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ADHF Diagnosis & Risk Stratification in the Emergency Setting
W. Frank Peacock, IV, MD

Management of AHF: Review of Contemporary Therapies and Current Guidelines
J. Douglas Kirk, MD

Future Directions in ADHF Treatment
Peter E. Carson, MD

Question & Answer Session

Live symposium was supported through an unrestricted educational grant from Otsuka America Pharmaceuticals, Inc.
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Learning Objectives
At the completion of this activity, participants will be able to:

• Review the definitions, prevalence and presentations of ADHF and AHF syndromes in the emergency department

• Compare currently available evidence-based clinical practice guidelines for ADHF and AHF for the emergency setting

• Identify optimal care pathways and multidisciplinary strategies for best patient outcomes for ADHF and AHF in the emergency setting

• Critically discuss current and future trends in the treatment of ADHF and AHF

Program Accreditation

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Target Audience:
This activity is intended for emergency physicians, nurses and nurse practitioners, cardiologists, and other specialists who care for patients in emergency settings with acute heart failure.

Activity Description
Estimated time for completion: 1 hour
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This CME program consists of text and a various presentation graphics taken from the individual faculty presentations. You should read the information, refer to the references, and complete the self-evaluation post-test in order to be awarded CME credit.
ADHF Diagnosis & Risk Stratification in the Emergency Setting

W. Frank Peacock, IV, MD

According to the demographics on heart failure, we spend more as a country on heart failure than any other disease. Heart failure is the number one reason people are admitted to the hospital in the United States. It's the number one reason they come back for a second admission. When heart failure shows up at the hospital, it comes as shortness of breath. It doesn't say heart failure across their forehead. And when you think about shortness of breath, what — everybody say, "Well, it's heart failure." Well, that's what you get at the end. When you start, there are a whole bunch of diagnoses; you've got to sort it out. And you have to sort it out quickly, and you have to be right. And I'm going to go through the process. But ultimately we're trying to get to that little slice on the bottom there called heart failure. And one of the problems with heart failure is that it is not a — it doesn't have one thing, you say, oh, you're done. It is a syndrome. No single test will determine the diagnosis.

Looking at the diagnosis accuracy in the published literature, in primary care the diagnosis has been reported to be falsely positive in over — in up to 50 percent. And there was another study done in an outpatient clinic where the correct diagnosis was right in 18 percent of women and 36 percent of men on the first time. Now, I'm not picking on primary care. When they show up in the emergency department they're a lot sicker, so it's a lot easier. And you can see that the confounders there are gender and obesity, both of which are common in the United States.

So the first thing we do in the ER is get an EKG, and that's because we're required to get at chest pain in 10 minutes, so everybody's got an EKG. And unfortunately the EKG in heart failure is about useless because it provides long-term prognostic info only — they'll tell you in five years if the patient has increased QRS duration they'll be dead. But the 5-year outcome does not help the emergency department. So unless there are ischemic changes, the EKG — we're just done with it.

So what do we do? We do an EKG. We do a physical exam. The physical exam is diagnostic in about a third. That leaves two-thirds of the people out in the cold. We do a chest x-ray. It's nondiagnostic in a quarter, and it also has some significant limitations. We can do other tests — blood gases and those sort of things that are absolutely useless in heart failure. If you want to know what is the best finding of heart failure, it's the history.

But here's the challenge for the emergency department. What if they're too sick to give a history? I mean, really sick people can't talk very well. What if they speak French? I don't speak French. What if they are drunk? The reality in the emergency department is some of my patients are. And when's the last time you got a great history from a 90-year-old? It's just not going to happen. And what if they're a nut and just want a warm place to sleep, or they're anxious and they just want to talk to somebody?
And what if it's Sunday night? Sunday night's the busiest night in the emergency department, and anybody who works there knows what it's like. This is what it looks like. And the challenge there is I've got seven minutes of patient contact time on Sunday night to get through and make an accurate diagnosis where history is the best. And how much time do you have when they're doing this, when they're laying flat? How good a history can you take?

So the next thing we ask, "Well, how -- are you short of breath?" And they say, "Yes." And if you look at sensitivities and specificities, you can flip a quarter and write on the chart, "It came up heads," and you'll be as accurate as shortness of breath. Shortness of breath is a useless finding in heart failure. It's what they all have. If you look at retrospective heart failure databases, 90 percent will have presented with shortness of breath. But as a predictor of a heart failure diagnosis, it's as good as a quarter.

Orthopnea is the other thing you ask: "Do you get short of breath when you lay down?" And if they do, that has a specificity of 88 percent, so that's pretty good. And sensitivity is useless. It misses a lot. There are plenty of people walking around with heart failure who do not have orthopnea.

The next piece is the S3, the extra heart sounds. So the S3 and S4, and if you remember from your early physiology, they come in diastole, and what you're looking for is the early diastolic extra heart sound. The advantage of this is when it's positive it's very helpful. The S3 has a specificity of 99 percent with a stethoscope. You can take it to the bank. The problem is that in an ER environment, you've got the drunk next door who's screaming about his mother and the kid down the hall, and you can't hear. And that's why the sensitivity is 20 percent.

We miss four out of five S3's. There is some new technology that allows us to do that better, and I'll show that to you in a minute. Rales, we all listen for rales. The problem is in old people, rales are very common, so the sensitivity is once again as good as a quarter. When they're there, they're helpful; when they're not, they're not very good at all.

And next, are there really good findings of jugular venous distention (JVD). You look at the specificity is 94 percent. If you can see JVD, you can take it to the bank. Probably a really good chance the patient has heart failure. The difficulty is we're in the middle of an obesity epidemic, and that's the big confounder for JVD. So the sensitivity runs about 40 percent. It's worse than a quarter. So when it's there it's helpful; when it's not there you don't learn anything.

And the last piece is edema, which sort of is considered the harbinger of heart failure. Look at the numbers. It's the 60-60 club: neither sensitive nor specific. There are plenty of people who show up in the emergency department, especially in the summer, with big feet. And your answer is they're big feet.

So here's the chest X-ray data. It's an extremely blunt tool. It misses 20 percent, one out of five, of echocardiographically proven cardiomegaly. All you have to be is a little bit turned and the heart doesn't look big anymore. And it misses a third of pleural effusions if they're done supine. How do you do
coughing, which is common in sick people? They lay on the bed. You take their chest x-ray. They do not stand up and get a good PA and lateral. If you do them portable, it's even worse. And reality be told, we do most of our chest x-rays portable because they're sick, and they don't want to -- the nursing staff and I don't want to take them down the hall. And they're hooked to all that spaghetti, and they're on the IV and the monitor, and it's just -- so we do them portable and miss a bunch. So now I'm 15 minutes into my case, which is all the data that I'm allowed to have because that's all you can get back in 15 minutes. I want to show you the time-dependent accuracy.

We just finished a study of 1,000 patients in the emergency department. Fifteen minutes into the door they asked the doc, 'What have they got?' The gold standard with two cardiologists at the end of the visit, five days later, and we looked at 30-day follow-up. An emergency doc was accurate in the first 15 minutes in a third. With history and physical, we missed two-thirds. And so that becomes real important for treatment.

In a study of 8300 patients transferred to the hospital by EMS, ultimately 500 were shown to be heart failure. And they got nitroglycerin, morphine, and furosemide. Now, I'm going to rant and rave about morphine. I think it's a terrible drug. It doesn't have any role in heart failure. However, this was a study done in 1992, so it was the standard of care. So 240 people got treated, and if they got treated it took an extra two minutes in the ambulance to treat them. And if they received -- if they had heart failure and they received treatment, their odds of survival was a 250 percent increase. Early treatment absolutely works. We should all do it.

