Risk of heart failure in patients with non-alcoholic fatty liver disease.

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BULLET POINTS

- Evidence supports an association between non-alcoholic fatty liver disease (NAFLD) and risk of heart failure (HF).
- The magnitude of this risk increases with severity of liver disease in NAFLD.
- Certain drugs for the treatment of diabetes may decrease risk of HF in NAFLD.
- It remains uncertain whether a NAFLD diagnosis improves risk prediction for HF.

Abstract

Heart failure (HF) and non-alcoholic fatty liver disease (NAFLD) are two conditions that have become important global public health problems. Emerging evidence supports a strong and independent association between NAFLD and the risk of new-onset HF, and there are multiple potential pathophysiological mechanisms by which NAFLD may increase risk of new-onset HF. The magnitude of this risk parallels the underlying severity of NAFLD, especially the level of liver fibrosis. Patients with NAFLD develop accelerated coronary atherosclerosis, myocardial alterations (mainly cardiac remodeling and hypertrophy), and certain arrhythmias (mainly atrial fibrillation), which may precede and promote the development of new-onset HF. This brief narrative Review aims to provide an overview of the association between NAFLD and increased risk of new-onset HF, discuss the underlying mechanisms that link these two diseases, and summarize targeted pharmacological treatments for NAFLD that might also reduce the risk of HF.

Condensed Abstract

Non-alcoholic fatty liver disease (NAFLD) is part of a “multisystem” disease that adversely affects multiple extra-hepatic organs, including the heart and vasculature. Evidence suggests that NAFLD promotes accelerated coronary atherosclerosis and adversely affects other anatomical structures of the heart, conferring an increased risk of myocardial abnormalities (cardiac remodeling and hypertrophy) and arrhythmias (atrial fibrillation) that contribute to the development of heart failure (HF). Because of the link between NAFLD and HF, more careful surveillance of these patients is needed. Further research is required to better elucidate whether ameliorating NAFLD will ultimately prevent or slow the development and progression of HF.

Introduction

Heart failure (HF) is a major public and economic health burden, paralleling general aging, and is associated with considerable hospitalization and mortality (1). The prevalence of HF increases steeply with age, especially amongst persons aged over 60 years. It has been estimated that HF has a prevalence rate of ~10% in community-dwelling people ≥60 years old, with HF with preserved ejection fraction (HFpEF) being more common than HF with reduced EF (HFrEF) (~5% vs. 3.5%) (2).

Non-alcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease worldwide, affecting up to ~30% of the word's adults (3). NAFLD represents a spectrum of liver conditions ranging from simple steatosis to non-alcoholic steatohepatitis (NASH with varying levels of fibrosis) and cirrhosis. The worldwide prevalence of NAFLD is expected to dramatically increase in the foreseeable future in parallel with the increasing epidemics of obesity and type 2 diabetes (T2D) (4). In 2019, NASH has become the most common indication for liver transplantation in the United States (5).

Strong evidence indicates that NAFLD is associated not only with increased liver-related complications, but also with an increased risk of developing coronary heart disease (CHD), T2D, chronic kidney disease, and certain extra-hepatic cancers (6,7). Additionally, there is evidence that NAFLD not only promotes accelerated coronary atherosclerosis, but also affects other anatomical structures of the heart, conferring an increased risk of myocardial alterations, mostly cardiac remodeling and hypertrophy that may lead to new-onset HF (8). These findings support the notion that NAFLD is a "multisystem" disease requiring a patient-centered, multidisciplinary and holistic approach to manage both liver disease and cardiometabolic risk (7).

This Review focuses on the rapidly expanding body of clinical evidence supporting a strong association between NAFLD and the risk of new-onset HF. We also discuss the putative pathophysiological mechanisms underpinning this association, and summarize targeted pharmacotherapies for NAFLD that may also beneficially affect cardiac complications leading to new-onset HF.

1.Risk of Cardiovascular Events and HF in NAFLD

NAFLD is recognized as a risk factor for major adverse cardiovascular events (MACE), which are the leading cause of death in NAFLD (9,10). An updated meta-analysis of 36 observational cohort studies (>5.8 million participants) indicates that the long-term risk of developing fatal or non-fatal MACE is increased in people with NAFLD [hazard ratio (HR) 1.45, 95%CI 1.31–1.61]. This risk is further increased with more advanced liver disease, especially with higher liver fibrosis stage, as assessed by histology or non-invasive fibrosis biomarkers (HR 2.50, 95%CI 1.68–3.72) (6). A recent prospective cohort study of 1,773 adults with biopsy-proven NAFLD followed for a median of 4 years did not show any associations between the severity of liver fibrosis and risk of MACE (11). Growing evidence also supports a strong and independent association between NAFLD and increased risk of cardiac (functional, structural, and arrhythmic) complications that may promote the development of HF (8-10), as discussed below.

