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Guideline-directed medical strategies for the co-management of heart failure and metabolic dysfunction-associated steatotic liver disease

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There is a high and rising global prevalence of people with both metabolic dysfunction-associated steatotic liver disease (MASLD) and heart failure, which has a severe impact, highlighting the need to address these conditions. However, the relationship between MASLD and heart failure remains underexplored. This comprehensive narrative review explores the shared pathophysiological mechanisms, diagnostic evaluations, and current medical and surgical recommendations for heart failure therapy in the context of co-existing MASLD. Here, we show the need for co-management of MASLD and the different subtypes of heart failure, integrating both standard and innovative heart failure treatments with those targeting MASLD. We highlight the benefits of certain drug classes and surgical interventions for both conditions while noting potential adverse outcomes with others. To address the global rise in metabolic diseases, a holistic, coordinated, and multidisciplinary approach is essential. Collaborative efforts between cardiologists and hepatologists are crucial for developing tailored interventional strategies to prevent and manage comorbid conditions, thereby mitigating the threats posed by MASLD and heart failure.

In the evolving landscape of metabolic research, the link between atherosclerotic cardiovascular disease (ASCVD) and metabolic-associated steatotic liver disease (MASLD) has received considerable attention because of their high prevalence, global health impact[1–3], and shared pathophysiologic mechanisms[4–6]. Major metabolic disorders, such as diabetes mellitus, hypercholesterolemia, dyslipidemia, obesity, and hypertension, play central roles in this association[7]. Type II diabetes (T2D) is characterized by insulin resistance and chronic hyperglycemia, which contribute to hepatic steatosis and promotes atherosclerotic processes-pathogenic mechanisms shared by both MASLD and ASCVD[7]. Hypercholesterolemia and dyslipidemia exacerbate liver disease by promoting lipid accumulation and hepatic inflammation while also accelerating vascular dysfunction[7]. Obesity, which is a global health crisis according to the World Health Organization[8], significantly impacts both diseases through systemic inflammation and oxidative stress[7]. Additionally, hypertension, often co-morbid with these metabolic conditions, worsens vascular damage and hepatic fibrosis, highlighting a shared pathophysiological pathway[7,9].

MASLD, formerly known as non-alcoholic fatty liver disease (NAFLD)[10], encompasses a spectrum of hepatic conditions where ≥5% of hepatocytes display macrovascular steatosis[1]. This occurs alongside

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metabolic comorbidities and the absence of other underlying etiologies, such as alcohol consumption, infections, or hepatotoxic medications. MASLD spans all degrees of hepatic steatosis, leading to inflammation, cellular injury, fibrosis, cirrhosis, and, ultimately, hepatocellular carcinoma[1]. An estimated 30% of the global adult population has been diagnosed with MASLD, with variations across geographical regions and the highest incidence in South-East Asia, North America, and Australasia[2]. The disease prevalence correlates with metabolic disorders, such as T2DM, dyslipidemia, central obesity, and hypertension[2]. Cumulative data from 245 articles involving nearly 2.7 million patients predict that over half of adults worldwide will develop some degree of MASLD by 2040[3]. Notably, metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH)[10], the most severe form of MASLD, already ranks as the primary indication for liver transplantation in women and those over age 65[1].

Like MASLD, heart failure is a serious condition whereby cardiac output is insufficient to achieve adequate oxygen delivery to facilitate normal cardiorespiratory metabolic functionality[11]. In the United States, approximately 6.7 million adults currently have heart failure, and this number is expected to rise to 8.5 million by 2030[12,13]. Globally, the disease affects approximately 60 million adults worldwide[14]. Black individuals demonstrate a higher incidence and prevalence of heart failure compared to other racial and ethnic groups, possibly due to distinct genetic and pathophysiological mechanisms, social determinants of health, and treatment disparities[12,13,15] In the United States, overall hospitalization and mortality rates related to heart failure have been steadily increasing since 2012, especially in rural areas compared to urban[12,13]. Notably, younger patients (aged 35–64 years) have experienced a more significant annual increase in heart failure-related mortality rates compared to older (65–84 years) adults[12,13]. Social determinants of health, including socioeconomic status, education, and access to healthcare, have a significant impact on heart failure risk factors and outcomes. Lower quality or limited availability of these determinants contribute to worse health outcomes and lower rates of guideline-directed medical therapy compared to those with more favorable social conditions[12,13,15]. Additionally, heart failure mortality rates are higher in rural areas compared to urban areas[12,13].

A retrospective study conducted in Japan investigated the incidence rate of cardiovascular disease in patients with MASLD[16]. The study estimated the incidence rate of cardiovascular disease to be 2.69 (95% confidence interval [CI] 2.64–3.01) per 1000 person-years in patients with MASLD compared to 1.01 (95% CI: 0.98–1.03) in non-MASLD controls[16]. Additionally, a separate retrospective cohort study involving Medicare beneficiaries with baseline MASLD revealed a significantly higher risk of new-onset heart failure in MASLD compared to controls (6.4% vs 5.0%; $P < 0.001$; adjusted hazard ratio [HR] 1.23, 95% CI: 1.18–1.29)[17]. Despite this correlation, several studies have shown that patients with MASLD are more likely to die from cirrhosis or end-stage liver disease rather than an adverse cardiovascular event[18–20].

In 2022, the American Heart Association issued a scientific statement identifying MASLD as a risk factor for ASCVD. They offered proposed pathophysiology, diagnostic and screening strategies, and potential interventions[21]. Other than this statement regarding MASLD and ASCVD, no formal guidance has been offered for the diagnosis and co-management of MASLD and heart failure. Although separate specialties typically manage MASLD and heart failure, their frequent coexistence calls for an integrated, multidisciplinary approach[22–24].

This comprehensive review explores the pathophysiological link between MASLD and the various heart failure subtypes, emphasizing preventative and therapeutic management strategies for patients with both conditions. It also discusses the diagnostic challenges of the two disease states and offers a combined, preventative, holistic strategy combining preventive hepatological and cardiological approaches. In those who have progressed to having concomitant MASLD and heart failure, drug classes such as angiotensin II converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, mineralocorticoid receptor antagonist (MRA), and sodium-glucose cotransporter-2 (SGLT2) inhibitors demonstrate benefits, while loop diuretics may worsen MASLD. Surgical interventions in heart failure with reduced ejection fraction (HFrEF), such as implantable cardioverter-defibrillator (ICD) placement or MitraClip devices, could offer advantages to those with severely reduced ejection fraction and MASLD. However, the demographic of patients with concurrent MASLD and heart failure remains insufficiently explored, presenting a challenge to researchers aiming to identify optimal co-management strategies for these diseases, especially given the growing need for coordinated interventions.

