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Emerging therapies for MASLD and their impact on plasma lipids

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ABSTRACT

Metabolic-dysfunction associated steatotic liver disease (MASLD) affects 1 out of every 3 individuals in the adult population and the disease prevalence is predicted to increase worldwide. Patients with MASLD are also burdened by cardiovascular disease, which is the leading cause of mortality in this population. Complex metabolic derangements such as insulin resistance and atherogenic dyslipidemia affect patients with MASLD. In patients with MASLD, treatment such as pharmacotherapy may be best directed towards improving the adverse concomitant metabolic disorders associated with MASLD, particularly the ones that may contribute to MASLD. Herein, we discuss conventional therapies that target cardiometabolic risk factors which have the potential to improve hepatic injury, and summarize emerging therapies that target hepatic receptors, fibrosis, and fatty acid oxidation in patients with MASLD. Given the relationship between hepatic injury which leads to MASLD, insulin resistance, and ultimately atherogenic dyslipidemia our review uniquely delves into the effects of conventional and emerging therapies for MASLD on plasma lipid parameters.

1. Introduction

Metabolic-dysfunction associated steatotic liver disease (MASLD) is defined as the presence of hepatic steatosis in addition to one or more cardiometabolic risk factors and absence of other identifiable causes. MetALD (metabolic and alcohol related/associated liver disease) comprises patients with MASLD and increased alcohol intake [1]. The global prevalence of MASLD in the adult population is estimated at 25–30 % [2]. Metabolic-dysfunction associated steatohepatitis (MASH), the clinically aggressive form of MASLD, is defined as the presence of hepatic steatosis and lobular inflammation with hepatocyte injury. MASH affects approximately 3–6% of the population in the United States [2]. Importantly, the prevalence of MASLD and MASH continues to increase worldwide as the population burden of obesity and metabolic diseases simultaneously increases. By 2030, it is estimated that decompensated cirrhosis, hepatocellular carcinoma (HCC), and MASH-related deaths will increase three-fold [3].

Patients with MASH are known to be at increased risk of cardiovascular disease (CVD) [4]. Studies have shown that MASLD is an independent predictor of CVD, even when adjusted for known cardiovascular risk factors [3,5]. CVD is the leading cause of mortality before later stages of the disease (such as bridging fibrosis and cirrhosis) develop. Several metabolic derangements including insulin resistance, atherogenic dyslipidemia, metabolic syndrome, lipodystrophy, hypertension, and defects in mitochondrial fatty acid oxidation cluster together in patients with MASLD [6]. These patients are at high risk for ectopic fat deposition in tissues other than the liver (including cardiac, pancreatic, and skeletal) which increases the risk of atherosclerotic cardiovascular disease (ASCVD). Increased epicardial fat deposition is associated with intramyocardial inflammation, endothelial dysfunction, and accelerated atherogenesis. Epicardial fat itself can become insulin-resistant and a source of atherogenic dyslipidemia [7].

An important pathologic feature of MASLD is the dysregulation of lipid homeostasis. This is characterized by increased hepatic fatty acid uptake, de novo lipogenesis, suppressed fatty acid oxidation, excessive very low-density lipoprotein (VLDL) secretion, and impaired high-density lipoprotein (HDL) cholesterol efflux capacity (Central Illustration). Within the liver, fatty acids can either undergo oxidation or esterification to form triglycerides that are then stored or exported into the circulation as VLDL particles. Lipid accumulation i.e., hepatic

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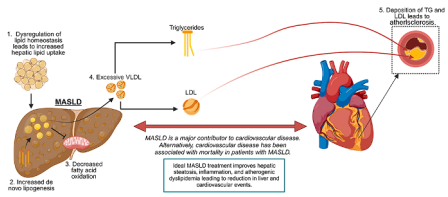

Central Illustration. Relationship between MASLD and Atherosclerosis
The biochemistry of lipid and lipoprotein abnormalities in MASLD is multifactorial. It includes dysregulation of lipid homeostasis which promotes hepatic fatty acid uptake, increased de novo lipogenesis, decreased fatty acid oxidation, and excessive VLDL secretion which consequently leads to elevated levels of triglyceride-rich lipoproteins in the circulation. These particles deposit in blood vessels (which is causal for atherosclerosis) and lead to complications such as acute coronary syndrome, peripheral artery disease, and ischemic stroke.
Abbreviations
MASLD: metabolic-dysfunction associated steatotic liver disease
VLDL: very low-density lipoprotein
TG: triglycerides
LDL: low-density lipoprotein.

steatosis, occurs when triglycerides conglomerate (primarily through excessive dietary intake or increased de novo lipogenesis) at a rate faster than triglyceride disposal [6]. Fatty acids are delivered to the liver after lipolysis of triglycerides primarily in the adipose tissue. Insulin resistance contributes significantly to this process and some treatments for MASLD are targeted toward weight loss and improving insulin sensitivity for this reason. Certain agents have been developed to pharmacologically target enzymes and transcription factors related to de novo lipogenesis such as stearoyl-Co-A response element binding protein-1c and farnesoid X receptor which are later discussed within novel therapies for MASH/MASLD [8].

There are currently no Food and Drug Administration approved medications for the treatment of MASLD and MASH [9]. An important challenge is designing agents that target MASLD without having a detrimental effect on plasma lipids as MASLD is intimately associated with lipid metabolism. In this review we will describe conventional and emerging MASLD therapies with a focus on their impact on lipid parameters and CVD risk.

2. Liver histology and imaging in MASLD

Per the American Association for the Study of Liver Diseases guidelines, patients with MASLD are typically asymptomatic and diagnosed once referred to gastroenterology for elevated liver chemistries or incidentally noted hepatic steatosis [10]. AST or ALT levels >30 U/L intermittently or chronically (≥6 months) suggests chronic liver injury and should be investigated. Metabolic comorbidities and evaluation of viral hepatitis serologies, autoimmune serologies, transferrin saturation, iron, ferritin, total iron binding capacity, ceruloplasmin, and alpha-1-antitrypsin genotype must be assessed in the initial evaluation phase. General screening for high-risk individuals such as those with type 2 diabetes mellitus (T2DM), obesity with metabolic complications, first degree relatives with cirrhosis due to MASH/MASLD, or moderate alcohol intake (21–39 grams daily in women and 31–59 grams daily in men) is recommended. Primary risk assessment includes determination of the fibrosis-4 index (FIB-4) which is valuable due to its high negative predictive value in case of FIB-4 <1.3. Patients at higher risk for MASLD progression include those with prediabetes, T2DM or ≥2 metabolic risk factors and require more frequent FIB-4 monitoring (every 1–2 years). FIB-4 scores are based on age, ALT, AST, and platelet count. Patients with FIB-4 ≥ 1.3 benefit from further assessment with vibration-controlled elastography (VCTE) or the Enhanced Liver Fibrosis (ELF) panel which measures hyaluronic acid, tissue inhibitor of metalloproteinase-1, and N-terminal procollagen III peptide in the serum. For patients in whom cirrhosis is suspected based on imaging and overall clinical picture, cirrhosis treatment can be initiated even in the absence of a liver biopsy. Conventional ultrasound can detect hepatic steatosis, but is not routinely recommended due to its low sensitivity for steatosis and low sensitivity in patients who are obese. The controlled attenuation parameter (CAP) measured with VCTE or MRI-PDFF are favored for the purposes of identifying and quantifying steatosis, respectively. If the diagnosis cannot be made based on history, laboratory testing, and non-invasive imaging, a liver biopsy is indicated and is the only definitive way to confirm the diagnosis of MASH and assess the severity.

The Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) developed the NAFLD activity score (NAS) as the gold standard for NASH histology assessment for clinical trials [11]. The components include steatosis (scores 0–3), inflammation (scores 0–3), and ballooning (scores 0–2) with the total score ranging from 0 to 8. Steatosis score of 0 indicates <5 % of the liver is affected by fatty changes, 1 indicates 5–33 %, 2 indicates 34–66 %, and 3 indicates >66 %. Inflammation score of 0 indicates no inflammatory foci, 1 indicates <2 foci/200x, 2 indicates 2–4 foci/200x, and 3 indicates >4 foci/200x. Ballooning score of 0 means none, 1 indicates few balloon cells, and 2 indicates many cells and prominent ballooning. MASH resolution requires absence or resolution of ballooning, with no or minimal inflammation confirmed by histology. In clinical trials, a reduction in NAS score by ≥2 points (with ≥1 point reduction in the ballooning category) is accepted as a marker of improvement if there is no progression of fibrosis [12].

The process of undergoing a liver biopsy utilizes time, financial resources, and posits risks to patients including infection (less than 1 %), moderate bleeding not requiring transfusions (0.2 %), severe bleeding (hemodynamic instability with radiographic evidence of intraperitoneal bleeding) between 0.01 % to 0.04 % and death (less than 0.01 %) [13]. There exist non-invasive imaging modalities to evaluate drug efficacy including vibration-controlled transient elastography (VCTE) also known as Fibroscan, magnetic resonance elastography (MRE), magnetic resonance spectroscopy (MRS), and magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) [14]. Fibroscan allows for measurement of hepatic fat, stiffness, and fibrosis with results readily available in clinic, however, limitations include lack of anatomic localization, low accuracy for quantifying the amount of steatosis, and cost prohibitive as a new Fibroscan machine costs $50,000 versus $34,000 for a portable machine and $8,500 for annual maintenance [15,16]. MRS allows for direct measurement of liver fat based on the signal peak of fat and advantages include disregard for iron deposition and fibrosis [17]. MRE converts wave images to cross-sectional images as a measurement of liver stiffness and is more costly than VCTE, yet more accurately diagnoses earlier stages of fibrosis [18]. MRI-PDFF is helpful in the study of drugs with high likelihood of anti-steatotic effect and in early trials to assess for reduction in liver fat content [14].

3. Off-label therapies for MASLD and MASH

The off-label therapies described in this section target cardiometabolic risk factors and have demonstrated potential efficacy in MASLD/MASH management [19]. These include metformin, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, vitamin E, pioglitazone, ezetimibe, and bariatric surgery and are summarized in Table 1.

Metformin has been investigated as a therapeutic option for MASH. Studies have been inconclusive due to challenges in differentiating whether effects from metformin are attributed to insulin-sensitization or its effect on weight loss. Loomba et al. found that metformin treatment for 48 weeks led to improvements in liver histology and ALT levels. These changes were suspected secondary to weight loss rather than effects on insulin as greater weight loss was associated with greater improvement in liver histology. There was a significant association between weight loss and improvements in NASH activity index and there

Table 1
Off-label therapies for MASLD/MASH.

Agent	Efficacy/safety	Baseline lipid parameters (mg/dL)	Effect on lipid parameters (mg/dL)	Baseline hepatic fat content	Effect on hepatic fat content
Liraglutide [22]	Liraglutide is effective for MASH resolution. More gastrointestinal side effects were noted in patients taking liraglutide compared to placebo.	Total cholesterol 174 liraglutide 193 placebo HDL-C 42 liraglutide 50 placebo LDL-C 100 liraglutide 112 placebo TG 168 liraglutide 159 placebo	At 48 weeks: Total cholesterol 174 liraglutide 188 placebo HDL-C 45 liraglutide 48 placebo LDL-C 96 liraglutide 108 placebo TG 170 liraglutide 175 placebo	Not reported	Not reported
Empagliflozin [23]	Empagliflozin reduces hepatic fat content and is associated with non-specific symptoms (fatigue, arthralgia, balanoposthitis).	HDL-C 45 control 42 empagliflozin LDL-C 114 control 95 empagliflozin TG 212 control 201 empagliflozin	At 20 weeks: HDL-C 47 control 45 empagliflozin LDL-C 96 control 95 empagliflozin TG 175 control 96 empagliflozin	Empagliflozin group 16.2 %, placebo group 16.4 % (MRI-PDFF)	Empagliflozin group 11.3 %, placebo group 15.5 %
Vitamin E [27]	Vitamin E was effective at improving MASH while pioglitazone was effective, but not in a significant manner. The regimen is generally safe.	Total cholesterol 199 placebo 195 vitamin E 195 pioglitazone HDL-C 43 placebo 44 vitamin E 45 pioglitazone LDL-C 125 placebo 119 vitamin E 126 pioglitazone TG 165 placebo 166 vitamin E 162 pioglitazone	At 96 weeks: Total cholesterol 189 placebo 181 vitamin E 183 pioglitazone HDL-C 41 placebo 43 vitamin E 46 pioglitazone LDL-C 119 placebo 107 vitamin E 118 pioglitazone TG 158 placebo 165 vitamin E 142 pioglitazone	Not reported	Not reported
Pioglitazone [29]	Pioglitazone led to metabolic and histologic improvements in MASH. Safe therapy with a few reports of non-specific fatigue.	Total cholesterol 189 placebo 188 pioglitazone HDL-C 37 placebo 40 pioglitazone LDL-C 117 placebo 118 pioglitazone TG 137 placebo 156 pioglitazone	At 24 weeks: Total cholesterol 191 placebo 193 pioglitazone HDL-C 39 placebo 43 pioglitazone LDL-C 115 placebo 120 pioglitazone TG 207 placebo 132 pioglitazone	Not reported	Pioglitazone led to decrease in hepatic fat content by 54 % at 6 months (magnetic resonance spectroscopy)
Pioglitazone [30]	Pioglitazone led to improvements in steatosis and inflammation. Generally safe. Weight gain seen with pioglitazone.	Total cholesterol 182 placebo 187 pioglitazone HDL-C 37 placebo 36 pioglitazone LDL-C 109 placebo 109 pioglitazone TG 179 placebo 224 pioglitazone	At 72 weeks: Total cholesterol 149 placebo 153 pioglitazone HDL-C 40 placebo 44 pioglitazone LDL-C 79 placebo 84 pioglitazone TG 149 placebo 127 pioglitazone	Pioglitazone group 19 % , placebo group 15 % (magnetic resonance spectroscopy)	Pioglitazone group 7 %, placebo group 11 %
Ezetimibe [33]	Ezetimibe does not effectively reduce liver fat in MASH. Safe.	Total cholesterol 182 ezetimibe 169 placebo	At 24 weeks: Total cholesterol 152 ezetimibe 175 placebo	Ezetimibe group 15 %, placebo group 18.5 % (MRI-PDFF)	Ezetimibe group 11.6 %, placebo group 16.4 %

