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Evolution of care in cirrhosis: Preventing hepatic decompensation through pharmacotherapy

Seohyuk Lee, Saad Saffo

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Abstract

Cirrhosis is a leading cause of morbidity and mortality, impacting more than 120 million people worldwide. Although geographic differences exist, etiologic factors such as alcohol use disorder, chronic viral hepatitis infections, and non-alcoholic fatty liver disease are prevalent in nearly every region. Historically, significant effort has been devoted to modifying these risks to prevent disease progression. Nevertheless, more than 11% of patients with compensated cirrhosis experience hepatic decompensation each year. This transition signifies the most important prognostic factor in the natural history of the disease, corresponding to a decline in median survival to below 2 years. Over the past decade, the need for pharmacotherapies aimed at reducing the risk for hepatic decompensation has been emphasized, and non-selective beta-blockers have emerged as the most effective option to date. However, a critical therapeutic gap still exists, and additional therapies have been proposed, including statins, rifaximin, and sodium-glucose cotransporter-2 inhibitors. Based on the results of innovative retrospective analyses and small-scale prospective trials, these pharmacotherapies represent promising options, but further studies, including randomized controlled trials, are necessary before they can be incorporated into clinical use. This report highlights the potential impact of these agents and others in preventing hepatic decompensation and discusses how this paradigm shift may pave the way for guideline-directed medical therapy in cirrhosis.

Key Words: Cirrhosis; Hepatic decompensation; Beta-blockers; Statins; Sodium-glucose cotransporter-2 inhibitors; Rifaximin

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Core Tip: Hepatic decompensation is the most important clinical predictor of morbidity and mortality among patients with cirrhosis. New pharmacotherapies aimed at preventing hepatic decompensation in high-risk patients are emerging, augmenting traditional management strategies. These treatments represent safe, accessible, and effective options that may improve quality of life and prolong transplant-free survival, regardless of the etiologic factors involved.

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INTRODUCTION

Cirrhosis reflects the end stage of all chronic liver diseases. It impacts more than 120 million people globally, largely in the context of common risk factors such as alcohol use disorder, chronic viral hepatitis, and non-alcoholic fatty liver disease (NAFLD)[1]. It represents the 8th leading cause of mortality in the United States and 13th in the world, with the number of attributable deaths worldwide having increased by approximately 50% between 1990 and 2013[2]. Regardless of etiology, the most important prognostic factor for survival is the presence or absence of hepatic decompensation, which includes complications such as ascites, variceal hemorrhage, hepatic encephalopathy, and jaundice[3,4]. Although patients with cirrhosis may remain compensated for extended periods of time, especially if their underlying risk factors are mitigated, approximately 11% of those with compensated disease experience new decompensations each year[5], and the progression from compensated to decompensated cirrhosis is associated with a decline in median survival from 12 years to less than 2 years[6]. Among individuals with compensated disease, the 10-year risks of developing ascites, gastrointestinal hemorrhage, hepatic encephalopathy, and jaundice are 40%, 25%, 28%, and 33%, respectively[6].

Beyond its burden on patient health and quality of life, cirrhosis also represents a critical healthcare challenge. According to the Global Burden of Disease Study 2017[1], there are 112 million and 10.6 million cases of compensated and decompensated cirrhosis worldwide, respectively. In the United States, this is associated with significant healthcare costs, including approximately \$2.5 billion annually for hospitalization and treatment and \$10.6 billion annually for losses in work productivity and health-related quality of life[7]. These costs are disproportionately borne in the management of complications among those with decompensated disease. Despite the significant health and socioeconomic burdens, it is only recently that management strategies have pivoted from focusing primarily on risk factor modification and the treatment of complications towards the prevention of hepatic decompensation in high-risk patients. Unlike the management of other common chronic diseases such as congestive heart failure, in which the implementation of guideline-directed medical therapy has resulted in significant reductions in morbidity and mortality, the long-term management of cirrhosis has been historically limited by a lack of robust chemoprevention[8,9]. In this report, we discuss the management of cirrhosis, focusing on pharmacotherapies aimed at preventing hepatic decompensation.

