Digoxin Toxicity: Awareness, Recognition, and Treatment CME

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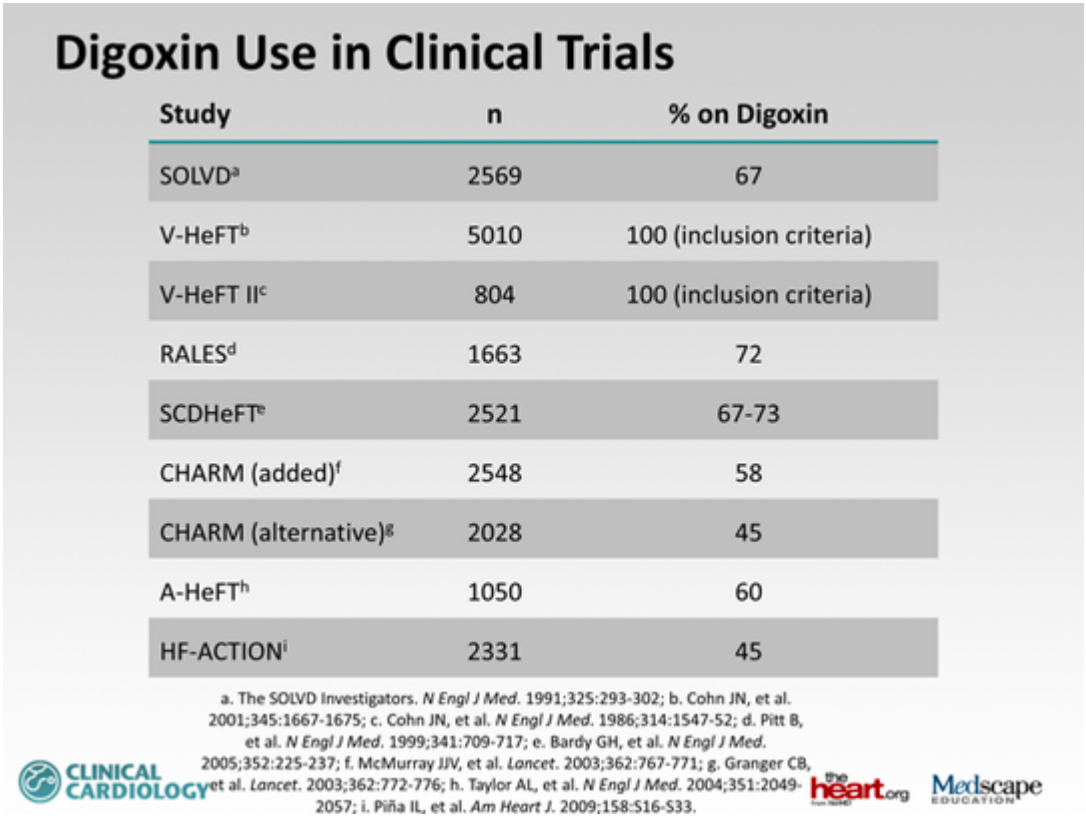
Slide 1.

Ileana L. Piña, MD: Hello. I am Dr Ileana Piña, professor of medicine, epidemiology, and population health at Albert Einstein in New York, and associate chief of cardiology at Montefiore Medical Center. I want to thank you for joining us today and welcome you. We have a very interesting program called "Digoxin Toxicity: Awareness, Recognition, and Treatment." We have a wonderful panel today, and I want to welcome them.

We have Dr Peter Carson, who is professor of clinical medicine at Georgetown in Washington. Welcome, Peter, and thank you for joining me. We also have Dr Paul Hauptman, who is professor of internal medicine in cardiology at St. Louis University in St. Louis, Missouri, and then last but not least, we have my friend Dr Peter Pang, who is associate chief of clinical affairs and associate professor of medicine in the Department of Emergency Medicine at Northwestern in the Feinberg School of Medicine in Chicago, Illinois. It is really good to have all 3 of you here.

We have some very specific goals that we want to achieve today. We would like to review the symptoms of digoxin toxicity. Some of you may be wondering why we are dealing with digoxin today as it is a drug that we do not hear much, but I think that we are going to give some important information and review some important studies that may help the clinician. And then secondly, we want to talk about treatment strategies for both acute and for chronic digoxin toxicity.



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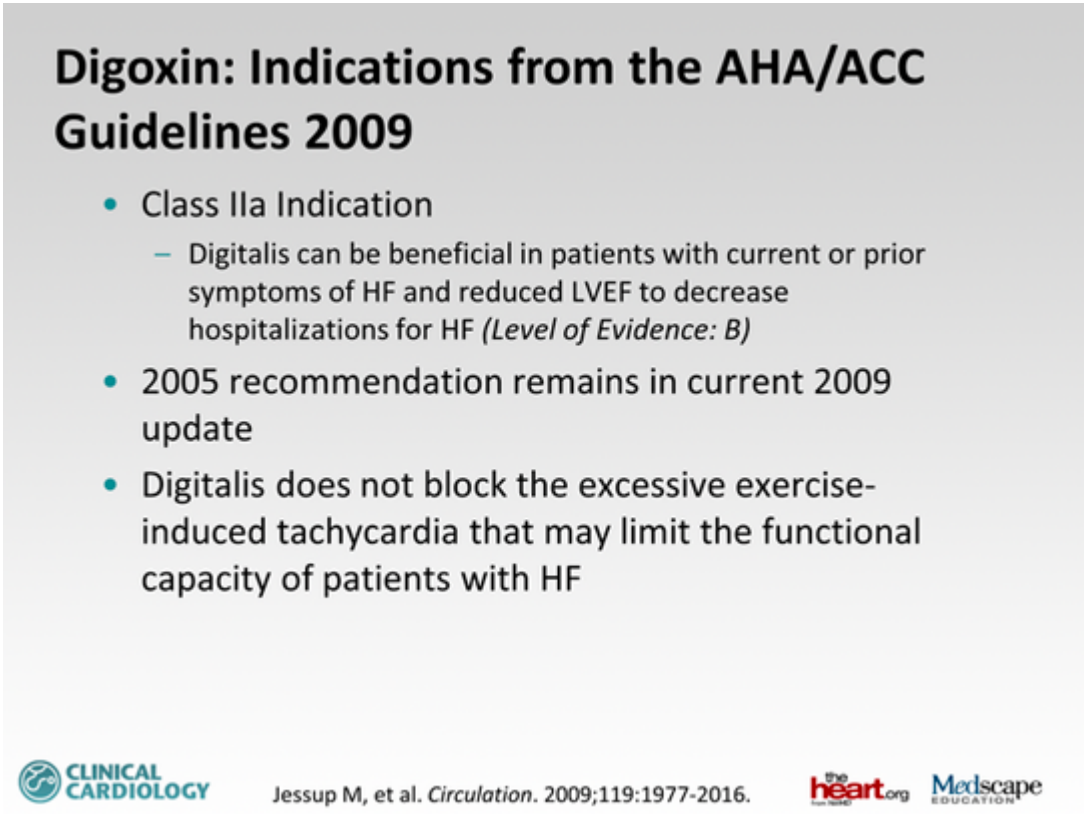
As we were sitting around talking about how to really approach the subject, I remembered that as we look at clinical trials -- and at this table, we are all clinical trialists -- we see less and less digoxin being used in the clinical trials. If we go back into V-HeFT I and V-HeFT II, digoxin use is not even reported because the patients who were entered into the trial were already on digoxin and diuretics. That is all that we had at that time. Then as we moved into the era of angiotensin-converting enzyme (ACE) inhibitors, we had everybody on digoxin and diuretics. But even then in SALT, 67% of patients were on digoxin.

