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Review Article

Pharmacological Interventions for Cirrhotic Ascites: From Challenges to Emerging Therapeutic Horizons

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Ascites is the most common complication in patients with decompensated cirrhosis. This condition results in a severely impaired quality of life, excessive healthcare use, recurrent hospitalizations and significant morbidity and mortality. While loop diuretics and mineralocorticoid receptor antagonists are commonly employed for symptom relief, our understanding of their impact on survival remains limited. A comprehensive understanding of the underlying pathophysiological mechanism of ascites is crucial for its optimal management. The renin-angiotensin-aldosterone system (RAAS) is increasingly believed to play a pivotal role in the formation of cirrhotic ascites, as RAAS overactivation leads to a reduction in urine sodium excretion then a decrease in the ability of the kidneys to excrete water. In this review, the authors provide an overview of the pathogenesis of cirrhotic ascites, the challenges associated with current pharmacologic treatments, and the previous attempts to modulate the RAAS, followed by a description of some emerging targeted RAAS agents with the potential to be used to treat ascites. **(Gut Liver 2024;18:934-948)**

Key Words: Renin-angiotensin system; Liver cirrhosis; Ascites; Finerenone; Sodium-glucose transporter 2 inhibitors

INTRODUCTION

The appearance of ascites is the most common sign indicating the entry of decompensated phase of cirrhosis, about 5% to 10% of patients with compensated liver cirrhosis would develop this complication each year.[1] Despite its prevalence in medical settings, its management remains a great challenge for physicians. The 1-year mortality rate of patients with cirrhotic ascites is close to 40%, and only half could survive over 2 years.[2] Moreover, ascites significantly impacts the quality of patient's life, results in a substantial disease burden, and requires significant health care resources. In Western countries, the 30-day unplanned readmission rate for ascites ranges from 37% to 52%, with costs exceeding 20,000 USD in the last year of life.[3,4]

PATHOGENESIS

Blood pressure is dictated by the dynamic interplay of cardiac output, systemic vascular resistance, and blood volume. The hallmark of hemodynamic disturbances in liver cirrhosis is a precarious balance to maintain the blood pressure on a setting of splanchnic arterial vasodilation. Compensated cirrhosis is characterized by a progressive decline in systemic vascular resistance, primarily due to splanchnic arterial dilatation, which is offset by an increase in cardiac output, without appreciable changes in blood

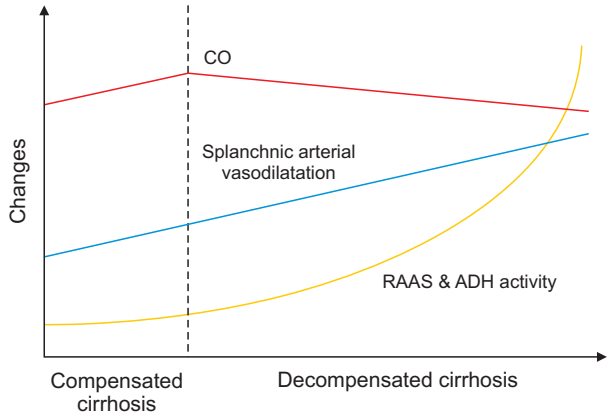

Fig. 1. Hemodynamic manifestations of liver cirrhosis. The main hemodynamic manifestation of liver cirrhosis is a progressive decrease in arterial vessel resistance due to splanchnic arterial vasodilatation. Initially, this is compensated by an increase in cardiac output (CO). However, compromised cardiac function in decompensated stage further deteriorates effective circulating blood volume insufficiency. Finally, the components in neurohumoral system have to be activated. RAAS, renin-angiotensin-aldosterone system; ADH, antidiuretic hormone. Adapted from Arroyo V, *et al.* Ann Hepatol 2011;10 Suppl 1:S6-S14.[5]