TRADITIONAL TREATMENT STRATEGIES

Chronic hepatitis C virus (HCV) infection, NAFLD, and alcohol-related liver disease are the three leading causes of cirrhosis in the United States[10]. For each of these etiologies, a critical component of the long-term management involves risk factor modification. Among patients with chronic HCV infection and compensated disease, the advent of direct-acting antiviral agents represents a landmark achievement that has been shown to reduce the risk for liver-related complications[11-14]. Unfortunately, more than 40% of HCV infections are diagnosed after hepatic decompensation has already occurred[10], at which point antiviral treatment is less effective and associated with a higher risk for adverse events[15]. For those with NAFLD, a growing body of literature supports the efficacy of a multimodal approach which integrates dietary changes, weight reduction, and restoring insulin sensitivity[16]. Glucagon-like peptide 1 receptor agonists such as semaglutide have an evolving role in the treatment in of NAFLD, offering both weight reduction and possible attenuation of steatohepatitis, and a number of other drugs aimed at reducing fibrosis progression and the risk for complications are currently being evaluated in phase II and phase III clinical trials[17]. However, to date, disease-specific pharmacologic treatments have yet to be approved. The prevalence of NAFLD and its associated complications continue to increase[18] such that it is currently the second leading cause of cirrhosis among patients awaiting liver transplantation in the United States[14] and is expected to overtake HCV-

related cirrhosis as the most frequent indication for liver transplantation[19]. Finally, alcohol-related liver disease remains highly prevalent worldwide[20] with increasing cirrhosis-related mortality in regions with high alcohol consumption[21]. Abstaining from alcohol significantly improves survival among patients with cirrhosis, but pharmacologic options for alcohol use disorder remain limited, partially due to concerns about hepatotoxicity[22]. For patients with less common causes of chronic liver disease, risk factor modification may include therapies such as immunosuppression (autoimmune hepatitis), ursodeoxycholic acid (primary biliary cholangitis), and phlebotomy or chelation (hemochromatosis). Unfortunately, the impact of some of these treatments is generally diminished in the context of cirrhosis.

Once hepatic decompensation has occurred, treatment strategies may be implemented to address specific complications. This includes pharmacotherapy to eliminate ascites (diuretics), reduce the risk of variceal rupture [non-selective beta-blockers (NSBBs)], and prevent recurrent encephalopathy (lactulose and rifaximin)[23-25]. Among patients with refractory ascites or variceal hemorrhage, transjugular intrahepatic portosystemic shunting (TIPS) reduces the risk of further decompensation and may improve survival in a subset of patients[26-28]. Finally, liver transplantation is the only durable curative option for patients with decompensated cirrhosis. However, resource limitations and host factors restrict the use of TIPS and liver transplantation to a relatively small number of patients in resource-rich settings. Furthermore, despite advances in the care of decompensated cirrhosis, the 30-d mortality following hospital discharges for hepatic decompensation remains largely unchanged[29]. Thus, significant interest exists in preventing the progression to decompensated cirrhosis.

CURRENT THERAPIES TO PREVENT HEPATIC DECOMPENSATION

NSBBs are currently the only agents recommended for the long-term management of portal hypertension in patients with compensated cirrhosis[30]. Traditional NSBBs such as propranolol and nadolol inhibit β_1 and β_2 receptors, mitigating the hyperdynamic response and splanchnic arteriolar vasodilation that occur in the context of cirrhosis. Carvedilol has additional α_1 inhibition that reduces intrahepatic vascular resistance[31,32]. Together, these hemodynamic effects attenuate portal hypertension, reducing the risk for hepatic decompensation. In addition, NSBBs impact the risk for liver-related complications through other mechanisms. For example, NSBBs reduce abnormal gastrointestinal permeability and bacterial translocation[33] and upregulate the phagocytic activity of monocytes and granulocytes after exposure to bacterial DNA[34]. As such, a recent prospective study demonstrated that NSBBs reduce the risk for bacterial infections [odds ratio = 0.46, 95% confidence interval (CI): 0.3-0.7; $P = 0.001$][35].