Here's the scary part. There were 106 of those patients who ultimately got treatment turned out not to be heart failure, and their mortality went from 3.8 percent to 13.6 percent. So if you have chronic obstructive pulmonary disease (COPD) and you get heart failure treatment, it's not cool. And that's a 250 percent increase in mortality. So if you're right there's a 250 percent increase in survival, and if you're wrong there's a 250 percent increase in mortality. So there's a two-way sword that you'd better be quick and you'd better be fast -- and you'd better be accurate.

We're 15 minutes in our case, and that's about the time the B-type natriuretic peptides (BNP) can come back. And what you see here is BNP synthesis. On the right side of this is proBNP. It's released in the wall stress of the myocardium. It is the N-terminal proBNP, or BNP. There are assays for both of those, and they are very accurate for ruling out heart failure. On the left side of this graph represents ANP levels. And if you're a fish in the water, you can see the ANP level's about 800. And think about it, that if you live in a salt water environment, you've got salt water leeching into you all the time, if you don't pee salt water, you're going to drown. It seems crazy that fish would drown. And it doesn't because it's got a ton of natriuretic peptides.

But as you move up the evolutionary scale to amphibian and reptiles, you can see those ANP levels drop. So by the time you're a mammal there's only two times in your life your natriuretic peptide
levels should be up, and that is during birth, as you shift from fetal to adult circulation, or pathologically. And that's why we can use it as a diagnostic. Conversely, renin is the darker yellow there. It goes up as you move up the evolutionary scale, and the reason is because we're out of the water. We walk around. We need to hold salt water inside of us. If we lose it, we'd be dehydrated to death.

When you look at BNP levels by diagnosis, you can see that in heart failure, it's about 1,000, whereas people who had COPD it was about 86. So a great discriminator early in the course. If you look at accuracy of physician assessment — this is a receiver operating characteristic curve — and if you look at the red dot in the left upper corner, that is where the perfect test would go, would be aligned. So you want to be as close up to that dot as you can. And the red line is doctors with their clinical judgment, and the blue line is doctors considering NT-proBNP. So what you see is that using natriuretic peptide gets you closer to that red dot. So this is the function of it. It's a better test for the patient.

I'm going to talk a little bit about mortality. This is BNP levels at the door. This was published by Gregg Fonarow and me about three months ago. And what you see, the higher the BNP level in that top graph is 1700, the mortality this week — this is not five years from now — the mortality this week is 6 percent. What does that look like in terms of your hospital? The death from a myocardial infarction in most hospitals is 4 percent. This is 50 percent higher. So if you have a big high BNP, you need to worry about that patient. BNP can be confounded by two things. One is renal failure. And what this is, is as you go across this graph from left to right, when you get to the right side, the kidney is essentially dead. That's a glomerular filtration rate (GFR) less than 30. And you can see that in both of the groups, with and without heart failure — without heart failure is the little orange ones, and the tall ones are with heart failure — that it goes up, so the more your kidneys are dead, the higher your BNP.

There's a big discrimination between these heart failure and non-heart failure populations. And we use a cut point of about 200 for BNP to say, "Well, even though they have some renal insufficiency, they still cannot be ruled out for heart failure." The other one is obesity. If you have a body mass index greater than 35, your BNP will be falsely low. This is really important. So you see somebody who's 350 — I work in Cleveland. We have a huge obesity problem. So you see someone who's 350 pounds, their BNP will come back and it'll be 200. And they look exactly like heart failure. And the answer is, they are. Because it's markedly decreased in the setting of high BMI.

The point being here is there are two things you can do. You can either double the cut point or double the BNP level. That's what I do. If it comes back at 200, I say, "Well, it's actually 400" in people with a high BMI. So this is how it turns out when you're all said and done. This — if you look on the left here, we can say that patients with a BNP less than 100 or an NT-pro less than 300 are very unlikely to have heart failure, less than 2 percent. You need to think of a different diagnosis causing that patient's shortness of breath.
If those are higher, if the BNPs more than 500 or the NT-pro is greater than 900, heart failure is very likely, and you can initiate treatment. In the gray zone – 1- to 500 BNP and 3- to 900 for NT-pro – you've got to work it out. You don't have a clean answer. You need to do a chest x-ray. You need to do a Q scan or CT angiogram, or do something additional – get an echo – to figure out what the diagnosis is.

When you use these markers for accuracy, what you can see here is we take the misdiagnosis rate, which in this on history and physical in this study was 25 percent, and you add BNP to it, now the misdiagnosis rate is 18 1/2 percent. We're not done, but it gets us right down to where we're wrong only one out of five times.

Now, this is a new device that's out. It's called the AUDICOR. And what it does is to substitute a microphone for the V3 and 4 leads in the EKG. You still get an EKG, but it allows you to use some digital technology. You hear the heart sound. And then you can look at the box on the right is the actual tracing itself, and it says S3 in that little wiggly line. And I don't make any pretenses that I can read these wiggly lines, but if it says S3 in the box in the middle at the top there, then you know that patients has an S3. And this does a lot more sophisticated sound analysis and it's a lot better at reading that background noise than I am.

When you look at the presence of an S3 versus left ventricular and diastolic pressure, the louder is the S3, the higher is the left ventricular and diastolic pressure, in other words, the harbinger of heart failure. The thing you need to know is that the S4, in the dark purple there, is much more common as you get older. This is age across the bottom. The S3 disappears. So when you're 28, you might have an S3. It happens in about a third of patients. But by the time you're in the heart failure years, you're 50 or 60 years old, an S3 is not a common event. It happens in less than 5 percent of patients.

The BNP is sensitive – BNP under 100 is highly sensitive (95 percent). The specificity is only 64 percent, so not the greatest for ruling in. It's a great test for ruling out HF at low levels, but if you add a BNP that's really high, now you're at 93 percent specificity. So the message here is that the BNP is really good when it's a low level rule-out, but we need something specific to add, and that's where the S3 comes in.

Sean Collins and I looked at several hundred patients – about 400 in total when we were done – but this is the analysis done in 133. And we said, "Well, let's see where the ER call it heart failure and the – or the ER said there wasn't heart failure and the final diagnosis five days later that says it was." And we ended up with 44 patients out of the total in that box there. We went back and looked at those 44, and 15 of them had an S3 that we didn't hear. And the point of that is if we would have known, we could have done the right thing for the patient: admitted them in the hospital, but as well started treatment.

When we went back and looked at those misses themselves, what it was, there was a three times incidence of COPD, that I called a COPD. All these
patients had lower BNPs, so they were in the gray zone, which was the challenge, and they stayed in the hospital a day longer. So there’s a penalty for missing the early diagnosis. If you want to put this in terms of likelihood ratios, BNPs under 100, you’re done, the likelihood ratio is .1, and that means you do not have heart failure. If you go into that BNP gray zone between 100 and 500, you can see the likelihood ratio is 9, and that gets you into the area where you can start considering treatment. So the gray zone disappears.

I’m going to talk a little bit about risk stratification. One of the controversies in heart failure is troponin. Everybody says, “Oh, troponin doesn’t mean anything. It’s always elevated in heart failure patients.” And I want to disabuse you of that. This is an analysis of 14,000 patients that we did with positive troponins. And what you’re looking at here is that if the troponin is positive at presentation, the mortality is 8 percent. That’s twice of a myocardial infarction. If the troponin is negative, it’s about 2 1/2 percent. More people intubated, they stay longer in the hospital, they stay longer in the ICU.