Understanding the shared pathogenesis of metabolic syndrome (MetS), ASCVD, and MASLD

MetS is a collection of several comorbidities associated with an increased risk of ASCVD, insulin resistance, DM, and neurovascular complications[25,26]. The estimated prevalence in the United States is 33.4%, with a higher prevalence in Hispanics and the lowest risk in African-Americans[27]. The strong correlation between MetS and MASLD led to the renaming of NAFLD to MASLD[10]. In a study of 1903 MASLD patients, hepatic steatosis was linked to central obesity (waist circumference ≥ 102/88 cm, 71.8% vs 37.1%, $P < 0.001$) and insulin resistance (47.1% vs 12.2%, $P < 0.001$)[4]. While the exact mechanism remains unclear, insulin resistance, impaired lipid metabolism, and systemic inflammation are pivotal in the development of MASLD/MASH and ASCVD (Fig. 1)[5,7,20–22].

As adipocyte dysfunction worsens, excess free fatty acids are delivered to various organs, including skeletal muscle, pancreas, and liver. This dysfunction is accompanied by a pro-inflammatory state, characterized by elevated levels of pro-inflammatory cytokines (tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1b (IL-1b)) and altered levels of metabolically active cytokines from adipose tissue called adipokines (increased leptin and decreased adiponectin). In insulin-resistant obese patients, skeletal muscle cells exhibit impaired insulin signaling pathways. Intramuscular lipid accumulation leads to reduced insulin sensitivity, glucose uptake, and glycogenesis. The liver, which has significant fat oxidation capacity, becomes the last defense against excess lipid storage. However, when overwhelmed by increased free fatty acid delivery and de novo lipogenesis, lipotoxic species accumulate, causing mitochondrial dysfunction, endoplasmic reticulum stress, oxidant stress, and inflammasome activation, resulting in hepatocyte injury. This intricate interplay between insulin resistance, hyperinsulinemia, and lipotoxicity drives the progression of MASLD and MASH, ultimately leading to fibrosis, end-organ failure, and mortality[4,5,28].

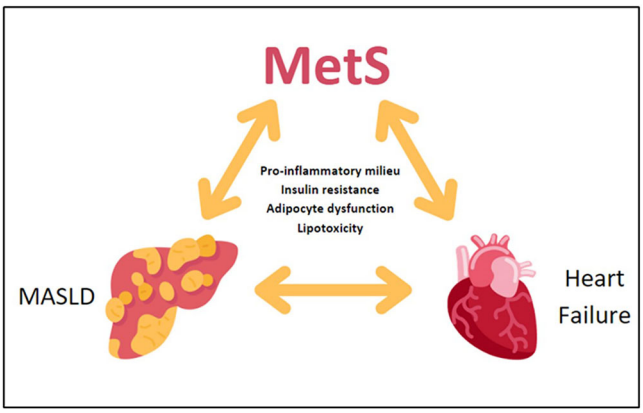
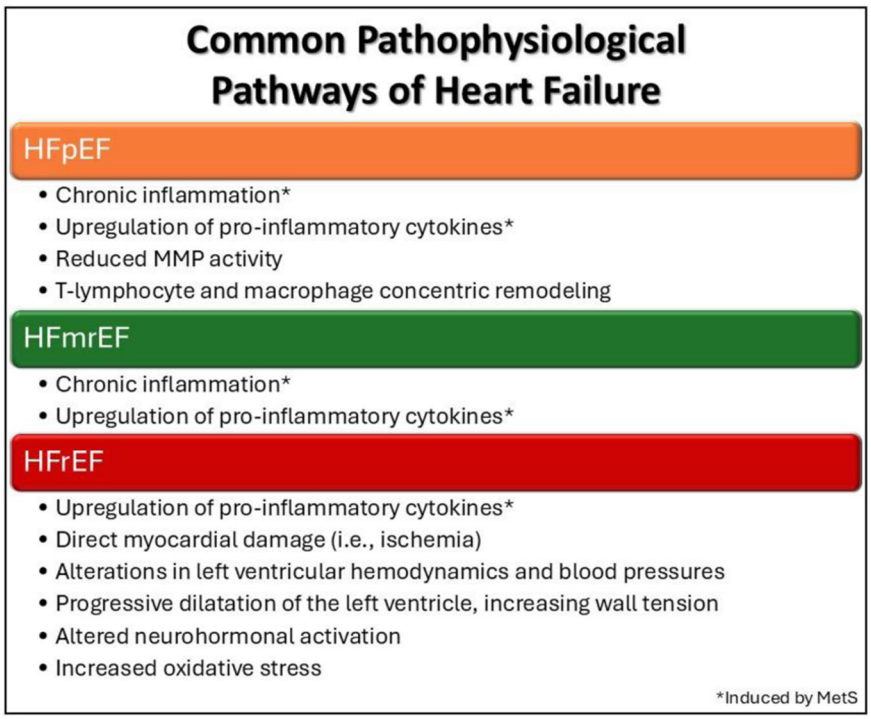


Fig. 1 | The inflammatory cascade and subsequent insulin resistance, adipocyte dysfunction, lipotoxicity, and pro-inflammatory milieu caused by MetS, and therefore heart failure and MASLD, produce bidirectional downstream multi-system adverse effects. Specifically, fatty deposits in the liver and heart heart failure potentiate inflammation, causing further damage, including fibrosis, atherosclerosis, prothrombotic states, etc. MASLD metabolic-dysfunction associated steatotic liver disease, MetS metabolic syndrome.

Box 1 | Summary of common pathophysiological pathways of each heart failure subtype

MetS contributes to each in varying degrees, mostly HFpEF, via chronic inflammation and upregulation of proinflammatory cytokines. HFrEF is most commonly due to ischemic events, which can be triggered by longstanding inflammation due to MetS. HFmrEF shares components of both HFpEF and HFrEF.



HFpEF heart failure with preserved ejection fraction, *HFmrEF* heart failure with mildly reduced ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *MetS* metabolic syndrome, *MMP* matrix metalloproteinase.