The landmark trial demonstrating the utility of NSBBs in preventing decompensation was the study on Beta-Blockers to Prevent Decompensation of Cirrhosis with Portal Hypertension (PREDESCI)[36]. In this multicenter, double-blind, randomized controlled trial (RCT), 201 patients with compensated cirrhosis and clinically-significant portal hypertension (CSPH) without high-risk varices were randomized to receive NSBBs (propranolol up to 160 mg twice daily or carvedilol up to 25 mg daily) or placebo. Over a median follow-up of 37 mo, the risk of hepatic decompensation, including ascites, variceal hemorrhage, or hepatic encephalopathy, was significantly lower among patients receiving NSBBs relative to those receiving placebo [hazard ratio (HR) = 0.51, 95% CI: 0.26-0.97; $P = 0.041$]. This difference was driven primarily by a reduction in ascites (HR = 0.42, 95% CI: 0.19-0.92; $P = 0.03$), although non-significant trends towards decreased progression to high-risk varices and improved survival were also observed. The number needed to treat for the prevention of a decompensation event over the follow-up period was 9, and the incidence of adverse events was similar between the treatment and placebo groups.

Prior to PREDESCI, other RCTs consistently demonstrated that propranolol and nadolol were effective in preventing variceal hemorrhage among patients with cirrhosis and large esophageal varices but without prior bleeding episodes. Pascal and Cales[37] found that patients receiving propranolol up to 320 mg daily were less likely to develop bleeding episodes compared to those in the placebo group (74% *vs* 39%; $P < 0.05$); Idéo *et al*[38] also observed significantly lower rates among those receiving nadolol up to 120 mg daily (94.4%) relative to those receiving placebo (70.2%). Other studies have reported similar risk reductions in initial[39,40] and subsequent[41] variceal bleeds, although one reported a significant difference only among patients who lacked ascites[42]. Given these data, NSBBs are currently recommended for the primary and secondary prophylaxis of variceal hemorrhage[37,41]. Notably, however, the Prevention of Esophageal Varices by Beta-Adrenergic Blockers trial observed no differences in the use of timolol up to 80 mg daily *vs* placebo in the development of varices among patients with compensated cirrhosis[43].

The potential benefits of carvedilol beyond those of traditional NSBBs have also been of great interest. Four studies have evaluated the impact of carvedilol in preventing hepatic decompensation or disease progression among patients with compensated cirrhosis and CSPH. A subgroup analysis of the PREDESCI trial[36] found a non-significant reduction in the risk for hepatic decompensation or death (HR = 0.39, 95% CI: 0.10-1.49; $P = 0.16$) and Bhardwaj *et al*[44] observed a significantly higher likelihood

of non-progression from small to large esophageal varices (79.4% *vs* 61.4%; $P = 0.04$). In comparing carvedilol to variceal band ligation, one study found carvedilol 12.5 mg daily to be associated with significantly lower rates of initial variceal hemorrhage (HR = 0.41, 95%CI: 0.19-0.96; $P = 0.04$) but similar rates of bleeding-related and overall mortality[45], while another reported comparable rates across all three outcomes with the same dosing[46]. Additionally, a recent meta-analysis of these four studies observed a significantly improved hazard ratio for decompensation among patients receiving carvedilol compared to control therapy (HR = 0.506, 95%CI: 0.289-0.887; $P = 0.017$)[47]. Finally, in comparison to propranolol, multiple studies, including PREDESCI, have suggested that carvedilol may be superior in reducing the hepatic venous pressure gradient[36,48]. However, it remains unclear whether this finding consistently translates into a difference in the risk for hepatic decompensation.

Although NSBBs have been extensively studied and represent the current treatment of choice for the prevention of hepatic decompensation, there is significant interest in identifying additional therapies for chemoprevention for a variety of reasons. First, most commonly, patients may have contraindications or intolerance to NSBBs. Common adverse effects include bradycardia, hypotension, and fatigue. Second, pharmacotherapy may be leveraged for pleiotropic benefits, and alternative therapies may provide an opportunity for enhanced personalized care. Finally, therapies may have additive or synergistic effects that may provide additional clinical benefit for high-risk patients. As such, a number of agents are currently under evaluation (Table 1).

EMERGING THERAPIES TO PREVENT HEPATIC DECOMPENSATION

Statins

These cholesterol-lowering drugs are a mainstay for the treatment of dyslipidemia and atherosclerotic cardiovascular disease but have diverse pleiotropic effects that may impact a wide range of other disease processes. Concerns regarding hepatotoxicity have historically limited their use among patients with chronic liver disease[49], but emerging evidence indicates that their anti-fibrotic, immunomodulatory, and antioxidant effects may attenuate portal hypertension and limit disease progression[50-53] without posing an excess safety risk among patients with compensated disease[54-56].

