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Learning objectives	• Discuss the screening, diagnostic and monitoring approaches to non-alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH). • Examine the updated Chest guidelines for anticoagulation perioperative bridging and anticoagulation in patients with atrial fibrillation. • Utilize medical management strategies regarding prostate cancer screening over age 69, and recognize the high prevalence of colonoscopy in the elderly without improved outcomes.

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Approach to non-alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH)

This article is an updated version of the 2018 summary of non-alcoholic fatty liver disease (NAFLD), including non-alcoholic steatohepatitis (NASH) previously published in this newsletter in 2018.[1,2,3] Updates include screening, diagnostic and monitoring approaches[4] and upcoming pharmacotherapeutic interventions.

Introduction

Now that close to 70% of Americans are overweight or obese, NAFLD has become the most common chronic liver disease in the U.S., representing ~75% of all cases. The annual direct cost attributable to NAFLD/NASH in the U.S. exceeds $100 billion. In a study of over 10,500 patients with biopsy-confirmed NAFLD, their risk of death over an average 14.2-year follow-up period was 41% higher than matched controls from the general population (16.9 vs. 28.6/1000 person-years [PY]; aHR=1.93).[5] This excess mortality was present in varying degrees in all categories of NAFLD (simple steatosis, NASH, and cirrhosis), but increased with increasing degrees of inflammation and fibrosis. However, because a large proportion of patients with NAFLD also have metabolic syndrome, it is still cardiovascular disease and not chronic liver disease that is the most common cause of death in these patients. It is estimated that 24% of the U.S. population has NAFLD and up to 6.5% has NASH, which is the next step in the evolution towards cirrhosis. Cirrhosis due to NASH will ultimately occur in 2% of the American population and will soon become the most common reason for liver transplantation. NASH is defined by the presence of hepatocyte damage with inflammation. The progression of NAFLD to NASH is linked to insulin resistance causing accumulation of toxic lipid metabolites and activation of inflammatory mediators, including TNF alpha. There may also be important contributions from an abnormal gut microbiome. Histologically, NASH is indistinguishable from alcohol related liver damage. Importantly, the most potent risk factors that predict the transition from NAFLD to NASH are Type 2 diabetes and the various components of the metabolic syndrome. The risk of hepatocellular carcinoma is similar to that from other causes of cirrhosis; therefore, patients with cirrhosis need yearly ultrasound surveillance for the development of hepatocellular carcinoma (HCC).

Diagnosis

Since it is impractical and inappropriate to perform liver biopsy on all patients with NAFLD to assess for NASH, a more focused approach to assessing for this condition has recently been put forth by the American Association for the Study of Liver Diseases (AASLD).[6] Patients with two metabolic risk factors or with Type 2 diabetes mellitus should be screened for NASH. Metabolic risk factors include central obesity, high triglycerides, low HDL cholesterol, hypertension, and insulin resistance. In addition to a detailed alcohol history, the following studies will exclude the vast majority of alternative diagnoses.

- Iron studies for hemochromatosis
- Hepatitis B and C serologies for chronic viral hepatitis
- ANA and anti-smooth muscle antibody for autoimmune hepatitis
- Anti-mitochondrial antibody for primary biliary cirrhosis
- Alpha-1 antitrypsin level for alpha-1 antitrypsin deficiency

Because alcohol excess causes identical histologic changes, it may be either the primary etiology or contributory depending on the level of alcohol intake. Moderate alcohol intake at one to two drinks daily has not been found to cause or adversely affect NAFLD.

Although the specificity of an elevated alanine aminotransferase (ALT) level for the diagnosis of NAFLD is 85%, the sensitivity is only 45% and patients can progress to cirrhosis with normal liver function tests (LFTs). The AST/ALT ratio is typically < 1. Clinical signs suggesting the progression to cirrhosis include progressive elevations of the AST/ALT with a ratio >1, increased bilirubin levels, thrombocytopenia, or exam stigmata of advanced liver disease.