Patients in RALES had a higher rate of digoxin use, which is interesting because that was a pretty sick cohort of patients. It was a class IV patient population. In SCD-HeFT, which is a more modern of trial of defibrillators and amiodarone, we saw the percentages of digoxin use anywhere from 67 to 73. As we start to move down into CHARM, then A-HeFT, and then finally in the HF-ACTION trial, which is probably the latest of the large clinical trials, where patients were very well medicated with ACE inhibitors and β-blockers, we only saw 45% of patients were on digoxin. We also have information from the registries. Paul, I know that you have some data from the ADHERE Registry, obviously of patients who were coming in decompensated. Can you share that with us?

Paul J. Hauptman, MD: Sure, we looked at dates from 2001 to 2004, and the overall background use on admission of digoxin was just under 24%. It is interesting that it is about half of what was seen in the clinical trials. It is a little bit disturbing, and perhaps we will get into this later, that use in the elderly was actually higher than the overall rate, and that is a group that is susceptible to digoxin toxicity.[1]



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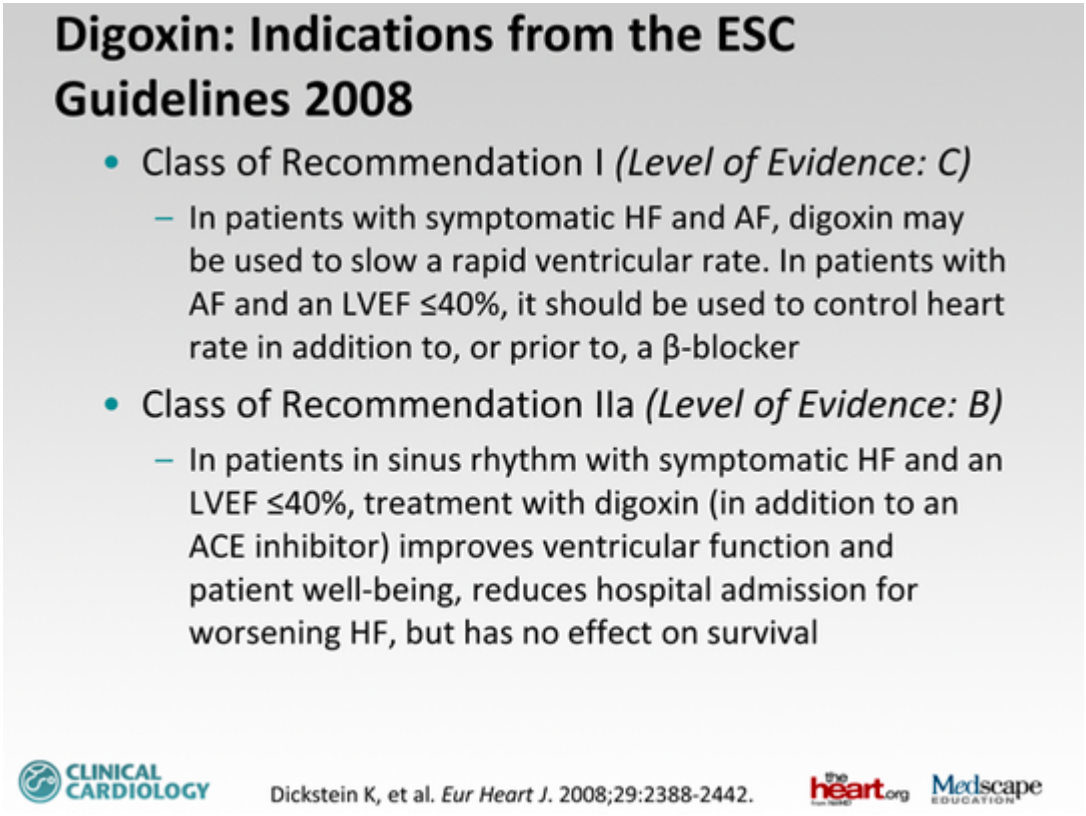
Dr Piña: Yes, and we will get into that as well. When we were planning this activity, we also talked about what the guidelines really say. These are the American Heart Association (AHA) and American College of Cardiology (ACC) guidelines from 2009; just to remind the audience, those guidelines were an update of the 2005 guidelines. Where changes had been made, the authors clearly said this is exactly like the 2005 or not. Digoxin has a class IIa indication.

The guidelines talk about digoxin being beneficial in patients who have prior symptoms and a reduced ejection fraction to decrease hospitalizations. The level of evidence B comes from the digoxin trial,[2] where hospitalizations were in fact reduced. Digoxin could be beneficial in patients who have current or prior symptoms to decrease hospitalizations, not only for new patients but also for patients with established symptoms. That recommendation remained identical in the 2009 update as in 2005. It states very clearly that it does not block the excessive exercise-induced tachycardia. Clinically, we talk about how we can control the heart rate of chronic atrial fibrillation (AF) patients who are active. We know that digoxin does not do well with exercise heart rates.



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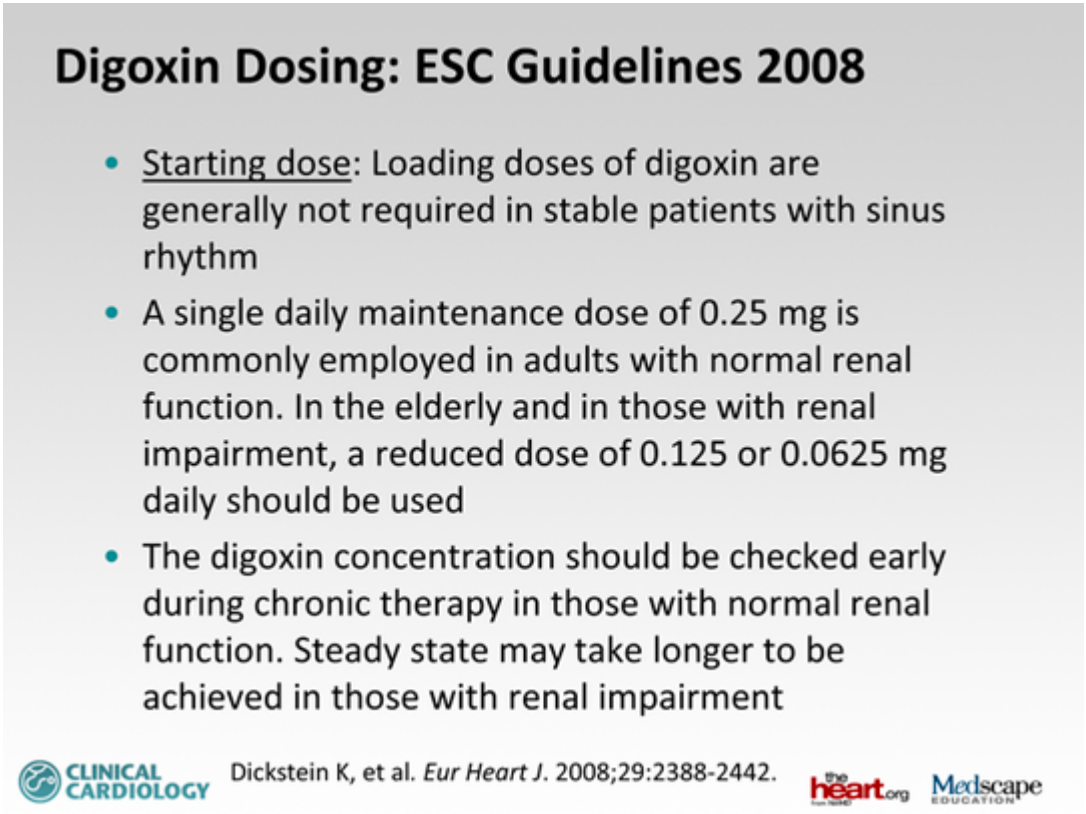
So I pulled the European Society of Cardiology (ESC) guidelines as well.