Coronary microvascular dysfunction

Coronary microvascular dysfunction is associated with left ventricular (LV) diastolic dysfunction and future risk of MACE, including HFpEF (12). Recently, in a retrospective cohort study of 886 patients without evidence of obstructive coronary artery disease and preserved LV ejection fraction, Vita et al. reported that coronary microvascular dysfunction was more prevalent and coronary flow reserve was lower in patients with computed tomography-detected NAFLD compared to those without NAFLD (13). Patients with NAFLD also had a higher risk of MACE, as did those with coronary microvascular disease, over a median follow-up of 5.6 years (13). An association between NAFLD (on magnetic resonance spectroscopy) and coronary microvascular dysfunction was also reported in 55 Finnish patients with known CHD (14).

Cardiac autonomic dysfunction

Cardiac autonomic dysfunction, which is implicated in HF pathogenesis, has also been reported in NAFLD. For instance, in a cross-sectional study involving 96 sedentary individuals, Houghton et al. showed that heart rate variability (HRV), diastolic variability and systolic variability were impaired in patients with NAFLD (diagnosed with magnetic resonance spectroscopy or biopsy) compared to controls. These differences were largely dependent on the degree of liver fat content and fibrosis staging (15). In another study of 496 individuals, Liu et al. reported that HRV measures, as detected by 5-min resting electrocardiograms, were lower in individuals with ultrasound-detected NAFLD than in those without NAFLD (16). Similarly, Clough et al. found that

dysregulated neurovascular control underlined declining microvascular functionality in 189 patients with radiological or biopsy-proven NAFLD (17). A strong association between NAFLD (on ultrasonography) and impaired cardiac sympathetic/parasympathetic balance, regardless of the presence or absence of T2D and other cardiometabolic risk factors, was also recently confirmed in the Cooperative Health Research in South Tyrol-NAFLD substudy (n=356 individuals included) (18).

Cardiac arrhythmias

Accumulating evidence supports the presence of an association between NAFLD and greater risk of arrhythmias, mostly permanent atrial fibrillation (AF), and QTc interval prolongation that predisposes subjects to life-threatening ventricular arrhythmias (7,8,10). A meta-analysis of six longitudinal cohort studies (614,763 participants) showed that imaging-defined NAFLD was associated with a ~1.2-fold higher risk of incident AF (adjusted-HR 1.19, 95%CI 1.04–1.31) over a median of 10 years (19). Also, imaging-defined NAFLD was found to be associated with higher arrhythmia recurrence rates in a retrospective cohort of 267 consecutive patients undergoing AF ablation during a mean follow-up of ~30 months (20). Some evidence also suggests an association between the presence of imaging-defined NAFLD and certain types of cardiac conduction defects (mainly left anterior hemiblock and right bundle branch block), irrespective of coexisting cardiometabolic risk factors (8,10).

Cardiac remodeling and hypertrophy

Cardiac remodeling is a pivotal process in the natural course of HF (21). Compelling evidence supports a strong association between NAFLD and higher risk of LV diastolic dysfunction, greater LV hypertrophy, or larger left atrial volume, independent of obesity, hypertension, and T2D (8-10). A meta-analysis of 16 cross-sectional studies (32,000 participants) showed that imaging-defined NAFLD was associated with subclinical myocardial structural alterations (increased LV mass), as well as lower early diastolic relaxation (e') velocity, higher LV filling pressure, and larger left atrial volume (22). In most of these studies, NAFLD remained significantly associated with subclinical cardiac remodeling after adjustment for established cardiometabolic risk factors, thus providing insight into a possible link between NAFLD and risk of new-onset HF (22). Consistently, an association between NAFLD and LV abnormality/dysfunction has also been reported in children (23). Some studies have shown that NAFLD-related cardiac abnormalities are further increased

with more advanced liver disease, especially with higher liver fibrosis, as assessed by histology or transient liver elastography (24,25). Finally, in a population-based cohort study of 1,827 adults followed for 5 years, NAFLD on computed tomography was associated with subclinical changes in LV function and structure over time (26).