The Fibrosis-4 index (FIB-4) is a rigorously studied score for NASH that uses age, AST, ALT, and platelet count to calculate. While it requires minimal and readily available data to calculate and has a high negative predictive value, it has a low positive predictive value and is less accurate in those >65 or <35 years of age. Additionally, roughly 30% of individuals have a score in the 'indeterminate' range, requiring further testing, such as with one of the direct serum fibrosis biomarker tests, or an imaging test for liver stiffness. Imaging includes vibration controlled transient elastography (VCTE – FibroScan®) and magnetic resonance elastography (MRE). Of the two imaging tests, MRE has slightly more favorable performance measures but may not be as widely available and is about 4 times more expensive than the FibroScan. All that said, a FIB-4 score in a person at risk for NASH of <1.3 likely has low risk of progression and can be safely managed in the primary care setting with regular follow-up. Scores in the indeterminate range of 1.3-2.67 should have a FibroScan performed. If this shows significant fibrosis, GI referral should be obtained. Scores >2.67 suggest more advanced fibrosis and likely would benefit from GI specialist management.

Management

Pharmacotherapy is not recommended in the absence of NASH, other than treatment that would otherwise be indicated for DM2 or obesity. There is ample data to support weight loss to reverse NAFLD/NASH and since there are available therapies for this, including drugs and bariatric surgery, weight loss should be considered the cornerstone of treatment. Sustained weight loss of at least 3-5% of body weight is needed to reduce steatosis, and 7-10% for patients with NASH. Additionally, Type 2 diabetes should be aggressively managed. Low carbohydrate diets have shown greater improvement in NAFLD compared to other types of diets. Bariatric surgery in 766 patients with paired liver biopsies showed improvement in NAFLD in 91%, NASH in 81%, and fibrosis in 65% of patients. There are no FDA approved drugs, and the best data to date show improvements in only ~50% of patients with any intervention other than weight loss. The Institute for Clinical and Economic Review (ICER), a non-profit research institute that examines value including cost-effectiveness for existing and emerging therapeutics, recently published a report on two new pharmaceuticals soon to be available (anticipated FDA decision in 2023) for the treatment of NASH.[7] Resmetirom is a small molecule agonist for the thyroid hormone receptor beta. Obeticholic acid is a bile acid analog. This group concluded that the two new agents improve liver histology but there is not yet evidence demonstrating improved long-term outcomes. As the pharmaceutical companies have not yet disclosed the intended price, it is not yet clear if these drugs will be cost-effective.

- **Vitamin E** at a dose of 800 IU daily has been shown in a randomized trial to improve both liver tests and histologic changes of both NAFLD and NASH including resolution of NASH in 36% of patients. However, fibrosis scores were not improved with vitamin E treatment.

- **Pioglitazone** also improves insulin sensitivity and is the best studied of the pharmacologic agents and has demonstrated clear benefits. This may be related to the fact that unlike metformin, pioglitazone improves adipocyte function, and thus increases fatty acid uptake in adipose tissue, decreasing the fatty acid load to the liver and thereby decreasing deposition of fat in the liver. This improves insulin sensitivity at the expense of the expansion of peripheral fat mass (thus the weight gain seen with this drug class). Improvements in the 35-50% range in liver functions and histologic changes have been seen in both diabetic and non-diabetic populations with the use of pioglitazone. The number needed to treat with pioglitazone for resolution of NASH ranges from 2-12, which makes it a reasonable treatment strategy if there are no contraindications.

- Importantly, **metformin** improves insulin sensitivity but has not been shown to improve liver histologic changes. This may be related to the fact that its main effects are on increasing muscle uptake of glucose and decreasing hepatic glucose production, with lesser effects on fat metabolism. If however, patients treated with metformin have significant weight loss and/or improvement in Type 2 diabetes, liver function is likely to secondarily improve.

- Phase II trials have shown improvements in NASH using the **GLP-1 agonist** class and phase III trials are ongoing. Smaller trials have shown benefits using probiotics and fish oil supplements, both of which have been shown to improve insulin sensitivity.

- Lastly, there are small trials showing benefits, including improved histologic changes with use of pentoxifylline which is a TNF alpha antagonist.

Summary

We are under diagnosing both NAFLD as well as NASH. Increased vigilance is required to screen and identify the subset of our patients with NAFLD who are progressing towards NASH and cirrhosis. Once identified by the FIB-4 test and Fibroscan when indicated, the first efforts should be directed at lifestyle modification including, when indicated, pharmacologic or surgical approaches to weight loss, and optimal control of Type 2 DM when present. Given the available data from the Phase II trials, GLP1-RA therapy is the preferred pharmacotherapy for obesity in the setting of NASH. If unsuccessful, the options are to initiate supplement therapies using probiotics, Vitamin E, and/or fish oils, versus initiation of pharmacotherapy using pioglitazone. Bariatric surgery has a clear role when obesity is resulting in the progression of NAFLD to NASH and cirrhosis and continues to be underutilized. NAFLD progressing to cirrhosis will likely be the most common form of cirrhosis and the most common reason for liver transplantation in the near future.

Evidence in favor of bariatric surgery to treat NASH

Recent publication of results from the BRAVES trial (bariatric-metabolic surgery vs. lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (NASH)) provides strong evidence for preferential treatment with surgery to treat NASH.[8] In this randomized controlled trial including 288 patients with biopsy-confirmed NASH, a third were randomized to intensive lifestyle intervention plus medications, a third to Roux-en Y gastric bypass and a third to sleeve gastrectomy. Intention-to-treat analysis showed that patients in both surgical groups had over 3.6 times greater chance of NASH resolution with no worsening fibrosis compared to the intensive lifestyle intervention with medication group at 1-year follow-up. This was even more favorable for the surgery groups when using a per-protocol analysis. The complications in the surgery groups were managed medically or endoscopically, and there were no serious adverse events reported. These findings comport with the 2017 publication of a study looking at the use of these bariatric surgeries in the treatment of patients with Type 2 diabetes mellitus and obesity in which the surgery arms had significantly better outcomes than the medical therapy arm.[9] In this report of a 5-year follow-up after randomization of the 150 patients, all relevant laboratory parameters (HgbA1c; lipid profile), body weight, and measured quality of life (QOL) were significantly better in the surgery groups. For HgbA1c, there was an average reduction of 2.1% in the surgery groups compared with 0.3% in the medical therapy group. For the other outcomes of interest, the numbers are as follows: body weight (-23%, -19%, and -5% in the gastric-bypass, sleeve-gastrectomy, and medical-therapy groups, respectively), triglyceride level (-40%, -29%, and -8%), use of insulin (-35%, -34%, and -13%), and QOL (general health score increases of 17, 16, and 0.3; scores on the RAND 36-item health survey ranged from 0 to 100, with higher scores indicating better health) ($P<0.05$ for all comparisons).

While bariatric surgery appears to perform better than intensive lifestyle intervention plus medical therapy, study limitations make the generalizability of the findings less robust. As always, individual patient factors must be considered when applying the evidence to an individual case. The results of the BRAVES trial add to our understanding of effective treatments of this disease.

Anticoagulation perioperative bridging guideline – Chest update

The updated Chest guideline includes 44 new recommendations of which only a subset is relevant to primary care.[10] Of note, almost all of the previous indications for heparin bridging have been removed. There are still circumstances where heparin bridging may be indicated based on a high risk of perioperative thromboembolism. See the accompanying **Table 1,** which is helpful in identifying this high-risk population. Below are the most important updates.

- Perioperative heparin bridging is no longer recommended in patients receiving vitamin K antagonists (VKA) therapy for atrial fibrillation, mechanical heart valves, or for VTE. The recommendation is to hold VKA therapy at least 5 days prior to the procedure.
- VKA interruption is not recommended for minor dermatologic, minor ophthalmologic procedures, or for colonoscopy with anticipated polypectomy.
- Heparin bridging is not recommended when DOAC therapy is temporarily held perioperatively. The recommendations for stopping specific DOAC therapies preoperatively are:
  - Apixiban, edoxaban, and rivaroxaban - stop 1-2 days before procedure
  - Dabigatran – stop 1-4 days before procedure
- In patients who require DOAC interruption for an elective surgery/procedure, perioperative heparin bridging is not recommended. Resumption of DOAC therapy is recommended not earlier than 24 hours post procedure.
- In patients receiving ASA for secondary prevention of stroke or MI, who are undergoing elective non-cardiac surgery, ASA continuation is recommended.