They have 2 recommendations. The first one is specifically for AF. Digoxin has a class I recommendation for the control of resting heart rate or rapid ventricular rate, and the ESC guidelines even say that in patients with AF and an ejection fraction (EF) of 40% or lower, digoxin should be used in addition to a β-blocker. The class IIa recommendation is very similar to the ACC/AHA guidelines, with the level of evidence B for the treatment of low EF patients, reducing hospital admissions, and again, these guidelines use the data from the DIG trial.[2]



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The ESC guidelines go 1 step further and talk about how to dose the drug and how to check it. So I turn to my panel here to ask, if you were going to start a new patient on digoxin, how would you do it? How would you begin, and when would you check the digoxin levels, if at all? Paul, do you want to start?

Dr Hauptman: Well, sure. I certainly do not load anybody anymore. I think those days are over, and most of the patients we initiate are on 0.125 mg a day. More frequently now, especially in the elderly cohort or in patients with renal insufficiency, digoxin may be administered every other day. We talk about a Monday-Wednesday-Friday regimen, for example. Now, admittedly, that has not been supported in the clinical trials, but the ESC guidelines do support that kind of dosing regimen

Dr Piña: And they also support a lower dose of 0.0625 mg in the patients with impaired renal function. Peter, how do you start digoxin?

Dr Carson: Well, I agree that starting with a load is generally not necessary. The data out of the large digoxin study really alerted us to the notion that a lower dose is what you want because when you look at the retrospective analysis of the digoxin data, serum levels below 1 were associated with favorable outcomes.[2] Higher serum levels were associated with worse outcomes, so out of that has come the idea that the standard dose for most patients ought to be 0.125. There was a day when we used higher doses than that.

Dr Piña: Even though it takes you a few days to get them up to a blood level. Would that be different, Peter, if you were deciding to use it on an acute heart failure patient that you saw in the emergency department (ED)?

Dr Pang: Right. In general, digoxin is rarely used. We tend to use it in patients who come in with AF with a rapid ventricular rate. It is usually a second-line therapy or a consideration as a second-line therapy, in which case we tend to use it intravenously. I guess I would not really say load per se, but we usually start at about 0.5 mg.

Dr Piña: 0.5?

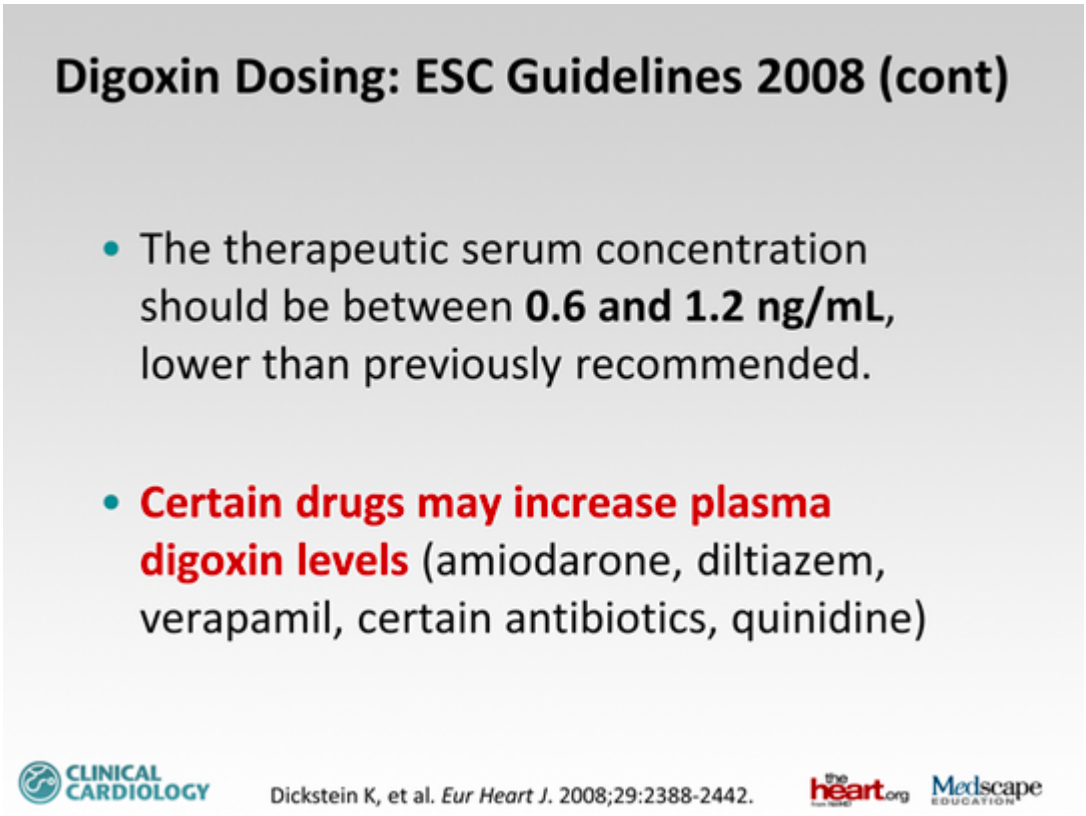
Dr Pang: Yes.

Dr Piña: Acutely given.

Dr Pang: Yes.

Dr Piña: When should you see benefits if the patient was going to get better?

Dr Pang: Well, we are traditionally taught that it takes a long period of time, up to 4 to 6 hours. However, *The Physicians' Desk Reference* says we should see some benefit in about 30 minutes.



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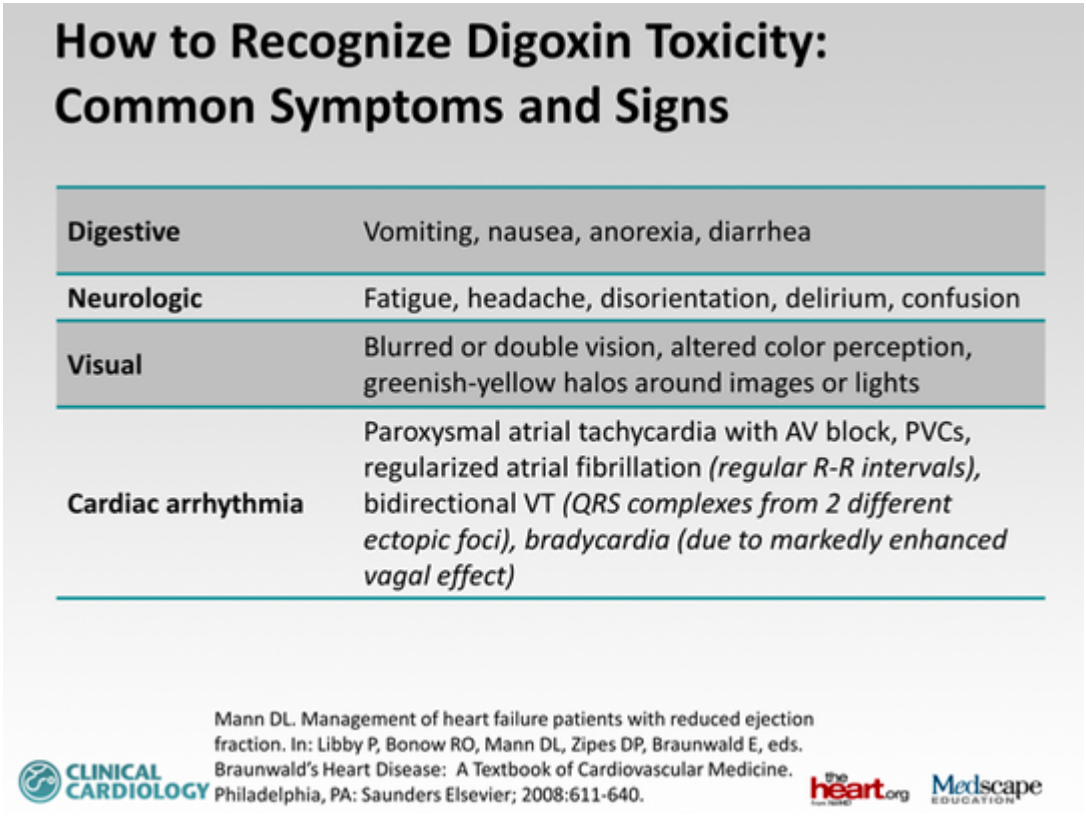
Dr Piña: I think that the ESC guidelines are also pretty cautious about digoxin toxicity and understanding which other drugs can combine and raise digoxin levels. I remember when the calcium channel blockers first came out, everybody was very worried about the digoxin levels rising with things like diltiazem and verapamil. Of course, amiodarone also increases digoxin level, and they may, in fact, be used together in some instances.