Risk for new-onset HF

Some community-based studies have shown that mildly elevated serum gamma-glutamyltransferase (GGT) concentrations (as a proxy for NAFLD) were associated with a higher risk of incident HF, independently of several risk factors for HF (27-29) (**Table 1**). Roh et al. reported that an increased fatty liver index (i.e., a validated biomarker score of hepatic steatosis that also includes serum GGT concentration) was associated with a higher risk of incident HF in a healthy population (30). Most interestingly, in a nationwide cohort study of 10,422 Swedish individuals with biopsy-proven NAFLD and ~50,000 matched controls, Simon et al. showed that NAFLD was associated with a ~65% increased risk of incident MACE (defined as non-fatal CHD, stroke, HF, or cardiovascular death) over a median of 13.6 years. This risk was independent of common cardiometabolic risk factors, and increased progressively with worsening liver disease severity (31). Furthermore, the risk of each of the individual components of MACE (including also that of new-onset HF) was increased across all NAFLD histological categories, with the highest risk found in patients with cirrhosis (31). Thus, the findings of this nationwide cohort study provide further evidence that NAFLD may be a risk factor for new-onset HF. Some studies also found a high prevalence of NAFLD with increased non-invasive liver fibrosis scores in patients with chronic HF, especially in those with HFpEF (32,33). Additionally, NAFLD with increased liver fibrosis scores was found to be associated with a higher risk of in-hospital and post-discharge mortality among elderly patients admitted for acute HF (34).

2.Putative Mechanisms Linking NAFLD to HF Development

There are likely multiple factors associated with T2D or derived from adipose tissue and gut microbiota, as well as liver-specific mediators, which have the potential to increase risk of NAFLD-related cardiac disease (**Central Illustration**). It is beyond the scope of this review to discuss all of the molecular mechanisms potentially involved in the development of NAFLD-related cardiac disease and these have been discussed in a recent review of the subject (35). In this section, we

have considered the putative mechanisms linking NAFLD to HF development that we consider may be clinically relevant and we have only considered studies in man.

Liver-specific mediators and genetic factors

With NAFLD, there is often an increase in hepatic synthesis of very-low density lipoprotein (VLDL). This increase in circulating VLDL is often accompanied by pro-atherogenic lipid changes in small dense low-density lipoprotein and high-density lipoprotein-cholesterol levels, which are referred to as the atherogenic lipoprotein phenotype. The role of atherogenic dyslipidemia in mediating NAFLD-associated CHD risk, and the modifying influence of specific NAFLD-related genotypes, have recently been discussed in detail (10). With the development of progressive NAFLD, there is also hepatic mitochondrial dysfunction (36). It is uncertain whether there is associated mitochondrial dysfunction in the heart, but cardiac mitochondrial dysfunction may regulate LV hypertrophy in maladaptive myocardial changes (37). Thus, mitochondrial dysfunction might be a therapeutic target in HF (37). Mitochondrial activity in any organ also increases the potential for the generation of reactive oxygen species (ROS), mainly due to the respiratory chain complexes I-III activity (38). Other non-mitochondrial enzymes and protein complexes also produce ROS and amongst these are nicotinamide adenine dinucleotide phosphate oxidase and nitric oxide synthases (39). Generation of ROS in combination with increased activation of the renin-angiotensin-aldosterone system (RAAS) also affects cardiac remodeling. With NAFLD, there is evidence of increased RAAS activation (40), which is a key mediator of HF progression (41).

Angiotensin-converting enzyme 2 (ACE2), a homolog of ACE, is a carboxypeptidase that converts angiotensin II into angiotensin 1-7 (Ang 1-7), and Ang 1-7 opposes the effects of angiotensin II. ACE2 is widely expressed in cardiomyocytes, endothelial cells and cardiac fibroblasts, and preclinical studies showed a key counter-regulatory role of the ACE2/Ang 1-7 axis on the activated RAAS that results in HFpEF (41). Although the loss of ACE2 enhances susceptibility to HF, increasing ACE2 level may prevent and reverse the HF phenotype, and both ACE2 and Ang 1-7 have emerged as an important protective pathway against HF development. Thus, the ACE2/Ang 1-7 axis with increased cardiac ROS may promote cardiac remodelling and increase risk of HF in NAFLD by activating the nuclear factor-κB/c-JNK pathway (41).