Several retrospective studies have evaluated the role of statins in preventing hepatic decompensation. In one case-control study of patients with predominantly early-stage cirrhosis, statin use was associated with a decreased risk of hepatic decompensation over 36 mo (HR = 0.58; $P = 0.04$)[57]. Similar findings have been reported in patients with cirrhosis due to chronic viral hepatitis; among statin users, the HR for hepatic decompensation was 0.39 (95%CI: 0.25-0.62)[58] for hepatitis B virus-related cirrhosis and 0.51 (95%CI: 0.29-0.93)[58] to 0.55 (95%CI: 0.39-0.77)[59] for HCV-related cirrhosis. A trend towards decreased hepatic decompensation was observed with among patients with alcohol-related cirrhosis (HR = 0.69, 95%CI: 0.45-1.07)[58]. A recent meta-analysis of these three observational studies found the pooled HR for hepatic decompensation to be 0.54 (95%CI: 0.46-0.65) with minimal heterogeneity ($I^2 = 0\%$)[60]. A similar meta-analysis using these studies also demonstrated that the association between statin use and an improved decompensation was independent of cirrhosis etiology[61].

In light of the encouraging findings reported in observational studies, RCTs evaluating the impact of statins in preventing hepatic decompensation are currently in progress. In the United States, the Statins and Cirrhosis: Reducing Events of Decompensation trial is studying simvastatin at a dose of 40 mg daily (ClinicalTrials.gov, NCT03654053)[62]. In Denmark, the Statins for Prevention of Disease Progression and Hospitalization in Liver Cirrhosis trial is studying atorvastatin at doses of 10-20 mg daily (ClinicalTrials.gov, NCT04072601).

Rifaximin

Patients with cirrhosis can experience increased bacterial translocation secondary to elevated portal pressures, increased gastrointestinal permeability, and altered gut microbiota, thereby contributing to the inflammatory milieu. Rifaximin is a safe poorly-absorbed oral antibiotic with broad gut-selective antimicrobial activity against gram-positive and gram-negative bacteria. Beyond its impacts on the intestinal microbiome, it may also attenuate inflammation, decrease bacterial interactions with enterocytes, and improve intestinal epithelial integrity[63,64]. Furthermore, the combination of propranolol and rifaximin compared to propranolol alone is associated with a more significant reduction in portal pressure[65]. Although rifaximin is currently approved for the prevention of recurrent hepatic encephalopathy[66], it may also have a role in preventing other hepatic decompensations.

A number of studies have evaluated the association between rifaximin use and liver-related complications, demonstrating that rifaximin may reduce the risk of further decompensation in patients with decompensated cirrhosis[63]. However, little is known about its role in those with high-risk compensated disease. Most notably, in a *post-hoc* analysis of a RCT comparing rifaximin 550 mg twice daily to placebo, Flamm *et al*[67] demonstrated that rifaximin reduces the risk for further hepatic decompensation (HR = 0.41, 95%CI: 0.25-0.67; $P < 0.001$). This finding was corroborated by Zeng *et al*[68] in a prospective randomized open-labelled study. Currently, there are no ongoing trials investigating

Table 1 Chemoprevention for hepatic decompensation in cirrhosis: Current and emerging therapies

Agents	Mechanism of action	Primary benefits	Potential adverse effects	Other limitations	Supported by RCT
NSBBs	β 1 and β 2 blockade; α 1 blockade (carvedilol)	Decreased portal pressure	Hypotension, bradycardia, fatigue	Dosing frequency (propranolol)	Yes
Statins	Inhibition of HMG-CoA reductase	Decreased inflammation and endothelial dysfunction	Myopathy, hepatitis, diabetes		Ongoing
Rifaximin	Broad-spectrum, gut-specific antibiotic	Reduced dysbiosis and bacterial translocation	Gastrointestinal upset	Cost	Included patients with prior decompensation
Anticoagulants	Inactivation of clotting factors	Reduced endothelial dysfunction	Hemorrhage	SQ injection (enoxaparin), dosing (warfarin)	Included patients with prior decompensation
ACE inhibitors	Inhibition of angiotensin II production	Decreased portal pressure ¹	Hypotension, AKI, electrolyte derangements, angioedema		No
ARBs	Inhibition of angiotensin II type 1 receptor	Decreased portal pressure	Hypotension, AKI, electrolyte derangements		No
MRAs	Inhibition of the aldosterone receptor in the distal nephron	Decreased portal pressure	Hypotension, AKI, electrolyte derangements	Gynecomastia (spironolactone)	Only in combination with NSBB
SGLT2 inhibitors	Inhibition of proximal tubule sodium-glucose cotransporter	Decreased portal pressure	Electrolyte derangements, mycotic genital infections	Cost, risk of ketoacidosis in AUD	No
Albumin	Anionic carrier protein with pleiotropic properties	Reduced inflammation; increased effective circulating volume	Volume overload	Cost, intravenous administration	Included patients with prior decompensation

¹Not demonstrated in prior clinical studies.

