was published. This leads to the next question.

Question #4

In the EMPEROR-Preserved trial, which studied empagliflozin compared with placebo in patients with heart failure with **preserved** ejection fraction (NYHA class II-IV, EF >40%), what was the main outcome?

A. Significantly reduced composite of CV death or hospitalization for heart failure vs. placebo (in patients with and without DM)
B. Significantly increased mortality in patients without DM
C. Significantly reduced CV death for heart failure vs. placebo
D. Similar reduction in CV death and all-cause mortality as placebo

Current guidelines now recommend SGLT2 inhibitors for patients with HF, with or without diabetes.

In heart failure with **reduced** ejection fraction (HFrEF), certain SGLT2 inhibitors were already approved for use. Specifically, dapagliflozin and empagliflozin are approved for patients with HF with reduced ejection fraction, regardless of diabetes status, while canagliflozin is only approved for those with diabetes and HFrEF. These approvals are based on several clinical trials that demonstrated reduced rates of hospitalization and/or reduced deaths for patients receiving the SGLT2 inhibitor: DAPA-HF (HFrEF),[16] CANVAS[17] and EMPEROR-Reduced.[18]

However, in heart failure with **preserved** ejection fraction (HFpEF), so far there are not many phamacotherapies targeting HFpEF directly.

In February 2022, based on results of the EMPEROR-Preserved trial, empagliflozin had its indication expanded to include the treatment of HFpEF.[19]

In the EMPEROR-Preserved trial, researchers randomly assigned 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% to receive empagliflozin or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

This primary outcome event was significantly reduced in the empagliflozin group compared with the placebo group (13.8% vs. 17.1%, respectively; HR, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes.

The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.

In August 2022, results from the DELIVER trial were released, showing that in patients with preserved EF (EF >40%), treatment with dapagliflozin reduced the combined risk of worsening heart failure or CV death.[20]

In the DELIVER trial, researchers randomly assigned 6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin or matching placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death.

The primary outcome was significantly reduced in the dapagliflozin group compared with the placebo group (16.4% vs. 19.5%, respectively; HR, 0.82; 95% CI, 0.73 to 0.92; P<0.001). Worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.91); cardiovascular death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (hazard ratio, 0.88; 95% CI, 0.74 to 1.05).

Results were similar among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, and results were similar in prespecified subgroups, including patients with or without diabetes. The incidence of adverse events was similar in the two groups.

Within the availability of your region and healthcare system, it is important to incorporate your healthcare team and other specialists in the care of patients with heart failure. The primary care provider, at times with the help of a CV specialist, is in the best place to treat CV risk factors and incorporate newer agents into routine clinical practice. Clinicians can now choose from several therapies that have positive CV benefits in addition to their effects on blood glucose.[21]

These therapies have improved clinical outcomes for those with heart failure with or without comorbid diabetes and should be actively considered in each appropriate patient. The choice of therapy should always be discussed proactively with the patient to meet each patient's needs. The patient's clinical profile and safety/ tolerance considerations will aid treatment decisions and thus, providers and patients should weigh the risks and benefits of therapies.

Clinicians should remember dosing and usage considerations in patients with renal impairment. SGLT-2 inhibitors require dose adjustments with reduced estimated glomerular filtration rates. Guidelines also indicate that caution should be taken when initiating or increasing SGLT-2 inhibitors' dosage because of acute kidney injury risk.[22] As well, for patients taking sacubitril/valsartan, clinicians should monitor for impaired renal function and increasing potassium levels.[12]

Case Continues

Chantal's vital signs and respiratory status have been stabilized. You order a repeat echocardiogram to re-stratify her heart failure, given her heart failure admission and pulmonary/pedal symptoms of fluid overload.

This brings us to our final clinical question.

Question #5

Based on Chantal's clinical history and preferences, which of the following changes to her treatment regimen would be most appropriate to reduce her risk of heart failure events based on current evidence?

A. Add an SGLT-2 inhibitor and discontinue her beta-blocker

B. Add an SGLT-2 inhibitor to her existing regimen

C. Discontinue her beta-blocker

D. Add ivabradine to her existing regimen

The ACC/AHA has released a set of treatment decision pathways to make treating HF with reduced ejection fraction (HFrEF) simpler.[23] New recommendations were made for the use of SGLT2i in HF.

In symptomatic patients with chronic HFrEF, SGLT2i is recommended to reduce hospitalization and cardiovascular mortality, regardless of the presence of type 2 diabetes. SGLT2i can also be beneficial in patients with HFmrEF and HFpEF.