Table 1: Adapted American College of Chest Physicians (CHEST) Suggested Risk Stratification for Patient-Specific Periprocedural Thromboembolism

Risk Category	Mechanical Heart Valve	Atrial Fibrillation	VTE
High (> 10%/y risk of ATE or > 10%/mo risk of VTE)	Mitral valve with major risk factors for stroke[b] Caged ball or tilting-disc valve in mitral/aortic position Recent (< 3 mo) stroke or TIA or other highrisk stroke situations[c]	CHA_2DS_2VASc score ≥ 7or $CHADS_2$ score of 5 or 6 Recent (< 3 mo) stroke or TIA Rheumatic valvular heart disease	Recent (< 3 mo and especially 1 mo) VTE Severe thrombophilia (deficiency of protein C, protein S or antithrombin; homozygous factor V Leiden or prothrombin gene G20210A mutation or double heterozygous for each mutation, multiple thrombophilias) Antiphospholipid antibodies Active cancer associated with high VTE risk[a]
Moderate (4%-10%/y risk of ATE or 4%-10%/mo risk of VTE)	Bileaflet AVR with major risk factors for $stroke_b$	CHA_2DS_2VASc score of 5 or 6 or $CHADS_2$ score of 3 or 4	VTE within past 3–12 mo Recurrent VTE Non-severe thrombophilia (heterozygous factor V Leiden or prothrombin gene G20210A mutation) Active cancer or recent history of cancer[c]
Low (< 4%/y risk of ATE or < 2%/mo risk of VTE)	Bileaflet AVR without major risk factors for $stroke_b$	CHA_2DS_2VASc score of 1–4 or $CHADS_2$ score of 0–2 (and no prior stroke or TIA)	VTE > 12 mo ago

This was an empiric risk classification, not prospectively validated. ATE = arterial thromboembolism; AVR = aortic valve replacement; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack; CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease history, age ≥ 65 years, female sex.

[a]Includes pancreatic cancer, myeloproliferative disorders, primary brain cancer, gastric cancer, and esophageal cancer.

[b]Includes multiple prior strokes, prior perioperative stroke, or prior valve thrombosis.

[c]Atrial fibrillation, prior stroke or transient ischemic attack (TIA), hypertension, diabetes, congestive heart failure, and age > 75 years.

Evidence of over and under anticoagulation in patients with atrial fibrillation

The Optum Center for Research and Innovation (OCRI), along with colleagues at the Mayo Clinic, published a study in the International Journal of Cardiology[11] looking at patterns of anticoagulation use in 339,000 patients with non-valvular atrial fibrillation (AF). An algorithm was created to estimate CHA_2DS_2-VASc scores from patient claims and applied to the multi-payor Optum Labs data warehouse database using a retrospective cohort design.

The findings of note included:

- In the ~14,000 patients who had scores of 0 in men or 1 in women, 29.6% of patients were on anticoagulation therapy which was potentially inappropriate.
- In the ~297,000 patients who had scores ≥ 2 in men or ≥3 in women, 52.2% were not taking anticoagulants, suggesting possible undertreatment of stroke prevention in this large group of patients.
- In the year prior to the index date, there was an increase in ER and hospitalization use in the high-risk patients who were not anticoagulated. Also, within the previous 3 months of the index date, patients in the non-OAC group had a slightly higher number of ischemic strokes/systemic embolization, major bleeding, and intracranial bleeding episodes.

These data suggest that there is a significant opportunity to improve anticoagulation prescribing based on the CHA_2DS_2-VASc score in non-valvular AF in both low risk and high-risk groups of patients.

Prostate cancer screening not indicated in those over age 69 years, though potentially helpful for younger cohorts

The 21-year follow-up of the Dutch arm of the European Randomised Study of Screening for Prostate Cancer (ERSPC) trial again highlights the lack of benefit of treatment for prostate cancer (CA) over age 70.[12] These findings comport with the USPSTF recommendation to avoid screening for prostate CA in those age 70 and older (grade D).[13] This update on a subset of the ERSPC patients from the Netherlands included over 42,000 men aged 55-74 years who were offered PSA-based screening for prostate CA every 4 years. Those invited for screening who were over 69 years at the time of randomization had no improvement in prostate-specific mortality compared with those not invited for screening (RR of 1.18 [95% CI: 0.87–1.62]). The reason for this likely is due to the fact that aggressive prostate cancers manifest well before age 70, so those of that age and above who do have prostate cancer usually have a more indolent form of the disease; one that does not affect mortality statistics. The 21-year follow-up study does reinforce the potential benefit of screening those in the 55–69-year age group, with a number needed to invite (NNI) of 246 and number needed to diagnose (NND) of 14, to prevent one death from prostate cancer. For the outcome of metastatic disease, the NNI was 121 and the NND was 7. These numbers are similar in magnitude to the Göteborg (Sweden) arm of the ERSPC study 22-year follow-up, in which the NNI was 221 and NND was 9.[14] In that arm of the study, 20,000 men were randomized into a screening invite group and a control group. Screening was offered using PSA every other year. For both studies, there was a noted tradeoff between potentially lower mortality in exchange for higher rates of identification of indolent disease that would not substantively have impacted the patient's health.