ACE: Angiotensin converting enzyme; AKI: Acute kidney injury; ARB: Angiotensin receptor blocker; AUD: Alcohol use disorder; BP: Blood pressure; HMG-CoA: Hydroxy β -methylglutaryl-CoA; MRA: Mineralocorticoid receptor antagonist; NSBB: Non-selective beta-blocker; SGLT2: Sodium-glucose cotransporter 2; SQ: Subcutaneous; RCT: Randomized controlled trial.

the impact of rifaximin in patients with compensated disease, although the Simvastatin Plus Rifaximin in Decompensated Cirrhosis study is examining the role of statins and rifaximin among patients with pre-existing decompensated disease (ClinicalTrials.gov, NCT03780673). Historically, a critical barrier to the study and use of rifaximin has been cost.

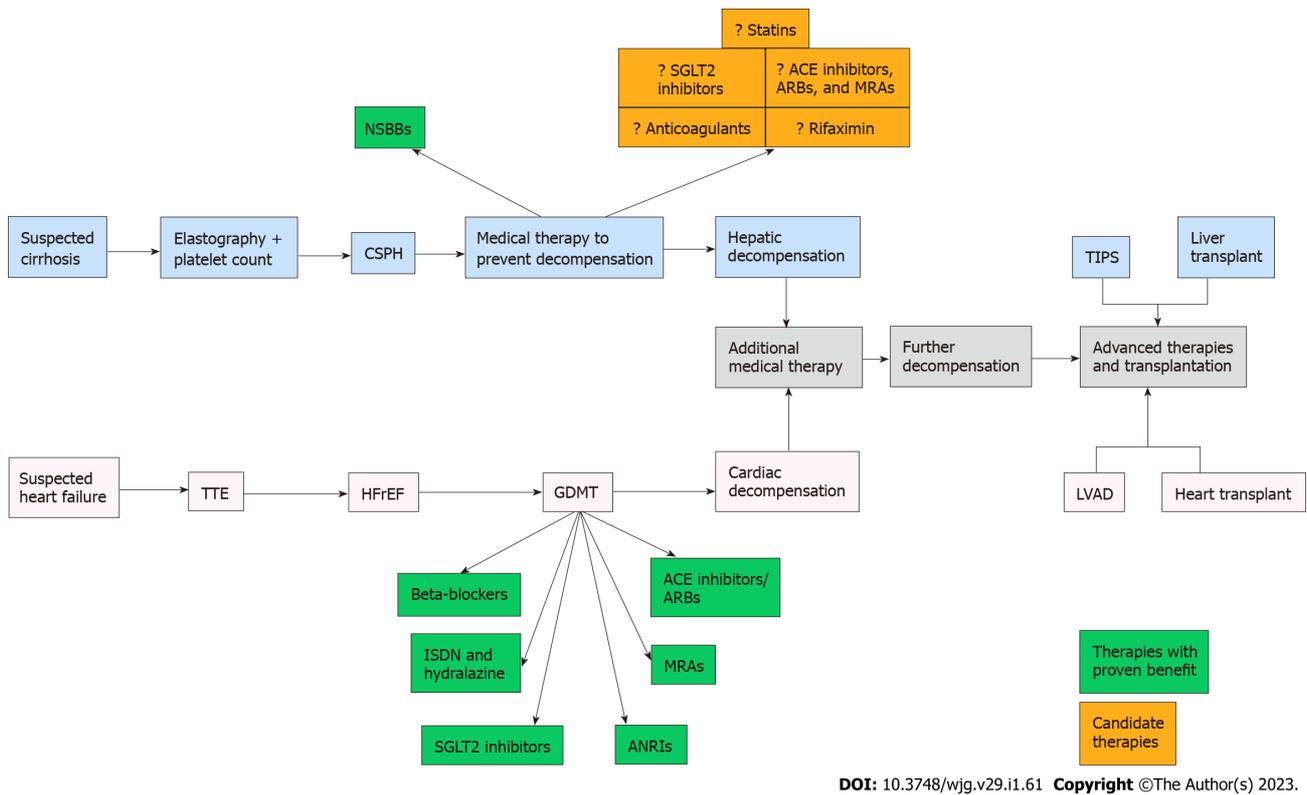
Anticoagulants

In light of the impaired synthesis of clotting factors and the presence of thrombocytopenia associated with cirrhosis, the risk of bleeding has historically been prioritized over thrombosis[69]. However, more recent evidence suggests that a new state of rebalanced hemostasis is achieved among those with stable cirrhosis in which decompensation can lead to increased risks of both hemorrhage and thrombosis, which in turn, can increase the risk for further decompensation[69]. Thrombin has been proposed to activate hepatic stellate cells and lead to upregulation of hepatic fibrosis, suggesting a potential role for anticoagulation in slowing cirrhosis disease progression[70].

Several studies have evaluated the efficacy and safety of anticoagulation in preventing or managing venous thrombotic events in patients with cirrhosis, but only two have specifically addressed its association with preventing decompensation[71-75]. In a RCT of patients with advanced cirrhosis randomized to receive enoxaparin 4000 IU/d or no treatment, decompensation was significantly less common among those receiving enoxaparin (11.7% vs 59.4%; $P < 0.0001$)[75]. Enoxaparin was independently associated with a reduced risk for hepatic decompensation (HR = 0.331, 95%CI: 0.148-0.741; $P = 0.007$). Notably, following cessation of enoxaparin receipt, rates of hepatic decompensation were similar between those in the control and treatment groups. In contrast, in a retrospective study of patients with cirrhosis and portal vein thrombosis, the 1-year probability of hepatic decompensation was not significantly different between patients who did or did not receive warfarin (15.6% vs 17.9%; $P = 0.847$)[72]. The ongoing CIRROXABAN phase III RCT (ClinicalTrials.gov, NCT02643212) aims to evaluate the effect of rivaroxaban in the development of decompensation among patients with cirrhosis.

Renin-angiotensin-aldosterone system antagonists

The renin-angiotensin-aldosterone system (RAAS) has a central role in the pathogenesis and progression of portal hypertension. Splanchnic and peripheral vasodilation in response to excess nitric