As discussed earlier, recent trial data show that SGLT-2 inhibitors positively impact HF hospitalization rates and mortality. Taking SGLT-2 inhibitors and beta-blockers together is not contraindicated. More importantly, beta-blockers prevent cardiac remodeling associated with heart failure, *providing a mortality benefit in heart failure patients*, as such they should be continued.[24]

Given that Chantal requires further treatment for heart failure, adding an SGLT-2 inhibitor is a reasonable option. Ivabradine is indicated in patients with heart failure. However, it is specifically indicated in patients with heart failure with **reduced** ejection fraction, with a heart rate ≥70 beats per minute who are in sinus rhythm.[11] This indicates the correct answer is B.

Other considerations include adding a mineralocorticoid receptor antagonist (e.g., spironolactone and eplerenone). These agents are associated with improved survival in patients with HF with reduced ejection fraction. Specifically, in the RALES trial, spironolactone showed a significant mortality benefit in patients with NYHA class III or IV HF and EF ≤35 percent.[25,26] The EMPHASIS-HF trial showed the benefit of eplerenone on reduced overall and cardiovascular mortality in patients with NYHA class II HF and either an EF ≤30 percent or LVEF >30 and ≤35 percent and QRS duration >130 ms.[27]

Case Continues

You and Chantal discuss the potential advantages and limitations of both classes of agents. You both decide that the SGLT2 inhibitor, empagliflozin, is a reasonable option given its favorable efficacy and safety profile and proven HF, CV and CKD benefits. She continues using her previous medications (including furosemide 40 mg PO QD, valsartan 160 mg PO BID, and carvedilol 12.5 mg PO BID) and begins taking empagliflozin 10 mg once daily.

With pharmacological interventions, you also help support lifestyle changes to improve her heart health. These interventions include weight-loss counseling, which may include the Dietary Approaches to Stop Hypertension (DASH) diet, and increasing omega-3 fatty acids, plant intake and physical activity.[28–30]

In 3 months, Chantal returns to the office and her breathing and lower limb edema have improved. Functionally, she has not quite returned to her previous exercise capacity, but is much improved. She can now climb one set of stairs without impairment. Her hemoglobin A1C has decreased slightly to 5.4%, and she reports no notable adverse effects since starting empagliflozin. You continue to monitor her renal function and note that a drop in eGFR to below 45 mL/min/1.73 m^2 would warrant discontinuation.[31]

Conclusions

HF is a serious condition with potentially devastating consequences. Its outcomes have remained relatively stagnant over the past years; however, new treatment options have emerged, showing promise. Still, PAs face knowledge gaps in the diagnosis and treatment of this condition. To treat HF effectively, it must first be diagnosed through effective history-taking and physical examination. Guideline updates have highlighted the use of investigational and newer biomarkers for diagnosis and disease stratification.

Evidence-based guidelines provide clinicians with a roadmap for providing patients with the best possible treatment. The implementation of these recommendations is crucial for maximizing the benefits of HF therapy in clinical practice. Similarly, type 2 diabetes is frequently comorbid with HF, so both conditions require effective co-management. SGLT-2 inhibitors have new evidence for their benefit in patients with heart failure, both with and without diabetes. Greater attention to all of these concerns will help patients derive maximum benefits from HF management and experience an improved quality of life.

CLINICAL PEARL

We hope you have enjoyed this *eCase Challenge*, and that you have increased your knowledge and confidence in diagnosing and managing patients with chronic heart failure. Chronic heart failure can be tricky to diagnose in its early stages. PAs must be mindful of careful history taking, especially regarding changing exercise ability and functional status. Echocardiography can help tease out the cause and type of heart failure, but heart failure remains a clinical diagnosis.

Upon diagnosis, the key is taking the initial time to explain what heart failure is and how this patient acquired it, and then how to manage it.

Remember to use your health care team to help in patient education.

Treatments for chronic heart failure are evolving. Ivabradine is recommended for lowering hospitalization rates and worsening heart failure in patients, one, with stable symptomatic chronic heart failure with a left ventricular ejection fraction of less than or equal to 35% or, two, those who are in sinus rhythm with a heart rate of greater than 70 bpm minute or, three, those who are taking maximally tolerated doses of beta-blockers or who have contraindications to them.

Sacubitril/valsartan and ARNI has shown positive results in lowering cardiovascular death and hospitalization in patients with N York Heart Association class II to IV heart failure with reduced ejection fraction.

More recently, SGLT-2 inhibitors have shown positive heart failure outcomes in patients with diabetes, and for some SGLT-2 inhibitors, even for patients without diabetes.

For heart failure with preserved ejection fraction, in February 2022, based on results of the EMPEROR-Preserved trial, empagliflozin had its indication expanded to include treatment of heart failure with preserved ejection fraction.