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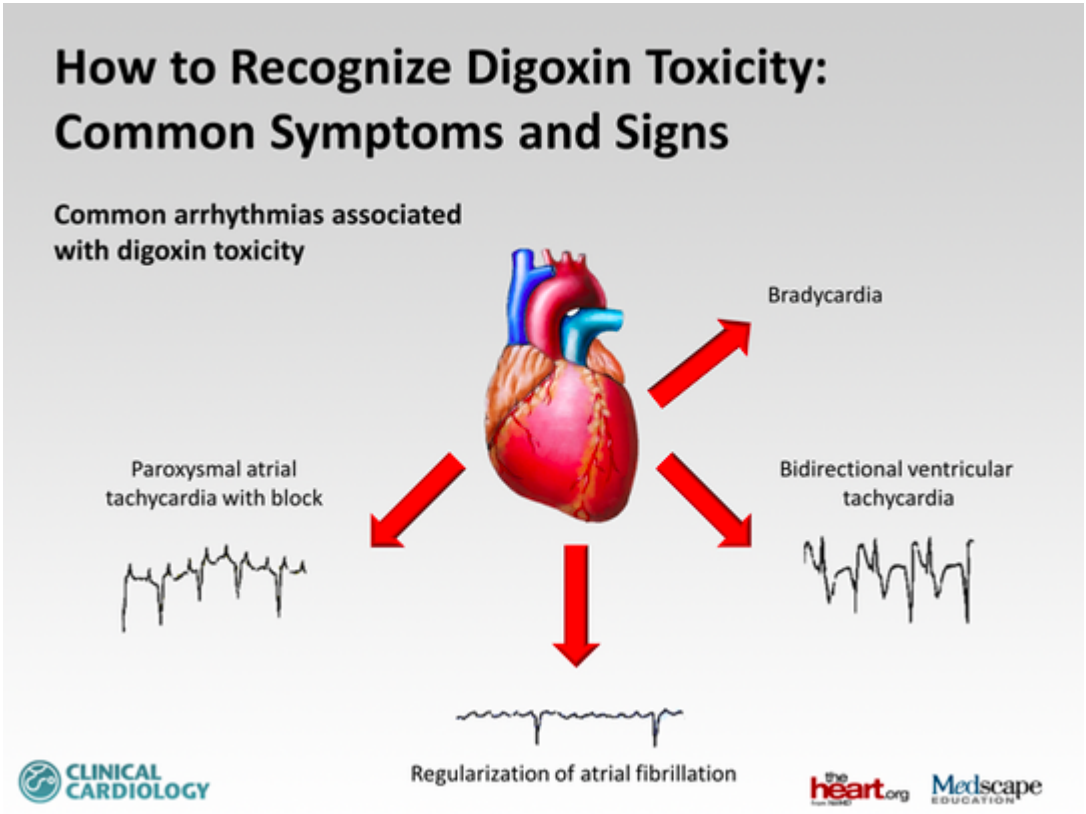
Since we are now getting into the symptoms of digoxin toxicity, let us go over how to recognize it. Paul, do you want to tell us some classic symptoms of digoxin toxicity?

Dr Hauptman: Well, sure. Patients can present with nausea, visual disturbance, failure to thrive, and then there are characteristic rhythm disturbances as well. It is usually not 1 particular symptom or finding that is characteristic for the family of it; it becomes a clinical diagnosis. You have to have a high degree of suspicion at the outset; otherwise, you will find that you miss cases. Many cases involve subclinical toxicity and patients continue to get dosed. Therein lies some danger.

Dr Piña: When we were studying for boards, there was an emphasis on recognition of digoxin toxicity. I do not think our house staff really thinks about that as much. Peter, what do you think about the way we are training our younger doctors?

Dr Carson: I totally agree. You need a high index of suspicion, just like Paul said, for digoxin toxicity, particularly in patients who are older and in patients with some degree of renal insufficiency. These are high-risk patients for the development of digoxin toxicity. If you do not think of it and test for it, then you may not find it.



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Dr Hauptman: I would also add that you do not have to have truly toxic levels in an older patient. For example, if you have a patient who has underlying sick sinus syndrome, it does not take much to tip them over. They are bradycardic and not doing well.

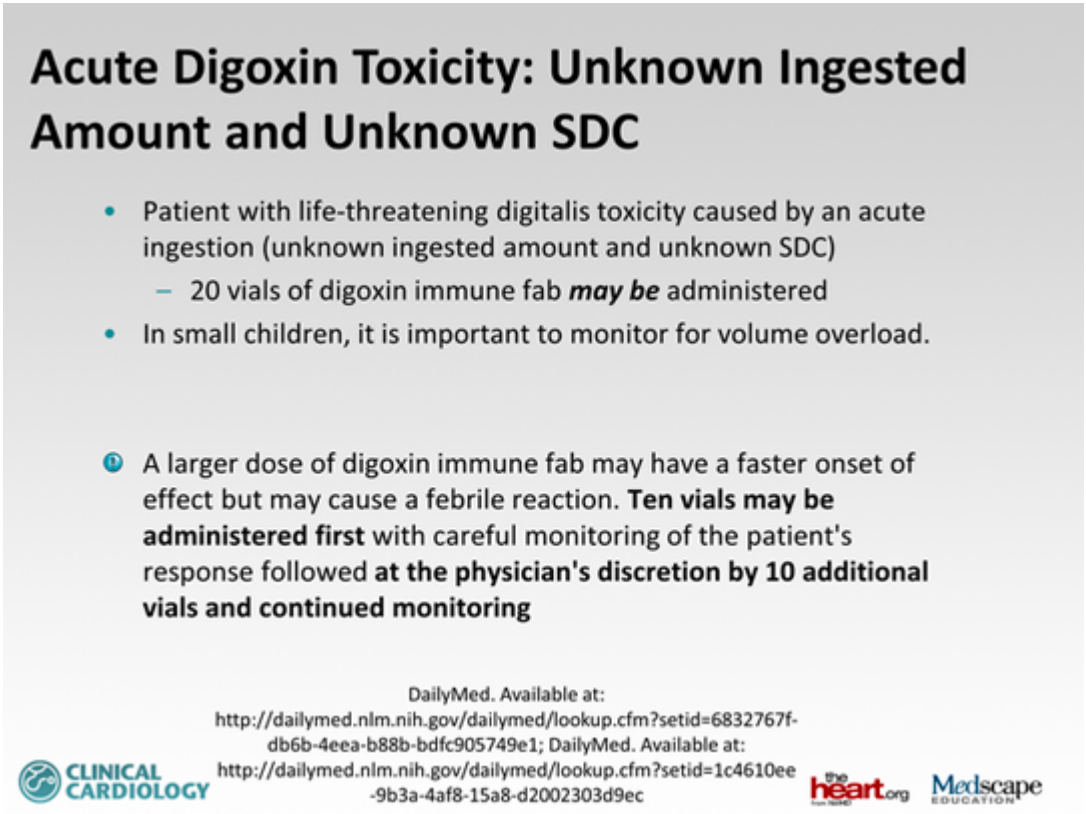
Dr Piña: Even sinus arrest.