Recent research has also suggested that gut microbiome composition plays a role in the development and progression of hepatic fibrosis. Notable alterations include decreased diversity, with an increase in certain gram-positive bacteria genera such as Streptococcus and gram-negative bacteria such as Bacteroides and Ruminococcus, which have been associated with hepatic fat-related inflammation, called steatohepatitis, and scarring, ultimately leading to fibrosis. Patients with advanced fibrosis exhibit elevated levels of other bacterial genera, such as gram-negative E. coli and proteobacteria, and significantly lower gram-positive Firmicutes. Multiple pathophysiological pathways have been suggested, including changes in glucose metabolism, inflammation via bacterial endotoxins binding to toll-like receptors, hepatic triglyceride deposition from microbial metabolites, and altered lipid and bile metabolism[9].

Pathophysiology of heart failure and the shared development of MASLD

Heart failure is categorized into three subtypes based on cardiac dysfunction: heart failure with preserved ejection fraction (HFpEF), reduced ejection fraction (HFrEF), and mildly reduced ejection fraction (HFmrEF)[29]. While each subtype has a distinct pathophysiology, they often intersect with the development of MASLD via the development of a pro-inflammatory milieu, insulin resistance, adipocyte dysfunction, and lipotoxicity (Box 1).

HFpEF

HFpEF is a clinical syndrome where patients exhibit heart failure symptoms despite normal or near-normal left ventricular ejection fraction[29]. It affects 1.1–5.5% of people worldwide, with higher incidence in older patients and women, a trend also observed in MASLD[30]. Studies suggest an association between MASLD and HFpEF, but the exact relationship remains uncertain.

In a retrospective study of Medicare beneficiaries, MASLD patients who developed heart failure were more likely to have HFpEF (adjusted HR 1.24, 95% CI: 1.14–1.34) than HFrEF (adjusted HR 1.09, 95% CI: 0.98–1.2)[17]. Another American prospective cohort study found that 27% of HFpEF patients met MASLD criteria, with ultrasound, computed tomography, or magnetic resonance imaging consistent with advanced stages and cirrhosis. Older age, higher body mass index (BMI), and DM significantly correlated with MASLD diagnosis in HFpEF patients[31].

Traditionally, HFpEF has been observed in patients with concentric hypertrophy of the left ventricular walls and normal chamber size. However, recent population-based studies have revealed HFpEF symptomatology even in patients with concentric remodeling (without hypertrophy) or those with a normal left ventricular geometry. Cardiomyocytes in HFpEF patients appear thicker and less elongated than those in patients with HFrEF. Additionally, these cardiomyocytes may exhibit increased collagen composition. Consequently, the left ventricular myocardium becomes stiff, less distensible, and often fibrotic, leading to oxidative stress and profibrotic cytokine production. Matrix metalloproteinases (MMPs), which were previously thought to limit cardiac fibrosis, have been found to potentially induce fibrosis. Altered levels of MMP-2 and MMP-9, along with reduced tissue inhibitors of MMPs (TIMP-1), correlate with diastolic dysfunction. Furthermore, mutations in cardiac myosin binding protein C (MyBP-C), as an essential protein involved in cross-bridge kinetics, impair diastolic function in HFpEF patients[32].

Inflammation plays a significant role in the development of HFpEF. Comorbidities associated with MetS, such as arterial hypertension, DM, and hypercholesterolemia, increase inflammatory markers (IL-1B, IL-6, ICAM-1, and VCAM-1) and reduce collagen-degrading MMP activity. Chronic inflammation leads to T-lymphocyte and macrophage remodeling, contributing to heart failure[11]. In patients with insulin resistance, increased adiposity triggers inflammatory cytokine release, altering cardiac remodeling, and promoting HFpEF development. Additionally, inflammation mobilizes fatty acids from skeletal muscle, contributing to hepatic deposition in MASLD[11]. Altered fatty acid metabolism, reduced nitric oxide levels, and advanced glycation end-products may further impact reverse remodeling and mortality[33].

In summary, the chronic pro-inflammatory milieu and altered fatty acid metabolism induced by MetS and MASLD, noted by increased pro-inflammatory cytokines, can lead to increased cardiac remodeling and HFpEF development.

HFrEF

A retrospective study from the National Inpatient Sample revealed that among nearly 1.9 million hospitalized patients with HFrEF, 43,400 had concomitant MASLD. Notably, patients with both MASLD and HFrEF tended to be younger and had a higher prevalence of T2DM, obesity, and renal failure compared to HFrEF patients without MASLD. Interestingly, HFrEF patients without MASLD showed a higher prevalence of previous myocardial infarction, percutaneous intervention, and prior stroke. These findings suggest that MASLD and HFrEF often coexist, and their development may involve non-traditional pathophysiological pathways beyond primary ischemic myocardial injury[34].

The pathophysiology of HFrEF involves cardiac remodeling due to direct myocardial damage, resulting in decreased left ventricular contractility during systole. Chronic alterations in left ventricular hemodynamics, blood pressure, and neurohormonal activation influence this remodeling process. Myocardial injuries, such as ischemic events, lead to progressive ventricular dilatation without sufficient hypertrophy, increasing ventricular wall tension, and contributing to heart failure. Neurohormonal compensatory mechanisms play a role, and drugs targeting the renin-angiotensin-aldosterone system provide mortality benefits[35]. Some emerging evidence also suggests pre-existing cardiac and circulatory dysfunction via maladaptive neurohormonal activation may significantly contribute to the onset of progression of hepatorenal syndrome in those with decompensated cirrhosis, a feared complication of MASLD[36]. Pro-inflammatory cytokines (TNF-α, IL-6, IL-1b, and IL-2) and oxidative stress also impact heart failure severity[35].

Population studies suggest that MetS contributes to the pathophysiology and progression of HFrEF. Previously, the 'obesity paradox' proposed that obesity is protective, while insulin resistance increases mortality in heart failure patients[37]. However, recent research highlights a direct link between waist-to-hip ratio (rather than BMI) and adverse outcomes in HFrEF[37]. Chronic inflammation, induced by adiposity and insulin resistance, likely plays a role in cardiac remodeling. Additionally, comorbidities like dyslipidemia directly impact coronary artery disease and heart failure progression[38,39].

HFmrEF

HFmrEF is a recently recognized classification that accounts for approximately 13–24% of heart failure cases[40,41]. Studies, such as the TIME-CHF and ALARM-CHF trials, indicate that HFmrEF often results from coronary artery disease, similar to HFrEF; however, the pathophysiology involves both systolic and diastolic dysfunction[40,42,43]. Biomarker studies reveal an intermediate profile, with interaction between cardiac stretch and inflammatory markers suggesting it may share similar pathophysiologic mechanisms with HFpEF as well[40,44]. Additionally, increased epicardial fat in HFmrEF patients, despite similar BMI, suggests a role for lipotoxicity alongside ischemic causes in myocardial injury[45].