An elevated troponin in the setting of heart failure is evil. It is not a normal thing. And the higher it is, the worse they do. And this is – you use both troponin I and T, in different colored bars. The point is you can see the shape of the curve: The higher the troponin, the worse they do. And this is the Kaplan-Meier curve. This is the death per day, and it separates at one day. So this is an acute, evil marker of death in a heart failure patient. This is coming out in the New England Journal in about two weeks.

Troponin can be used with BNP. If you look at the BNP being low and the troponin low, the risk of death is 2 percent. If both are high, the risk of death is 10 percent, and then in the middle it’s about 4 1/2 percent, either one being elevated – and elevated here was considered greater than 840 on your BNP – and the troponin was positive, meaning it wasn’t zero.

The other important piece is renal function. This is the ADHERE CART analysis (Figure 1), where they stratify patients by what is the most important predictor. Everyone said, “Oh, it’s troponin, it’s injection fractions, age, it’s something else.” It’s actually blood urea nitrogen (BUN). If your BUN is greater than 43, your risk of death this week is about 10 percent, that box on the right. And if you add to that a systolic blood pressure of 115 or lower, your risk of death is now about 15 percent, and an elevated creatinine, it’s 22 percent, one in four dead this week.

Renal function becomes critical. And I’ll tell you right now that patients in your hospital, the BUNs are 50 on a regular medical floor. And my opinion is
that is not right. If your BUN is up that high, you
should be getting aggressive care because that's a
death rate twice of a myocardial infarction. And your
CCUs are full of people with lower death rates.

This is what we do at my hospital. You show up at
the door, age greater than 40 and asthma not clearly
present. You automatically get an EKG, a troponin,
and a BNP. They're all done at point-of-care. By the
time I see that patient 15 minutes later, I'm ready to
make a decision. I talk to them for a few minutes, and
we're done. If they have a BUN less than 30 or blood
pressure greater than 160 at presentation – these
come from a couple studies that show these people
do very well. They go home in 24 hours. They don't
die. They don't come back within a month. Or if the
BNP is less than 500, that's the low-risk group. Now,
we may keep them and hold them overnight and take
a couple liters off of them, but this is a low-risk group.
They do well. BUN greater than 43, low blood
pressure, high creatinine, these people do terrible, or
BNP greater than 1700. They should go to a unit and
get aggressive care. And the S3 in the middle if you
have it pushes you to the right, as well. So you're left
with a little group in the middle, that's your gestalt
group. We don't have that completely worked out. But
we certainly have the parameters to pick out heart
failure and make a decision where it goes.

In summary, heart failure is a hard diagnosis.
Errors are common. They are time-dependent. The
longer I have the patient, the more accurate I am.
The problem is that the longer I have the patient
and they're not getting treated, the patient's not
benefiting. We've got to be fast, and we've got to
be right.
Management of AHF: Review of Contemporary Therapies and Current Guidelines

J. Douglas Kirk, MD

I will continue this whirlwind tour through heart failure with basically covering some of the contemporary management strategies, as well as the current guidelines. As Frank alluded to, many of these guidelines are lacking and don't really hit the mark with respect to the acute management of heart failure that we see in the emergency department. The goals of therapy for ADHF are predominantly for us in the emergency department to relieve symptoms, and obviously that for the most part are patients who present with dyspnea, as Dr. Peacock has just described. We also want to attack the congestion that these patients have, both in the pulmonary vasculature, as well as in the systemic vasculature, predominantly with general edema.

We also want to improve hemodynamics. And again, this for the most part is really a target towards reducing left and right heart filling pressures because those are what have led to this pulmonary congestion and the symptoms that the patients typically present with. Improving cardiac output may be important, but it may not be important, as well. Peter may talk about this further in a moment. But that probably shouldn't be our predominant target as much as reducing filling pressures.

The most important thing that Frank just kind of gave you a little segue to this is that you need to do all this, but you can't hurt the kidneys because if you hurt the kidneys, you're going to kill the patient. And I think that's becoming more and more clear, and I'll show you some evidence to support that. So if you look at a number of studies that have looked at the relationship between worsening renal function and the management of ADHF, you'll see, whether or not you look at creatinine bumps of greater than .3 or .5, or increases in creatinines greater than 2, that all of these are related to an increase in mortality.

Forman and colleagues looked at 1,000 patients who were admitted with ADHF. This was a multicenter trial. And this was defined as a creatinine increase of greater than .3, and this was seen in about 27 percent of patients within just a short time after admission. And the particulars of this worsening renal function were probably what you'd expect in the most part: a prior history of heart failure. As we know, many people with heart failure continue to return with heart failure, and they have a gradual decline in both their function, as well as in their survivability from the subsequent admissions; if they had diabetes; or if they admission creatinines greater than 1.5; or in this study, in fact, a blood pressure that was exceedingly high. Those were all patients who had a sense -- or a more common sense of increasing their risk of renal dysfunction.

Regarding the relationship between this worsening renal function and hospital death, it is dramatically worse with an adjusted relative risk of approximately 7.5 for hospital death; a complicated hospital course was about twofold higher; and length of stay, which we all know is quite important to us in this era of
resource management, was about threefold higher if these patients developed worsening renal function during this hospital admission.

We have numerous therapies that have been investigated, and we’ve identified a number of them that improve outcomes for heart failure patients when we use them for their management. But what you’ll look here, whether you look at those that are associated with improved survival – such as ACE inhibitors or ARBs or beta blockers or aldosterone antagonists – or those that reduced hospitalization, what’s the striking part of this is that these are none of the drugs that we use in the emergency department to treat heart failure. There really is no proven benefit to the things that we typically use, which I’ll show you here in just a few moments, to treat heart failure. These really are all predicated and targeted at the outpatient chronic management of heart failure. And that’s a real problem for us in the ED.

I’ll give you a snapshot of what our current pharmacologic armamentarium is to treat these patients. It starts with diuretics. And most of us, if you look at the ADHERE database or any of the registries of heart failure, you’ll see that a predominant tool for treating these patients are diuretic therapies. And that’s really targeted to reduce the extracellular fluid volume. We use IV loop diuretics predominantly, but occasionally we’ll use diuretics, such as metolazone or thiazides that affect the proximal tubule to effect a more rigorous diuresis, particularly if these patients have diuretic resistance and we’re having to use exceedingly higher doses of loop diuretics to effect the same amount of urine output. Now, the problem with this is that it may unfavorably affect renal function. As we know, that might be tied directly to poorer outcomes.

We also use vasodilators to reduce filling pressure. This is predominantly true in those patients who present with acute pulmonary edema and are often quite hypertensive. The agents we use here predominantly are nitroglycerin, nesiritide to a lesser degree, and nitroprusside to a much lesser degree unless the patient is markedly, markedly hypertensive. We all know, or I suspect most of you know that there are safety concerns with at least one of these agents, nesiritide, which is certainly being investigated. And so it’s kind of curtailed some of the use of that particular agent for this group of patients.

Last but certainly not least are the inotropes. Now, I think any of us who have trained back in the past 20 to 25 years, this was really the mainstay – one of the mainstays of therapy, even for the patients that we typically see in an emergency department that don’t have cardiogenic shock.

We know now that there are substantial safety concerns with using inotropes to treat the garden variety, if you will, heart failure patient. And these consist of sympathomimetic agents that you’re all familiar with, as well as some phosphodiesterase inhibitors. They’re very effective if the patient has a frank low cardiac output state or cardiogenic shock, but they’re very ineffective and in fact can be harmful in the patients that don’t have these presentations. And of course this only affects about 5 percent or so of the patients that we typically see in the emergency department. So they’re really not a
predominant tool for us to use currently.