Dr Hauptman: Sinus arrest, and that whole family of diagnoses. We saw a patient not that long ago -- you and I have discussed the case -- of a woman who had heart failure, failure to thrive, inanition, and some mental status changes. We were called in to consult about the possibility of heart failure. I noticed that she was on digoxin and amiodarone. We asked them to get a level. It came back 1.9. I made the decision to actually treat it because I thought for that individual, a level of 1.9 really was toxic, and the manifestations were reasonably classic.

Dr Piña: It was keeping her in the hospital.

Dr Hauptman: Well, it was the reason for admission.

Dr Piña: That is very interesting. We have been reading cases that are accumulating in the literature, so I wonder if we are going to be seeing more and more.



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Have you seen any of these digoxin toxicity patients come to the ED with this nausea, vomiting, not feeling well, even the visual changes?

Dr Pang: We do see it. I would agree that given the lower use of digoxin, it is not common, but we do still see it. I think the emergency department offers a unique perspective because sometimes the patients will, for whatever various reasons, intentionally try to overdose on digoxin. I think that is important. If intentional overdose is the case, we know how to treat those patients. I would agree that when a case involves chronic toxicity, the symptoms can be subtle. Manifestations such as gastrointestinal or neurologic symptoms are sometimes difficult to find. A lot of times, family members bring in patients and and say that they are not quite acting the same; they have altered mental status, a little bit of fatigue.

Dr Piña: That is interesting. Altered mental status in an elderly patient can be so many things. It could be a metabolic issue. But if you do not think about it, you are not going to identify it.

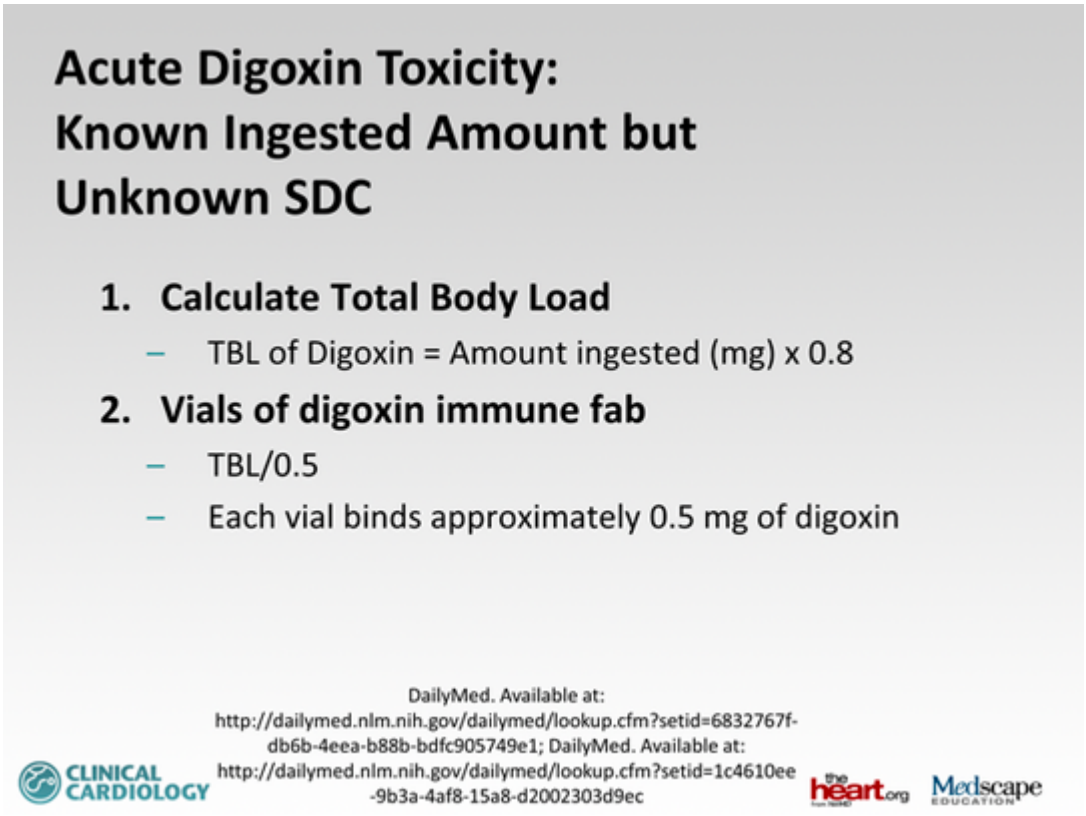
Dr Hauptman: Correct.

Dr Piña: How do you do it? What do you do in the ED?

Dr Pang: Well, I think that when it is an acute ingestion, and if the amount or the dose is unknown, it is just empiric treatment. Usually, we are concerned if they manifest any evidence of, of course, life-threatening arrhythmia. Even hyperkalemia greater than 5.0 has been recommended to treat empirically if the dose ingested is not known. Also, end-organ dysfunction, say for renal dysfunction, or altered mental status are also potential indications to treat empirically. Treatment would be 10 vials of digoxin immune fab. basically fab or DigiFab or Digibind, which essentially are interchangeable.

I think there are other avenues of therapy as well. I think if you know that patients have ingested more than 10 mg of digoxin, you can go ahead and treat those patients empirically as well. The one important lesson is to be careful about the serum digoxin concentration (SDC). If you acutely ingest digoxin, given its large volume of distribution, you cannot measure it right away. The SDC will give you a falsely elevated reading. It takes about 6

hours after oral doses for patients to get to a rough steady state, where you could correctly assess the SDC, so asking when patients took the digoxin would also be important.



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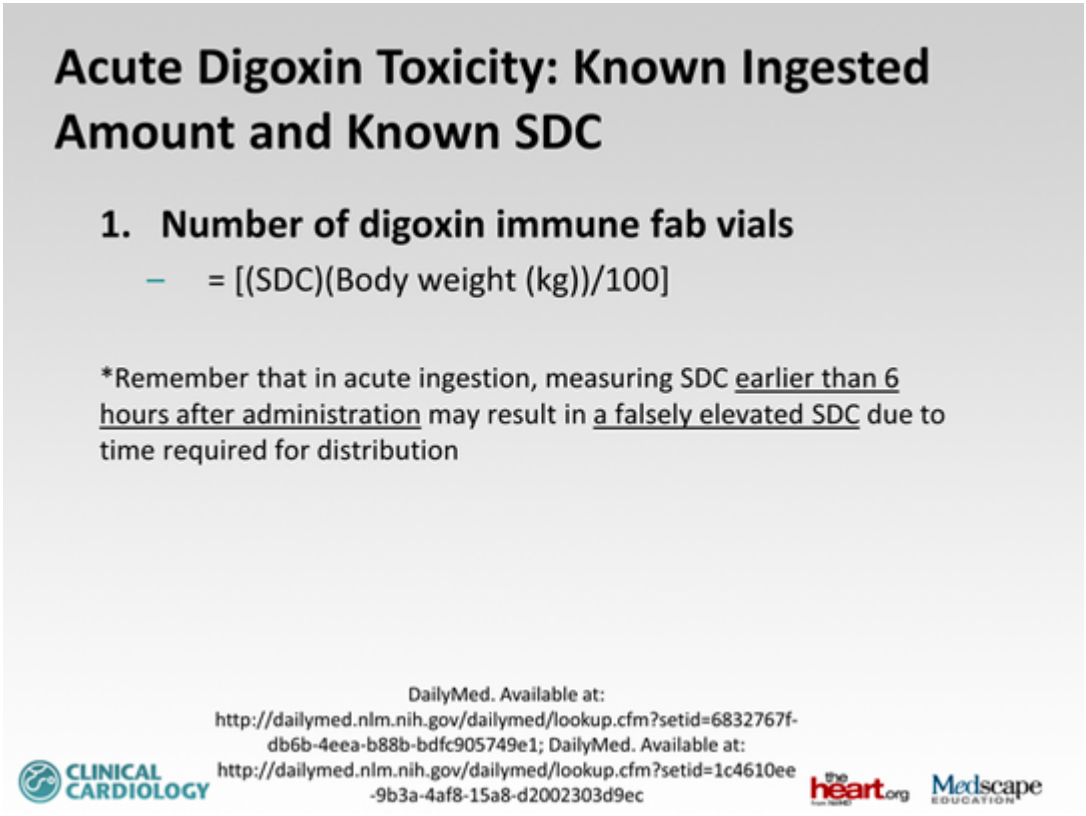
If you do know the actual amount they ingested but not the serum digoxin concentration, there are some formulas that you can use to figure it out. Frankly, I usually end up looking these up to make sure that I have got them down, and we put them up here as well.