Diagnostic challenges of heart failure with MASLD

Diagnosing heart failure using traditional methods such as the Framingham Heart Failure Diagnostic Criteria or newer scoring tools such as the H_2FPEF (Heavy (BMI > 30 kgm^3), Hypertensive (two or more antihypertensive medications), atrial Fibrillation (paroxysmal or persistent), pulmonary hypertension (Doppler echocardiography estimated pulmonary artery systolic pressure > 35 mmHg), elder (age > 60 years), Filling pressure) score for HFpEF can be challenging, especially when comorbid MASLD is present. Advanced liver disease shares similar symptoms with heart failure, complicating diagnosis. The AHA staging and New York Heart Association (NYHA) classifications rely on functional limitations, and MASLD exacerbates these restrictions. Even in the absence of clinical heart failure, underlying metabolic disease meets AHA stage A criteria. Unfortunately, current diagnostic tools do not adequately differentiate similar clinical conditions, potentially leading to misdiagnosis and inappropriate interventions[46–48].

Melding preventative hepatology with preventative cardiology in the co-management of MASLD and heart failure

Preventive medicine is crucial in managing MASLD and heart failure. Both hepatology and cardiology emphasize lifestyle changes to prevent, slow down, or even reverse the adverse effects of insulin resistance[49,50]. Key strategies include achieving a 7–10% weight loss through a healthy diet tailored to individual comorbidities and regular exercise[51]. The Mediterranean diet, rich in vegetables, whole grains, omega-3 fatty acids, and olive oil, has shown benefits for MetS and MASLD, even reducing the risk of hepatic fibrosis and lowering all-cause and cardiovascular mortalities[52,53]. The AHA recommends a combination of aerobic and muscle-strengthening exercises to reduce cardiovascular risk (Box 2)[50,54,55].

Tobacco and alcohol cessation are crucial due to their impact on MetS, liver disease, and heart failure. Significant alcohol consumption places further oxidative stress on the liver, exacerbating underlying MASLD[9]. Recent studies show that tobacco use, especially in combination with insulin resistance and DM, increases the risk of hepatic fibrosis and MetS[56,57]. Smoking cessation reduced heart failure risk, while continued tobacco use escalates it[56]. Multimodal strategies, including drug therapy, support groups, rehabilitation, and motivational interviewing, are essential for successful cessation[51,56].

Social determinants of health

Clinicians must recognize how commercial and social determinants of health affect MetS, MASLD, and ASCVD. Access to affordable, healthy, and high-quality foods, time constraints, sedentary lifestyles, and mental health barriers hinder progress. Resources, including food banks, farmers markets, nutritionists, and low-cost gyms, should promote health equity[51].

Time is also a commodity that may prevent exercise or shopping for healthy food options, leading to sedentary lifestyles and the consumption of high-fat, low-protein foods. Poor mental health and health literacy may also provide barriers to success. Resources such as food banks, farmers markets, nutritionists, psychologists, low-cost public gyms, equipment-free exercise regimens, and disease-specific literature should be made available to all patients to create and maintain health equity across socioeconomic backgrounds[51].

When behavioral changes fail to produce meaningful weight loss, medications or surgical interventions can be considered. Anti-obesity medications (e.g., orlistat, phentermine/topiramate, naltrexone/bupropion, glucagon-like peptide-1 receptor agonists [GLP-1 RA]) are recommended for patients with a BMI ≥ 30 kg/m^2 or ≥27 kg/m^2 in the presence of one or more co-morbidities[58,59]. Bariatric-metabolic surgery is also recommended for patients with a BMI ≥ 35 kg/m^2, regardless of the presence, absence, or severity of comorbidities, or in patients with metabolic disease and a BMI of 30–34.9 kg/m^2. Bariatric surgery has consistently demonstrated safety and efficacy and has been shown to improve or reverse MASLD/MASH[60–66].

Box 2. | Summary of preventative measures to prevent progression or onset of MetS, MASLD, or heart failure

Preventative measures for MetS, MASLD, and heart failure
Weight loss (7–10% of body weight)
Mediterranean diet
• (−) Refined grains, fructose, processed meats, saturated fatty acids, alcohol • (+) Vegetables, whole grains, omega-3 fatty acids, and olive oil
Aerobic activity and resistance training
• ≥150 min of moderate-intensity aerobic exercise per week or vigorous aerobic activity for 75 min per week in combination with moderate to high-intensity muscle-strengthening activity (resistance or weights) at least 2 days per week to lower ASCVD risk
Illicit substance, alcohol, and tobacco cessation

MetS metabolic syndrome, *MASLD* metabolic-dysfunction associated steatotic liver disease, *ASCVD* atherosclerotic cardiovascular disease.

Table 1 | Summary of the shared benefits or risks of common HFpEF medications in patients with MASLD

Drug class	HFpEF benefit	MASLD benefit
SGLT2 inhibitors	Yes	Yes
GLP-1 receptor agonists	Unclear	Yes
MRAs	No	Yes
ACE inhibitors	Unclear	Unclear
ARNIs	Unclear	Unclear

HFpEF heart failure with preserved ejection fraction, *MASLD* metabolic-associated steatotic liver disease, *SGLT2* sodium-glucose transport protein 2, *GLP-1* glucagon-like peptide-1, *MRA* mineralocorticoid receptor antagonist, *ACE* angiotensin-converting enzyme, *ARNI* angiotensin receptor-neprilysin inhibitor.

Goal-directed medical therapy of heart failure in patients with MASLD

Guideline-directed medication therapy for heart failure varies based on the subtype of heart failure. These differing yet targeted strategies are crucial in managing heart failure, especially in patients with MASLD, where appropriate therapy can attempt to mitigate the cardiovascular risk associated with liver disease.

HFpEF

Guideline-directed medical therapy of HFpEF traditionally focuses on risk factor management. Recent landmark trials (e.g., DELIVER, PRESERVED-HF, EMPEROR-Preserved, EMPULSE, and SOLOIST-WHF) have suggested that sodium-glucose transport protein 2 (SGLT2) inhibitors and MRAs reduce hospitalizations and improve diastolic dysfunction[45,67–72]. Loop diuretics alleviate symptoms, but their impact on overall cardiac function is limited. Angiotensin receptor blockers (ARB) and ARNI are approved for HFpEF, but further evidence is needed to grade their efficacy[46]. Considering the shared development pathway with MASLD, clinicians should carefully consider how drug therapies for HFpEF affect MASLD (Table 1).