Genetic polymorphisms may predispose individuals to develop more severe liver disease in NAFLD, e.g., patatin-like phospholipase domain-containing protein-3 (*PNPLA3*); trans-membrane 6 super family-2 (*TM6SF2*); membrane-bound O-acyltransferase domain containing-7 (*MBOAT7*) (42). In a multi-cohort exome-wide association study focused on serum aminotransferase levels, a sequence variant of APOE has also been identified that is associated with NAFLD (43). This genetic variant is also known to be associated with a higher risk of dyslipidemia (44). Although there are limited data to date testing the influence of genetic polymorphisms on cardiac disease in NAFLD, two genetic polymorphisms (*PNPLA3* rs738409-I148M and *TM6SF2* rs58542926-E167K) may modify the strength of the association between NAFLD and CHD risk. Despite both genotypes increasing the risk of more severe liver disease in NAFLD, both genotypes also decrease plasma VLDL concentrations, and thereby potentially attenuate the strength of the association between NAFLD and CHD risk (10). Thus, it will be interesting to see whether these genotypes have any effect on the strength of the association between NAFLD and risk of HF.

Intestinal dysbiosis

With dysbiosis, gastrointestinal tract-derived factors, such as lipopolysaccharide (LPS), aromatic acid metabolites, ethanol, *p*-cresyl sulphate, short-chain fatty acids, incretins and modified bile acids may contribute to the severity of liver disease (45,46), and also act directly on the cardiovascular system to influence cardiac disease (47). One of the most commonly observed changes with dysbiosis is an increase in Gram-*negative* bacteria and a decrease in Gram-*positive* bacteria (48). With an increase in Gram-*negative* bacteria and intestinal permeability, the endotoxin's potential to enter the portal circulation and promote a pro-inflammatory response in the liver is increased. Many nutritional compounds, e.g. red meat, contain a trimethylamine group (TMA), and in the liver TMA is oxidized by flavin mono-oxygenases to trimethylamine oxide (TMAO) (47). Studies have shown that increased TMAO levels are associated with CHD, chronic kidney disease, T2D or NAFLD (49,50), and TMAO therefore also has the potential to adversely influence cardiac disease (51).

Gut microbiota affects energy harvesting, inflammation, and immunity. A role for gut microbiota and changes in its composition has been proposed in the development of liver fibrosis (52) that may further increase risk of cardiac disease (31). Loomba et al. (52) provided interesting evidence for a fecal-microbiome derived metagenomic signature to detect advanced fibrosis in NAFLD; in particular, there was an increase in E. coli and Proteobacteria. Both of these bacteria are Gram-

negative organisms that may induce systemic/hepatic inflammation via increasing LPS concentrations in the portal and systemic circulations. Moreover, an increase in Proteobacteria has also been associated with increased endogenous alcohol production (53) that occurs because of greater microbial synthesis and/or lower alcohol dehydrogenase activity (46), and has the potential to further increase liver fibrosis and also induce cardiac dysfunction.

Expanded adipose tissue

Increased pro-inflammatory cytokines and lower plasma adiponectin concentrations originating from expanded/dysfunctional adipose tissue may contribute not only to the development and progression of NAFLD via effects on glucose and lipid metabolism, or insulin resistance, but may also directly influence coronary arteries and cause cardiac disease. Increased serum interleukin (IL)-6 levels have also been associated with subclinical atherosclerosis in population-based studies (54). Expanded/dysfunctional visceral adipose tissue expresses much higher levels of IL-6, IL-1β and tumor necrosis factor-α than the liver, and marked weight loss attenuates the expression of these pro-inflammatory cytokines (55,56). A meta-analysis has shown that higher plasma IL-6 and C-reactive protein levels are associated with increased AF incidence, as well as with AF recurrence after ablation (57). Other ectopic fat depots, such as increased pericardial fat, may also contribute to increase risk of incident HF (particularly risk of HFpEF) (58). Presently, it remains uncertain whether specifically targeting inflammation in NAFLD benefits liver disease or risk of HF. Recently, a phase 2 randomized controlled trial (RCT), the CENTAUR trial involving 289 NASH patients showed that a 1-year treatment with cenicriviroc (a dual C-C chemokine receptor antagonist) did not improve histological features of NASH, but did improve liver fibrosis by ≥1 stage compared with placebo (59). Moreover, the majority of cenicriviroc-treated NASH patients, who achieved a fibrosis response at year 1, maintained the benefit after two years treatment (60). It is uncertain whether any benefit on liver fibrosis with this agent influences risk of HF.

Although aspirin treatment has effects both on the hemostatic system and inflammation, it also limits hepatic stellate cell activation and may therefore attenuate liver fibrogenesis in NAFLD. A prospective cohort study of 361 adults with biopsy-proven NAFLD showed that daily aspirin use was associated with less severe histologic features of NAFLD/NASH, and lower risk of liver fibrosis progression over time (61). Although it is plausible that daily low-dose aspirin may benefit both the liver and the heart in NAFLD, further research is needed before treatment with aspirin could

be advocated. A placebo-controlled RCT involving 10,061 patients with previous myocardial infarction showed that treatment with canakinumab (an anti-inflammatory monoclonal antibody targeting interleukin-1β) led to a lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering therapy (62). However, it remains uncertain whether canakinumab may also have any hepato-protective effect in NAFLD.