If we hone down on the diuretics, we're going to see in the next couple of minutes here, I'm going to kind of pick on the drugs, if you will, and show you some of their weaknesses and what I think is fertile ground for further research and further investigation about what's the optimal use of these agents and in which particular patients. So if you look at diuretics, the thing that's interesting is that although with use them in great amounts, there really are no randomized clinical trials (RCTs) that show the efficacy of diuretics for the treatment of heart failure. That's very surprising I suspect for most of you. But what we do know is that there is pretty decent data that shows it actually impacts GFR in a negative way: It decreases it, it may activate neurohormones, it may cause re-accumulation of sodium, which often leads to diuretic resistance.

I'm sure everyone has seen this in your practice, or you've seen in your hospital us using exceedingly higher doses of diuretics to try to affect the same amount of diuresis in these patients. We give hundreds and hundreds of milligrams of furosemide at a time to try to squeeze those kidneys to get some urine out. And unfortunately that leads to negative effects in the long run for these patients. And that negative impact on clinical outcome actually can be both with the amount of resources you consume, but more importantly is actually that you can increase the mortality of these patients.

If you read heart failure literature or you go to any of these talks, you'll see this slide frequently. I think it's a great slide. This is a study by Gottlieb that looked at patients who got 80 milligrams of intravenous furosemide, which is not an uncommon dose, but a little on the high side for most de novo patients, but not uncommon. In fact, this is what most of our paramedic units use in the field for patients they suspect have ADHF. But they looked at these patients and they measured their GFR as a response to this versus placebo. And they also measured their urine output. And as you can see in the little box to the left, the placebo group had really little – small change if any in the GFR, and really had no effect on urine output, whereas the IV furosemide, while it did effect a very brisk diuresis, about 1600 cc's of urine in eight hours, it also resulted in about a 20 percent drop in the GFR.

And as I showed you earlier, a drop in the GFR is not what we're trying to do with these patients. In fact, if you look at the study by Hasselblad, this comes from the ESCAPE database, this is a post hoc analysis that looked at the relationship between diuretic dose and mortality, you can see a pretty sharp increase in mortality in these patients treated with diuretics. You see the inflection point. It's really at a dose that most of us not uncommonly use: right around between 100 milligrams of furosemide up to around 200 milligrams. You can see a sharp increase in the mortality rate of these patients. So again, using high doses of diuretics to affect the treatment change that you're looking for – i.e., a reduction in congestion – may be good on the front end – i.e., in the emergency department – but you may be mortgaging the future of these patients on the back side because you've affected their renal function.
Moving on to vasodilators, again, these are very effective agents in people with high filling pressures, and again not particularly if they have significant hypertension. But nitroglycerin and nitroprusside are fraught with some difficulties in the management. Nitroglycerin can be very effective, but there are some side effects, it does require titration, tachyphylaxis or tolerance does develop fairly quickly with relatively small doses, so you have to continue to uptitrated, and then we all know of the concerns or problems with headache in these patients, as well. Nitroprusside is equally effective, but again, a very difficult drug to titrate because of its effect on the blood pressure, making patients hypertensive.

These often require ICU monitoring and frequently arterial lines. And it also has some negative impact on patients particularly if you have acute coronary syndrome that there may be some relationship with increased mortality in those patients who happen to have heart failure, as well. Nesiritide I mentioned earlier, very effective at lowering the wedge pressure, very effective at lowering – improving dyspnea. But there is some concern that’s currently being investigated about an increased signal of mortality and renal dysfunction. And the recently released FUSION-2 study by Clyde Yancy showed that it really had no favorable effect on mortality or renal function. You can look at that as the glass half-empty or the glass half-full. I would say it’s actually half-full because the patients improved symptomatic-wise and there was no increased safety signal. So that was a good thing, I think, in the big picture. And again, this is being studied further under a current trial that’s being investigated.

Inotropic therapy is likewise fraught with some complications, particularly increased mortality as well as aggravation of the arrhythmogenic potential for these patients, increasing heart rate and neurohormonal activations, as well. So again, these drugs while they can be quite effective in that cardiogenic shock patient really don’t have much role in the again garden variety patient with ADHF we see in the ED.

If you look at the broad scope of this problem, as I’ve already described to you, there’s no good RCT data to support these drugs’ use. And we’ve showed you that of all the drugs that improvement mortality, none of these drugs are really on the list. And while they might improve short-term prognosis, they may seem – excuse me, short-term symptoms and signs, they may be related with long-term harm. I’m going to segue into the guidelines portion of this talk, and you’ll see as we describe this there’s really no universally accepted guidelines for the management of heart failure. That’s true whether you look at the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, the European Society of Cardiology (ESC), the Heart Failure Society of America (HFSA), or our own American College of Emergency Physicians (ACEP) guidelines, there’s little consensus regarding the management. And this creates very inconsistent care. We know one of the things tied to outcomes is variability in treatment. So you don’t want to have a broad range of therapeutic treatment in these patients because that leads to poorer outcomes.
We're trying to tie conclusive evidence to particular therapies to try to find out what works in what patients. And I'll tell you at the end of this talk about our efforts, as Frank alluded to earlier, from the Society's approach to managing these patients. If you look at the ACC/AHA guidelines, they really pertain to chronic heart failure and not acute decompensated heart failure. They really classify patients in ways that we don't -- really aren't even familiar and helpful to us: stage A, that they're at increased risk for heart failure versus stage D, and these are the patients with refractory heart failure, patients that need LVADs or need transplant to survive even for 30 days. So not very helpful in the acute world.

The European Society of Cardiology, again, if you look at the document, 80 percent of the document if not more really pertains to chronic heart failure management. There are some guidelines or recommendations for the acute management. And again, they've held a comparison to the chronic therapy. They do have some useful things as far as particular clinical scenarios -- and we're going to talk about that in a few moments -- that can help us try to be patient-specific with some of the recommendations.

The HFSA, a great organization that's addressing this problem, but again, if you look at the guidelines released in 2006, again predominantly regarding chronic management, there are some management recommendations, but they're not very patient-specific. They're very broad-based, and they're very - - they're not as useful for that honed down patient that we may see in the ED.

Last but not least, the American College of Emergency Physicians has recently published, in the last two years, a clinical policy statement regarding management, but it's very narrow in scope. In fact, it addresses four very specific questions. The first is the diagnostic use of BNP that Frank just discussed a few moments ago. And from a therapeutic side, it actually addresses the utility of noninvasive ventilation, diuretics, and vasodilators. And I'll go over those in just a second.

Now, as I said, there were four questions. This comes from the ACEP policy statement which was published in 2007. We'll focus on the last two: vasodilator use, as well as diuretic therapy. And the way these guidelines are set up is that they recommend things in three groups: Level A are recommendations that reflect a very high degree of clinical certainty; Level B is mild to moderate clinical certainty; and Level C really is expert panel consensus, so there’s not a lot of good data to support a Level C recommendation.

So if you look at their comments on diuretics, the first thing you'll notice is there's no Level A recommendations because there's no good data. There are no RCTs that support their use. Now, from a Level B standpoint, some moderate certainty, they again in a broad sense recommend to treat patients with moderate to severe pulmonary edema with furosemide in combination with nitrate therapy. And a Level C recommendation is aggressive diuretic monotherapy, so by itself, is unlikely to prevent the need for intubation compared with aggressive
nitrate therapy. Okay? And they also make a comment with respect to safety, that diuretics should be administered judiciously because of their association with renal dysfunction and the potential for long-term mortality.

