Good afternoon. Thanks, John, very much for the invitation to be here today. I am delighted to discuss elevated transaminases in the setting of heart failure.
I have nothing to disclose, and the opinions expressed here are my own.
The objectives of my presentation today are to review the effects of acute and chronic heart failure on acute and chronic liver injury, respectively, and also to discuss how challenging it can be to assess the potential for a drug product to cause drug-induced liver injury in the setting of heart failure.
As John has mentioned, there is a mutual relationship between the liver and the heart. Hepatocardiatomic diseases can be divided into three categories: heart diseases affecting the liver such as heart failure, which will be the focus of my discussion today; liver diseases affecting the heart such as chronic hepatitis C, which will be discussed by Dr. Wendy Carter to follow, and conditions affecting the heart and the liver at the same time. If you would really like to find out more about all three of these conditions, I recommend the review article by Fouad which was included in the references.
As we all know, acute heart failure can lead to acute liver injury, also known as acute ischemic hepatitis (acute liver injury), and chronic heart failure can lead to chronic congestive hepatopathy ("nutmeg liver"). But, as John has mentioned, the goal is to treat the underlying heart disease, because usually the hepatic abnormalities will improve.

*Goal is to treat the underlying heart disease*
Well, what in the world is a nutmeg liver and how did we ever come up with that term? I am not a histopathologist. But, if you looked at the picture on the right, those are normal liver cells. You see a picture of the nutmeg on the left. If you remember only one slide from my presentation today, I hope it is this. And if you play Pictionary, you may want to keep this in your back pocket.
But a nutmeg liver is not a happy liver. This is what it looks like. The term "nutmeg liver" was coined by Kiernan in the 1830s and, subsequently, by two others in the 1870s, by looking at autopsy specimens. And then, Mallory came along in the 1900s and determined that these brownish-red spots throughout the liver are actually due to centrilobular necrosis. I should say that medical history could have been very different if all three of these individuals had thought about cinnamon first.

I don't know what it is, but after being here at the agency for over 11 years, I find that sponsors, in particular, don't really know when the FDA may be trying to make a joke. (Laughter.) I'm glad I got your attention.
So, let's be very simplistic. Liver injury can be divided into acute liver injury, acute ischemic hepatitis, or chronic liver injury. Let's talk about acute liver injury first. As John has also mentioned, the liver has a great capacity to compensate for significant insults such as hypotension and decreased blood flow and hypoxemia.
What it does is try to extract more oxygen from the blood that does flow through the liver. But sometimes even that compensatory mechanism can be so overwhelmed, and you end up with hypoxic damage and get hepatocellular injury.
Acute Liver Injury

- Hypotension
- Hypoxemia
- Increased metabolic demand
Profound hypotension can be caused by acute cardiopulmonary arrest such as in the setting of acute myocardial infarction. It can also be caused as a result of heart failure in and of itself, but also associated with acute myocardial infarction, like a Killip III or IV infarct. You can also see hypotension with pulmonary embolism or sustained arrhythmia such as atrial fibrillation or flutter with a rapid ventricular response. Observationally, heart failure accounts for most cases of acute liver injury.
Hypoxemia can be due to respiratory failure or obstructive sleep apnea. With all of the obesity that we have in this country right now, obstructive sleep apnea is a big problem. There is a lot of people on CPAP.
Toxic or septic shock can also cause increased metabolic demand and contribute to acute liver injury.
What are the signs, symptoms, and physical examination findings that we see in acute liver injury? The patient can either be asymptomatic or have some non-specific symptoms, such as nausea or vomiting, anorexia, malaise, right upper quadrant discomfort, jaundice, decreased urine output, or flapping tremors, which are due to cerebral hypoperfusion and not hepatic encephalopathy.
With respect to the laboratory evaluation, we typically see sharp increases in the transaminases, total bilirubin, alk phos, LDH, and PT, occasionally accompanied by renal impairment. These liver abnormalities typically peak one to three days after the onset of the insult and normalize within five to ten days. You will also typically see an ALT/LDH ratio of less than 1.5. That helps to differentiate acute liver injury from viral hepatitis or even DILI.
Pathophysiologically, what we see is centrilobular necrosis of the zone 3 hepatocytes. I am not a histopathologist, but there are three Rappaport zones in the liver.
And so, zone 1 is highly-oxygenated. Zone 3 is not and is most susceptible to anoxic and hypoxic injury.
Liver Injury