Growing, robust evidence exists regarding the benefits of SGLT2 inhibitors on cardiovascular mortality and hospitalizations[73], however recent a recent meta-analysis has shown that SGLT2 inhibitors may also benefit patients with MASLD[74]. Liver fibrosis and steatosis indicators, including liver stiffness measurement (LSM), controlled attenuation parameter (CAP), serum ferritin, serum type 4 collagen 7s, and FIB-4 index, were measured in 699 patients from 16 trials[74]. Results indicated that significant reductions in LSM, CAP, serum ferritin, serum type 4 collagen 7s, liver biomarkers, and FIB-4 index were associated with SGLT2 inhibition. Triglycerides and insulin resistance (HOMA-IR) also decreased significantly[74]. Body composition improved, including reduced BMI, visceral adipose tissue (VAT) area, and liver fat content[74]. Conversely, another meta-analysis involving 1595 participants from 25 studies found that SGLT2 inhibitors did not significantly impact HOMA-IR, VAT area, or triglyceride reduction. However, this study had limitations due to clinical trial heterogeneity[75].

The hypothesized pathophysiological mechanisms of SGLT2 inhibition on the liver are multifold[76]. First, glucosuria has been associated with weight loss, mainly fat loss, primarily through improved insulin resistance and liver steatosis[76]. Second, glucosuria also promotes decreases in blood glucose levels and a downregulation of carbohydrate-responsive element-binding protein, a transcription factor responsible for activating fatty acid synthesis[76]. This, in turn, blocks de novo lipogenesis[76]. Third, reducing the inflammatory markers associated with insulin resistance can increase the oxidation of free fatty acids and prevent hepatic deposition[76]. Finally, SGLT2 inhibition can also increase glucagon levels, which has been associated with decreased development of fatty liver in human and animal models[76].

Overall, SGLT2 inhibitors should be considered as concomitant therapy in patients with both HFpEF and MASLD, even if the benefits in MASLD are modest. Any improvement in cardiac function may reduce hepatic congestion and improve liver stiffness and enzymes.

Recent evidence suggests GLP-1 RAs benefit patients with HFpEF[77,78]. In the STEP-HFpEF trial, semaglutide, a GLP-1 RA, significantly improved patient-oriented quality of life, body weight, and exercise function compared to placebo. Serious adverse events were lower in the treatment group (13.3% vs 71%; $P < 0.001$)[79]. The SUMMIT trial recently evaluated the effect of tirzepatide, another GLP-1 RA, in people with obesity related HfpEF and found treatment with tirzepatide to be associated with a lower risk of composite death from cardiovascular causes or worsening heart failure in patients with HFpEF and obesity, compared to placebo, suggesting tirzepatide use may be on the horizon for the co-management of MASLD and HFpEF[80]. In patients with MASLD and T2DM, the drug has shown efficacy in lowering glucose levels and reducing weight[81]. It also has demonstrated the ability to reduce liver fat content in patients with MASLD and T2DM, with a relative reduction of 47%[82]. Other randomized controlled trials, such as SYNERGY-NASH, have also shown successful treatment of MASLD and MASH resolution without worsening of fibrosis[83].

MRAs have demonstrated significant benefits in patients with HFpEF. In the TOPCAT trial, spironolactone, an MRA, reduced hospitalizations for heart failure (HF 0.83, 95% CI: 0.69–0.99), but it did not significantly impact overall mortality[84]. Finerenone, a novel non-steroidal MRA, has shown cardiorenal protective benefits in patients with chronic HFpEF and

Table 2 | Summary of the shared benefits or risks of common HFrEF medications in patients with MASLD

Drug class	HFrEF benefit	MASLD benefit
ACEi	Yes	Yes
ARB	Yes	Unclear
ARNI	Yes	Unknown
MRA	Yes	Yes
Beta-blocker	Yes	Unclear**
SGLT2 inhibitor	Yes	Yes
Hydralazine	Yes	Unknown
Isosorbide mononitrate	Yes	Unknown
Loop diuretics	Yes*	Unknown**
Digoxin	Yes*	Unknown
GLP-1 receptor agonists	No	Yes

HFrEF heart failure with reduced ejection fraction, *MASLD* metabolic-associated steatotic liver disease, *ACEi* angiotensin-converting enzyme inhibitor, *ARNI* angiotensin receptor-neprilysin inhibitor, *ARB* angiotensin II receptor blocker, *MRA* mineralocorticoid receptor antagonist, *SGLT2* sodium-glucose transport protein 2, *GLP-1* glucagon-like peptide-1.

*Safe to use in patients with HFrEF for symptom control but without mortality benefit.

**Likely safe to use in patients with MASLD, but with an unknown direct MASLD.

T2DM[85–87]. The FINEARTS-HF trial, a recently concluded randomized, double-blind, placebo-controlled trial, compared finerenone with placebo in patients with HFpEF and HfmrEF who were using either a loop or thiazide diuretic at baseline. Finerenone was found to reduce the total worsening heart failure events classified as (hospitalization or urgent care visit requiring intravenous diuresis) and cardiovascular death by 16%, suggesting finerenone may be the superior MRA when compared to spironolactone in the treatment of HFpEF and HfmrEF[88]. However, more research is needed to determine the superior drug, especially in patients living with concomitant MASLD.

MRAs are considered first-line agents for patients with refractory ascites in decompensated cirrhosis, a potential complication of MASLD[89]. Their potential utility has also been demonstrated in patients with MASLD. A small single-center randomized controlled trial assessed the effect of spironolactone plus vitamin E in patients with biopsy-proven MASLD[90]. After an 8-week follow-up, there were significant reductions in insulin resistance (HOMA-IR) (4.4 ± 0.9 at baseline vs 2.8 ± 0.5 at week 8, $P = 0.047$) and total insulin levels compared to baseline (15.3 ± 2.7 at baseline vs 10.3 at week 8 ± 5.0, $P = 0.013$)[90]. Low-dose spironolactone was found to combat dyslipidemia and hepatic inflammation via a PCSK9-dependent mechanism[91]. Eplerenone was also found to prevent the development of MASH and metabolic abnormalities by inhibiting inflammatory responses in both Kupffer cells and macrophages by suppressing lipopolysaccharide-induced TNF-α production[92,93]. Other studies have suggested MRAs may have anti-inflammatory properties and prevent the onset and progression of MASLD and MASH[94,95].