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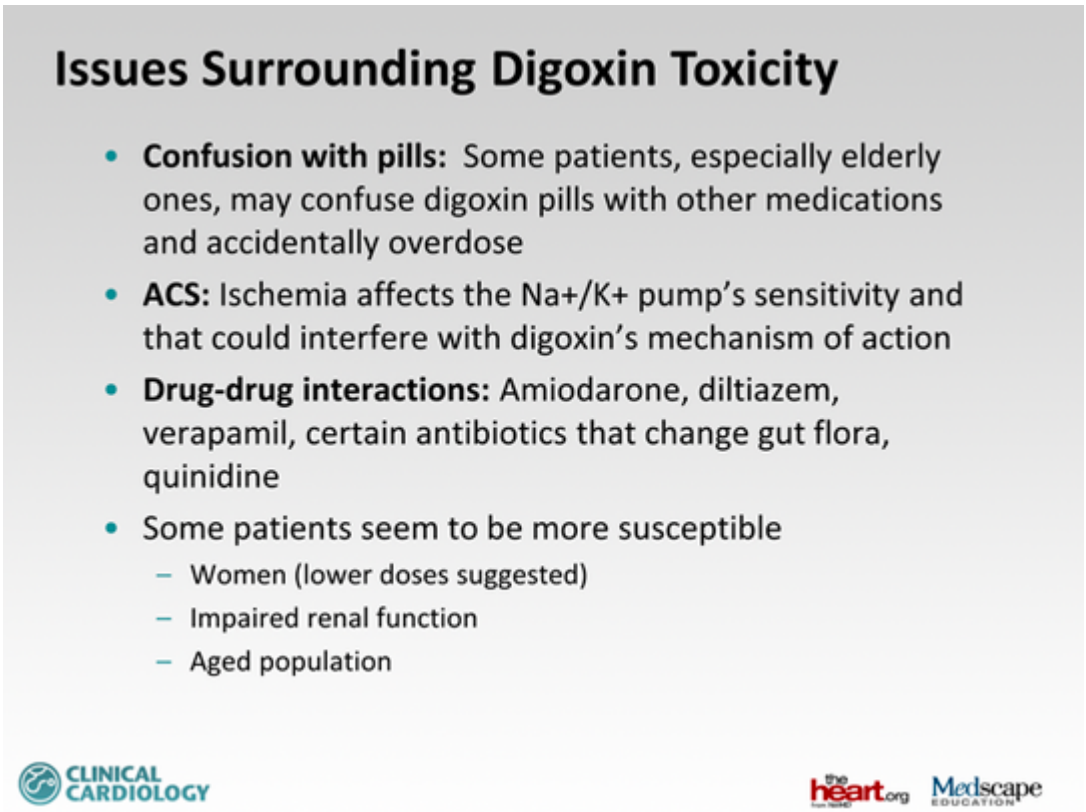
Essentially, first you want to calculate the total body load (TBL). Once you calculate the TBL of digoxin, the number of vials of fab that you give is essentially divided by half. So the TBL of digoxin divided by 0.5 will give you the number of vials that you want to give to bind the digoxin.



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Dr Piña: It is interesting that we are talking about the elderly. When elderly patients get confused with all these pills, we find that they could in fact be ingesting more of each of the drugs that we think they are. Just asking that question, getting the level, is important because you do not know if they may have taken digoxin more often than it was prescribed. It is a little white pill, which can look like a lot of our generic ACE inhibitors. The β-blockers are also generic, and they can appear very similar. Even spironolactone can look very, very similar to digoxin, and it is relatively inexpensive on the market.

So I want to go over the patients who would be most susceptible to digoxin toxicity. We have had discussions about acute coronary syndrome (ACS). If a patient comes in with pulmonary edema, there are some people who believe that intravenous (IV) digoxin acutely is a drug to use in this population. Peter, what do you think about that? Do you know any data?

Dr Carson: On IV use in acute decompensated heart failure?

Dr Piña: Right, due to an ischemic event.

Dr Carson: Well, no, I do not. I do think, though, that there is a concern that acute ischemia can alter the sensitivity of the sodium pump that is part of the mechanism of digoxin's action. Patients might have some enhanced risk of digoxin toxicity symptoms and findings in that circumstance.

Dr Piña: So, that may be a patient in whom you would want to do something else, like vasodilator therapy?

Dr Carson: It would not be the first card out of my deck for treating that patient.

Dr Piña: And then I think we need to recognize the drug-drug interactions with, for example, diltiazem, verapamil, and amiodarone. Can you think of any others? How about warfarin?

Dr Hauptman: I would think about antibiotics. Some of the breakdown of digoxin is through gut flora when you take it orally, so if you change the gut flora, you might absorb more digoxin. Cyclosporine for the renal transplant population can also increase digoxin levels. The P-glycoprotein inhibitors, amiodarone and verapamil, as you have already mentioned, decrease excretion of digoxin. There are many drugs. It is one of those sentinel drugs, like warfarin. I think when you have a patient on digoxin, you really should look at the medication list in the same way you might with a patient on warfarin.