- Acute (ischemic hepatitis)
- Chronic

What are the signs, symptoms, and physical examination findings that we see in acute liver injury? The patient can either be asymptomatic or have some non-specific symptoms, such as nausea or vomiting, anorexia, malaise, right upper quadrant discomfort, jaundice, decreased urine output, or flapping tremors, which are due to cerebral hypoperfusion and not hepatic encephalopathy.
Now let's move on to talk briefly about chronic liver injury in the time that we have left. Chronic heart failure and hepatic dysfunction can be due to a number of conditions, such as ischemic or non-ischemic cardiomyopathies, pulmonary arterial hypertension, valvular heart disease such as mitral stenosis or tricuspid regurgitation, constrictive pericarditis, and postoperative consequences of the Fontan procedure.
What are some of the symptoms and the signs and the physical examination findings we see in chronic liver injury? Well, you could have mild, dull right upper quadrant pain, hepatomegaly, peripheral edema, ascites, and jaundice, although jaundice is uncommon. Ascites can occur in up to 25 percent of patients.
From a laboratory perspective, you will have two- to threefold increases in AST, ALT, LDH, GGT, and ALP. The total bilirubin will be increased, but it rarely exceeds 3 milligrams per deciliter, and the albumin can be low.
Pathophysiologically, what we have here is we have right ventricular dysfunction which increases venous pressures. You end up with atrophy of hepatocytes, perisinusoidal edema, increased lymph formation, thrombosis due to the stasis of the blood flow within the sinusoids, the hepatic venules, and portal tracts. And you see an alternating pattern of hemorrhage and necrosis in zone 3 and normal or slightly steatotic areas in zones 1 and 2.
So, if we compare acute liver injury versus chronic liver injury, the point I just want to make is that, typically, in acute liver injury and acute heart failure there are marked increases in the total bilirubin and the transaminases compared to mild increases in the setting of chronic heart failure. With respect to acute liver injury, usually it is benign and a self-limited course. With chronic liver injury and chronic heart failure, if you treat the underlying heart failure, in the near-term the liver abnormalities can improve, but overall there is going to be a slowly progressive course due to the chronic heart failure.
Severe Drug-Induced Liver Injury

- Hepatocellular injury
- Aminotransferase (AT) elevations (ALT, AST) > 3x ULN and TB > 2x ULN
- Normal ALP
- No other reasons to explain the combination of increased AT and TB (e.g., hepatitis, preexisting or acute liver disease, another drug capable of causing the observed injury, PK interactions)
- May not be dose-related or evident nonclinically (exception: acetaminophen)
- Idiosyncratic hepatotoxicity (e.g., bromfenac, troglitazone, ximelagatran)

So, to contrast heart failure versus drug-induced liver injury, this has been covered by all of our other speakers this morning, including that very interesting talk by Dr. Seeff, I am sure as you all know. Where is Dr. Seeff? Did he leave? I did not find his lecture to be boring.

So, what you get with DILI is hepatocellular injury, elevations in the aminotransferases of greater than threefold upper limits of normal, total bilirubin greater than two times upper limit of normal, a normal alk phos, and there can be no other reasons to explain these abnormalities.

In many cases, DILI is not dose-related or evident non-clinically. In some cases, it can be idiosyncratic.
In summary, there is a mutual relationship between the heart and the liver. Acute heart failure can lead to acute liver injury (acute ischemic hepatitis). Chronic heart failure can lead to chronic liver injury (chronic congestive hepatopathy). Treat the underlying heart failure. In the setting of heart failure, it can be challenging to assess whether a drug product can cause drug-induced liver injury. That is why I want to say that I am so grateful to have a colleague like Dr. Senior who can help us sort through these very challenging cases. Thank you very much for your attention.
Back-Up Slides
Profound hypotension (often as a consequence of acute cardiopulmonary collapse)