volume. However, as cirrhosis progresses to the decompensated stage, cardiac output cannot increase further, as a result, a compromised cardiac performance occurs (Fig. 1).[5] Concomitantly, splanchnic arterial vasodilation continues to advance, accompanied by related changes in the molecule profile.[6] For instance, portal hypertension induces overproduction of nitric oxide (NO) by endothelial cells, which, regarded as the strongest vasodilator molecule, contributes to excessive vasodilation in both splanchnic arterial vessels and systemic circulation.[7] In addition, several other vasodilatory molecules have also been identified as a contributory role in the pathogenesis of portal hypertension in cirrhotic patients and experimental rodent models.[8,9] Carbon monoxide, which is sourced from heme oxygenase-1, may serve as an endogenous regulator of vascular tone and exhibit anti-inflammatory and anti-apoptotic properties.[10] Similarly, prostacyclin is another potent vasodilator, as well as inhibitor of platelet thrombus formation.[11] Endocannabinoids are lipid-mediated signaling molecules that increase activity of vasodilatory-related pathways and modulate diverse physiological functions, including regulating inflammation status.[12] Their upregulation in the setting of cirrhosis and portal hypertension suggests a potential role in the modulation of splanchnic vascular resistance and the maintenance of portal blood flow.

As discussed above, pathophysiological changes in patients with cirrhosis give rise to a decrease in the effective circulating blood volume and consequent circulatory dysfunction. To maintain blood pressure despite these hemodynamic abnormalities, the renin-angiotensin-aldosterone system (RAAS) is activated, leading to a significant increase in the reabsorption of sodium and water in the kidney.[6,13] The aldosterone secreted during this process can stimulate the mineralocorticoid receptor, which acts as a transcription factor to elevate the expression of inflammatory cytokines and activate genes targeting water resorption.[14] This process ultimately leads to disproportionate water retention and results in dilutional hyponatremia. Additionally, relative hypovolemia reduces the afferent impulses from baroreceptors in the atria, ventricles, carotid sinus, and aortic arch that communicate with the hypothalamus through the vagus nerve. This process triggers non-osmotic secretion of antidiuretic hormone (ADH), which, by binding to V2 receptors on the basolateral membrane of the collecting duct, increases cyclic AMP production and activates protein kinase A. These facilitate the translocation of aquaporin-2 from the cytoplasm to the apical plasma membrane of the lumen side, altering water permeability.[15]

The above pathophysiological mechanisms collectively contribute to the most common complication in patients with decompensated cirrhosis-ascites.

THE DILEMMA IN THE CURRENT CHOICE FOR ASCITES MANAGEMENT

Current guidelines recommend several treatment strategies for patients with decompensated cirrhosis and ascites. Non-pharmacologic options include sodium restriction and large-volume paracentesis. Mineralocorticoid receptor antagonists (MRAs) and loop diuretics form the mainstay of pharmacologic treatments for alleviating ascites.[1,16] The basic principle of using diuretics to manage ascites is to promote natriuresis by blocking ion channels in renal tubular epithelial cells. This action subsequently leads to osmotic diuresis, a process that reduces the passive reabsorption of water and ions. Despite these agents have been widely used for decades, they are considered as symptom relievers without proven evidence on survival benefits.[1]

LOOP DIURETICS

Loop diuretics exhibit a potent natriuretic effect by interfering with the sodium-potassium-chloride cotransporter 2 (NKCC2) located at the thick segment of the ascending limb. By increasing the sodium chloride concentration in the luminal fluid of the distal convoluted tubule, these agents have been found to remarkably increase urine production. However, this pronounced natriuretic effect

is limited to an acute setting. Inhibiting NKCC2 located at the macula densa can increase renin secretion, potentially exacerbating RAAS overactivation, leading to greater reabsorption of sodium. Prolonged use of loop diuretics leads to a gradual decline in net sodium excretion, which is termed "braking phenomenon."[17] Despite guidelines allow titrating the maximum furosemide dosage up to 160 mg/day, clinicians often consider the dose-effect relationship of loop diuretic to be linear. In fact, these agents demonstrate steep dose-response curves, with minimal effects observed until a threshold dose is reached. Beyond this threshold, response rapidly peaks, a phenomenon known as the "ceiling effect." Consequently, once the ceiling is achieved, further increases in diuretic dosages no longer enhance urinary sodium excretion.[17] Yet, in patients with cirrhotic ascites, the dose-response curve shifts downward and to the right, reducing the ceiling height, as observed in heart failure cases. These suggest that increasing loop diuretic dosage is futile for urine volume improvement.