(*continued on next page*)

Table 1 (*continued*)

Agent	Efficacy/safety	Baseline lipid parameters (mg/dL)	Effect on lipid parameters (mg/dL)	Baseline hepatic fat content	Effect on hepatic fat content
		LDL-C 100 ezetimibe 89 placebo TG 152 ezetimibe 144 placebo	LDL-C 76 ezetimibe 90 placebo TG 125 ezetimibe 142 placebo		
Ezetimibe [32]	Ezetimibe led to histologic improvement in MASLD and lipid parameters including most atherogenic forms, oxLDL and emLDL.	Total cholesterol 228 HDL-C 49 LDL-C 136 TG 168	Total cholesterol 193 (48 weeks) 194 (96 weeks) HDL-C 53 (48 weeks) 52 (96 weeks) LDL-C 117 (48 weeks) 114 (96 weeks) TG 136 (48 weeks) 138 (96 weeks)	Not reported	Not reported
Bariatric Surgery [35]	Surgical treatment associated with MASH resolution. Generally safe with expected outcomes after bariatric surgery (constipation, GERD, nausea).	Total cholesterol 190 lifestyle 199 Roux-en-Y 193 sleeve gastrectomy HDL-C 44 lifestyle 43 Roux-en-Y 42 sleeve gastrectomy LDL-C 114 lifestyle 124 Roux-en-Y 120 sleeve gastrectomy TG 152 lifestyle 160 Roux-en-Y 155 sleeve gastrectomy	At 48 weeks: Total cholesterol 174 lifestyle 158 Roux-en-Y 182 sleeve gastrectomy HDL-C 46 lifestyle 52 Roux-en-Y 49 sleeve gastrectomy LDL-C 102 lifestyle 85 Roux-en-Y 109 sleeve gastrectomy TG 131 lifestyle 98 Roux-en-Y 116 sleeve gastrectomy	Not reported	Not reported

was a −10.5 kg weight change in responders compared to −4 kg in non-responders [20]. However, in a pooled meta-analysis of three trials using metformin, none were associated with improvement in histological and biochemical parameters [21].

The phase 2 study LEAN [Liraglutide Safety and Efficacy in Patients with Non-Alcoholic Steatohepatitis] found that 39 % of patients with MASH treated with liraglutide (a GLP-1 agonist) had resolution of MASH compared to 9 % of the placebo group at 48 weeks. Fewer patients treated with liraglutide had progression of fibrosis (9 %) compared to placebo (36 %). There was no significant difference in HDL-C, LDL-C, triglycerides, or total cholesterol at 48 weeks [22]. There was a negligible decrease in LDL-C in patients treated with liraglutide (pre-treatment LDL-C 100.54 mg/dL versus 96.67 mg/dL at 48 weeks). Triglyceride levels did not change in patients treated with liraglutide. In the placebo group, there was a small increase in triglycerides from 69.61 mg/dL to 76.57 mg/dL at 48 weeks. At week 48, patients treated with liraglutide had a greater decrease from baseline weight of 5.5 % compared to 0.7 % in the placebo group. Weight loss was achieved by week 12 and weight started to increase 12 weeks after discontinuation of liraglutide.

The E-LIFT [Effect of Empagliflozin on Liver Fat Content in Patients with Type 2 Diabetes] trial demonstrated a reduction in liver fat measured by MRI-PDFF in patients treated with empagliflozin (a SGLT2-inhibitor) 10 mg daily compared to placebo. In patients treated with empagliflozin, liver fat was reduced from 16.2 % to 11.3 % compared to smaller decrease from 16.4 % to 15.5 % in the control group. Both empagliflozin and placebo led to a decrease in plasma triglycerides. However, a decrease in LDL-C was seen only in the placebo group [23]. Notably, SGLT2-inhibitors have been shown to increase LDL levels by ~25 % [24,25]. Another randomized trial identified a significant decrease in controlled attenuation parameters (CAP) in patients with MASLD who were randomized to empagliflozin 10 mg daily or placebo. Liver stiffness measurement decreased in patients treated with empagliflozin while no change was identified in the placebo group [26]. Baseline lipid values were not available in this trial by Taheri and colleagues.

The PIVENS trial [Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis] randomized patients with biopsy-proven MASH to receive vitamin E 800 IU daily, pioglitazone 30 mg daily, or placebo. Patients administered vitamin E had significant improvement in liver enzyme levels compared to placebo. MASH resolution was observed in 21 %, 36 %, and 47 % of placebo, vitamin E, and pioglitazone groups, respectively. The primary endpoint was improvement in histologic findings (which encompassed improvement in the ballooning category and decrease in total NAS to ≤3 points or ≥2-point decrease in NAS from baseline) and this was observed in 19 %, 43 %, and 34 % of placebo, vitamin E, and pioglitazone groups, respectively. There was no difference in liver enzymes between patients who received pioglitazone 30 mg daily compared to placebo [27]. Per the American Association for the Study of Liver Disease (AASLD) guidelines, vitamin E can be *considered* in patients with biopsy-proven MASH without diabetes. The phase 2 VEDS (Vitamin E Dosing Study) aims to determine the minimum effective dose of vitamin E (patients treated with vitamin E 200 IU, 400 IU, or 800 IU or placebo) required for relative change in ALT from baseline at 24 weeks [28]. The VEDS study is performed with Vitamin E D-alpha-tocopherol,

while the RRR-alpha tocopherol formulation was used in the PIVENS trial.