Now, the vasodilator statement they made, again the thing you see quickly is that there really are no Level A recommendations again because no good RCT data from which to build from. They do have Level B recommendations, which are to administer an intravenous nitrate therapy, so nitroglycerin, to patients with acute heart failure syndrome who present with dyspnea. And then from a Level C standpoint, they actually -- they suggest not to use nesiritide instead of nitroglycerin because of the safety concerns, and that ACE inhibitors may be used, but you should be cautious about first dose hypotension. Very nondescript suggestions for the use of these agents in this group of patients.

We then move on to the Heart Failure Society of America's guidelines. These were published in 2006. And they make some broad statements regarding fluid and sodium restricted diuretic therapy, ultrafiltration, which I think Peter may talk about in a moment, vasodilator therapy, as well as inotropes. Now, their recommendations are similar in that they from a stronger standpoint they make the term -- use the term "is recommended" and then next down would be "should be considered" and then next down is "may be considered" and then last but no least is "is not recommended". But you can see how strong their statements are. So "is recommended" really is part of routine care, so it kind of sets the standard of care, if you will, in these patients. Their guidelines are again pretty short and sweet, but it is recommended that patients with AHF and increased fluid overload should be treated initially with loop diuretics given intravenously rather than orally, and it is recommended that diuretics be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status control and relief of signs and symptoms. So again pretty broad statements.

The other thing they do is that they kind of put all their eggs in a diuretic basket, at least on the initial management of patients, and that's irrespective of their presentation or hemodynamics. Now, they also go on to state that when congestion fails to improve with these diuretic therapies, you can add these other measures. So you can fluid restrict them, sodium restrict them, increase their doses of loop diuretics, so you can give a continuous infusion of a loop diuretic, or you can add one of those proximal loop diuretics to effect a great and more brisk diuresis. And then last but not least, ultrafiltration may be considered in these patients.

In the absence of symptomatic hypotension, you can use vasodilators. They can be considered in these patients, but again, lower level of evidence, B, and obviously frequency of blood pressure monitoring is recommended. And then you can use a combination of IV vasodilators and diuretics are recommended for rapid symptom relief. And these are the patients with acute pulmonary edema. So they present with acute symptoms. If they have pulmonary edema either on clinical exam or chest x-
ray, those are important patients to use this combination of therapy. And then IV inotropes really are only indicated for those patients who have advanced heart failure and end-stage heart failure.

Moving on to the ESC guidelines, you can see just a quick snapshot here of what they recommend. They actually do recommend morphine, although Frank and I are both in agreement that this is not a very good drug for these patients for reasons that we’ll be happy to discuss later because of the interests of time. Vasodilators are indicated. They’re a Class 1 for nitroglycerin and Class 1 for nitroprusside. Nesiritide is not used in Europe, so it really has no recommendation. They don’t recommend ACE inhibitors in Europe to be used acutely for these patients. They do indicate that diuretics are a very effective Class 1 recommendation. And again, beta blockers as you can imagine have a role but not again as much in the acute treatment of these patients. And inotropes are only recommended if they have hypoperfusion.

There are a group of folks that have kind of jumped off of the ESC guidelines and broken these into five different groups. And they treat them based on if the patient is hypertensive, hypotensive, or normotensive. And I think this is a very effective way. In fact, this is kind of similar to what we’ve done with the Society of Chest Pain Centers (SCPC) guidelines.

So the patients who present with hypertension and congestion, we use or we recommend the addition of noninvasive ventilation, nitrates as your first-line therapy, with diuretics to follow if the patients have ongoing signs of volume overload, whereas those patients who are normotensive, diuretics have more of a role, particularly if they are obviously volume overloaded, and again, those patients who are hypotensive we really don’t recommend either of those agents. In fact, volume loading sometimes is helpful for these patients and obviously PA catheter management with inotropes is sometimes indicated.

They also go on to make comments about acute heart failure with acute coronary syndrome, and it really depends on what they present with for blood pressures. In the interests of time, I won’t go into these in great detail. And then right ventricular heart failure very uncommon to present do novo by itself, but those patients typically if their blood pressure is high you can manage them with diuretic therapy; if it’s low, often inotropes are indicated and needed to bail these patients out.

Now, my last slide here, and again, just to move forward, is just kind of an invitation to you, if you will, to come to our session this afternoon in the heart failure track, which will cover the guidelines that we produce. And this is a report from the Society of Chest Pain Centers. I was responsible just for the treatment guidelines. Frank Peacock, who spoke earlier, is the – one of the co-chairs of the overall guidelines, and you’ll hear us talk about from A to Z, all the guidelines and recommendations we’ll make, and you’ll see where we’ve taken these other guidelines and tried to meld them into a patient-centric useful guideline that you can use at the bedside for managing these patients.
And these are two of the graphics that we have, and we again break these up based on the patient's presentation, predominantly with their blood pressure at presentation (Figure 2). So I will just give you a little glimpse of this. This afternoon you'll see these.

**FIGURE 2.** Society of Chest Pain Centers Treatment Algorithm for the AHF Patient. **Top panel:** Patients with normal systolic blood pressure (SBP) at presentation. **Bottom panel:** Patients with elevated SBP at presentation.

So in summary, contemporary therapies are reasonably effective to relieve symptoms and congestion, but they may be associated with some deleterious effects. There may be some possible prognostic implications. Current guidelines are lacking with respect to management. No universally accepted approach. So hopefully the SECP guidelines will be very helpful, and please come to this afternoon's session and take a look at those. Thank you.

**Dr. Peacock:** So we have rapidly gone through the world of heart failure. Dr. Carson, Peter Carson, is from Georgetown. He's a cardiologist. This is the part of the meeting that I think is the coolest part because he's going to talk about what's coming down the pike. I think you learn more about physiology by seeing this kind of thing than a lot of the stuff that we've been talking about.
Future Directions in ADHF Treatment

Peter E. Carson, MD

Thanks very much, Frank. It’s a pleasure to be here this morning. It’s a bit eye-opening to me, this meeting and this interaction between emergency rooms and heart failure. I was interested talking to Frank earlier that he and I had intersected at – although not temporally, at Wayne State in Detroit, and I noticed one of the participants in the session this afternoon is from Detroit Receiving Hospital because when I was at Wayne State Hospital in downtown Detroit, in the emergency room at Detroit Receiving when I used to go down there from the CCU, frankly, if you hadn’t been shot you hadn’t been stabbed, there wasn’t a whole lot of interest in you. So it’s – I’m delighted to see heart failure begin to take this place.

And I loved the last couple slides that Doug Kirk showed that indicated this interaction phase in the ER where you might take a patient with acute heart failure and work with the patient there to decongest them and treat them, and you might not even admit them, which expands then the role of emergency department observation units to the place where chest pain center and chest pain units are now developing, that you now have the potential for a heart failure unit, you may be able to treat a patient, make them better and not even have to admit them to hospital, and get them on the way to be able to receive the kind of chronic therapies that have been shown to be effective.

So from both speakers, let’s just say that – we’re going to say that the diagnosis of heart failure has been established, a la Frank Peacock, so that’s been already done. And Doug Kirk has already shown you many things about the – both the limitations of what we know about what works in heart failure. So I’m just going to talk to you a little bit more in detail about those things that work or don’t work, and why we think they do.

And Doug set the stage for me very nicely to be able to say currently nothing about dosage and side effects, which is not appearing on this slide here. But I’m just going to say to you that unfortunately diuretics, it’s kind of like I look out at the audience, some of you are familiar with this comment that, you know, it’s like teenagers: You can’t live with them, and you can’t live without them, with your teenaged children.