MINERALOCORTICOID RECEPTOR ANTAGONISTS

As the most commonly used neurohormonal modulator, spironolactone was developed over 60 years ago as a class of potent MRAs. It was primarily used for the clinical treatment of congestive heart failure, primary aldosteronism, essential hypertension, and other pathologies associated with aldosteronism, such as ascites secondary to decompensated cirrhosis. Spironolactone is metabolized in the liver into three active metabolites that bind to cytoplasmic mineralocorticoid receptors, functioning as aldosterone antagonists, and produce a potassium-sparing diuretic effect in the distal tubules. All three active metabolites have demonstrated long half-life (range, 13.8 to 16.5 hours).[18] However, liver cirrhosis can significantly impair the metabolic process, extending the metabolites' half-lives from 23.9 hours to 126 hours.[19] In clinical practice, this slows pharmacokinetic characteristics poses a challenge for physicians in titrating the optimal dose of spironolactone. Optimal dosage adjustment can take several weeks and is often accompanied by electrolyte disturbances related to the accumulation of active constituents during the treatment.[20] Due to its simultaneous blockage of progesterone receptors and androgen receptors, spironolactone also commonly causes challenging side effects such as menstrual irregularities, impotence, and gynecomastia.

Unlike spironolactone, novel nonsteroidal MRAs showed significantly higher selectivity for aldosterone receptors and greater affinity in head-to-head trials.[21] Its nonsteroidal structure allows for more efficient binding to aldosterone receptors, inhibiting inflammatory and pro-fibrotic gene expression due to hyperaldosteronemia, thus slowing the pace of kidney structure remodeling and functional deterioration among diabetic patients.[22] The advantages of nonsteroidal MRAs are evidenced not only by their higher selectivity and affinity for mineral receptor but also by their inactive metabolites, rapid onset of action, and significantly shorter half-life, lasting only 2 hours.[23] In addition, nonsteroidal MRAs have shown a better safety profile regarding hyperkalemia, with incidence less than half those associated with spironolactone (5.3% for finerenone vs 12.7% for spironolactone) in a phase II clinical trial.[24]

In the FIDELIO-DKD research, the nonsteroidal MRA finerenone considerably decreased the renal composite endpoint by 18% in patients with type 2 diabetes and chronic kidney diseases. The study also indicated a potential reduction in the incidence of hospitalization due to heart failure (hazard ratio, 0.86; 95% confidence interval, 0.68 to 1.08).[25] Another phase III trial investigated the compositecardiovascular events (including death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, or hospitalization caused by heart failure) in patients withchronic kidney disease and type 2 diabetes. Finerenone decreased the incidence of heart failure hospitalization by 29%, while only 1.2% of the finerenone group discontinued treatment due to hyperkalemia, compared to 0.4% in the placebo group.[26] Importantly, neither of these trials reported any hepatotoxicity-related adverse events. Currently, there is no direct evidence supporting the use of nonsteroidal MRAs in the management of cirrhotic ascites. However, given that RAAS overactivation is a common pathogenic mechanism in cirrhotic ascites, heart failure and diabetes mellitus, further investigation into nonsteroidal MRAs is warranted.

VAPTANS

Vaptans, also known as vasopressin receptor antagonists, disrupt the interaction between ADH and vasopressin V2 receptors, thereby facilitating the excretion of free water. Mechanistically, these medications do not affect the RAAS activity as they merely mitigate water retention without concomitant excretion of urine sodium. This action can lead to sodium retention and subsequent recurrence of water retention.[27] Moreover, a rapid elevation of serum sodium concentrations could further stimulate osmotic ADH production,[28] and volume depletion would further compromise hemodynamics. Given these limita-

tions, vaptans cannot provide long-term relief from cirrhotic ascites.

Several clinical studies have reported favorable outcomes with short-term (≤2 weeks) weight reduction, coupled with the correction of hyponatremia, in patients with cirrhotic ascites.[29] However, a 12-week study showed satavaptan offered no significant advantages over placebo in terms of ascites regression or large-volume paracentesis requirements.[30] Interestingly, similar findings have also been observed in the treatment of heart failure. Although tolvaptan alleviated dyspnea symptoms among hospitalized patients with acute congestive heart failure,[31,32] it did not offer any long-term clinical benefits.[33] Notably, vaptans were associated with hepatic toxicity as an adverse effect in patients without underlying liver diseases.[34] Accordingly, current guidelines do not endorse the routine use of vaptans in treating cirrhotic ascites.[1,35]