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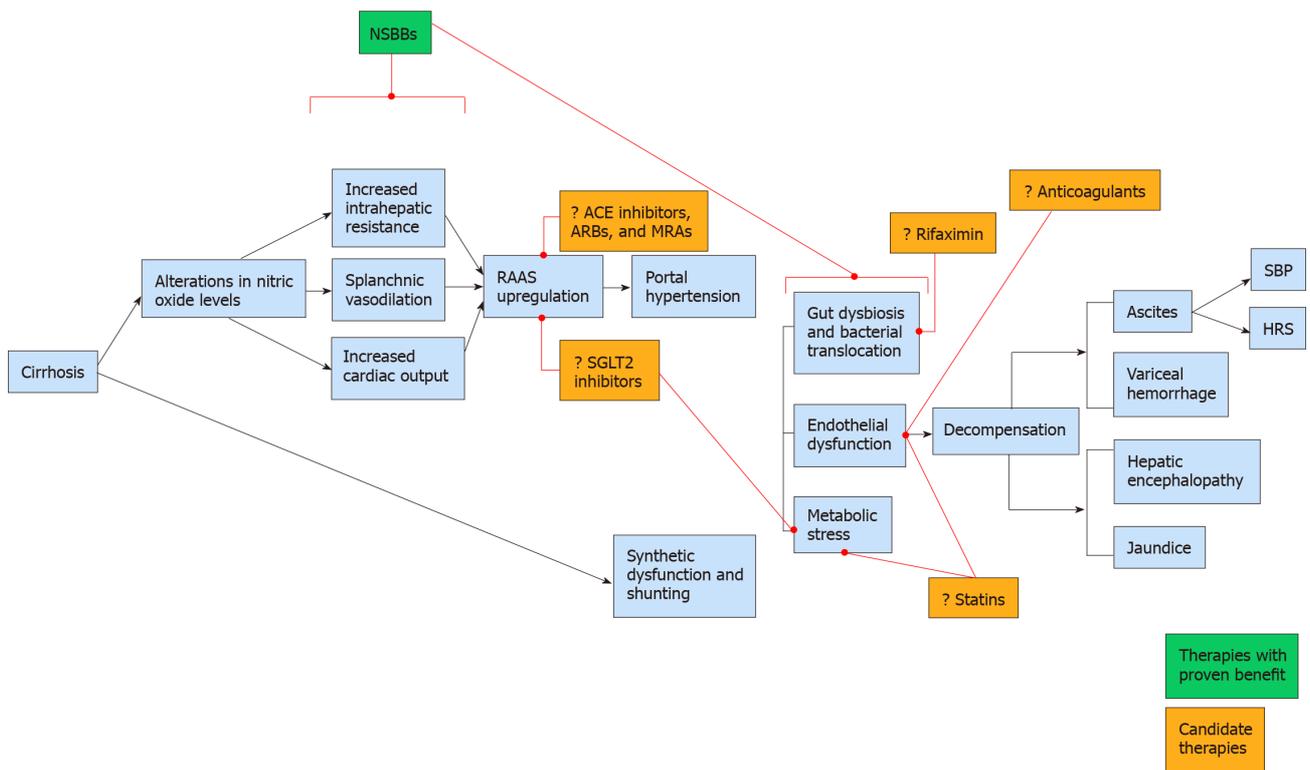
Figure 1 Management of cirrhosis in comparison to congestive heart failure. ACE: Angiotensin converting enzyme; ANRI: Angiotensin receptor-neprilysin inhibitor; ARB: Angiotensin receptor blocker; CSPH: Clinically-significant portal hypertension; GDMT: Guideline-directed medical therapy; HFrEF: Heart failure with reduced ejection fraction; LVAD: Left ventricular assist device; MRA: Mineralocorticoid receptor antagonist; NSBB: Non-selective beta-blocker; SGLT2: Sodium-glucose cotransporter 2; TIPS: Transjugular intrahepatic portosystemic shunting; TTE: Transthoracic echocardiogram.

oxide stimulate the renin-angiotensin-aldosterone and sympathetic nervous systems, triggering a number of mechanisms that further exacerbate portal hypertension. Mediators of these pathways have been directly linked to mortality in patients with cirrhosis[76,77]. Thus, a number of drugs which attenuate the RAAS have been evaluated with mixed results. These include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists such as spironolactone, and sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Both ACE inhibitors and ARBs have been studied in portal hypertension, but their impact in preventing hepatic decompensation remains unclear. Current evidence suggests that ARBs may reduce portal pressures[78-84], but they have yet to be evaluated in RCTs. In contrast, ACE inhibitors have not been shown to reduce portal pressures[85], but a recent large retrospective analysis suggest that they may reduce the risk for liver-related complications in patients with NAFLD[86]. Regardless, while both agents may be safe and potentially beneficial in patients with early-stage disease, their side-effect profile may be deleterious among patients with CSPH.