ARNIs combine an ARB with a neprilysin inhibitor, which affects the degradation of natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides[96]. A recent randomized clinical trial called the PARABLE trial randomized 250 asymptomatic patients with pre-HFpEF (or AHA stage B HFpEF) to receive either an ARNI (sacubitril-valsartan) or ARB (valsartan) alone for 18 months. The results indicated that treatment with an ARNI was associated with a significantly greater increase in left atrial volume index and improved NT-pro BNP compared to ARB alone[97]. A recent prospective cohort trial with a small sample size of 27 participants found that sacubitril-valsartan led to an overall improvement in both left ventricular ejection fraction from 30% to 38% over six months. In nine patients with hepatic fibrosis, there was a significant decrease in LSM, a noninvasive measurement of hepatic fibrosis, from 9.8 kPa to 7.8 kPa. This data suggests ARNIs may also be beneficial in managing MASLD; however, larger studies are needed to corroborate this finding[98].

Overall, MRAs and SGLT2 inhibitors have independently demonstrated safety in efficacy in both heart failure and MASLD; however, trials are lacking in patients with concomitant disease. GLP-1 RAs show promising benefits for both HFpEF and MASLD, but more studies are necessary to determine their therapeutic roles and standardized treatment regimens.

A recent retrospective study using the National Inpatient Sample analyzed the outcomes of patients with HFpEF and MASLD. After multivariate adjustments, admissions in patients with both HFpEF and MASLD were associated with higher odds of in-hospital mortality, length of stay, vasopressor use, cardiogenic shock, cardiac arrest, acute kidney injury, and need for dialysis compared to HFpEF admissions without MASLD. Hospitalizations with HFpEF-MASLD also had a longer length of stay and incurred more hospitalization cost[34]. Developing optimized outpatient and inpatient therapeutic strategies is necessary to reduce adverse patient outcomes associated with both diseases.

HFrEF

Goal-directed medical therapy for HFrEF has a robust evidence base compared to HFpEF. In HFrEF, medications are titrated to their maximally tolerated doses for proven mortality or functional benefit[96]. These drug classes include the following: (1) renin-angiotensin system in inhibition with angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), or angiotensin receptor/neprilysin inhibitor (ARNI); (2) beta-blockers; (3) MRAs; (4) sodium-glucose cotransporter 2 (SGLT2) inhibitor; and (5) hydralazine and isosorbide dinitrate in black patients[96]. Diuretics, such as loop diuretics, can be useful in managing heart failure symptoms, with newer studies demonstrating their short-term clinical benefits (Table 2)[96]. Digoxin, when combined with beta-blockade, has also demonstrated lower 30-day all-cause readmission rates but no benefits to mortality[99]. Surgical management of HFrEF can include placement of an intracardiac defibrillator and/or Mitraclip in the appropriate patients[96].

Randomized controlled trials have consistently demonstrated the morbidity and mortality benefit of ACEi[100–105], ARBs[106–108], and, more recently, ARNIs. Landmark trials (e.g., PARADIGM-HF, PIONEER-HF, and TRANSITION) have highlighted the efficacy of ARNIs in HFrEF, leading to their recommendation as first-line therapy for HFrEF patients[96,109–111]. If patients cannot tolerate ARNIs, ACEi or ARBs are suitable alternatives[96].

Despite its success in HFrEF patients, the available research on the effect of RAAS inhibition with ARNIs, ARBs, or ACEi in patients with MASLD is limited. One randomized controlled trial investigated the impact of telmisartan on MASLD activity and fibrosis scores in patients with MASH. After 1 year, the telmisartan group showed improved MASLD activity and fibrosis scores compared to controls (regression analysis, OR 92.07, 95% CI: 1.39–6106, $P = 0.035$). Adverse events were mild and similar in both groups[112]. Additionally, a prospective cohort study evaluated the effectiveness of ACEi in improving insulin resistance (HOMA-IR) and its effect on alanine aminotransferase (ALT). Both HOMA-IR and ALT significantly decreased following 2-month trials of olmesartan and telmisartan[113]. A randomized controlled trial-based and single-arm meta-analyses were conducted to assess the safety and efficacy of ARBs in managing MASLD. Low-density lipoprotein levels and total cholesterol levels were significantly decreased without affecting ALT levels[114]. However, fibrosis and MASLD activity scores were not significantly improved by ARB treatment[114].

Early initiation of beta-blocker therapy (bisoprolol, extended-release metoprolol succinate, and carvedilol) in patients with HFrEF has been shown to reduce the mortality rate and the combined risk of death or hospitalization[115–118]. Like with RAAS blockade, the use of beta-blockers in the co-management of HFrEF and MASLD has not been extensively studied. However, nonselective beta-blockers, such as propranolol, have been demonstrated to be beneficial in patients with cirrhosis due to their effects

Table 3 | Summary of the shared benefits or risks of common HFmrEF medications in patients with MASLD

Drug class	HFmrEF benefit	MASLD benefit
SGLT2 inhibitors	Likely	Yes
GLP-1 receptor agonists	Likely	Yes

HFpEF heart failure with mildly reduced ejection fraction, *MASLD* metabolic-associated steatotic liver disease, *SGLT2* sodium-glucose transport protein 2, *GLP-1* glucagon-like peptide-1.

on reducing portal hypertension[119]. Furthermore, carvedilol is now the first-line therapy to prevent esophageal variceal bleeding or the onset of ascites for those meeting Baveno VII criteria and thus may be the best choice in this patient population[120]. Murine models have suggested that beta-blockers may decrease insulin resistance, improve dyslipidemia, and increase liver expression of GLUT4[121], while another model suggested they may worsen liver injury in MASH[122]. Further research needs to be performed to quantify their effects (Table 3).

MRAs, such as spironolactone and eplerenone, consistently improve survival, reduce heart failure hospitalizations, and prevent sudden cardiac death in patients with HFrEF[96]. They are recommended for any degree of HFrEF based on positive results from clinical trials (RALES, EPHESUS, and EMPHASIS-HF)[96,123–125]. As with ACEi, ARBs, and ARNIs, disruption of the RAAS blockade has been shown to be beneficial in patients with insulin resistance and lipid dysregulation. Aldosterone receptor antagonism has not been extensively studied in patients with MASLD, especially with concomitant HFrEF. However, eplerenone and spironolactone are frequently and safely used in decompensated hepatic cirrhosis due to their positive effect on portal hypertension[119,120].