3.Lifestyle Modifications and Pharmacological Treatments to Benefit Both NAFLD and HF

It is not our aim in this review to describe the effects of all drugs that have been tested in NAFLD/NASH. Rather, it is our intention to illustrate the effects of lifestyle modifications, bariatric surgery and some drugs that may benefit the liver and have clinically important benefits on the cardiovascular system.

Lifestyle modifications and bariatric surgery

Lifestyle modifications are the cornerstone of treatment for NAFLD since no specific pharmacotherapies have been licensed for use by regulatory agencies to date. Weight reduction results in improvement/resolution of NAFLD and, importantly, also decreases the risk of CHD (63). Specifically, weight reduction of ≥10% promotes histological resolution of NASH and fibrosis improvement (63). Conversely, 5-10% weight reduction improves hepatic steatosis, necro-inflammation, but not fibrosis (63). Based on this evidence, current guidelines for NAFLD management strongly recommend a weight reduction of ≥5% in most individuals with NAFLD, irrespective of body weight (3,64). Bariatric surgery is an effective treatment for advanced NAFLD (including NASH-related cirrhosis) in selected patients with morbid obesity (3,64). Cirrhosis due to NASH or other etiologies represents a (relative) contraindication for the eligibility of HF patients to cardiac transplantation. Evidence suggests that bariatric surgery may also be considered for treating morbidly obese patients with advanced HF (65), enabling successful cardiac transplantation. In some patients, cardiac transplantation may be avoided through surgical weight loss (66).

Pioglitazone

The current guidelines for NAFLD management recommend the use of pioglitazone in adults with biopsy-proven NASH (**Table 2**), regardless of the presence or absence of T2D (3,64). However,

pioglitazone is not yet approved by most national Medicines agencies outside of T2D treatment. Pioglitazone is a selective ligand of the PPAR-γ, a nuclear regulatory factor modulating key pathways involved in glucose and lipid metabolism (67). A systematic review of RCTs assessing the efficacy of anti-hyperglycemic agents to specifically treat NAFLD or NASH in adults with or without T2D showed that pioglitazone use was associated with improvement in individual histologic features of NASH and resolution of NASH without worsening of fibrosis (68). A phase-2 RCT showed that long-term use of pioglitazone (45 mg/day for 72 weeks) was better than placebo in improving fibrosis stage amongst patients with biopsy-confirmed NASH and T2D or prediabetes (69). This finding was corroborated by a meta-analysis of eight phase-2 RCTs (70). Strong evidence shows that pioglitazone exerts cardiovascular benefits, as it reduces the risk of myocardial infarction and ischemic stroke in patients with T2D or prediabetes (71). Safety concerns (moderate weight gain, peripheral edema, and risk of distal bone fractures) may limit its long-term use in clinical practice. Peripheral edema is seen in ~5-10% of patients treated with pioglitazone and, similar to weight gain, is dose related (67). Supposing fluid retention occurs during pioglitazone treatment in patients with NAFLD and undiagnosed cardiomyopathy, pioglitazone might trigger HF (67). Therefore, pioglitazone is contraindicated in patients with overt HF and in those at high risk of HF (67) (**Table 3**).

Glucagon-like peptide 1 receptor agonists

GLP-1RAs are a class of glucose-lowering drugs approved for the treatment of T2D, which improve glycemic control, insulin resistance and promote weight loss (on average 3-5 kg). Two phase-2 placebo-controlled RCTs (72,73), involving patients with biopsy-confirmed NASH, showed that once-daily subcutaneous treatment with either liraglutide (72) or semaglutide (73) resulted in significantly higher percentage of patients with histologic resolution of NASH than placebo. However, these two trials did not show any improvement in liver fibrosis (72,73). Considering also the published phase-2 RCTs that used magnetic resonance-based techniques for diagnosing NAFLD, treatment with GLP-1RAs decreased liver fat content (74) (**Table 2**). However, since no robust evidence from large RCTs with liver histological endpoints is available thus far, current guidelines do not recommend the use of GLP-1RAs in patients with NAFLD/NASH (3,64). RCT evidence also indicates that GLP-1RAs have consistent cardiovascular benefits in T2D individuals (75). A recent meta-analysis of eight RCTs (~60,000 T2D participants) reported that GLP-1RAs significantly reduced all-cause mortality, cardiovascular mortality, and also hospitalization for HF (75).