Diuretics are a lot like that. Patients come in, and they’re congested. That is the vast majority of heart failure patients. They come in, they’re congested, and you’ve got to do something about it then. And one of the problems that we have in terms of figuring out what works and what doesn’t work is that the evaluation of what works is often seen in terms of what works over a long-term outcome – 30 days, six months, a year – based on what you had to do immediately in the emergency room. There’s a bit of a disconnect there because lots of things then go bump in the night after a patient leaves the hospital that interferes with your ability to say what’s good for a patient long term: So how do you prove that something really works has been
a major problem for us.

The next slide shows a series of doses of diuretics that you all know to use. The only comments I want to make to you acutely is to say, “Sorry, folks, about the diuretics. I know they do bad things, but you've got to get the patient decongested and feeling better immediately in that — soon after that 15-minute phase in the emergency room, and diuretics in the end are what you're going to use a lot. And the common mistake I see in our emergency room is that people don't give enough early, and they don't also repeat the dose. So remember that furosemide is going to have about a 15-, 20-minute, half-hour maximal onset of action. If nothing's happened by then and the patient is still congested, they're not doing well, give some more and maybe you're going to induce a diuresis.

Maybe you're going to improve symptoms on that basis and you're not going to end up having to do something like acutely intubating the patient. So an intubated patient that's alive is better than one that's dead, but on the other hand you want to be able to move quickly to avoid taking that kind of step. We do know that diuretics do have untoward effects. Doug Kirk said to you you see this slide all the time in heart failure talks, and you're going to see it twice this morning. This is from a study that Steve Gottlieb did looking at the effects of diuretics because he was comparing them to a new agent that I'll talk about in a moment, the adenosine antagonists, and Steve did indeed show that GFR did change in a negative direction with an 80 milligram dose of furosemide.

Now, the question of why that happens is kind of interesting: Is the molecule toxic to the kidney itself? Well, probably not. But what does happen is that if — number two there is the afferent arterial, and the afferent arterial, if there's less blood flow through it to the glomerulus then you're going to find then that your GFR is going to drop. So if you drop volume by virtue of the diuretic then your GFR is going to drop because your flow through the kidney is dropping.

There's also this interest in the phenomenon of plasma refill rate, and that is the idea that as you pull fluid out of the vascular — as you take fluid out of the vasculature, well, all that edema that you see on the patient's exam or the pleural fluid or the fluid within the abdominal cavity, well, that fluid then, that's excess fluid. You're trying to remove that fluid, and the idea is you're going to pull that out of the extravascular space and into the vascular space.

Unfortunately that doesn't always quite happen as the rate that you're pulling out of the vascular space, and so this concept of plasma refill rate is one of the things people talk about when you look at the GFR decreasing and the creatinine and the BUN going up, it's going up sometimes because you're not replacing what you've taken out of the vasculature from the third space.

It also was commented about the bad things diuretics do in other ways, particularly in neurohormonal stimulation. This is one of a couple studies, and maybe this is the best one that's shown that. It's an older study, goes back to the 1980s. This was published by a now colleague of Frank's, Gary Francis, who's now at the Cleveland Clinic. And what Gary did was to take a group of chronic heart failure patients and give them IV furosemide and to look at
their hemodynamics. Interestingly, at that point in time, something like 20 years ago, there was the idea that there was a vasodilating effect from a loop diuretic, particularly furosemide, and Gary was interested in showing this. But what's interesting is he showed the opposite. If you note the second panel in the middle on the top, systemic vascular resistance, interestingly enough it goes up with the use of intravenous furosemide.

I actually use this slide in another way when I show it to our house staff because I'm always hearing the story about the patient who was clearly congested and with pulmonary edema with a blood pressure of 100 and therefore they can't be diuresed because they'll get more hypotensive. And I always say, 'Look folks, when you actually give an IV diuretic, it doesn't happen that way. It does remove fluid, but your hypotension if that's what you think you have is not actually going to get worse.' Well, it may not get more hypotensive, but you may actually get this vasoconstricting effect that is mediated by plasma norepinephrine and plasma renin activity. These are the two things incidentally that we worry about with chronic use of diuretics and maybe even a risk of acute use because you have this spike of sympathetic activity and activation of the renin angiotensin system. You also notice that vasopressin, which is another vasoconstricting substance, also rises acutely with the use of intravenous furosemide. These things then do resolve over time, and you notice that left ventricular filling pressure also falls. But this is probably one of the best examples of one of the untoward effects of diuretics.

What about vasodilators? And vasodilators then have been nicely gone over by Doug Kirk in terms of things they do. Let me just show you some data. I have to say that all of us in the heart failure world like to say when we are trying to be all so virtuous to each other, that, "Oh, yes, nitroprusside is the thing that we think is the best to use pharmacologically. It has an immediate action of vasodilating both the venous system and the arterial system." So the idea is that the filling pressures would go down as you see on this slide along the bottom on the left, the pulmonary capillary wedge pressure goes down and systemic vascular resistance also goes down, and your cardiac output to some extent goes up.

Unfortunately, though, they're a bit cumbersome to use, and frankly the amount of use that gets done acutely I think is quite low and even chronically outside of most heart failure centers. So pharmacologically this is the most attractive agent to use of the vasodilators because it has an acute onset and acute offset, and it does all the things you would like it to do. Unfortunately, most people don't actually use it. Interestingly, I had to search far and wide to find a slide anymore that even illustrates what it does. And it may interest you to know that this is from an article on the treatment of aortic stenosis with a vasodilator therapy that was also published by Frank Peacock's friends at the Cleveland Clinic a couple years ago in the New England Journal.

How about nitroglycerin? Well, nitroglycerin has a lot of the same pharmacologic activities, but do remember that nitroglycerin doesn't become very active in the arterial system until you've given a lot if
it unless you're having a massive effect on filling pressure. And so therefore all of these nice effects that you see are the result of large-scale nitrate doses, and commonly they don't – people don't use these kind of doses acutely, and I'll come back to that in just a moment.

It is worthwhile saying that the patient who comes in with acute pulmonary edema and they're hypertensive, a very quick way to get the show on the road if you want would be to give two nitroglycerins under the tongue, which is going to give you some kind of systemic effect that will be brief, both on the venous system and on the arterial system.

Now, this is nesiritide, and Doug mentioned to you that nesiritide has been a great triumph of marketing, if you will. There is effective data on nesiritide that involves symptoms to some extent, and also a vasodilating effect. What you see here is the vasodilating effect with a change in wedge pressure in the VMAC trial, and what you see is placebo, nitroglycerin, and nitroprusside. VMAC did meet its primary endpoint, which was an improvement in dyspnea at a 3-hour point, and there was once again with nesiritide an improvement, as you see, in hemodynamics.

Now, VMAC had its controversial aspects, too, one of which was that the nitroglycerin dose was quite low. It was on average about 50 milligrams. There were those who felt it wasn't really a fair comparison of nitroglycerin and nesiritide. It's also true that if you look carefully at the VMAC data, that all three groups had significant improvement in dyspnea, suggesting that conventional therapy of heart failure patients when they come in the hospital in terms of making them feel better is quite effective. This has limited our ability to show things actually work because the therapies we do actually do improve some improvement – do improve symptoms in patients when you go and measure them.

There has been a signal with nesiritide with worsening renal function, and worsening renal function in most scenarios of heart failure is associated with a worse outcome if the worsening renal function persists. This has been an arguable signal in the nesiritide database, but has worried many and has prompted a large clinical trial called ASCEND, which is ongoing, to look at the long-term effects of nesiritide.