SGLT2 inhibitors work by promoting urinary excretion of glucose, improving insulin resistance in DM, and showing benefits in managing HFrEF[96,126,127]. Trials such as DAPA-HF and EMPEROR-Reduced demonstrated over 30% reduction in heart failure hospitalizations and lowered all-cause mortality[96,128,129]. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, also reduced cardiovascular death and urgent heart failure visits by 33%[71,96]. These drugs have also been well-tolerated, aside from an increased risk of urinary tract infections due to induced glycosuria and rarely euglycemic ketoacidosis[96]. Overall, SGLT2 inhibitors are likely safe and beneficial in patients with HFrEF and concomitant MASLD. Any improvement in cardiac function may reduce hepatic congestion and improve liver stiffness and enzymes[130,131].

As demonstrated above, GLP-1 receptor agonism has been shown to be beneficial in the management of MASLD and HFpEF; however, small trials performed with liraglutide have been less favorable for patients with HFrEF. The LIVE (effect of liraglutide on left ventricular function in stable chronic heart failure patients) trial randomized 241 patients with HFrEF with or without DM to receive either liraglutide 1.8 mg weekly or placebo for 24 weeks[132]. There were no significant changes in LVEF, health status, or functional class, but serious cardiac events, including sustained ventricular tachycardia, atrial fibrillation requiring intervention, aggravation of ischemic heart disease, and worsening of heart failure, were significantly increased in the treatment group ($n = 12$, 10.0% vs $n = 3$, 3.0%; $P = 0.04$)[132]. Another trial called the FIGHT (Functional Impact of GLP-1 for HF Treatment) randomized 300 patients with HFrEF and recent decompensation to receive liraglutide or placebo for 6 months[133]. Again, there were no positive changes in LVEF, but there were higher associations with the composite outcomes of death or heart failure hospitalization (HR 1.30; 95% CI: 0.92–1.83; $P = 0.14$), especially in patients with diabetes (HR 1.54; 95% CI: 0.97–2.46; $P = 0.07$)[133]. However, neither study was sufficiently powered to produce meaningful conclusions about GLP-1 receptor agonists in HFrEF[132,133]. Importantly, neither of these trials was limited to study participants with obesity, and so the impact of weight loss among patients with obesity and comorbid HFrEF remains unclear. In the SELECT trial, of the 17,604 pts (BMI ≥ 27 kg/m^2) with pre-existing CV disease without diabetes (HbA1c < 6.5%) enrolled in the study had an investigator-reported history of HF at randomization that included 2268 patients with HFpEF and 1341 patients with HfrEF[134,135]. This represents the largest population of patients with HFrEF studied with a pharmacologic weight loss intervention to date. SELECT reported a 20% relative risk reduction in the primary composite outcome. Results from additional endpoints and subgroup analyses, especially those related to HFrEF, are still awaited[134,135].

Hydralazine and isosorbide nitrate are recommended in Black patients with HFrEF who remain symptomatic despite ACEi (or ARB), beta-blockers, and MRA due to reduced all-cause mortality and heart failure hospitalizations and improved quality of life in this population[96,136]. Unfortunately, studies on the safety and efficacy of these medications in MASLD patients are lacking.

Loop diuretics, such as furosemide, torsemide, and bumetanide, are often used as rescue therapy for overt hypervolemia in patients with poorly controlled HFrEF or decompensated HFrEF[96,137]. Traditionally, these drugs have not been associated with morbidity or mortality benefits; however, a study using the OPTIMIZE-HF registry in 2020 demonstrated a short-term benefit with loop diuretics in loop-diuretic naïve patients. This study indicated that prescription of a loop diuretic following hospitalization for an index decompensated heart failure event reduced 30-day all-cause mortality (HR 0.73; 95% CI: 0.57–0.94; $P = 0.016$) and lowered 30-day HF-readmission rates (HR 0.79; 95% CI: 0.63–0.99; $P = 0.037$)[138]. Interestingly, there were no statistically significant differences when divided into HFrEF or HFpEF, but overall, this study shows potential, previously unrecognized benefits of loop diuretics in patients with heart failure.

Like MRAs, loop diuretics have been the mainstay of therapy for patients with overt hypervolemia due to decompensated cirrhosis; however, their benefits in patients with MASLD are not as appreciated. Murine model studies have suggested that loop diuretic-induced prerenal azotemia can increase plasma IL-6 expression and the acute phase response, as well as disrupt physiologic insulin-induced cellular swelling, an important factor in hepatic proteolysis inhibition[139]. A retrospective study found furosemide (OR = 1.9; 95% CI: 1.4–2.5, $P < 0.001$) and spironolactone (OR = 3.1; 95% CI: 2.0–4.6, $P < 0.001$) to be associated with an increased risk of advanced fibrosis[140]. While these findings do not imply a causal relation and may be because furosemide and spironolactone are used in advanced decompensated cirrhotic patients, they do signify further need for research about their safety in patients with MASLD.

Digoxin has been traditionally utilized as a last-line therapy for patients with HFrEF due to its potential cardiotoxicity with a narrow therapeutic window and limited mortality benefit[98]. Recent studies have shown that when combined with beta-blockade, patients demonstrate a statistically significant reduction in symptomatic improvement and rehospitalization rates, but fail to improve mortality[98]. Preclinical studies have also shown promise in managing MetS and MASLD, likely due to an observed immunomodulating effect[141]. At high doses, digoxin binds to the ligand-binding domain of the NR RORγT, inhibiting its transcriptional activity, leading to inhibition of Th17 and IL-17 related and suppression of nuclear factor kappaB activity[141]. At lower doses, digoxin activates RORγT signaling, leading to the induction of several Th17-specific genes, suggesting a potential role of digoxin in adoptive cell therapy[141]. However, these effects have yet to be established clinically.

In patients with HFrEF prescribed maximally tolerated GDMT who still have bothersome symptoms, surgical management may be indicated[96]. An implantable cardiac defibrillator (ICD) or cardiac resynchronization therapy may be considered in patients with nonischemic cardiomyopathy or ischemic heart disease at least 40 days post-myocardial infarction and NYHA class II or III symptoms on chronic goal-directed medical therapy, who have a reasonable expectation of meaningful survival for more than 1 year[96]. Many studies have consistently demonstrated the mortality benefits of ICDs if the previous criteria are met; better outcomes have been appreciated in patients with ischemic etiologies[96,142–150].

While there are no studies evaluating the use of ICDs in patients with concomitant HF and MASLD, there may be clinical indications for them in

both conditions. Previous studies have demonstrated increased rates of arrhythmias in patients with MASLD, including ventricular arrhythmias, atrial fibrillation, and heart blocks[151–153]. A recent retrospective cohort study using the TriNetX Research Network found MASLD to be associated with significantly higher odds of ventricular arrhythmias (OR 2.75, 95% CI: 2.54–2.98, $P < 0.0001$) and hospital admission (OR 1.05, 95% CI: 1.03–1.08, $P < 0.0001$) at 3-years, suggesting ICDs should be strongly considered in patients with concomitant HFrEF[154].

Severe mitral regurgitation is an independent predictor of mortality and HF hospitalization in both ischemic and nonischemic cardiomyopathy patients[155]. Evidence of the MitraClip has shown promise in patients with HFrEF and severe primary or secondary mitral regurgitation, however, no studies exist for patients with MASLD[96,156–158]. A subgroup analysis of a retrospective cohort study using the 2013–2017 National Inpatient Sample database of adults who were hospitalized for MitraClip repair of the mitral valve indicated that patients with cirrhosis were more likely to develop cardiogenic shock than those without cirrhosis (13.3% vs 3.9%, $P = 0.032$)[159]. No statistically significant differences in in-hospital mortality, length of stay, or total hospital cost were appreciated[159]. This suggests that MitraClip procedures are likely safe for patients with co-morbid HFrEF and MSLD, but more studies are needed.

HFmrEF

Unfortunately, there are no randomized controlled trials investigating the optimal medical therapies for patients with HFmrEF[96]. Most recommendations are supplied using post-hoc or subset analyses of previous HF trials with patients now classified as HFmrEF[96]. Loop diuretics are strongly recommended for symptoms of decompensation. SGLT2 inhibitors are also recommended due to evidence extrapolated from the EMPEROR-Preserved trial that suggested a reduced risk of the primary composite endpoint of cardiovascular death or hospitalization in HF in patients with a left ventricular ejection fraction between 41% and 49%[21]. Other post-hoc and subset analyses of HFrEF that included patients with HFmrEF have suggested benefit from the use of GDMT, including ACEi, ARBs, ARNIs, MRAs, and beta-blockers[160–164].

As discussed in previous sections, studies have consistently demonstrated the many benefits of SGLT2 inhibitors in patients with all forms of heart failure, as well as with MASLD, from the reduction of cardiovascular death and heart failure hospitalizations to improvement in glycemic control, insulin resistance, and lipid oxidation in patients with MetS. Clinicians should strongly consider an SGLT2 inhibitor in patients with any degree of MASLD or cardiac dysfunction. Extrapolations from previous studies also favor the use of RAAS blockade with ACEi, ARBs, and ARNIs in patients with MASLD and concomitant HFmrEF, while suggesting judicious use of loop diuretics and MRAs due to conflicting results showing potential adverse hepatic lipid deposition with these drugs.

A subgroup analysis of the STEP-HFpEF trial showed favorable safety and efficacy results of GLP-1 receptor agonists in the small sample size of HFmrEF patients[79]. These drugs are likely safe in this population; however, further dedicated trials in patients with HFmrEF and, ideally, MASLD, are necessary to compare their efficacy and safety in this population.

Outlook

The strong associations, shared pathophysiologic pathways, and increasing global prevalence and mortality rates of MASLD and heart failure express the need for optimized multidisciplinary diagnostic and management strategies[165]. Carefully coordinated preventative, holistic hepatological and cardiological approaches to patients with MetS should be implemented in those at risk for the onset or progression of MASLD or heart failure[24]. In those who have progressed to having concomitant MASLD and heart failure, drug classes such as ACEi, ARBs, ARNIs, beta-blockers, MRAs, and SGLT2 inhibitors demonstrate benefits, while loop diuretics may worsen MASLD. Surgical interventions in HFrEF, such as ICD placement or MitraClip devices, could offer advantages to those with severely reduced ejection fraction and MASLD. However, the demographic of patients with concurrent MASLD and heart failure remains insufficiently explored, presenting a challenge to researchers aiming to identify optimal co-management strategies for these diseases, especially given the growing need for coordinated interventions.

There is a significant deficit and necessity for further research into the cardiometabolic spectrum of diseases that encompasses heart failure and MASLD, especially when large landmark heart failure trials fail to report baseline MASLD characteristics or endpoints specific to MASLD. Although shared pathophysiology and comorbidities have been clearly established, their coexistence continues to pose a challenge to diagnosis, prevention, and intervention for each disease. Diagnostic and classification algorithms of heart failure may not adequately represent the disease when concomitant MASLD is present due to the often-confounding symptomatology. Studies should focus on how to effectively diagnose heart failure in the presence of MASLD and determine their respective contribution to the clinical picture, which can, in turn, guide targeted therapeutic strategies. Moreover, most studies simply report MASLD by the presence of steatosis without adequate characterization of the degree of fibrosis. The correlation of liver fibrosis with heart failure is understudied but is critical to better understand common pathogenic mechanisms.

Furthermore, very few randomized controlled trials explore the therapeutic benefits of heart failure GDMT in patients with MASLD. Loop diuretics and MRAs are commonly used medications in heart failure patients, but their safety profile and pathophysiologic effectiveness have yet to be understood in patients with MASLD. Existing literature suggests a hastening of hepatic lipid deposition, but larger randomized studies are needed to corroborate these findings. The effects of beta-blockers and digoxin in MASLD should also be explored. Further studies need to be conducted to identify the optimal medical treatment of HFmrEF, regardless of MASLD presence, as existing recommendations have been extrapolated from randomized controlled trials involving patients with HFrEF or HFpEF.

It is worth noting that newer drugs and alternative applications of existing drugs are on the horizon. GLP-1 agonists are gaining popularity due to their antihyperglycemic and weight loss benefits in those with MetS. This drug class has also been shown to reduce ASCVD risk in patients with T2DM, as well as demonstrate a significant impact on clinical, biochemical, and histological markers of fatty liver and fibrosis in patients with MASLD. Emerging evidence suggests that GLP-1 agonists may benefit heart failure patients, especially those with MetS or obesity-related HFpEF. As demonstrated in the STEP-HFpEF trial, which found improved heart failure-related symptoms and functional status, in addition to weight loss[71].

The rapidly growing prevalence of metabolic disease worldwide necessitates a holistic, coordinated, multidisciplinary approach to formulate a standardized optimal interventional algorithm that can be tailored to individual needs. Collaborations between cardiologists and hepatologists in the prevention and co-management of comorbid disease in this patient population are vital to mitigate the global threats of MetS, MASLD, and heart failure. As our current understanding of the complex cardiometabolic disease spectrum evolves, frequent advancements in research and collective global efforts offer optimism for the coming years.

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Competing interests

The authors declare no competing interests.

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