Consequently, GLP-1RAs are an attractive therapeutic option for NAFLD patients with/without coexisting HF (**Table 3**).

Sodium-glucose cotransporter-2 inhibitors

SGLT-2 inhibitors are a class of glucose-lowering drugs that act by inhibiting SGLT2 in the proximal convoluted tubule of the kidney, thereby preventing glucose reabsorption and promoting its excretion in urine. Preclinical data showed favorable effects of SGLT-2 inhibitors on NAFLD histology (68). A meta-analysis of twelve RCTs (850 participants, most of whom with T2D) supported the efficacy of SGLT-2 inhibitors in improving serum liver enzymes and liver fat content, as assessed by magnetic resonance-based techniques (68,76). SGLT-2 inhibitors had a similar adverse event profile to placebo, excluding for higher risk of genitourinary infections. However, due to the lack of any RCT with histological liver endpoints, it is still premature to recommend the use of SGLT-2 inhibitors in patients with NAFLD/NASH (**Table 2**) (3,64). Strong evidence indicates that SGLT-2 inhibitors exert significant cardio-renal benefits, regardless of T2D status (77). In a meta-analysis of eight RCTs (including ~60,000 individuals), Salah et al. reported that SGLT-2 inhibitors reduced all-cause mortality (HR 0.84, 95%CI 0.78-0.91), cardiovascular mortality (HR 0.84, 95%CI 0.76-0.93), and also hospitalization for HF (HR 0.69, 95%CI 0.64-0.74) (78). Interestingly, the EMPEROR-Reduced (79) and DAPA-HF trials (80) showed that empagliflozin and dapagliflozin reduced the risk of HF hospitalization and death in patients with HFrEF, irrespective of T2D status. The EMPEROR-Preserved trial showed that empagliflozin also reduced the risk of HF hospitalization and death in those with HFpEF (81). These findings emphasize the potential therapeutic benefit of SGLT-2 inhibitors in patients with NAFLD and coexisting chronic HF (**Table 3**).

Other drugs, such as statins and RAAS inhibitors, are widely used in patients with HF and in those with NAFLD (**Table 2**). There is no convincing evidence that these classes of drugs are beneficial for liver disease in patients with NAFLD/NASH; however, they can be safely prescribed for conventional indications.

Conclusion

There is a strong association between NAFLD and increased risk of new-onset HF, regardless of the presence or absence of T2D and other coexisting cardiometabolic risk factors. The magnitude

of this risk increases with the severity of liver disease in NAFLD. The strong association between NAFLD and the risk of new-onset HF deserves particular attention in view of its potential implications for screening and surveillance strategies in clinical practice. Further research is needed to better decipher the complex pathophysiological mechanisms by which NAFLD/NASH may contribute to the risk of new-onset HF, and to elucidate whether ameliorating NAFLD/NASH will ultimately prevent or slow the development and progression of HF.

FIGURE LEGEND

CENTRAL ILLUSTRATION. Hepatic and extra-hepatic factors affecting risk of HF in NAFLD.

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Table 1. Principal prospective cohort studies assessing the association between NAFLD and the risk of new-onset HF.