Nesiritide has very much gone out of favor recently for all these reasons. But also I think when people look back at the data, it really wasn't entirely clear that it was all that effective on top of conventional therapy, so these are the two reasons why nesiritide has largely gone out of favor.

What about inotropes? Well, the dirty little secret that many of us in heart failure have is, yes, we do use inotropes on occasion, even though we talk about how bad they are. This is looking at dobutamine and milrinone and is just giving you the notion that both of these agents are effective in terms of improving cardiac index and mean capillary wedge pressure. They're effective agents when we use them in appropriate patients.

However, it is also true there has never been a study that has shown a favorable signal with inotropic
therapy in frankly any setting, whether it's acute or chronic heart failure. Acute heart failure has been very difficult to study. This is the OPTIME trial, which was the best attempt to be able to do that, comparing milrinone to placebo in ADHF patients. As you can see here, on outcomes there is no benefit for milrinone-treated patients compared to placebo, and there is a worse adverse outcome profile, which is on the upper part of the screen.

This is unfortunately once again a study where there has been some controversy, partly because the population enrolled is really not the population that most of us would have used an inotrope in anyway. These were relatively mild to moderately sick ADHF patients. They weren't the kind of end-stage heart failure patients or even shock-like patients that we often are using inotropes in, even though we don't want to. So this kind of data doesn't really apply to the patients that we use – that we are using inotropes in these days and have for some years. We don't have a study on that basis on that group of patients because frankly physicians won't randomize those kind of patients into a clinical trial.

Are there any data or anything in the future that would be helpful? And I'm just going to show you some data that was presented at the American College of Cardiology. This is the HORIZON heart failure study with istaroxime. Now, no one wants to call their drug an inotrope anymore because that immediately is a bad label to put on it, so this is a drug that was called a calcium sensitizer, a lot like the drug levosimendan that had a brief star turn in the United States, but again produced data that was very much like you saw with OPTIME.

A lot of different squiggles and lines on this slide, but good things were happening in terms of hemodynamics with istaroxime in HORIZON-HF, but this is an early phase trial. Dr. Mihai Gheorghiade presented this data, and if you want to find out a little bit more about it, I think he's on the program later today and could talk to you more about it.

But people are looking for something to use in this sort of patient that has a low output and is in shock, and a calcium sensitizer, which is a little different than milrinone, a phosphodiesterase inhibitor, or a sympathomimetic like dobutamine, this kind of agent like levosimendan has been attractive to some with the idea that maybe there is not the same kind of adverse event kind of experience with it, but you would still get the kind of benefit we have seen.

Okay. Now what about other things? And this is investigational therapies. And in investigational therapies, one interesting one is the A1 adenosine antagonists in heart failure. This is -- if you think you've seen this slide before, it's because you have, now twice. This is a continuation of the data looking at GFR, furosemide and placebo by Steve Gottlieb. As I mentioned to you, this was really designed to look at an adenosine antagonist, looking at the effect of an adenosine antagonist with or without furosemide on GFR.

BG9719 is this adenosine antagonist, and GFR does not decrease even though urine output is augmented, particularly with the furosemide used in combination with this agent. Now, what's happening
here is that when you give a diuretic and you introduce more salt and water to the inside of the kidney, the macula densa towards the bottom of the cartoon on the right, what you find then is that there is a feedback mechanism that occurs, tubuloglomerular feedback is the expression nephrologists always use. That is an adenosine-mediated effect that inhibits sodium reabsorption in the proximal tubule, number 1 on this slide, and also produces vasoconstriction of the afferent arterial, that's number 2 on this slide. And what an adenosine antagonist does then is to impact on these two effects.

The agent that is furthest along in development is rolofylline, and rolofylline is shown here in an early study looking at change in plasma – in renal plasma flow and change in GFR. And as you can see over time for rolofylline there are favorable effects in both these parameters. There was a pilot study presented at the American College of Cardiology for dose ranging with rolofylline in what is called the PROTECT trial. And this is looking at a primary outcome which is kind of complicated to go through and I don't unfortunately have time to do that. But looking at three doses of rolofylline, and there was a favorable effect on a primary outcome which involved improvement of patient symptoms and a lack of adverse events during a short-term time period, as well as no worsening in renal function, so a dose-related favorable effect on this complicated primary outcome.

Even more interesting are two other things, perhaps. That is to say that for change in creatinine, interestingly if you particularly look out over time at day 7, but more at day 14, there was this inverse relationship between placebo – now placebo is getting diuretics – and the dosing of rolofylline so you're seeing a dose-related favorable effect in creatinine over time at day 14. This trial was very careful to look at the fact of what creatinine did over time, not just a one-shot or short-term effect, but looking at day 14 to see whether renal function stayed different as opposed to just a short-term change.

What about 60-day outcomes, was there an early effect that looked favorable? Yes, there was. This is looking at placebo and three doses of rolofylline. And you'd want to look at combined outcome there at the top. Small numbers of patients, but a favorable signal going across the board in terms of the number of patients who had death or cardiovascular or renal hospitalization over this time period. So some very favorable signals with rolofylline in the PROTECT pilot.

How about ultrafiltration? Ultrafiltration is a bit cumbersome to use acutely, as you all know, but certainly for patients who are admitted into hospital, there is some interesting data. This is the UNLOAD trial. UNLOAD looked at two primary outcomes of ultrafiltration added on to conventional therapy: dyspnea or weight loss. As I pointed out to you earlier, it's hard to show convincingly that dyspnea is improved in patients with new therapies, and UNLOAD did not, either, although there was a favorable effect on weight loss over time.

People were pretty interested in that, partly because outcomes in a 90-day period were also improved with the ultrafiltration system. So it was more effective acutely at drawing off weight and also a decrease in clinical events. Unfortunately this was
blinded, not a lot of events over this 90-day period, and that’s why I put this under the investigational category. People would like to see more data with it, particularly because there was a question about what happened to creatinine over time. There were a number of intervals in which creatinine was actually worse in the ultrafiltration arm.

The last group to talk about is the vasopressin antagonists. Vasopressin is a substance that acts both in the vasculature and on the kidneys. There are V2 receptors within the kidneys, V1 receptors in the vasculature. They go under the term aquaretics, if you will, for their renal effects, where they mediate salt and water metabolism through the aquapurines.

And just very quickly, these agents – and there are now about four of them that have been investigated - - have shown favorable effects on urine output. This is conivaptan, which is an intravenous agent, and you see a dose-related effect for conivaptan on urine output over time. For an oral agent, this is tolvaptan, and tolvaptan shows a favorable effect on hemodynamics, then looking at change in wedge pressure at three doses.

Now, what about clinical data beyond the just hemodynamics? And the large-scale database that we have now is the EVEREST trial. The EVEREST trial was a brilliantly designed study in that it took a group of decompensated heart failure patients in hospital and looked at both short-term and long-term outcomes. The short-term outcomes are seen in Trial A and Trial B. So the 4,000 patients were basically divided into two 2,000-patient trials and then reconstituted in their original treatment group looking at then the long-term effect of the vasopressin antagonist, which occurred then until a prespecified endpoint went on.

I’m just going to talk to you for a moment today about this primary composite on short-term effect. This is looking at change from baseline at day 7 or hospital discharge on a composite scale of patient global assessment and body weight. It was a combined outcome. Both trials were favorable, both Trial A and Trial B. The part of the composite that was favorable was once again weight loss: The patient global assessment was not favorable. This is what you see here: This is the change in body weight, and this is the change in patient global assessment on the right (Figure 3). So a little bit like the ultrafiltration data, the effect here was seen on weight loss.