Pioglitazone is a thiazolidinedione that improves insulin sensitivity through the activation of peroxisome proliferator-activated receptor (PPAR). Patients with prediabetes or type 2 diabetes and biopsy-confirmed MASH were randomized to receive 6 months of pioglitazone 45 mg daily or placebo. Both groups were placed on a hypocaloric diet. Pioglitazone improved liver enzymes, decreased hepatic fat content by 54 % at 6 months, increased hepatic insulin sensitivity, and improved histologic steatosis without significant effect on lipid parameters [29]. Improvements in liver fibrosis were not significant (33 % in placebo and 46 % in pioglitazone; *p*-value 0.08). The decrease in hepatic fat content in patients treated with pioglitazone was suspected due to thiazolidinediones reducing excessive rates of lipolysis which act as a substrate for the liver. In another study, 51 % of patients who received pioglitazone 45 mg daily for 18 months had resolution of MASH and improvement in histologic scores at 18 months compared to 19 % in the placebo group [30]. NAS improvement of $\geq$2 points was observed in 17 % of the placebo and 58 % of the pioglitazone groups. Hepatic triglyceride content measured by MRS was reduced from 19 % to 7 % in the pioglitazone group. Patients treated with pioglitazone experienced decreases in total cholesterol (187 to 153 mg/dL), LDL-C (109 to 84 mg/dL), and triglycerides (224 to 127 mg/dL) and increase in HDL-C (36 to 44 mg/dL). The placebo group exhibited the same patterns of change in lipid parameters, albeit to a lesser extent. AASLD guidelines suggest pioglitazone as a potential therapy for patients with biopsy-proven MASH who concurrently have diabetes, however, weight gain is a limiting side effect [10].

Ezetimibe, which inhibits cholesterol absorption and promotes upregulation of hepatic LDL receptors, has been studied in patients with MASLD, with some studies showing histologic improvement in steatosis and inflammation after ezetimibe treatment compared to control arms in a small population of <100 patients. However, the MOZART study [Ezetimibe for the Treatment of Nonalcoholic Steatohepatitis: Assessment by Novel Magnetic Resonance Imaging and Magnetic Resonance Elastography in a Randomized Trial] failed to demonstrate the efficacy of ezetimibe 10 mg orally daily for 24 weeks to improve hepatic steatosis or NAS in a significant manner ($\geq$2 point improvement seen in 27 % of the placebo and 33 % of the ezetimibe groups) [31–33]. At 24 weeks, patients treated with ezetimibe had a decrease in triglycerides, total cholesterol, and LDL-C. These changes were not seen in the placebo group. There was a 15.3 % decrease in liver fat content measured by MRI-PDFF in patients treated with ezetimibe and 4.2 % decrease in the placebo group; however, this was not statistically significant. Park et al. showed that in patients with biopsy-proven MASLD, ezetimibe 10 mg daily for 24 months led to improvements in triglycerides, total cholesterol, LDL-C, and estimated desaturase activity [32]. The suspected mechanism of action is the reduction in absorption of monosaturated fatty acids, especially palmitic acid.

Lifestyle modifications such as weight loss, exercise, and dietary changes are recommended in patients with MASLD. However, weight loss can be difficult to achieve and maintain and improvements in MASH and fibrosis are typically only seen in instances of >10 % weight loss [10]. Weight loss improves peripheral insulin sensitivity. Dietary adjustments leading to summative caloric deficit such as low-carbohydrate, low-fat, high-fiber and the Mediterranean diet seem to have some benefit in patients with MASH/MASLD. Studies have found that moderate exercise at least 5 times weekly for 150 minutes or an overall increase in activity by 60 minutes weekly can prevent or improve MASLD, noting that these plans are highly individualized. Meta-analyses have shown improvement in steatosis, steatohepatitis, and fibrosis from weight loss after bariatric surgery [34]. In the BRAVES study [Bariatric-metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis], patients with histologically confirmed MASH and body mass index (BMI) $\geq$30 kg/m^2 were randomized to Roux-en-Y gastric bypass, sleeve gastrectomy, or lifestyle modification. Patients who underwent Roux-en-Y gastric bypass were more likely to have MASH resolution. HDL-C increased, and LDL-C, total cholesterol, and triglycerides decreased most significantly in the Roux-en-Y gastric bypass group. These changes were also seen with lifestyle changes and in the sleeve gastrectomy group, but to a lesser extent, and may be attributed to a threshold in weight loss that is necessary to resolve MASH [35]. Unfortunately, weight regain (defined as $\geq$25 % of nadir weight prior to surgery) has been identified in 35–75 % of study groups followed for up to 7 years with the greatest rate in weight regained occurring one year postoperatively [36–38].

4. Novel therapies for MASLD and MASH

The emerging therapies for MASLD and MASH described in this section target specific pathophysiologic pathways that are key to hepatic disease initiation and progression. While none of these therapies have been FDA-approved for management, this is an area of active research with emerging therapies summarized in Table 2. Several theoretical pathways exist for the treatment of MASH/MASLD, and initial data has appeared promising. Some of these drugs failed to demonstrate efficacy in clinical trials leading to study termination while other studies are ongoing. The FDA requires both resolution of steatohepatitis on overall histopathological reports and improvement in liver fibrosis greater than or equal to one stage for approval of MASLD therapies. Challenges related to drug approval include the requirement of baseline and follow-up liver biopsies, inter-reader reliability without standardized reading protocols, difficulty determining optimal study duration given the complex nature of the disease, and comorbidities that influence therapeutic effects [39].

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors found in the liver, adipose tissue, heart, skeletal muscle, and kidney. PPARα pushes hepatic metabolism towards fatty acid oxidation and upregulates the expression of lipoprotein lipase while down-regulating lipoprotein lipase inhibitors. Elafibranor (GFT-505) is a dual agonist of PPARα/δ receptors. It has been shown to improve steatosis, inflammation, and fibrosis in murine models with MASLD [40]. The phase 2b GOLDEN study demonstrated a greater proportion of MASH resolution without worsening fibrosis in the elafibranor 120 mg group (26 %) compared to placebo (5 %) [41]. NAS improvement of $\geq$2 points was observed in 21 % of placebo, 18 % elafibranor 80 mg, and 48 % elafibranor 120 mg groups. Patients treated with elafibranor had improved triglycerides, LDL-C, and HDL-C levels. A multicenter, phase 3 study RESOLVE-IT [Study to Evaluate the Safety and Efficacy of Elafibranor versus Placebo in Patients with Nonalcoholic Steatohepatitis] did not demonstrate significant effect on MASH resolution between elafibranor and placebo. There were reductions in triglyceride and HDL-C in patients treated with elafibranor [42]. The compound is no longer being investigated for the treatment of MASH.