In August 2022, results from the DELIVER trial were released, showing that patients with preserved ejection fraction or those with ejection fractions greater than 40%, treatment with dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death.

But it's important not to forget the importance of lifestyle modification in helping patients with and at risk for heart failure. Key elements for counseling include smoking cessation, alcohol reduction, weight loss and perhaps sodium and fluid restriction.

Thank you again for your participation in this *eCase Challenge*.

References

1. Yancy CW, Bozkurt B, Butler J, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):e240-327. doi:10.1161/CIR.0b013e31829e8776
2. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136(6):e137-e161. doi:10.1161/CIR.0000000000000509
3. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18):e895-e1032. doi:10.1161/CIR.0000000000001063
4. Peacock WF, De Marco T, Fonarow GC, et al. Cardiac troponin and outcome in acute heart failure. *N Engl J Med*. 2008;358(20):2117-2126. doi:10.1056/NEJMoa0706824
5. Cataliotti A, Malatino LS, Jougasaki M, et al. Circulating natriuretic peptide concentrations in patients with end-stage renal disease: role of brain natriuretic peptide as a biomarker for ventricular remodeling. *Mayo Clin Proc*. 2001;76(11):1111-1119. doi:10.4065/76.11.1111
6. Das SR, Drazner MH, Dries DL, et al. Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study. *Circulation*. 2005;112(14):2163-2168. doi:10.1161/CIRCULATIONAHA.105.555573
7. McCord J, Mundy BJ, Hudson MP, et al. Relationship between obesity and B-type natriuretic peptide levels. *Arch Intern Med*. 2004;164(20):2247-2252. doi:10.1001/archinte.164.20.2247
8. Packer M, McMurray JJV, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. 2015;131(1):54-61. doi:10.1161/CIRCULATIONAHA.114.013748
9. Shen L, Jhund PS, Petrie MC, et al. Declining Risk of Sudden Death in Heart Failure. *N Engl J Med*. 2017;377(1):41-51. doi:10.1056/NEJMoa1609758

10. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376(9744):875-885. doi:10.1016/S0140-6736(10)61198-1
11. *Ivabradine Prescribing Information*. Amgen Inc.; 2019.
12. *Sacubitril/Valsartan Prescribing Information*. Novartis Pharmaceuticals Corporation; 2015.
13. Mair J, Lindahl B, Giannitsis E, et al. Will sacubitril-valsartan diminish the clinical utility of B-type natriuretic peptide testing in acute cardiac care? *Eur Heart J Acute Cardiovasc Care*. 2017;6(4):321-328. doi:10.1177/2048872615626355
14. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077
15. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2019;381(17):1609-1620. doi:10.1056/NEJMoa1908655
16. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. Published online September 19, 2019. doi:10.1056/NEJMoa1911303
17. *INVOKANA [Prescribing Information]*.; 2018. Accessed December 18, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204042s027lbl.pdf
18. FDA fast track designation for treatment of heart failure | Press. boehringer-ingelheim.com. Published November 17, 2019. Accessed November 17, 2019. https://www.boehringer-ingelheim.com/press-release/fda-fast-track-designation-chronic-heart-failure
19. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021;385(16):1451-1461. doi:10.1056/NEJMoa2107038
20. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. Published online August 27, 2022. doi:10.1056/NEJMoa2206286
21. Das SR, Everett BM, Birtcher KK, et al. 2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2018;72(24):3200-3223. doi:10.1016/j.jacc.2018.09.020
22. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2020. *Diabetes Care*. 2020;43(Suppl 1):S98-S110. doi:10.2337/dc20-S009
23. Writing Committee, Maddox TM, Januzzi JL, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;77(6):772-810. doi:10.1016/j.jacc.2020.11.022
24. Sabbah HN. The cellular and physiologic effects of beta blockers in heart failure. *Clinical Cardiology*. 1999;22 Suppl 5:V16-20.
25. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *The New England Journal of Medicine*. 1999;341(10):709-717. doi:10.1056/NEJM199909023411001
26. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *The American Journal of Cardiology*. 1996;78(8):902-907. doi:10.1016/s0002-9149(96)00465-1
27. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *The New England Journal of Medicine*. 2011;364(1):11-21. doi:10.1056/NEJMoa1009492
28. Djoussé L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. *JAMA*. 2009;302(4):394-400. doi:10.1001/jama.2009.1062
29. Agha G, Loucks EB, Tinker LF, et al. Healthy lifestyle and decreasing risk of heart failure in women: the Women's Health Initiative observational study. *Journal of the American College of Cardiology*. 2014;64(17):1777-1785. doi:10.1016/j.jacc.2014.07.981
30. Del Gobbo LC, Kalantarian S, Imamura F, et al. Contribution of Major Lifestyle Risk Factors for Incident Heart Failure in Older Adults: The Cardiovascular Health Study. *JACC Heart failure*. 2015;3(7):520-528. doi:10.1016/j.jchf.2015.02.009
31. Empagliflozin [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2018.