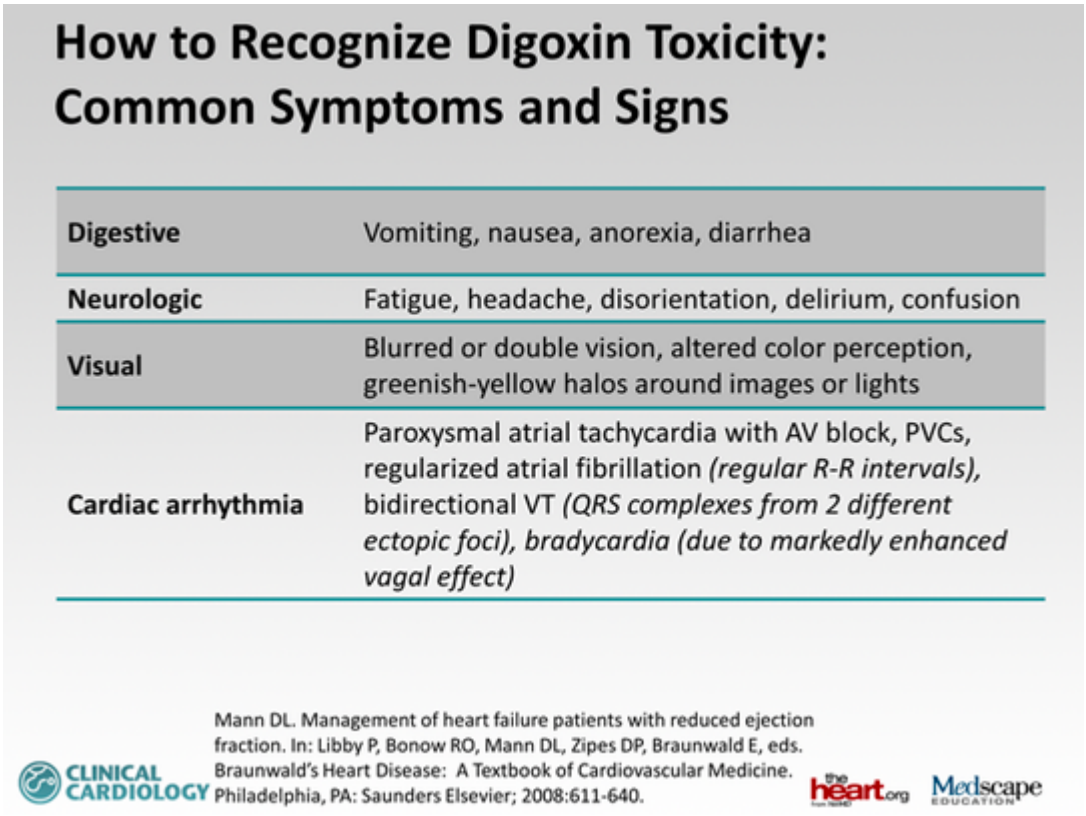
Dr Piña: It is a good thing to be reviewed when you suspect that a patient could be in digoxin toxicity. Of course, with our older patients who already have a lower body mass and whose renal function may be lower than we think, we can assess digoxin just by looking at the creatinine. Would you start those patients on 0.125 or 0.0625 mg, and would you start them on every other day?

Dr Hauptman: Well, I personally would start them on a low dose. If the patient is cognitively impaired, an every-other-day regimen might be difficult for them to follow, if there really is a need to initiate digoxin at all. It is interesting because the pendulum has swung. I do not know about my colleagues here, but when I first started out, digoxin levels were frequently checked, and then we reached a point where no one checked digoxin levels. Now, based on these data, we are checking them again. We really do want to see levels less than 1 and ideally maybe 0.5 to 0.8, especially in the heart failure cohort.

Dr Piña: Do you think it is different for women? Do we want to see lower levels in women? How about the digoxin trial in women?

Dr Carson: Well, I think there is concern about whether there are more adverse consequences for digoxin in women, but I wanted tocome back to a point that Paul made. I also think it can be very confusing for patients in general, but particularly for older patients, to take drugs a couple of times a week, as opposed to every day. They get the day wrong, and then they are completely out of sync. Maybe their level is double, et cetera, so I tend to avoid every-other-day dosing. I tend to give lower doses rather than do that.

Dr Piña: Okay, so high index of suspicion, we need to think about it. I think we need to teach our house staff to think about it because it is really not in the forefront when you have failure to thrive.



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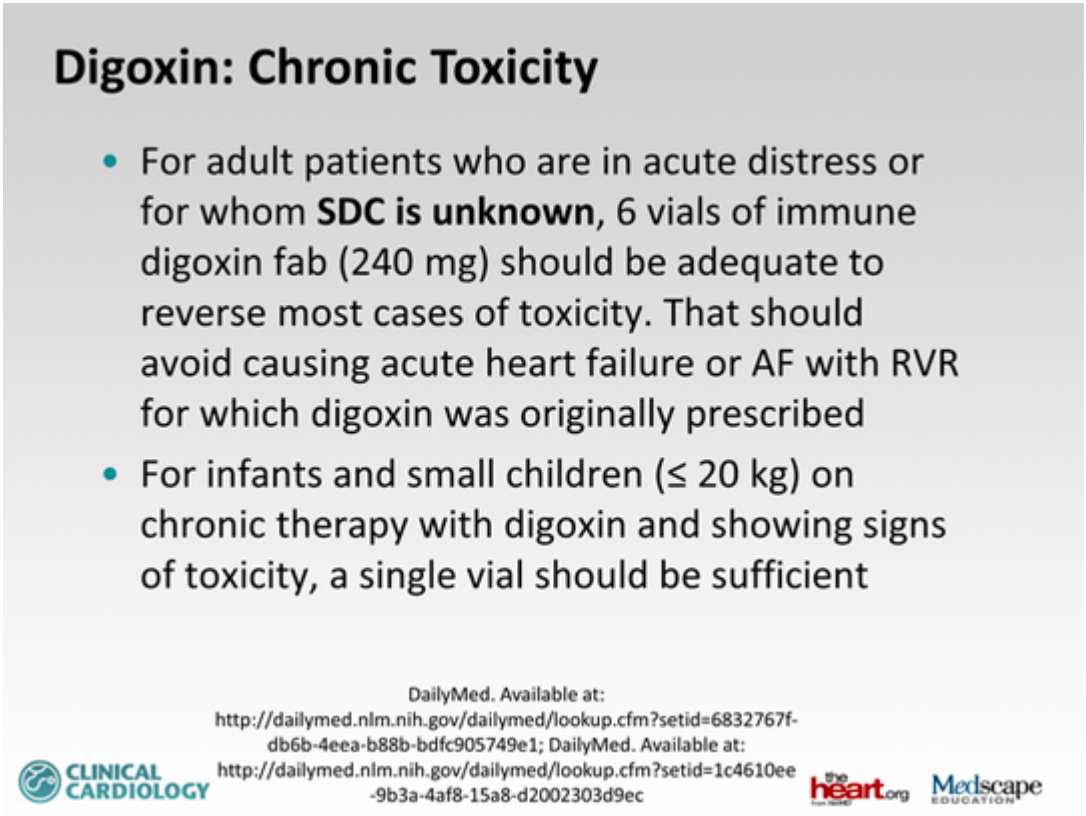
In an older patient, a woman with some nondescript symptoms, probably arrhythmia, the classic symptom of digoxin toxicity is atrial tachycardia with block. That is in the test, but there are other arrhythmias, like ventricular tachycardia. Also potassium. Do you check the potassium level in someone that you suspect could have digoxin toxicity?

Dr Pang: Yes, absolutely. Depending on the situation, the important thing is to always have a high index of suspicion, and be concerned about co-ingestions as well. I think the chemistry and the electrocardiogram (ECG) are some of the tests you are going to order first. Obviously, you will need a glucose test if there is an altered mental status. It has been recommended by the NIH that if the potassium level is greater than 5.0 mEq, then that could be 1 indication to go ahead and empirically treat with digoxin immune fab, so absolutely, I would check for the potassium.[3]

Dr Hauptman: I do not think it takes much in the way of an elevated level to trigger at least the thought of using digoxin immune fab, and I think there is a misunderstanding that anyone who is toxic needs 20 vials. If I am not mistaken, that amount is really for someone who actually has an acute ingestion -- let us say, a suicide attempt -- and you have no idea how many tablets they have taken. But especially for a patient who is in steady state, there is a set formula and often it comes down to be 2 or 3 vials worth of antidote.



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Dr Pang: Correct. One of the potential risks for the chronic patient who is stable is that you do not want to withdraw the digoxin so quickly that it might re-initiate the reason why the patient got treated in the first place.

Dr Piña: Yes, and there is a school of thought that digoxin withdrawal is not a good thing and that patients can get worse. I know that was one of the earlier concerns in the digoxin trial because 50% of those patients, I believe, were on digoxin coming into the trial, and so some of those in randomization would have their digoxin withdrawn.[2] I remember everybody was very concerned about that. Do you remember what happened to those patients?

Dr Hauptman: I do not know if that has been published, but I thought you were going to mention that β-blocker use in that trial was not even reported.