Obeticholic acid (OCA) is farnesoid X receptor (FXR) ligand. OCA is a synthetic variant of the natural bile acid chenodeoxycholic acid (CDCA) with 100 times the affinity for the FXR receptor compared to CDCA [43]. FXR activation has demonstrated the ability to reduce hepatic gluconeogenesis, lipogenesis, and steatosis. In the FLINT trial [The Farnesoid X receptor FXR Ligand Obeticholic Acid in Nonalcoholic Steatohepatitis [NASH] Treatment Study], OCA achieved a primary outcome of improving necro-inflammation without worsening fibrosis (equivalent to NAS improvement by $\geq$2 points) in 45 % of patients who received OCA compared to 21 % of the placebo group [8]. MASH resolution was observed in 13 % and 22 % of placebo and OCA groups, respectively. This difference was not significant. Unfortunately, OCA has been associated with elevated LDL-C and decreased HDL-C levels. Lipid parameters normalized with the withdrawal of OCA and were not associated with adverse cardiovascular events over a short follow-up period [9]. Additionally, the unfavorable increases in total cholesterol and LDL-C and decrease in HDL-C were mitigated with concurrent administration of atorvastatin 10 or 20 mg daily in the CONTROL trial [44]. Changes in

Table 2
Emerging therapies for MASLD/MASH.

Agent	Efficacy/safety	Baseline lipid parameters (mg/dL)	Effect on lipid parameters (mg/dL)	Baseline hepatic fat content	Effect on hepatic fat content
Elafibranor (GFT505) [41]	Elafibranor 120 mg led to MASH resolution. Generally safe, most common adverse effects were nausea and headaches.	Total cholesterol 185 placebo 197 elafibranor 80 mg 185 elafibranor 120 mg HDL-C 50 placebo 50 elafibranor 80 mg 46 elafibranor 120 mg LDL-C 108 placebo 116 elafibranor 80 mg 104 elafibranor 120 mg TG 159 placebo 159 elafibranor 80 mg 177 elafibranor 120 mg	At 48 weeks: Actual values not reported. Patients treated with elafibranor had decreased LDL-C and TG and increased HDL-C.	Not reported	Not reported
Elafibranor (GFT505) [42]	Elafibranor did not lead to MASH resolution. Safe.	Actual values not reported.	Reduction in TG (−0.3179 treatment difference between elafibranor and placebo) and HDL-C (−0.174) in patients treated with elafibranor	Not reported	Not reported
Obeticholic acid (OCA) [8]	OCA improved necroinflammation without worsening fibrosis. More patients taking OCA developed pruritus. More data needed regarding safety.	Total cholesterol 189 OCA 185 placebo HDL-C 42 OCA 42 placebo LDL-C 112 OCA 112 placebo TG 194 OCA 177 in placebo	At 72 weeks: Total cholesterol 195 OCA 178 placebo HDL-C 41 OCA 43 placebo LDL-C 120 OCA 103 placebo TG 175 OCA 170 placebo	Not reported	Not reported
Obeticholic acid (OCA) [45]	OCA 25 mg significantly improved fibrosis by at least one stage. Safe. Most common adverse effect was pruritus.	Total cholesterol 184 placebo 185 OCA 10 mg 183 OCA 25 mg HDL-C 45 placebo 44 OCA 10 mg 44 OCA 25 mg LDL-C 114 placebo 113 OCA 10 mg 113 OCA 25 mg	At 4 weeks: Total cholesterol not reported HDL-C 44 placebo 42 OCA 10 mg 39 OCA 25 mg LDL-C 117 placebo 130 OCA 10 mg 136 OCA 25 mg At month 18: LDL-C reverted to baseline	Not reported	Not reported
Tropifexor (LJN452) [48]	Tropifexor resulted in dose-dependent decrease in liver fat content. Safe. Adverse effects include pruritus, fatigue, nasopharyngitis.	HDL-C 54 placebo, 52 tropifexor 10 μg, 48 tropifexor 30 μg, 50 tropifexor 60 μg, 51 tropifexor 90 μg,	At 12 weeks, mean change: HDL-C tropifexor 10–90 μg ranged +1 to −4; tropifexor 140–200 μg −7 to −10 At week 12: Changes stabilized	Actual values not reported (MRI-PDFF)	At 12 weeks: Decrease from 7 to 15 % tropifexor 10–90 μg group, 19 % tropifexor 140 μg group, 39 % tropifexor 200 μg group. Placebo decreased 10 %

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Table 2 (*continued*)

Agent	Efficacy/safety	Baseline lipid parameters (mg/dL)	Effect on lipid parameters (mg/dL)	Baseline hepatic fat content	Effect on hepatic fat content
		50 tropifexor 140 μg, 50 tropifexor 200 μg			Hepatic fat content decreased further at 48 weeks (31 % in tropifexor 140 μg group and 39 % in tropifexor 200 μg group). Placebo decreased 3.58 %
		LDL-C 118 placebo, 106 tropifexor 10 μg, 107 tropifexor 30 μg, 118 tropifexor 60 μg, 124 tropifexor 90 μg, 118 tropifexor 140 μg, 101 tropifexor 200 μg	LDL-C tropifexor 10–90 μg ranged −2 to +11; tropifexor 140–200 μg +20 to +30		
Cenicriviroc [54, 55]	Not effective when study extended to 2 years.	Not reported	Not reported	Not reported	Not reported
Cenicriviroc [56]	Not effective at improving fibrosis. Safe.	Not reported	Not reported	Not reported	Not reported
Aramchol [60]	Aramchol led to dose-dependent reduction in liver fat content. Safe. Headache was most common adverse event. Pruritus resolved after drug discontinued.	Total cholesterol 189 placebo 179 aramchol 400 mg 188 aramchol 600 mg HDL-C 45 placebo 45 aramchol 400 mg 46 aramchol 600 mg LDL-C 119 placebo 110 aramchol 400 mg 117 aramchol 600 mg TG 170 placebo 175 aramchol 400 mg 170 aramchol 600 mg	At 52 weeks: Total cholesterol 193 placebo 183 aramchol 400 mg 192 aramchol 600 mg HDL-C 44 placebo 43 aramchol 400 mg 46 aramchol 600 mg LDL-C 125 placebo 120 aramchol 400 mg 124 aramchol 600 mg TG 178 placebo 178 aramchol 400 mg 184 aramchol 600 mg	Placebo 27.5 % Aramchol 400 mg 27.3 % Aramchol 600 mg 30.2 % (Magnetic resonance spectroscopy)	Placebo 27 % Aramchol 400 mg 23.8 % Aramchol 600 mg 27 %
Aramchol Ongoing, will be completed in 2024	In process	In process	In process	In process	In process
Resmetirom (MGL-3196) [65]	Resmetirom led to reduction in hepatic fat and lipid parameters. Adverse events included diarrhea and nausea, which were limited to duration of therapy. More studies needed regarding safety.	HDL-C 45 placebo 43 resmetirom LDL-C 116 placebo 111 resmetirom TG 161 placebo 178 resmetirom	HDL-C 46 placebo 44 resmetirom LDL-C 123 placebo 98 resmetirom TG 194 placebo 150 resmetirom	Not reported	At 12 weeks: Absolute reduction in hepatic fat 27 % placebo, 7 % resmetirom 80 mg At week 36: 28 % placebo, 8.2 % resmetirom 80 mg (MRI-PDFF)
Resmetirom (MGL-3196) [66] Ongoing, will be completed in 2024	In process	In process	In process	In process	In process