For adverse events, this was a very well-tolerated agent. The vasopressin antagonists do show a change in dry mouth and thirst because this vasopressin is one of the things that regulates when we want to drink water and things and when we don’t, when we become hypertonic in our serum – in
our blood solution. But otherwise a very well-tolerated agent.

So to finish up very quickly then, as the other speakers have said that large registries confirm the incidence and prevalence of acute decompensated heart failure, we have very high hospitalization rates of death and rehospitalization. I totally echo Frank Peacock's comments that this has a lot of morbidity, this syndrome: In fact in many cases this is higher than acute coronary syndromes, where we're all running around transferring patients and taking them off to catheterization labs. But somehow acute decompensated heart failure and the importance of what happens to patients is only recently coming into people's eyes as being so important.

Diuretics still are first-line agents, but when initial therapy fails, then modified diuretics. We didn't talk in the interests of time very much about adding on agents like metolazone, although Doug Kirk I think did touch on that.

Torasemide is also an agent that has had some benefit in the diuretic-resistant patients. Adding vasodilators and ultrafiltration we've touched on. Inotropes then we would consider only as a resort in patients with poor ventricular function and decreased perfusion, the sort of shocky type patients with end organ dysfunction. The new agents in development include calcium sensitizers, like istaroxime, adenosine antagonists, and vasopressin receptor antagonists. I'd like to stop there and thank you all for your attention.
Q&A Session

**Dr. Peacock:** Thank you, Peter. You talked about tolvaptan at the end there. And the thing that’s always sort of been the question is, it's an oral agent. And Dr. Kirk, maybe you want to chime in on this, too. But let’s assume that gets approved. How do you anticipate that being used for acute heart failure?

**Dr. Carson:** Well, I wonder about it as an agent in the emergency room where you’re talking about say the first few hours of therapy. That may not be an agent that would have a whole lot emergency room use, but I think for the patient who is hospitalized, this is where the benefit was shown on weight loss: It does induce an increase in weight loss and without a commensurate worsening of any adverse event that was material.

**Dr. Kirk:** I would agree in general, but a slightly different angle that one of the patient groups as we wrote these guidelines that we found difficult for us to manage were those patients who presented with roughly normal blood pressures, who often had renal insufficiency and were refractory to diuretic therapy. And that’s a group of patients where this drug may be actually fairly useful.

And although you think of oral drugs in the ED as not kind of, you know, the acute therapy, but in fact there are some advantages to oral therapies in the ED because it’s less cumbersome for us to use than a lot of the drugs that we’ve talked about. Peter mentioned this, as did I, you know, IV nitroglycerin and nitroprusside are hardly used. They’re just difficult to titrate, et cetera, so giving an oral drug may be, you know, very easy and beneficial for some of these patients, you know, particularly those patients who are refractory to other therapies.

**Dr. Peacock:** I think your point’s right. I use PO nitroglycerin as my first-line drug because I don’t have to have a line or anything. Another question was about hyponatremia and volume overload, the combination. Peter, do you want to comment on that?

**Dr. Carson:** The place that these agents were initially developed first was in the treatment of hyponatremia. And hyponatremia in heart failure patients is exceedingly difficult to treat, particularly when it's significant. We don't see a lot of it anymore, but when we see it, it is exceedingly difficult to treat, and these agents are quite effective at increasing the serum sodium without producing untoward effects. And that’s going to be one level of approval that the FDA is going to be considering. So that’s a very obvious effective place for these kind of agents.

And it is interesting to note that hyponatremia, even at very modest levels, is associated with worse outcome. The question that the FDA is going to be exploring is whether the correction of hyponatremia, what’s the data that that’s associated with improvement if you look at that as being the target.

And I think that if – considering that, I think Doug makes a very good point that the patient who is – has renal insufficiency and we worry about worsening that, particularly with a diuretic, the use
of an agent that is -- that does not appear to affect renal function, and tolvaptan does not appear to affect it in any material way, then becomes very attractive.

**Dr. Kirk:** And it looked like this and the adenosine receptor, you know, the ADH antagonists and the

**Dr. Carson:** Yes. Of course the adenosine receptor antagonists look like the next big promising thing for heart failure in terms of renal protection, which is clearly what we're all trying to get.

**Selected References**


POST-TEST

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1. Which of the following diagnostic tools has the lowest sensitivity for ADHF in patients presenting to the ED with dyspnea?
   A. Chest x-Ray
   B. Third (S3) heart Sound
   C. Serum BNP
   D. Troponin Level

2. Which of the following is a predictor of in-hospital mortality among ADHF patients?
   A. BUN >43 mg/dL
   B. Serum Creatinine >2.75 mg/dL
   C. Systolic BP <115 MM Hg
   D. All of the above

3. The safety and efficacy of diuretic use in patients with ADHF is supported by randomized placebo-controlled clinical trials
   A. True
   B. False

4. In patients with ADHF, nesiritide is associated with:
   A. Improved hemodynamics with 15 minutes of administration
   B. Worsening serum creatinine at higher doses
   C. Both A and B
   D. None of the above

5. In EVEREST, treatment with tolvaptan improved the composite endpoint of patient global assessment and changed in body weight at 7 days or hospital discharge.
   A. True
   B. False
Evaluation

This page is provided for review only. You will be asked to answer the following activity evaluation questions when completing the online evaluation. Please evaluate your experience while participating in this CME/CE activity. Your feedback is greatly valued and will help us continue to deliver educational activities that are both relevant and significant to healthcare providers. Be sure to answer all questions, once completed be sure to submit your answers.

1. Please evaluate the overall quality of this CME activity.
   - [ ] Excellent
   - [ ] Very Good
   - [ ] Fair
   - [ ] Unsatisfactory

2. How effective was this activity in meeting the stated learning objectives?
   - [ ] Excellent
   - [ ] Very Good
   - [ ] Fair
   - [ ] Unsatisfactory

3. Evaluate how relevant this information is to your practice.
   - [ ] Excellent
   - [ ] Very Good
   - [ ] Fair
   - [ ] Unsatisfactory

4. How effective was this activity in enhancing your knowledge?
   - [ ] Excellent
   - [ ] Very Good
   - [ ] Fair
   - [ ] Unsatisfactory

5. How effective was this activity in enhancing your confidence in diagnosing and treating patients with the condition(s) presented?
   - [ ] Excellent
   - [ ] Very Good
   - [ ] Fair
   - [ ] Unsatisfactory

6. How likely are you to make changes in your practice based on the information presented during this CME activity?
   - [ ] Very Likely
   - [ ] Likely
   - [ ] Somewhat Likely
   - [ ] Not Likely

7. In what areas will you make changes in your practice? (Please check all that apply.)
   - [ ] Screening/diagnosis
   - [ ] Treatment/management
   - [ ] Staff Education
   - [ ] Patient Education
   - [ ] Other
   - [ ] I do not plan to incorporate this information in my practice.

8. How soon will you incorporate the information from this CME activity into your practice?
   - [ ] Within one month
   - [ ] 1-3 months
   - [ ] 4-6 months
   - [ ] I am already implementing in my practice
   - [ ] I do not plan to incorporate this information in my practice.

9. To what degree do you believe that the subject matter was presented fair, balanced and free of commercial bias?
   - [ ] Excellent
   - [ ] Very Good
   - [ ] Fair
   - [ ] Unsatisfactory

10. Which statement(s) best reflects your reasons for participating in this activity? (Please check all that apply.)
    - [ ] Topics covered
    - [ ] Location/ease of access
    - [ ] Faculty
    - [ ] Opportunity to earn CME credits

11. What topics would you like to see offered as CME activities in the future?

12. Additional comments: