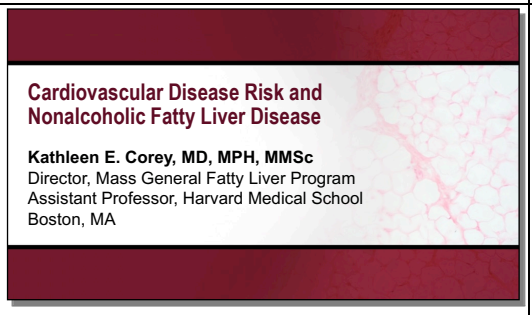
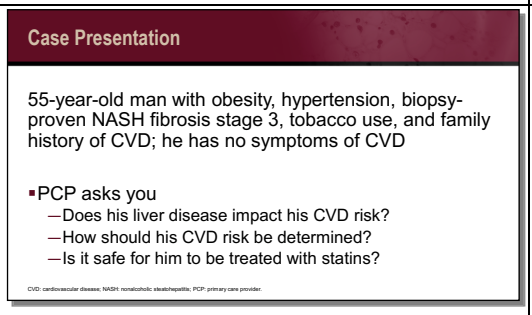
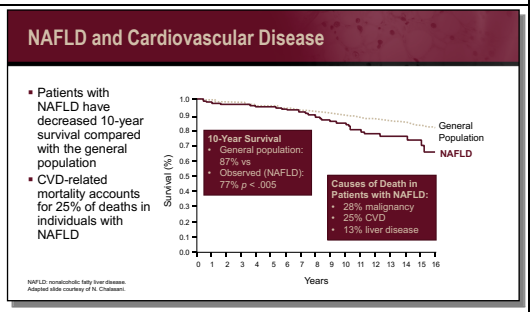
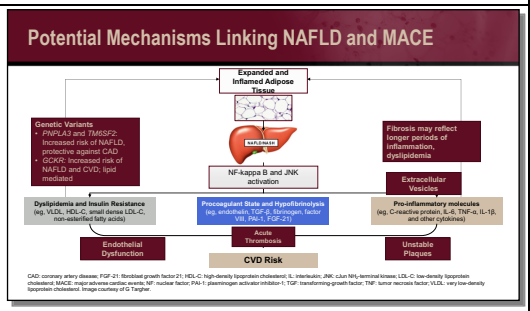
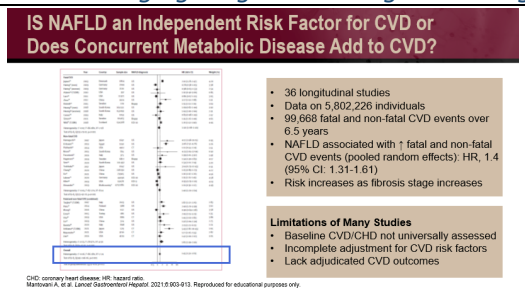
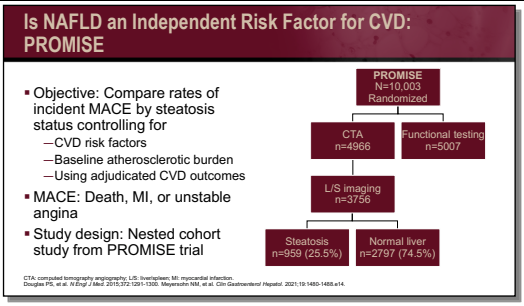
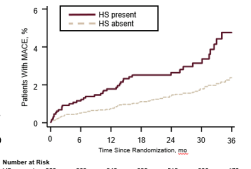
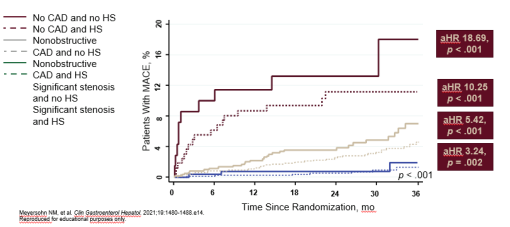
1		
2		Hi, I'm Kathleen Corey. I'm the director of the Mass General Hospital non-alcoholic fatty liver disease program, and an assistant professor at Harvard Medical School. And I'll be talking about cardiovascular disease risk in non-alcoholic fatty liver disease. For more information on the treatments for non-alcoholic fatty liver disease, especially emerging therapies, please see my colleague Dr. Zobair Younossi's talk.
3		We'll start off with a case presentation. We have a 55-year-old man who has obesity, hypertension and biopsy-proven NASH with fibrosis stage three out of four, tobacco use, and a family history of cardiovascular disease, who comes to us. He has no ongoing symptoms of cardiovascular disease. And his primary care physician asks you several questions: Does his liver disease impact his cardiovascular disease risk? How should his CVD risk be determined? And is it safe for him to be treated with things like statins?

4		We know that patients with NAFLD have a decreased overall survival, compared to the general population. And we know that's in part driven by cardiovascular disease. Patients with NAFLD have a ten-year survival that is decreased, about 77%, compared to 87% in the general population. And a large proportion of that mortality comes from cardiovascular disease, upwards of 25%.
5		There's several potential mechanisms linking NAFLD and what we call major adverse cardiovascular events, or MACE. We know that patients with NAFLD have increased rates of dyslipidemia, insulin resistance, procoagulant states and hypofibrinolysis, and proinflammatory molecules that can lead to endothelial dysfunction, acute thrombosis and unstable plaques, and increase their cardiovascular disease risk.

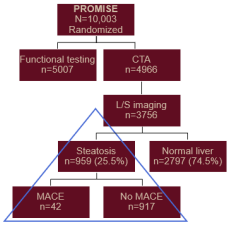
6		However, we know that many patients with NAFLD have other risk factors for cardiovascular disease. And we always are asked, is NAFLD an independent risk factor for CVD? And does the concurrent metabolic disease they have add to the CVD risk? This was a study that was published just recently in *Lancet Gastroenterology and Hepatology*, and it was a metanalysis seeking to address this question. They looked at 36 longitudinal studies with data on over 5.8 million individuals with nearly 100,000 fatal and non-fatal cardiovascular disease events over 6.5 years. NAFLD, they found, was associated with an increase in fatal and non-fatal cardiovascular events with a hazard ratio of 1.4, as you can see here. This risk increased as the fibrosis stage increased, suggesting that the more advanced NAFLD is, the more likely patients are to have cardiovascular disease events. However, several of these studies have important limitations that our group and others have sought to address. Their baseline amount of cardiovascular disease or coronary heart disease in each patient was not universally assessed in some of these studies. There was incomplete adjustment for cardiovascular disease risk factors. And there was a lack of adjudicated cardiovascular disease outcomes.

7		What we sought to do was to further evaluate whether NAFLD was truly an independent risk for cardiovascular disease through the PROMISE trial. And what we decided to do in this trial was compare rates of incident MACE – again, that's major adverse cardiovascular events, defined as death, MI or unstable angina. And we looked at them by steatosis status, controlling for some of those things that had been missing in previous trials: CVD risk factors that were comprehensively collected, baseline atherosclerotic burden by coronary CT, and using adjudicated cardiovascular disease outcomes. This study was a nested cohort control from the PROMISE trial. The PROMISE trial was a study of individuals with stable chest pain who were randomized to either receive functional testing, like a stress test, or anatomic testing with a coronary CT to determine if that ultimately changed outcomes. With those who underwent CT, about 3756, also had liver/spleen imaging, and that allowed us to determine whether patients had steatosis – about 25.5%, as we would expect in the general population – or had normal liver – 74.5% – and then allow us to compare rates of MACE, as well as risk factors for MACE.

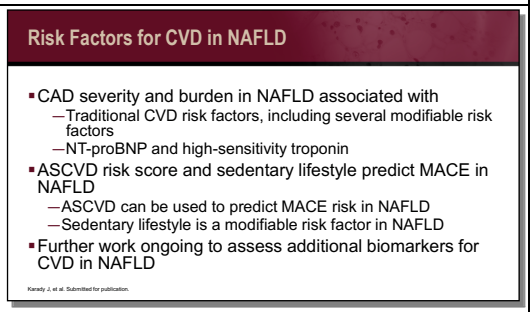
8	**NAFLD and MACE: PROMISE Trial** ▪Steatosis at baseline associated with higher prevalence of —Obesity (62% vs 41%) —Metabolic syndrome (53% vs 30%) —T2D (31% vs 16%) —Higher CV risk factor burden by ASCVD[a] risk score (12.3 vs 10.7) [a]ASCVD risk score is a composite score based on age, gender, race, total cholesterol, SBP/hypertension medicine, tobacco use, and T2D. ASCVD: atherosclerotic cardiovascular disease; CV: cardiovascular; SBP: systolic blood pressure; T2D: type 2 diabetes. Meyersohn NM, et al. *Clin Gastroenterol Hepatol*. 2021;19:1480-1488.e14.	Now, at baseline we found that those with steatosis, or fat on imaging, had higher prevalence of obesity, metabolic syndrome, and Type 2 diabetes. And they had a higher cardiovascular disease risk factor burden, as defined by the ASCVD risk score. And this is a risk score that we'll talk a lot about. It's largely replaced the Framingham risk score, and is used commonly by primary care doctors and cardiologists to predict 10-year cardiovascular disease risk in patients.
9	**NAFLD and MACE: PROMISE Trial (cont)** ▪At baseline, differences in atherosclerotic burden by steatosis status were small ▪No difference in high-risk plaques, calcified or non-calcified plaques ▪Steatosis associated with higher mean Leaman score (total obstructive and non-obstructive burden) and Agatston scores (coronary artery calcification) Meyersohn NM, et al. *Clin Gastroenterol Hepatol*. 2021;19:1480-1488.e14.	What we found also at baseline was that the differences in atherosclerotic burden by steatosis were small. Those with and without steatosis had no difference in the prevalence of high-risk plaques or calcified or non-calcified plaques. Although steatosis was associated with a higher mean Leaman score – which is a score that is a composite score for total obstructive and non-obstructive cardiovascular disease burden – and Agatston score, which is a coronary artery calcification score.
10	**Steatosis Associated With Higher Rates of MACE After Adjustment for Baseline CHD** ▪Median follow-up: 25.5 months ▪Overall rate of MACE: 3.1% (n=115) ▪Baseline steatosis associated with significantly higher rates of MACE: 4.4% vs 2.6% aHR 1.72,[a] $p = .007$  Adjusted for significant stenosis, ASCVD risk score, obesity, and metabolic syndrome. [a]Remained significant after adjustment for all CT measures of plaque and stenosis. aHR: adjusted hazard ratio; CT: computed tomography; HS: hepatic steatosis. Meyersohn NM, et al. *Clin Gastroenterol Hepatol*. 2021;19:1480-1488.e14. Reproduced for educational purposes only.	Importantly, what we found is that steatosis was associated with higher rates of MACE after adjustment for relevant covariants, cardiovascular risk factors and baseline coronary heart disease. Patients were followed after their coronary CT for 25.5 months on median, and their rate of MACE was about 3.1%. You can see here that those with hepatic steatosis had significantly higher rates of major adverse cardiovascular events, 4.4% over 25.5 months compared to only 2.6% in those without steatosis.

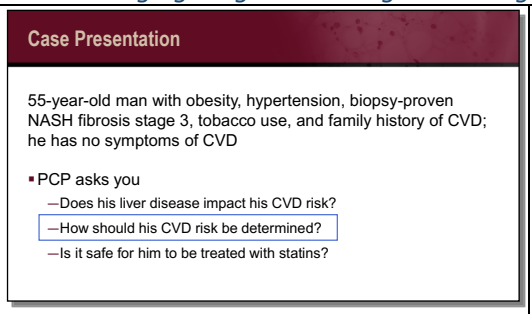
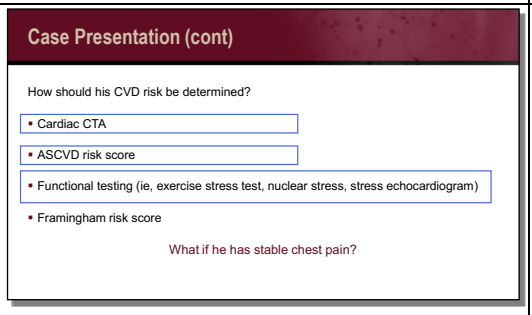
		And this remains significant after adjustment for all relent covariates and all the CT measures of plaque and stenosis that I just mentioned.
11	**Higher Rates of MACE With Steatosis and Both Obstructive and Nonobstructive CAD**  Meyersohn NM, et al. *Clin Gastroenterol Hepatol.* 2021;19:1480-1488.e14. Reproduced for educational purposes only	Interestingly further, when you took CAD and added steatosis, it also increased the risk of MACE. You can see here that these are patients with non-obstructive CAD. Those in the dashed line don't have hepatic steatosis, and when you add hepatic steatosis, their hazard ratio for major adverse cardiovascular events increases significantly. Likewise, these patients have obstructive cardiovascular disease. And their rates of major adverse cardiovascular events with obstructive disease is significantly higher if they have steatosis.
12	**NAFLD and MACE: PROMISE Trial Conclusion** ▪ *Baseline HS associated with a 70% increased risk of MACEs* ▪ *Increased risk independent of traditional CV risk factors and presence/extent of CAD including obstructive CAD and measures of plaque burden* Meyersohn NM, et al. *Clin Gastroenterol Hepatol.* 2021;19:1480-1488.e14.	What we found is that baseline hepatic steatosis was associated with a 70% increased risk of major cardiovascular disease events. And this increased risk was independent of traditional cardiovascular risk factors and the presence and extent of CAD, including prevalent obstructive CAD and measures of plaque burden.

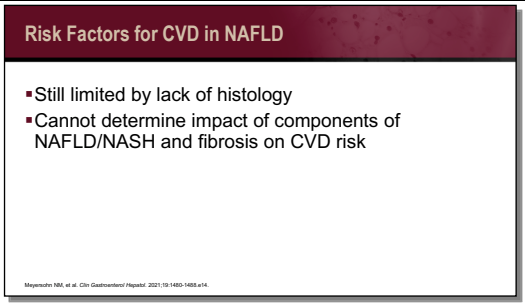
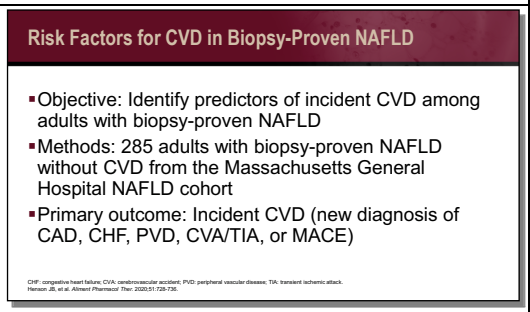
13	**Case Presentation** 55-year-old man with obesity, hypertension, biopsy-proven NASH fibrosis stage 3, tobacco use, and family history of CVD; he has no symptoms of CVD ▪PCP asks you —Does his liver disease impact his CVD risk? —How should his CVD risk be determined? —Is it safe for him to be treated with statins?	Back to our case. The PCP has asked us, does his liver disease impact his cardiovascular disease risk?
14	**Case Presentation (cont)** Does his liver disease impact his CVD risk? ▪Yes, it increases his CVD risk ▪No, it has no impact on his CVD risk ▪Unsure; his NAFLD may increase his risk but unsure how his advanced fibrosis impacts his CVD risk	The choices are: Yes, it increases his CVD risk. No, it has no impact on his CVD risk. Or unsure; his NAFLD may increase his risk, but we're unsure about how his advanced fibrosis, that stage three or four, impacts his CVD risk. We know that this liver disease, as I've shown you from this data and the metanalysis presented, that his NAFLD does increase his CVD risk. However, if you answered "unsure," that isn't wrong. His NAFLD does increase his CVD risk, but I haven't talked to you about how his advanced fibrosis may impact this risk. And we'll get to that later in the talk.

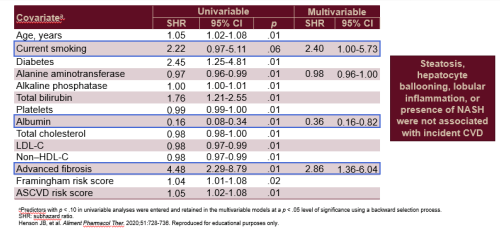
15	**Are traditional CVD risk factors valid in NAFLD and are there unique risk factors for CVD in NAFLD?** 1. Radiographic NAFLD 2. Biopsy-proven NAFLD	What we need to answer next are: Are traditional CVD risk factors valid in NAFLD? And are there any unique risk factors, including NAFLD histology, that occur in NAFLD?
16	**Risk Factors for CVD in NAFLD: PROMISE** ▪Nested cohort study from PROMISE trial ▪Limited to those with steatosis on imaging ▪MACE: Death, MI, or unstable angina  Douglas PS, et al. *N Engl J Med*. 2015;372:1291-1300. Kenady J, et al. Submitted for publication.	When we turn back to the PROMISE trial to try to evaluate this first question of, are there unique risk factors for CVD among patients with NAFLD? We again conducted a nested cohort study from the PROMISE study; this time focusing on this triangle here, of just patients with steatosis who had MACE, 42, or did not experience MACE, 917. The MACE, again, was defined as death, myocardial infarction, or unstable angina.
17	**Risk Factors for Significant CAD (>50% Stenosis) at Baseline in NAFLD** Dependent Variable: CAD (>50% stenosis) Unadjusted: OR, 95% CI, *p*; Adjusted[a]: OR, 95% CI, *p* **Demographics** Age (years): 1.04, 1.02-1.07, **< .001**; 1.06, 1.04-1.09, **< .001** Gender, % (males): 2.04, 1.40-2.97, **< .001**; 2.72, 1.82-4.06, **< .001** Race, % (ethnic minority): 0.72, 0.46-1.13, .150; 0.80, 0.50-1.26, .326 **CV risk factors** Hypertension, %: 1.20, 0.80-1.78, .376; 1.21, 0.80-1.82, .364 Diabetes, %: 1.74, 1.21-2.50, **.003**; 1.92, 1.32-2.80, **.001** Hyperlipidemia, %: 1.54, 1.02-2.33, **.042**; 1.60, 1.05-2.45, **.029** Smoker, % (current, past): 2.39, 1.63-3.50, **< .001**; 2.26, 1.53-3.33, **< .001** Obese, % (BMI >30 kg/m²): 0.66, 0.46-0.94, **.023**; 0.76, 0.52-1.10, .141 Sedentary lifestyle: 1.05, 0.74-1.50, .768; 1.14, 0.79-1.63, .491 ASCVD risk score: 1.05, 1.04-1.07, **< .001**; 1.05, 1.03-1.07, **< .001** ▪ All significant risk factors here are also associated with increased plaque burden (Leaman score). [a]Adjusted for gender and age. BMI: body mass index; OR: odds ratio. Kenady J, et al. Submitted for publication. Reproduced for educational purposes only.	What we found here is that there were significant interesting risk factors for significant CAD, which is defined as greater than 50% stenosis at baseline in those with NAFLD. We would expect that age and gender, male gender, are associated with CVD, and that diabetes, hyperlipidemia and, very importantly, smoking are associated with prevalent significant CAD. Something that we don't think about enough in our patients is the tobacco use. We also found that the ASCVD risk score – again, the risk score that's commonly used in the general population but hasn't been proven to be predictive

		in NAFLD – was indeed predictive of significant CAD in a NAFLD population.
18	**Risk Factors for Significant CAD (>50% Stenosis) in NAFLD** ▪Other risk factors identified —Lipids: LDL, total cholesterol, triglyceride, and apolipoprotein B levels —NT-proBNP —High sensitivity troponin NT-proBNP: N-terminal pro-brain natriuretic peptide. Karady J, et al. Submitted for publication.	We also identified other risk factors for prevalent CAD, including lipids, NT-proBNP, and high-sensitivity troponin.
19	**Risk Factors for MACE in NAFLD** Dependent Variable: Death, Non-fatal MI, or Hospitalization for UAP Unadjusted: HR, 95% CI, p Adjusted*: HR, 95% CI, p **Demographics** Age (years) 1.02 0.99-1.06 .224 1.03 0.99-1.07 .106 Gender, % (males) 1.45 0.77-2.72 .249 1.67 0.87-3.21 .124 Race, % (ethnic minority) 1.12 0.55-2.27 .759 1.18 0.58-2.41 .642 **CV risk factors** Hypertension, % 1.05 0.54-2.05 .887 1.04 0.53-2.04 .909 Diabetes, % 1.40 0.75-2.60 .295 1.45 0.77-2.72 .249 Hyperlipidemia, % 0.77 0.41-1.44 .408 0.78 0.42-1.48 .453 Smoker, % (current, past) 1.43 0.77-2.66 .261 1.36 0.73-2.55 .335 Obese, % (BMI >30 kg/m²) 0.64 0.35-1.17 .150 0.69 0.38-1.28 .245 Sedentary lifestyle 2.57 1.29-5.11 .007 2.68 1.34-5.34 **.005** ASCVD risk score 1.03 1.01-1.05 .002 1.03 1.00-1.06 **.022** **CAD equivalent** Positive family history, % 0.54 0.26-1.14 .106 0.58 0.28-1.22 .149 PAD, % (44 pad) 0.91 0.22-3.79 .902 0.82 0.19-3.45 .787 Stroke, % (1 stroke) – – – – – – CAD equivalent, % 1.38 0.71-2.45 .371 1.34 0.72-2.51 .353 *Adjusted for gender and age. PAD: peripheral artery disease; UAP: unstable angina pectoris. Karady J, et al. Submitted for publication. Reproduced for educational purposes only.	Importantly then, we went on to look at risk factors for incident MACE, incident major adverse cardiovascular disease events in those with NAFLD. And while we didn't see a lot of traditional risk factors, we did see two important risk factors that were at baseline predictive of future cardiovascular disease events. That's sedentary lifestyle and the ASCVD risk score. We've shown that a modifiable risk factor, sedentary lifestyle, can predict future cardiovascular disease events, and the ASCVD risk score and predict both prevalent and incident major adverse cardiovascular disease events.

20		The CAD severity and burden in NAFLD, therefore, is associated with our traditional risk factors that we think about in many patients, like age, gender and tobacco use, as well as NT-proBNP and high-sensitivity troponin. And importantly, the ASCVD risk score is a valid score that can be used, and I would say should be used, in all of our patients with NAFLD to assess their future cardiovascular disease risk. And sedentary lifestyle is a strong but modifiable risk factor for cardiovascular disease events in NAFLD. And further work is ongoing to evaluate additional biomarkers for prediction of CVD in NAFLD.

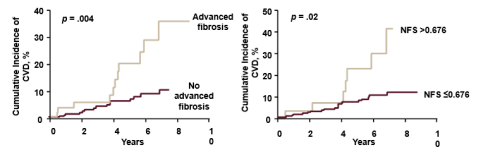
21		When we think about our patient now, we've answered one of our questions. We think his liver disease does impact CVD risk. But how should his CVD risk be determined?
22		Should we use a cardiac CT, as I've shown in the PROMISE trial? The ASCVD risk score? Functional testing, like exercise stress test, nuclear stress or stress echocardiogram? Or the Framingham risk score? Well, I hope I've convinced you that we should be using, for all of our patients, the ASCVD risk score, a calculator that you can find online and put in a patient's demographics and laboratory values; and that will predict their ten-year risk; and that we've validated this in patients with NAFLD. However, it's different if this patient has stable chest pain, or other symptoms of cardiovascular disease. For that patient, the CVD risk should be evaluated and determined either using a coronary CTA or functional testing. Both have been shown to be valid predictors of major adverse cardiovascular events, and can be used, of course in conjunction with consultation with our cardiology colleagues, to determine if a patient's stable chest pain is from cardiovascular disease.

23		Now, the problem with the studies I've discussed so far is they are limited by a lack of histology. We don't know if these patients have steatosis, NASH or any fibrosis. And we therefore can't determine the impact of the individual histologic components of NAFLD and fibrosis on cardiovascular disease risk.
24		I'll talk about a final study that looked at risk factors for CVD in biopsy-proven NAFLD. The objective was to identify predictors of incident CVD among adults with biopsy-proven NAFLD. And 285 patients were evaluated who had biopsy-proven NAFLD, but who did not have baseline cardiovascular disease, from our Mass General Hospital NAFLD cohort. The primary outcome was incident cardiovascular disease, including a new diagnosis of coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular accident, or major adverse cardiovascular event.

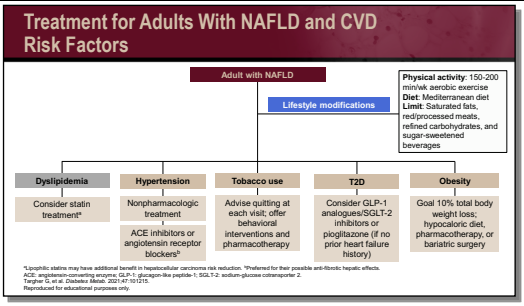
25	**Risk Factors for CVD in Biopsy-Proven NAFLD (cont)** ▪Followed prospectively to the first incident CVD, liver transplant, death, or end of follow-up —Mean 5.2 years ▪Incident CV events occurred in 26 individuals (9.1%) Henson JB, et al. *Aliment Pharmacol Ther.* 2020;51:728-736.	Patients were followed prospectively to the first incident of CVD, liver transplant, death or the end of follow-up for a mean of 5.2 years. And over that time, 26 individuals, or 9.1% of the total cohort, had a new CV event.
26	**Risk Factors for CVD in Biopsy-Proven NAFLD (cont)**  [1]Predictors with $p < .10$ in univariable analyses were entered and retained in the multivariable models at a $p < .05$ level of significance using a backward selection process. SHR: subhazard ratio. Henson JB, et al. *Aliment Pharmacol Ther.* 2020;51:728-736. Reproduced for educational purposes only.	What we found is similar to what we found in the PROMISE trial; again, emphasizing the importance of risk factor monitoring. Current smoking on multivariate analysis was a strong predictor of future cardiovascular disease events. Albumin, that being a low albumin, was associated with cardiovascular disease events. And advanced fibrosis was a strong predictor. Steatosis, hepatocyte ballooning, lobular inflammation or the presence of NASH were not associated with incident CVD. Only the presence of either stage three or four fibrosis was strongly predictive and remained so on multivariate analysis for cardiovascular disease events.

Covariate[1]	Univariable			Multivariable	
	SHR	95% CI	*p*	SHR	95% CI
Age, years	1.05	1.02-1.08	.01		
Current smoking	2.22	0.97-5.11	.06	2.40	1.00-5.73
Diabetes	2.45	1.25-4.81	.01		
Alanine aminotransferase	0.97	0.96-0.99	.01	0.98	0.96-1.00
Alkaline phosphatase	1.00	1.00-1.01	.01		
Total bilirubin	1.76	1.21-2.55	.01		
Platelets	0.99	0.99-1.00	.01		
Albumin	0.16	0.08-0.34	.01	0.36	0.16-0.82
Total cholesterol	0.98	0.98-1.00	.01		
LDL-C	0.98	0.97-0.99	.01		
Non–HDL-C	0.98	0.97-0.99	.01		
Advanced fibrosis	4.48	2.29-8.79	.01	2.86	1.36-6.04
Framingham risk score	1.04	1.01-1.08	.02		
ASCVD risk score	1.05	1.02-1.08	.01		

Steatosis, hepatocyte ballooning, lobular inflammation, or presence of NASH were not associated with incident CVD

27	**Risk Factors for CVD in Biopsy-Proven NAFLD (cont)**  **Incident CV Event:** 19.6% fibrosis stage 3-4 vs 6.6% fibrosis stage 0-2 (*p* = .01) Attributable risk of advanced fibrosis for CVD: 66.6% NFS: NAFLD fibrosis score. Henson JB, et al. *Aliment Pharmacol Ther.* 2020;51:728-736. Reproduced for educational purposes only.	As you can see here, those patients with advanced fibrosis had significantly higher cumulative incident cardiovascular disease, and this was by histology. And when we used the NAFLD fibrosis score to predict advanced fibrosis, this was also predictive of cumulative incident CVD.
28	**Risk Factors for CVD in NAFLD** ▪Adults with advanced fibrosis at baseline had significantly higher rates of incident CVD compared with those with fibrosis stage 0-2 ▪Among those with biopsy-proven NASH, smoking and advanced fibrosis were strongest predictors of incident CVD	In adults with advanced fibrosis at baseline, there was significantly higher rates of incident CVD compared to those with fibrosis, stage zero to two. And among those with biopsy-proven NASH, smoking and advanced fibrosis were the strongest predictors of future cardiovascular disease events.
29	**Case Presentation** Does his liver disease impact his CVD risk? ▪Yes, it increases his CVD risk ▪No, it has no impact on his CVD risk ▪Unsure; his NAFLD may increase his risk but unsure how his advanced fibrosis impacts his CVD risk	Does his liver disease impact his cardiovascular disease risk? Yes, it increases his risk. No, it has no impact on his risk. Or, his NAFLD may increase his risk, but unsure about how his advanced fibrosis impacts his CVD risk. Well, as I mentioned before, yes, we know that NAFLD overall increases his risk. And we also know – now I hope I've convinced you again – the presence of advanced fibrosis also contributes to his overall cardiovascular disease risk.

30



What do we do about this? We really want to focus on similar methods and changes as we do for our treatment of NAFLD. And that focuses on lifestyle modification.

We want to make sure that our patients are engaging in physical activity – 150 to 200 minutes per week of aerobic exercise. Or for those who can't engage in aerobic exercise, resistance training. Because as you saw, sedentary lifestyle was an independent predictor of future cardiovascular disease events.

The diet should be a Mediterranean diet, which has also been shown to decrease cardiovascular events in the general population. And patients should limit saturated fat, red or processed meats, refined carbohydrates and sugar-sweetened beverages.

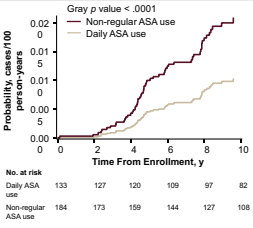
Then we should focus on the treatment of dyslipidemia, including statin treatment. And the ASCVD risk score can help us determine who should be on a statin.

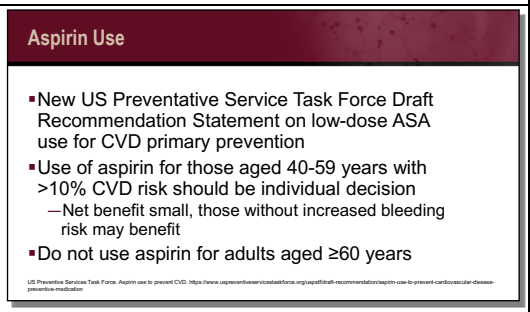
Treatment of hypertension.

Tobacco use cessation.

Treatment of Type 2 diabetes; specifically considering GLP-1 analogues and SGLT-2 inhibitors, which have been shown to decrease cardiovascular events in the general population and may be beneficial for NAFLD.

And then focus on the treatment of obesity with a goal of at least 10% total body weight loss, a hypocaloric diet, pharmacotherapy or bariatric surgery where appropriate.

31	**Case Presentation** 55-year-old man with obesity, hypertension, biopsy-proven NASH fibrosis stage 3, tobacco use, and family history of CVD; he has no symptoms of CVD ▪ PCP asks you —Does his liver disease impact his CVD risk? —How should his CVD risk be determined? —Is it safe for him to be treated with statins, ASA, or antihypertensives? ASA: acetylsalicylic acid.	Back to our patient. One of the most common questions that we get as gastroenterologists and hepatologists is about adjuvant therapy for cardiovascular disease and risk modification. And should we be treating our patients with things like statins and aspirin?
32	**Case Presentation** Is it safe for him to be treated with statins, ASA, or antihypertensives? ▪ Yes ▪ No ▪ Unsure Lipophilic statins include atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin, and pitavastatin	Well, is it safe for him to be treated with statins, aspirin, or antihypertensives?
33	**Aspirin and NASH** ▪ 361 adults with biopsy-confirmed NAFLD examined every 3-12 months for incident advanced fibrosis using NITs ▪ Compared with non-regular use, daily ASA use associated with lower odds of —NASH (aOR, 0.68; 95% CI: 0.37-0.89) —Fibrosis (aOR, 0.54; 95% CI: 0.31-0.82) ▪ Daily ASA users had lower risk of incident advanced fibrosis vs non-regular users (aHR, 0.63; 95% CI: 0.43-0.85) ▪ Effect was duration dependent; greatest benefit found ≥4 years of aspirin use (aHR, 0.50; 95% CI: 0.35-0.73)  aOR: adjusted odds ratio; NIT: noninvasive test Simon TG, et al. *Clin Gastroenterol Hepatol*. 2019;17:2776-2784.e4. Reproduced for educational purposes only.	The answer is, aspirin is safe for our patients and may be beneficial. This is a study that looked at 361 adults with biopsy-confirmed NAFLD or examined every three to 12 months over multiple years. And they found that those who are regular aspirin users had significantly lower odds of NASH and of fibrosis. And that daily aspirin users had a lower risk for incident advanced fibrosis. This effect was duration-dependent with the greatest benefit found after four years of aspirin use.

		We already know that aspirin is commonly used for the prevention of cardiovascular disease, and based on this study it may be beneficial for the treatment of NASH and fibrosis.
34		But there are new guidelines about this that have caused some confusion. The new US Preventative Service Task Force Draft Recommendation Statement on low-dose aspirin advises the use of aspirin for those age 40 to 59 with a greater than 10% CVD risk should be made by an individual decision between the patient and the primary care doctor. The net benefit in this group is probably small and should be used in those without an increased risk of bleeding. For those adults aged greater than or equal to 60, aspirin should not be used for primary prevention. This is distinct from secondary prevention. For our patients who've already had cardiovascular disease events, aspirin is something that we use, and can benefit their NASH. But for patients, for primary prevention, we really want to limit it to those age 40 to 59 who are high risk for cardiovascular disease, and who understand the risks and benefits.

35	**Take-Home Points** ▪ HS is associated with 70% increased risk of MACE, independent of traditional CV risk factors, compared with adults without steatosis ▪ Among those with NAFLD – Baseline CAD severity and burden in NAFLD associated with traditional CVD risk factors – ASCVD risk score and sedentary lifestyle predict MACE in NAFLD – Advanced fibrosis is associated with incident CV events ▪ Further studies needed to determine mechanism/association between fibrosis and CVD	To summarize, hepatic steatosis is associated with a 70% increased risk of MACE, independent of traditional CVD risk factors, compared with adults without steatosis. Among those with NAFLD, baseline CAD severity and burden in NAFLD is associated with traditional CVD risk factors, as well as an elevated ASCVD risk score and sedentary lifestyle. And advanced fibrosis is also associated with incident CVD events. Further studies are needed to understand this mechanism or association that links fibrosis and cardiovascular disease.
36	**Take-Home Points (cont)** ▪ Treatment calculators, including the ASCVD risk calculator, can determine when and how much lipid-lowering medication to start ▪ Lifestyle intervention with weight loss, smoking cessation, Mediterranean diet, and physical activity should be recommended to all individuals American College of Cardiology. ASCVD risk estimator plus. https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate	Treatment calculators – specifically the ASCVD risk calculator – can determine when and how much lipid-lowering medication to start, and help predict our patients' future cardiovascular disease risk. And lifestyle intervention with weight loss, smoking cessation, Mediterranean diet, and physical activity should be recommended to all of our patients with NAFLD.

37		Thank you so much for your time and attention.