(*continued on next page*)

Table 2 (*continued*)

Agent	Efficacy/safety	Baseline lipid parameters (mg/dL)	Effect on lipid parameters (mg/dL)	Baseline hepatic fat content	Effect on hepatic fat content
Aldafermin (NGM282 or M70) [67]	Aldafermin improved liver fibrosis and liver fat content. Generally safe although larger studies are needed.	Total cholesterol 171 placebo 173 aldafermin HDL-C 34 placebo 31 aldafermin LDL-C 95 placebo 95 aldafermin TG 167 placebo 194 aldafermin	At 24 weeks: Total cholesterol 150 placebo 147 aldafermin HDL-C 33 placebo 33 aldafermin LDL-C 79 placebo 76 aldafermin TG 139 placebo 132 aldafermin	Actual values not reported	Aldafermin reduced liver fat content by 7.7 % compared to 2.7 % in placebo (MRI-PDFF)
Pegozafermin [68]	Pegozafermin improved liver fibrosis. Generally safe. Most common side effects were nausea and diarrhea.	TG 170 placebo 186 pegozafermin 15 mg, 175 pegozafermin 30 mg, 164 pegozafermin 44 mg	TG 162 placebo 177 pegozafermin 15 mg, 135 pegozafermin 30 mg, 150 pegozafermin 44 mg	Actual values not reported	At 24 weeks: Decreased 27 % pegozafermin 15 mg group, 48 % pegozafermin 30 mg group, 41 % pegozafermin 44 mg group Placebo decreased 5 % (MRI-PDFF)
Efruxifermin[69]	Efruxifermin reduced hepatic fat content and improved NAS scoring. Most common side effects were diarrhea, nausea, and vomiting.	Total cholesterol 204 placebo, 189 efruxifermin 28 mg, 182 efruxifermin 50 mg, 175 efruxifermin 75 mg HDL-C 45 placebo, 42 efruxifermin 28 mg, 40 efruxifermin 50 mg, 41 efruxifermin 75 mg LDL-C 116 placebo, 111 efruxifermin 28 mg, 107 efruxifermin 50 mg, 99 efruxifermin 75 mg TG 208 placebo, 176 efruxifermin 28 mg, 176 efruxifermin 50 mg, 180 efruxifermin 75 mg	At 16 weeks: Total cholesterol 173 efruxifermin 28 mg, 175 efruxifermin 50 mg, 168 efruxifermin 75 mg HDL-C 55 efruxifermin 28 mg, 54 efruxifermin 50 mg, 56 efruxifermin 75 mg LDL-C 96 efruxifermin 28 mg, 103 efruxifermin 50 mg, 93 efruxifermin 75 mg TG 87 efruxifermin 28 mg, 69 efruxifermin 50 mg, 78 efruxifermin 75 mg	Placebo 19 %, 21 % efruxifermin 28 mg, 18 % efruxifermin 50 mg, 10 % efruxifermin 75 mg (MRI-PDFF)	At 16 weeks: Placebo increased 0.3 %, decreased 12 % efruxifermin 28 mg, 13 % efruxifermin 50 mg, 14 % efruxifermin 75 mg

CCR2/CCR5: C—C chemokine receptor types 2/5.
FGF: fibroblast growth factor.
FXR: farnesoid X receptor.
GERD: gastroesophageal reflux disease.
GLP1: glucagon-like peptide 1.
HDL-C: high-density lipoprotein cholesterol.
LDL-C: low-density lipoprotein cholesterol.
MASH: metabolic-dysfunction associated steatohepatitis.
OCA: obeticholic acid.
PPAR: peroxisome proliferator-activated receptor.
SCD-1: stearoyl-CoA desaturase-1.
SGLT2-i: sodium-glucose cotransporter-2 inhibitors.
TG: triglycerides.
THR: thyroid hormone receptor.

lipid parameters were suspected due to OCA blocking the conversion of cholesterol to bile acids which consequently increases serum cholesterol levels. The phase 3 REGENERATE [Research Study for Treatment of NASH (Non-Alcoholic Steato-Hepatitis)/Advanced Fatty-Liver Disease] study aimed to investigate the long-term clinical benefit of OCA treatment for patients with fibrosis due to MASH. Patients were randomized to receive placebo, OCA 10 mg, or OCA 25 mg daily. There was a 20 % increase in LDL-C in patients treated with OCA. LDL-C levels returned to baseline by month 6 and remained stable through month 18 regardless of statin initiation [45]. About 22 % of patients with MASH achieved improvement in ≥1 stage fibrosis without worsening of MASH compared to 9 % in the placebo group. Furthermore, 6 % of patients who received OCA exhibited MASH resolution compared to 3 % of the placebo group [46]. The compound is no longer being investigated for the treatment of MASH. The drug HTD1801 (berberine ursodeoxycholate or BUDCA) was compared against placebo in 100 subjects with diabetes and MASH in a phase 2 randomized trial [47]. BUDCA is ingested as a salt form that dissociates within the gastrointestinal tract. Individuals who received HTD1801 1000 mg twice daily had significantly greater absolute reduction in liver fat content (4.8 %) compared to placebo (2 %) measured by MRI-PDFF. In addition, LDL-cholesterol decreased by 16 ml/dL and weight decreased by 3.5 kgs in the high dose group (1000 mg twice daily) compared to no change in LDL-cholesterol and weight loss of 1.1 kg in the placebo group.

Alternative non-bile acid FXR agonists are being explored with the hope that these will not be associated with an increase in serum LDL-C. The FLIGHT-FXR phase 2 study of tropifexor (LJN452), a potent non-bile acid FXR agonist, showed that tropifexor led to decreases in aspartate transaminase (AST), alanine transaminase (ALT), HDL-C and liver fat content with increase in LDL-C. The most common adverse event with tropifexor was pruritus which occurred in a dose-dependent manner [48]. Changes in lipid parameters stabilized at week 12 when compared to week 48. Hepatic fat fraction measured by MRI-PDFF decreased by week 12, ranging from 7.48 % to 15 % in tropifexor 10–90 μg group, and was greater than the placebo group at 6.19 %. Further decreases at week 48 to 31 % in the tropifexor 140 μg and 39 % in the tropifexor 200 μg groups were reported. Dose-dependent decreases in hepatic fat content were also reported in the tropifexor 140–200 μg groups. A greater proportion of patients achieved hepatic fat reduction with tropifexor 140 μg (55 %) and 200 μg (68 %) compared to placebo (28 %). MASH resolution was observed in 0 % of the placebo group, 5 % of the tropifexor 140 μg group, and 6 % of the tropifexor 200 μg group. There were no significant differences in the proportion of patients achieving NAS improvement at 48 weeks (21 % in the placebo, 26 % in the tropifexor 140 μg group, and 26 % in the tropifexor 200 μg group). This study has since been terminated.