Spironolactone is critical in the management of cirrhotic ascites. However, the drug has been investigated as an adjunctive agent to NSBBs in the prevention of variceal hemorrhage. A prospective trial demonstrated that the addition of spironolactone 100 mg daily to nadolol reduced the risk of a combined endpoint of variceal hemorrhage and ascites (39% vs 20%; $P < 0.04$)[87]. Further trials exploring the utility of spironolactone in preventing hepatic decompensation among compensated patients have not been pursued, and thus the agent is currently not recommended for chemoprevention.

Initially introduced as antidiabetic drugs, SGLT2 inhibitors have become mainstays in the management of cardiovascular disease and chronic kidney disease among diabetic and nondiabetic patients due to their broad pleiotropic effects[88-93]. By inhibiting sodium and glucose reabsorption in the proximal convoluted tubule, SGLT2 inhibitors restore tubuloglomerular feedback, attenuate overactivation of the RAAS and the sympathetic nervous system, and promote natriuresis, thereby overcoming key mechanisms that are also implicated in the pathogenesis of portal hypertension in cirrhosis[9]. Unlike ACE inhibitors, ARBs, and spironolactone, SGLT2 inhibitors have limited effects on systemic blood pressure and may be better tolerated among patients with CSPH. Although RCTs in cirrhosis are currently lacking, retrospective studies suggest that these agents, namely empagliflozin, are likely safe and warrant further investigation[94-98].