For those of our patients who choose to be screened and who are subsequently diagnosed with low-grade prostate CA, patient education and shared decision-making around the beneficial use of active surveillance should be pursued.[15]

Low-value prostate cancer screening in those over age 69 associated with clinician behaviors

Based on robust evidence, the U.S. Preventive Services Task Force (USPSTF) recommends against screening for prostate cancer with a serum prostate-specific antigen (PSA) test in those over age 69 due to the risk of false positives and of overdiagnosis with resultant overtreatment.[16] Treatment of clinically localized prostate cancer in those over age 69 has not been shown to improve outcomes,[17] while it causes harm in virtually all men.[18] Despite this, screening in this age group remains common in clinical practice. A recent cohort study included over 32,000 males aged 70 and older who had a PSA, to better characterize factors associated with this low-value practice.[19] One of the factors associated with this over screening was a clinician discussing the advantages of PSA testing with their patient (odds ratio [OR], 9.09; 95% CI, 7.60-11.40; P<.001). This increased odds of having had a PSA test was not present when the clinician discussed the disadvantages of PSA testing (OR, 0.95; 95% CI, 0.77-1.17; P=.60). These findings suggest a central role of the clinician in providing evidence-based guidance in the shared decision-making discussion to decrease this low-value practice. Screening with serum PSA for prostate cancer is not indicated for average risk patients over age 69. Patient education and shared decision-making should be employed for those wanting screening.

High prevalence of colonoscopy in the elderly without improved outcomes

A recent article by Halabi et al. highlights the continued high prevalence of screening colonoscopies in patients who are asymptomatic for colorectal cancer (CRC), over 75 years old, and with a life expectancy of <10 years.[20] This may be evidence of ongoing low value care. The benefits of CRC screening take 10-15 years to manifest due to the time it takes for typical adenomas to progress to CRC, [21] and therefore would not benefit patients with a life expectancy <10 years. The study by Halabi et al. was a cross-sectional design with a nested cohort that included 7,067 patients over 75 years old and demonstrated a high percentage of those with life expectancy <10 years undergoing colonoscopy, with a very low percentage of actionable findings. Adverse events requiring hospitalization within 10 days of colonoscopy occurred in 13.58 per 1,000 patients in all patients. Those with life expectancy <10 years had double the complication rate compared with those with longer life expectancy. Only 2 per 1,000 patients were found to have invasive colorectal cancer. Of those 9 patients with life expectancy <10 years who were discovered to have colorectal cancer, only 1 out of the total screened population elected to undergo cancer treatment. Even with including the other 6 patients found to have cancer for a total of 15, at an estimated $1,000 per colonoscopy this means roughly $470,000 per cancer found, which is clearly not cost effective.

Colonoscopy complication rates are higher in the elderly for GI complications (e.g., perforation, bleeding) and non-GI complications (e.g., myocardial infarction, stroke).[22,23] Stool-based tests are safer in this population and are preferred for those in whom ongoing screening is indicated. For those with a life expectancy less than 10 years, there are no data supporting improved outcomes with CRC screening. The U.S. Preventive Services Task Force (USPSTF) 2021 guideline recommends discontinuing screening after age 85, and for those age 76-84, the decision to screen or not should be individualized, as the benefits are small.[24] Even if colorectal cancer is found, patients may elect for palliative, rather than attempting curative care.

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Dr. Kenneth Cohen is an experienced physician leader, practicing internist and researcher who has attained national recognition for health care quality improvement. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of Optum Care. He served as Chief Medical Officer from 1995 - 2020. He now serves as the Executive Director of Translational Research for Optum Care and co-leads the Optum Center for Research and Innovation. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the CDC Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine and School of Pharmacy. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

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With over 20 years of clinical, academic and leadership experience regionally, nationally and internationally, Dr. Jacobs currently serves as primary care engagement lead national Medical Director for Optimal Care within Clinical Performance at Optum Care. He is a Clinical Professor of Family Medicine at the Washington State University College of Medicine. He graduated from Pomona College with honors and from the John A. Burns School of Medicine as a member of the Alpha Omega Alpha honor society.

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