In patients with MASLD, increased levels of a chemokine subtype, C—C ligand 2 (CCL2), promotes the pooling of CCR2-positive monocytes in the liver which worsens hepatic inflammation, fibrosis, and steatosis [49,50]. Previous studies have found higher concentrations of CCL2 in patients with MASH compared to placebo [51]. CCR2 is regulated by obesity and the presence of CCR2 in myeloid cells promotes hepatosteatosis. Thus, blocking this receptor may reduce or even reverse hepatic steatosis [49]. CCL5 is induced in hepatic injury and in vivo studies have shown that CCL5 antagonism inhibits hepatic stellate cell migration and proliferation and accelerates fibrosis regression [52]. CCR1 (affects Kupffer cells) and CCR5 (affects hepatic stellate cells) are both required for hepatic fibrogenesis and have synergistic effects. In the absence of both CCR1 and CCR5, there was a greater decrease in fibrogenesis in comparison to eliminating only one of the receptors [53]. CCR2 and CCR5 ligands play an important role in liver fibrosis through inflammatory signaling and immune cell infiltration. CENTAUR [Efficacy and Safety Study of Cenicriviroc (CVC) for the Treatment of Nonalcoholic Steatohepatitis (NASH) in Adult Subjects with Liver Fibrosis] is a phase 2b study of Cenicriviroc, a dual CCR2/CCR5 antagonist. Data from the 1-year interim analysis did not achieve the primary endpoint of histological improvement in NAS by ≥2 points without worsening of fibrosis in patients treated with CVC (16 %) or placebo (19 %). Improvement in liver fibrosis by ≥1 stage was observed in a greater portion of patients treated with CVC (20 %) compared to placebo (10 %). Extension of treatment with CVC for 2 years did not lead to further improvement in fibrosis when compared to placebo [54,55]. AURORA [A Study for the Efficacy and Safety of CVC for the Treatment of Liver Fibrosis in Adults With NASH] is a phase 3 study which demonstrated that patients treated with CVC 150 mg daily for 12 months did not have improvement in fibrosis, but was well tolerated with similar safety profile compared to placebo [56]. The primary endpoint of fibrosis improvement by ≥1 stage was achieved in 22 % of patients treated with CVC and 25 % of patients treated with placebo. Baseline lipid studies and liver fat content are not available for this study. The AURORA trial was terminated.

Stearoyl-CoA desaturase-1 (SCD-1) is an enzyme that plays a crucial role in hepatic lipogenesis. In the process of de novo lipogenesis, SCD-1 catalyzes the conversion of stearoyl-CoA to oleoyl-CoA which is required for triglyceride synthesis [57]. SCD-1 inhibition decreases the synthesis of fatty acids and increases beta oxidation, resulting in decreased hepatic storage of triglycerides and fatty acids. SCD-1 deficiency activates the PPARα pathway, shifts metabolic pathways towards oxidation, and reduces lipogenesis and lipid storage [58]. Aramchol (arachidyl amido cholanoic acid) is a synthetic compound comprised of a bile acid (cholic acid) and a fatty acid (arachidic acid) [59]. Aramchol is a SCD-1 inhibitor. The phase 2b study ARREST [Aramchol for the REsolution of Steatohepatitis] included 247 patients with MASH who were randomized to aramchol 400 mg, 600 mg, or placebo. Aramchol 600 mg was associated with a 3.2 % reduction in liver fat content (measured by MRS) compared to 0.1 % reduction in placebo [60]. MASH resolution without worsening fibrosis was achieved in 16 % of patients treated with aramchol 600 mg compared to 5 % in the placebo group. Consistent increases in total cholesterol, LDL-C, and triglycerides were seen in all three groups. The changes were not significant. The phase 3/4 trial ARMOR [A Study to Evaluate the Effectiveness and Safety of Aramchol Versus Placebo in Subjects with MASH] began in 2019 with results expected in 2024.

There have been associations between hypothyroidism and dyslipidemia [61]. While hypothyroidism leads to decreased hepatic cholesterol synthesis, it increases gastrointestinal cholesterol absorption and decreases LDL-C receptors to a greater degree, ultimately leading to a reduction in LDL-C clearance and an increase in apo-B lipoproteins [62,63]. Thyroid hormone receptor isoform THR-α mediates thyroid effect on the heart and adipose tissues while THR-β affects cholesterol metabolism. Specifically, THR-β1 is found in the liver, brain, and kidney [61]. Through activation of β-receptors in hepatocytes, thyroxine regulates mitochondrial activity such as hepatic lipolysis and reduces serum-free fatty acids and triglycerides [64]. Resmetirom (MGL-3196) is a selective THR-β agonist which avoids unwanted effects on the central thyroid axis (i.e., causing hyperthyroidism and thyrotoxicosis) and targets the liver specifically. Patients treated with resmetirom 80 mg daily had a greater reduction in hepatic fat measured by MRI-PDFF compared to placebo at weeks 12 and 36 [65]. Patients treated with resmetirom also had 30 % reduction in LDL-C, 25 % reduction in apolipoprotein-B, and 60 % reduction in triglycerides [66]. Resmetirom was generally well tolerated with the most common adverse events being diarrhea and nausea. Resmetirom may decrease hepatic fat content due to increasing mitochondrial beta oxidation and restoring regular mitochondrial function in patients with MASH. The reduction in atherogenic lipoprotein particles associated with cardiovascular disease (e.g. small dense LDL particles and large VLDL) makes this drug enticing as emerging relationships between MASLD and cardiovascular disease have evolved. Significant reduction in NAS was only observed in patients who also lost <5 % of total body weight (1 % of placebo and 1.4 % of resmetirom groups). MASH resolution was observed in 27 % of patients treated with resmetirom compared to 6 % of the placebo group. The MAESTRO NASH

study [A Phase 3 Study to Evaluate the Efficacy and Safety of MGL-3196 (Resmetirom) in Patients With NASH and Fibrosis] will evaluate all-cause mortality and liver-related events up to 54 months after drug initiation is set to be completed in March 2024. [66]