Dr Piña: It was not reported.

Dr Hauptman: That is remarkable. What a change in such a short period of time.

Dr Carson: But I think it is possible that we will see more digoxin use going forward.

Dr Piña: Why do you say that?

Dr Carson: The heart failure population is an older population. We often talk about this being increasingly so. We have got a lot of people who are on ACE inhibitors, β-blockers, aldosterone antagonists, diuretics, even at appropriate doses, who remain symptomatic.

Dr Piña: Right.

Dr Carson: Then, digoxin is an add-on therapy, and that is the way the recommendations read.

Dr Piña: These patients may not be transplant candidates if they are older or left ventricular assist device

(LVAD) candidates.

Dr Carson: That is absolutely right. We also know that that elderly group also is prone to development of AF.

Dr Piña: Right.

Dr Carson: And digitalis and a β-blocker together is a very good combination to provide effective rate control in this group of patients.

Dr Hauptman: I want to ask Dr Carson on diastolic heart failure about the use of digoxin in that cohort.

Dr Piña: That is a great question.

Dr Hauptman: That remains, I think, a glaring uncertainty, even when you look at the guidelines, which usually specify EF, as opposed to just symptoms alone. So in your practice, in an elderly patient whose EF is 50%, would you use digoxin?

Dr Carson: Well, that is a very interesting question because when you look at the compiled clinical trials -- I-PRESERVE, CHARM-Preserved, PEP-CHF,[4-6] even the fragment with seniors -- you do not see a lot of positive data out of those trials. In the group of patients in the digoxin study, about 1,000 patients had an ejection fraction above 45%. There were some clearly positive signals for a reduction in mortality and heart failure hospitalizations, just like the overall digoxin trial.[2] I actually think that when you look at a large, combined population like that, you end up sliding a little bit of the preserved EF population into systolic heart failure. That is why the result looks the same. Digoxin is not really at the top of my list of medications to use for heart failure with preserved EF, but, as we all know, it is hard to come up with a list at all for that group.

Dr Piña: You do not have much of anything.

Dr Carson: It is possible that the favorable things that digoxin does, such as reduction in neurohormones, improvement in baroreceptor sensitivity --

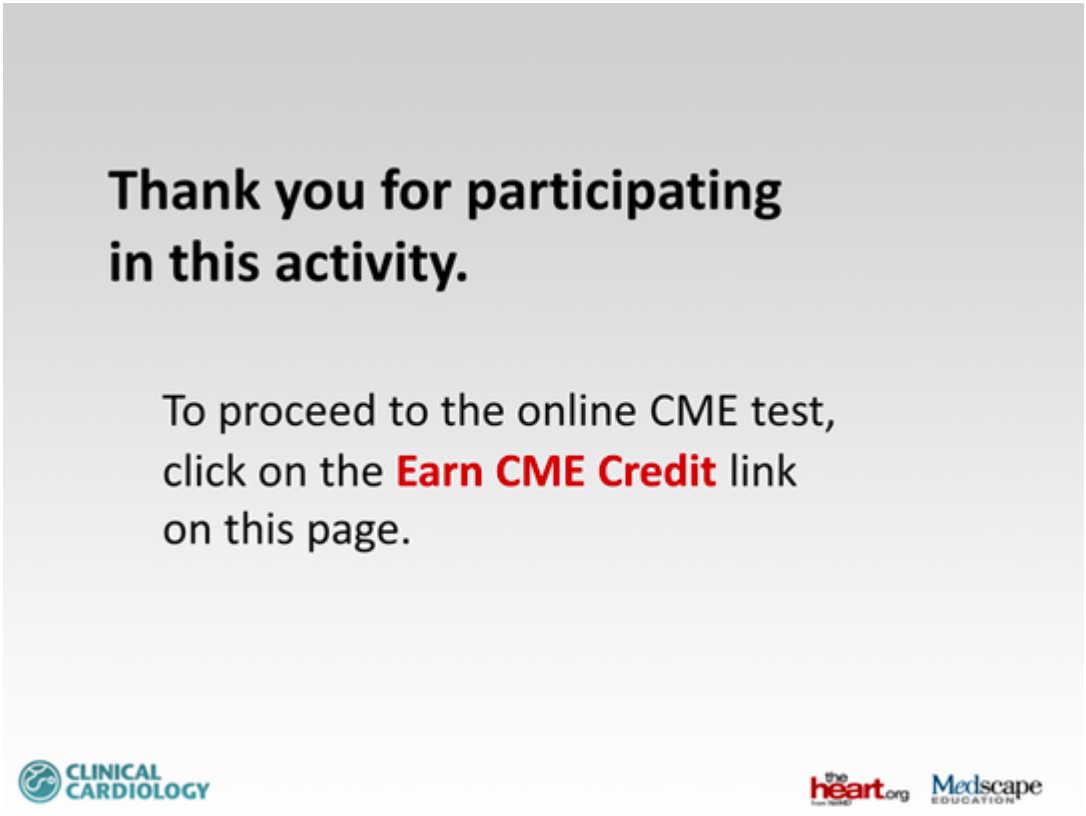
Dr Piña: Parasympathetic.

Dr Carson: -- May be a restoration of a parasympathetic tone. Those may be benefits in this older population, but I would still be very cautious using it in the preserved EF patient who is older and certainly may have renal insufficiency, too.

Dr Piña: Maybe it is time for a trial in that population.

Dr Hauptman: Or at least going back to look at those studies, I do not know if that has been done. You mentioned the pivotal study. We could just pull out those patients on digoxin and then compare active therapy versus placebo. That would be great.

Dr Piña: If we have echocardiographic data on those patients, we may be able to segment out the ones that have probably true, if there is anything like that, heart failure with preserved ejection fraction **(**HF-PEF) , with the big left atria, which is probably one of the most consistent findings.



Slide 15.

I want to wrap it up for today, and I want to thank my great panel here for a very good discussion. Hopefully, our listeners and our watchers will enjoy this and take it back to their patient population. I want to thank everyone for participating today. Now you may take the CME posttest by clicking on the Earn CME Credit link. Please also take a moment to complete the program evaluation that follows. We do read your evaluations and take your good suggestions very seriously; we always want to improve our programs. We are thrilled to have had you here today. This is Ileana Piña, signing off. Have a great day.

This transcript has been edited for style and clarity.

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ACC = American College of Cardiology
ACE = angiotensin-converting enzyme
ACS = acute coronary syndrome
ADHERE = Acute Decompensated Heart Failure National Registry
AF = atrial fibrillation
AHA = American Heart Association
A-HeFT = African-American Heart Failure Trial
AV = atrioventricular
CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
CHARM-Preserved = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity: Patients with Preserved Left Ventricular Function
ECG = electrocardiogram
ED = emergency department
EF = ejection fraction
ESC = European Society of Cardiology
HF = heart failure

HF-ACTION = Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HF-PEF = heart failure with preserved ejection fraction
I-PRESERVE = Irbesartan in Heart Failure with Preserved Systolic Function
IV = intravenous
LVAD = left ventricular assist device
PEP-CHF = Perindopril in Elderly People with Chronic Heart Failure
PVC = premature ventricular contraction
RALES = Randomized Aldactone Evaluation Study
RVR = rapid ventricular rate
SALT = Study of Ascending Levels of Tolvaptan in Hyponatremia
SCD-HeFT = Sudden Cardiac Death in Heart FailureTrial
SDC = serum digoxin concentration
SOLVD = Studies of Left Ventricular Dysfunction
TBL = total body load
V-HeFT I = Veterans Administration Cooperative Vasodilator–Heart Failure Trial I
V-HeFT II = Veterans Administration Cooperative Vasodilator–Heart Failure Trial II
VT = ventricular tachycardia

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