Author, Year, (Ref.)	Study Characteristics	NAFLD Diagnosis	Outcome (number of incident HF events)	Main Results	Covariate Adjustments
Dhingra R *et al*. 2010 (26)	Community-based cohort (Framingham Heart study): 3,544 United States participants (mean age 44.5 years; 1,833 women and 1,711 men), who were free of HF at baseline. Mean follow-up: 23.6 years	Serum GGT levels	Incident HF (n=188)	Higher serum GGT concentrations within the "normal" range were associated with greater risk of incident HF and incrementally improved prediction of HF risk. Participants with a serum GGT level at the median or greater had a 1.7-fold risk of incident HF (95% CI 1.21-2.41) compared with those with GGT concentrations less than the median	Age, sex, body mass index, diabetes, smoking, systolic blood pressure, treatment for hypertension, alcohol intake, total to HDL cholesterol ratio, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, valve disease, prior history of myocardial infarction
Wannamethee SG *et al*. 2012 (27)	Community-based cohort (British Regional Heart Study): 3,494 British men aged 60 to 79 years, who were free of HF and myocardial infarction at baseline. Mean follow-up: 9 years	Serum GGT levels	Incident HF (n=168)	Elevated serum GGT concentrations (top quartile, ≥38 U/L) were associated with greater risk of increased risk of HF in men aged <70 years	Age, body mass index, smoking, social class, physical activity, alcohol intake, diabetes, systolic blood pressure, antihypertensive treatment, prior stroke, left ventricular hypertrophy, atrial fibrillation, forced expiratory volume in 1 sec, C-reactive protein, leptin, von Willebrand factor, aspartate aminotransferase, alanine aminotransferase, homeostasis model assessment-insulin resistance, NT-proBNP
Wang Y *et al*. 2013 (28)	Community-based cohort (FINRISK cohort study): 38,079 Finnish participants aged 25-74 years (19,726 women and 18,353 men), who were free of HF at baseline. Mean follow-up: 14.5 years	Serum GGT levels	Incident HF (n=1,081)	Moderate to high levels of serum GGT (from the 50th to the 90th percentiles) were associated with greater risk of incident HF in men and women, and the predictive power was stronger in subjects aged <60 years	Age, sex, body mass index, study area, study year, smoking, education, alcohol consumption, physical activity, systolic blood pressure, total cholesterol, valvular heart disease, myocardial infarction and diabetes at baseline and during follow-up
Roh JH *et al*. 2020 (29)	308,578 healthy South Korean individuals (49% men) aged >20 years without comorbidities, who underwent the National Health check-ups in the Republic of Korea from 2009 to 2014 (National Health Insurance Service). Median follow-up: 5.4 years	Fatty liver index	Incident HF (n=2,532)	Higher fatty liver index (top quartile, >30) was associated with greater risk of incident HF risk in both sexes in a healthy Korean population	Age, sex, smoking, alcohol consumption, physical activity, blood pressure, fasting glucose, total cholesterol

Simon TG *et al*. 2021 (30)	This nationwide histology cohort included all Swedish adults with biopsy-confirmed NAFLD and without pre-existing cardiovascular disease at baseline (1966-2016, n=10,422; mean age 52.3 years; 55% men). NAFLD patients were matched to ≤5 population controls without NAFLD or cardiovascular disease, by age, sex, calendar year, and county (n=46,517). Median follow-up: 13.6 years	Liver biopsy	MACE (including cardiovascular death, non-fatal CHD, ischemic stroke, or congestive HF) (n=1,119 HF events)	Patients with NAFLD had higher incidence of MACE than controls (24.3 vs. 16.0/1000 person-years (PY); difference=8.3/1000 PY; adjusted-HR 1.63, 95% CI 1.56-1.70), including higher rates of CHD (difference=4.2/1000 PY; adjusted-HR 1.64, 95% CI 1.54-1.75), HF (difference=3.3/1000 PY; adjusted-HR 1.75, 95% CI 1.63-1.87), stroke (difference=2.4/1000 PY; adjusted-HR 1.58, 95% CI 1.46-1.71) and cardiovascular death (difference=1.2/1000 PY; adjusted-HR 1.37, 95% CI 1.27-1.48). Rates of each individual MACE outcome (including incident HF) increased progressively with worsening NAFLD severity, with the highest incidence observed with cirrhosis	Age, sex, calendar year, county of residence, education, number of recorded hospital visits in the 1 year prior to the index date, diabetes, obesity, hypertension, dyslipidemia, chronic kidney disease, family history of premature CHD, statin use, and alcohol use disorder during follow-up (defined as a time-varying covariate)

Abbreviations: CHD, coronary heart disease; GGT, gamma-glutamyltransferase; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; NAFLD, non-alcoholic fatty liver disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 2. Drugs that may benefit NAFLD/NASH and that also benefit risk of cardiovascular or cardiac diseases.