Fibroblast growth factors inhibit bile acid synthesis and regulate metabolic homeostasis. FGF19 is secreted from the ileum after farnesoid X receptor activation and inhibits gluconeogenesis and regulates bile acid synthesis [59]. In a phase 2 study, Aldafermin (also known as NGM282 or M70), a FGF19 analogue, improved liver fibrosis and led to reduction in absolute liver fat content (measured by MRI-PDFF) by 7.7 % compared to 2.7 % in placebo [67]. LDL-C initially increased at week 2 in patients receiving aldafermin due to inhibition of cholesterol conversion to bile acids. These changes were mitigated with rosuvastatin. MASH resolution was observed in 9 % and 24 % of the placebo and aldafermin groups, respectively. NAS improvement by $\geq$2 points was observed in 9 % and 62 % of the placebo and aldafermin groups, respectively. In another phase 2b study of 222 patients, Pegozafermin, a FGF21 analogue, improved liver fibrosis in a dose dependent manner at 24 weeks [68]. The percentage of patients with MASH resolution without worsening of fibrosis was greater in the pegozafermin groups (37 % in pegozafermin 15 mg weekly, 23 % in pegozafermin 30 mg weekly, 26 % in pegozafermin 44 mg every 2 weeks) compared to 2% in placebo. NAS improvement by $\geq$2 points was seen in 24 % of the placebo group, 37 % of the pegozafermin 15 mg group, 65 % of the pegozafermin 30 mg group, and 62 % of the pegozafermin 44 mg group. There were greater decreases in triglycerides and increase in HDL-C in the pegozafermin groups (greatest reduction achieved with pegozafermin 30 mg weekly) compared to placebo. Efruxifermin is a Fc-FGF21 fusion protein. In the phase 2a trial BALANCED, patients were randomized to receive placebo, efruxifermin 28 mg, efruxifermin 50 mg, or efruxifermin 70 mg once weekly for 16 weeks. Hepatic fat content measured by MRI-PDFF decreased in all treatment groups (12.3 % in the efruxifermin 28 mg group, 13.4 % in the efruxifermin 50 mg group, and 14.1 % in the efruxifermin 70 mg group) compared to placebo (0.3 %). Improvement in NAS score $\geq$2 points without worsening of fibrosis was achieved in 92 % of patients treated with efruxifermin 28 mg, 77 % of patients treated with efruxifermin 50 mg, and 86 % of patients treated with efruxifermin 70 mg compared to 50 % of the placebo group. MASH resolution was observed in 50 % of the placebo group, 46 % of the efruxifermin 28 mg group, 54 % of the efruxifermin 50 mg group, and 43 % of the efruxifermin 70 mg group. LDL-C was reduced by 16 % in the efruxifermin 28 mg group but unchanged in the efruxifermin 50 mg and 70 mg groups compared to placebo. Decreases in triglycerides, apolipoprotein B, and total cholesterol were also observed [69].

5. Summary

In summary, there are several promising agents currently being evaluated for the management of MASLD and MASH. Herein, we have discussed therapies including agents that have been approved for conditions other than MASLD but may be safe and effective in MASLD. We also discuss emerging agents that have been developed with the intent of treating patients with MASH/MASLD specifically. Our review focused on the impact of these therapies on plasma lipid parameters, as ASCVD is one of the leading causes of mortality in patients with MASLD. Treatment is challenging as it is multi-factorial with the overarching goals of halting the progression from MASLD to MASH and reducing cardiovascular disease burden. Treatment of the disease requires simultaneous treatment of metabolic comorbidities including diabetes, hypertension, and hyperlipidemia with preventive cardiology measures such as weight loss, dietary changes, increased exercise, smoking cessation, glycemic control, and blood pressure control remaining the crux of the solution [70].

The intricate relationship between MASLD and lipid metabolism underscores the need for effective therapies that not only target hepatic fat accumulation but also beneficially modulate lipoprotein metabolism. Furthermore, drugs targeting MASH need to demonstrate the ability to improve fibrosis and/or resolve MASH. Drugs that limit MASH progression do not meet the FDA criteria for approval. Our comprehensive review of the available literature reveals that several medications used for MASLD treatment have varied effects on lipid parameters. While some therapies present potential dual benefits by improving liver fat content and optimizing plasma lipids, others might exacerbate dyslipidemia, necessitating vigilant monitoring. These findings highlight the importance of individualized therapeutic approaches while considering both hepatic outcomes and cardiovascular risk profiles. As the global prevalence of MASLD continues to rise, it is paramount for clinicians and researchers to be cognizant of these dual effects to ensure holistic patient care.

However, there exist notable gaps in the current body of knowledge, necessitating further rigorous research to elucidate the underlying mechanisms of the observed lipid alterations and to develop therapeutic strategies with enhanced liver and cardiovascular efficacy and safety profiles. Understanding the interplay between MASLD medications and lipid and lipoprotein parameters is paramount for achieving a comprehensive therapeutic strategy that aims not only to manage liver disease but also to improve cardiovascular health. Innovations in pharmaceutical interventions may offer a deeper understanding of the hepatic-lipid-cardiovascular interactions that pave the way for more targeted and effective treatment modalities for MASLD that reduce the associated liver and cardiovascular morbidity and mortality (Central Illustration).

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Amon Asgharpour, M.D. is a consultant for Galectin and Madrigal.

Dave Dixon, PharmD receives grant funding from Boehringer Ingelheim, Inc.

Arun J. Sanyal, M.D. has stock options in Genfit, Tiziana, Durect, Inversago, Hemoshear. He has also served as a consultant to Merck, Pfizer, Eli Lilly, Novo Nordisk, Boehringer Ingelhiem, Astra Zeneca, Akero, Intercept, Madrigal, Northsea, Takeda, Regeneron, Genentech, Alnylam, Roche, Arrowhead, Aligos, Glaxo Smith Kline, Novartis, Tern, Fractyl, Inventiva, Intercept, Gilead and Target Pharmasolutions, Histoindex, Path-AI. He receives royalties from Uptodate and Elsevier. His institution has received grants from Intercept, Pfizer, Merck, Bristol Myers Squibb, Eli Lilly, Novo Nordisk, Boehringer Ingelhiem, Astra Zeneca, Novartis, Madrigal. VCU has a collaborative agreement with Avant Sante.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dave Dixon reports a relationship with Boehringer Ingelheim, Inc. that includes: funding grants. Arun J. Sanyal reports a relationship with Genfit, Tiziana, Durect, Inversago, Hemoshear that includes: equity or stocks. Arun J. Sanyal reports a relationship with Merck, Pfizer, Eli Lilly, Novo Nordisk, Boehringer Ingelhiem, Astra Zeneca, Akero, Intercept, Madrigal, Northsea, Takeda, Regeneron, Genentech, Alnylam, Roche, Arrowhead, Aligos, Glaxo Smith Kline, Novartis that includes: consulting or advisory. Arun J. Sanyal reports a relationship with Tern, Fractyl,

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