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Figure 2 Therapeutic targets in the prevention of hepatic decompensation. ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; HRS: Hepatorenal syndrome; MRA: Mineralocorticoid receptor antagonist; NSBB: Non-selective beta-blocker; RAAS: Renin-angiotensin-aldosterone system; SBP: Spontaneous bacterial peritonitis; SGLT2: Sodium-glucose cotransporter 2.

Albumin

Albumin has versatile anti-inflammatory and plasma expansion properties that may also mitigate mechanisms implicated in hepatic decompensation. To our knowledge, no study has investigated the role of albumin in preventing hepatic decompensation among patients with compensated disease. However, the Human Albumin for the Treatment of Ascites in Patients with Hepatic Cirrhosis study assessed the impact of human albumin in patients with uncomplicated ascites[99]. Although the primary outcome was mortality, secondary analyses demonstrated that weekly 40-gram albumin infusions reduced the risk for refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy in comparison to standard medical therapy alone. Notably, the study was limited by the fact that the treatment group received more frequent outpatient evaluations, allowing providers to address potential impending complications in a more proactive manner. Because of accessibility and cost limitations, in addition to other factors that restrict widespread use, it is unlikely that albumin will receive significant consideration as a potential therapeutic option in patients with compensated cirrhosis.

Other candidate pharmacotherapies

Numerous other agents hypothesized to decrease the risk of hepatic decompensation have been evaluated. Despite early studies suggesting indirect benefits, there is a paucity of consistent, rigorous clinical evidence demonstrating a direct role for nitrates[100-103], endothelin-A antagonists[104,105], farnesoid X receptor agonists[106], phosphodiesterase-5 inhibitors[107-111], serelaxin[112], sorafenib [113-115], taurine[116], and thalidomide[117] in the prevention of hepatic decompensation. Furthermore, it has been postulated that aspirin and metformin could be attractive targets. However, at this time, a number of prospective and retrospective studies have only demonstrated that these agents may reduce the risk of hepatocellular carcinoma without necessarily impacting the risk for hepatic decompensation[118-120].

A NEW PARADIGM: CHEMOPREVENTION IN THE MODERN ERA

Until PREDESCI validated the use of NSBBs for chemoprevention, the pharmacologic management of cirrhosis had experienced little progress over the preceding half century. In contrast, over the same period of time, incremental advances in the medical management of systolic heart failure, a condition

that mechanistically mimics portal hypertension, led to the widespread implementation of guideline-directed medical therapy, which significantly improved survival (Figure 1). In the past, the lack of non-invasive tools to identify high-risk patients hindered the development and application of chemoprevention in cirrhosis. However, with the advent of elastography and the validation of clinical prediction tools that incorporate laboratory markers such as platelet count, clinicians are now able to risk-stratify patients more efficiently, paving the way for more robust medical management. Based on the findings of the ANTICIPATE study and the guidelines proposed in the Baveno VII workshop[121, 122], patients who have a high likelihood for CSPH based on a combination of liver stiffness measurements and platelet count should be initiated on appropriate chemoprevention with a NSBB in the absence of contraindications to therapy. As additional agents for chemoprevention are evaluated over the coming years, a diverse multi-targeted strategy (Figure 2) may become feasible, mimicking the approach currently utilized for congestive heart failure. Although there are a number of candidate drugs, statins, rifaximin, and SGLT2 inhibitors currently offer the most promise, combining potential efficacy with other important considerations such as safety, accessibility, and systemic benefits.

CONCLUSION

The development of hepatic decompensation represents the most important prognostic factor in the natural history of cirrhosis. Treatments that mitigate this risk have an important role in the management of patients with CSPH. In light of the development of robust non-invasive tools that allow for the timely and accurate risk stratification of patients with cirrhosis, the application of chemoprevention is becoming increasingly feasible. NSBBs are currently the mainstays of treatment in this regard, but emerging therapies such as statins, rifaximin, and SGLT2 inhibitors, may offer hope for personalized multimodal strategies in the future. This paradigm shift may ultimately reduce liver-related morbidity and mortality, improve quality of life, and limit the socioeconomic burden of cirrhosis regardless of the etiologic factors involved.

FOOTNOTES

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