Drugs	Serum liver enzymes	Liver fat content*	Liver inflammation**	NASH resolution**	Liver fibrosis**	Cardiovascular benefits	Adverse effects	Comments
Pioglitazone	Improved	Improved	Improved	Improved	Improved (mildly)	Pioglitazone reduces the risk of myocardial infarction and ischemic stroke in patients with T2D or prediabetes	Weight gain (usually 2-4% of body weight, dose related), fluid retention (in around 5-10% of patients, dose related), bone fractures (mostly in post-menopausal women)	Guidelines recommend pioglitazone in adults with biopsy-proven NASH, irrespective of T2D status. It may also benefit liver fibrosis. Not yet approved by most national Medicine agencies outside T2D. The risk/benefit balance related to pioglitazone should be discussed with each patient. Pioglitazone is contraindicated in patients with symptomatic HF or in those with a high risk of HF
GLP-1RAs (exenatide, liraglutide, dulaglutide, semaglutide)	Improved	Improved	Improved¶	Improved ¶	No effect¶	GLP-1RAs reduce MACE outcomes by 14%, all-cause mortality by 12%, and hospitalization for HF by 11% in patients with T2D	Loss of appetite, and gastrointestinal side effects (nausea, constipation, abdominal pain, diarrhea)	Premature to consider in NASH, unless specifically being used as a treatment for T2D and obesity. Current controlled trials with histological liver endpoints are available only for liraglutide and semaglutide
SGLT-2 inhibitors (mainly empagliflozin, dapagliflozin, canagliflozin)	Improved	Improved	Unknown§	Unknown§	Unknown§	SGLT-2 inhibitors reduce MACE outcomes by 16%, all-cause mortality by 16%, and HF hospitalization by 31% (such benefit is consistent both in patients with HFrEF and in those with HFpEF), regardless of the presence or absence of T2D	Genitourinary (mycotic) infections (~10% of women and 2-3% of men), hypotension, diabetic ketoacidosis (<0.1%), Fournier's gangrene (very rare)	Premature to consider in NASH, unless specifically being used as a treatment for T2D. No current randomized trials with histological liver endpoints are available. The Federal Drug Administration and European Medicines Agency just approved the use of dapagliflozin and empagliflozin in patients with HFrEF, regardless of the presence of T2D status. The EMPEROR-Preserved trial showed that empagliflozin was effective on risk of cardiac death and hospitalization for HF in patients with HFpEF, irrespective of T2D status
Statins	Improved	Unknown#	Unknown#	Unknown#	Unknown#	Statin use is associated with significant reduction of cardiovascular mortality and morbidity in primary	Muscle pain, elevation of serum liver enzymes (<1%), rhabdomyolysis	These drugs are strongly recommended for the management of dyslipidemia in NAFLD/NASH patients with or without HF. Their use in NAFLD patients is safe with no increased risk of hepatotoxicity. However, their use does not seem to improve liver

						and secondary prevention. A reduction in risk of new-onset HF (mainly in patients at high cardiovascular risk) and hospitalization for HF has also been reported		histology in NASH
ACE-inhibitors or Angiotensin II receptor blockers	Improved	Unknown[#]	Unknown[#]	Unknown[#]	Unknown[#]	These drugs reduce the risk of death, hospitalization for HF, and improve symptoms in patients with HFrEF	Cough (for ACE-inhibitors only), iperkalemia, hypotension, dizziness, headache, weakness	These drugs are strongly recommended for management of hypertension in NAFLD/NASH patients with or without HF. Larger RCTs are required to provide consistent data on their possible hepatic anti-fibrotic effects

NB: Data included in the table are derived mainly from scientific guidelines, systematic reviews or meta-analyses (1,3,9,10,63,64,67,68,74-77).

Abbreviations: ACE, angiotensin converting enzyme inhibitors; GLP-1RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction, MACE, major adverse cardiovascular events; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RCT, randomized controlled trial; SGLT-2, sodium-glucose cotransporter-2, T2D, type 2 diabetes.

[*] Data derived from phase-2 RCTs where liver fat content was assessed by imaging techniques (mostly magnetic resonance imaging).
[**]Data derived from phase-2 RCTs where changes in liver inflammation, fibrosis and resolution of NASH were assessed by liver biopsy.
[§]There are no current RCTs with paired liver biopsy data for these drugs.
[¶]Phase-2 placebo-controlled RCTs with paired liver biopsy data are available only for liraglutide or semaglutide.
[#]There is no convincing evidence that these classes of drugs are beneficial for liver disease in patients with NAFLD/NASH; however, they can be safely prescribed for conventional indications.

Table 3. Potential therapeutic approaches to NAFLD/NASH patients with, and without, coexisting HF to treat cardiometabolic comorbidities.

	Cardiometabolic risk factors (with and without coexisting HF)	Drugs and drug classes that have potential hepato-protective effects in NAFLD/NASH
NAFLD/NASH without HF	T2D	Pioglitazone/GLP-1RAs/SGLT2-inhibitors
	Obesity	High dose GLP-1RAs (bariatric surgery in selected morbidly obese patients)
	Dyslipidemia	Statins
	Hypertension	ACE-inhibitors/ARBs
NAFLD/NASH with HF	T2D	GLP-1RAs/SGLT2-inhibitors (pioglitazone is contraindicated in patients with established HF)
	Obesity	High dose GLP-1RAs (bariatric surgery in selected morbidly obese patients)
	Dyslipidemia	Statins
	Hypertension	ACE-inhibitors/ARBs
	HF	SGLT2-inhibitors/GLP-1RAs

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; GLP-1RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SGLT-2, sodium-glucose cotransporter-2, T2D, type 2 diabetes.