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Question #1
When examining a patient and hearing an S3 heart sound, a primary care provider should always consider the possibility of which of the following?

- **A.** Atrial fibrillation
- **B.** Cardiomegaly
- **C.** Hypertension
- **D.** Volume overload

Question #2
Which class of antihypertensives has NOT been shown to improve mortality in HF?

- **A.** ACE inhibitors
- **B.** Angiotensin II Receptor Blockers (ARBs)
- **C.** Beta-blockers
- **D.** Loop diuretics

Question #3
Which of the following are other conditions, aside from heart failure, that may cause elevated BNP?

- **A.** Valvular heart disease
- **B.** Syncope
- **C.** Hypotension
- **D.** Cerebrovascular accident

Question #4
The 2022 ACC/AHA guidelines update recommend an angiotensin receptor-neprilysin inhibitor (ARNI) for which specific patient populations?

- **A.** Chronic heart failure and left ventricular dysfunction
- **B.** Chronic heart failure with reduced ejection fraction, NYHA Functional Class II-III, who are able to tolerate an ACEi or ARB
- **C.** Heart failure in patients with type 2 diabetes (and established cardiovascular disease or multiple cardiovascular risk factors)
- **D.** Symptomatic chronic heart failure, with ejection fraction ≤ 35%, in sinus rhythm, with HR ≥ 70 bpm, and already taking maximally tolerated doses of beta-blockers or contraindication to beta-blockers

Question #5
Which of the following is true about SGLT-2 inhibitors?

- **A.** Certain agents have shown benefit in clinical trials for heart failure with preserved ejection fraction without diabetes
- **B.** Common adverse events include hypertension and palpitations
- **C.** No evidence for benefit in heart failure with reduced ejection fraction
- **D.** No evidence for benefit in chronic kidney disease

Question #6
What consideration must be made when prescribing an ARNI?

- **A.** Hypertension is a potential adverse effect
- **B.** ARNIs are preferred over ACE inhibitors and ARBs in many cases
- **C.** In patients taking beta-blockers, the beta-blocker must be discontinued
- **D.** Monitor BNP levels to assess therapeutic response

Question #7
Which of the following can falsely LOWER brain natriuretic peptide (BNP) levels? When examining a patient and hearing an S3 heart sound, a primary care provider should always consider the possibility of which of the following?

- **A.** Angiotensin receptor-neprilysin inhibitor (ARNI)
- **B.** Pulmonary hypertension
- **C.** Myocardial infarction
- **D.** Obesity

Question #8
Which of the following has NOT been shown to improve mortality in heart failure (HF)?

- **A.** ACE inhibitors
- **B.** Beta-blockers
- **C.** Loop diuretics
- **D.** Sacubitril/valsartan

Question #9
Which of the following tools is considered "gold standard" for the diagnosis of HF?

- **A.** Brain natriuretic peptide (BNP)
- **B.** Cardiac CT scan
- **C.** Echocardiogram
- **D.** EKG

Question #10
The 2022 ACC/AHA guidelines update recommend which agent for patients with chronic HF with reduced ejection fraction, NYHA Functional Class II-III, and who are able to tolerate an ACEi or ARB, to reduce risk of hospitalization and death from HF?

- **A.** Canagliflozin (SGLT-2 inhibitor)
- **B.** Empagliflozin (SGLT-2 inhibitor)
- **C.** Ivabradine
- **D.** Sacubitril/valsartan (ARNI)

Question #11
Which of the following is true about SGLT-2 inhibitors?

- **A.** Some agents have demonstrated benefit in heart failure with preserved ejection fraction without diabetes in clinical trials
- **B.** Common adverse events include hypertension and palpitations
- **C.** No evidence for benefit in heart failure with reduced ejection fraction
- **D.** No evidence for benefit in chronic kidney disease

Question #12

A 56-year-old Caucasian man with a history of a large anterior wall myocardial infarction and an EF of 35% presents to your clinic. He notes shortness of breath after climbing two flights of stairs and after walking four or five blocks but denies PND or orthopnea. On examination he is in sinus rhythm with a resting heart rate of 95 beats per minute. He takes aspirin, atorvastatin, metoprolol, lisinopril, and eplerenone. After diuresis, which of the following is the best step in managing his heart failure?

A. Start hydralazine and isosorbide dinitrate
B. Start digoxin
C. Start ivabradine
D. Hospitalization for intravenous dobutamine infusion

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