THE EXPLORATION OF RAAS BASED INTERVENTION

Liver cirrhosis and chronic heart failure share similar pathophysiological mechanism (Fig. 2).[36] Generally, the reduction in effective arterial blood volume, whether due to splanchnic vasodilation in decompensated liver cirrhosis or the loss of cardiac output in heart failure, can increase RAAS activity. In addition, non-osmotic ADH release is further increased by sympathetic excitation due to relative hypovolemia,[37] which in turn enhances RAAS activity through renal β-adrenergic stimulation.[38] These neurohumoral system changes trigger clinical symptoms linked to water and sodium retention, such as ascites in liver cirrhosis and acute pulmonary edema in heart failure, along with a commonly observed abnormality in laboratory assay, dilutional hyponatremia. Numerous RAAS-modulating agents, which have demonstrated efficacy in the management of heart failure, have been explored for their utility in the treatment of hepatic ascites. Regrettably, unlike the favorable outcomes with angiotensin-converting enzyme inhibitors (ACEIs) and nonselective β-blockers in heart failure patients, these agents have not shown clinical benefits among decompensated cirrhosis patients with ascites.[39,40]

1. Angiotensin-converting enzyme inhibitors

This class of agents disrupts RAAS activity, yet does not directly impact renin levels. ACEIs block the angiotensin-converting enzyme that transforms angiotensin I to angiotensin II, thereby reducing the production of angiotensin II. A double-blind randomized controlled trial suggested that captopril substantially reduced glomerular filtration rate and urine sodium excretion in individuals with cirrhosis.[41] Further research demonstrated that in patients with cirrhotic ascites, captopril dramatically reduced natriuresis, urine production, and impeded the natriuretic effect of loop diuretics.[42] Pathophysiologically, ACEIs dilate the efferent arterioles and drastically diminish the glomerular filtration rate, leading to reduced urine sodium and urine volume, ultimately exacerbating the water and sodium retention. Further investigations have revealed that, contrary to expectations, ACEIs could not suppress RAAS activity among cirrhotic patients but instead increased plasma renin activity.[43] Since the vasodilatory impact by ACEIs

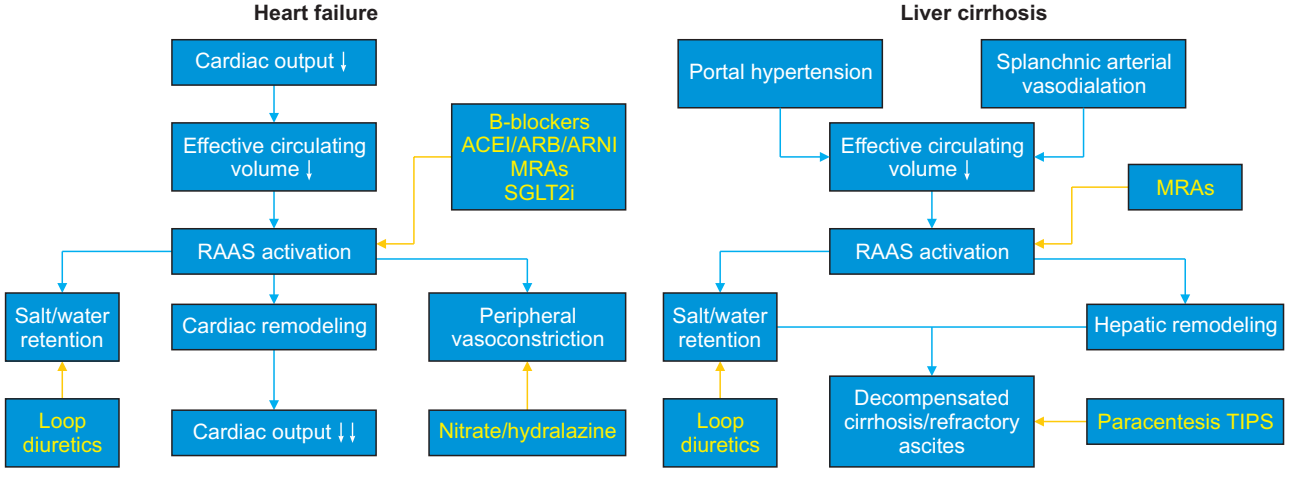

Fig. 2. The common mechanism between heart failure and liver cirrhosis. The activation of the RAAS takes the pivotal place in the pathophysiology of chronic heart failure and decompensated cirrhosis. NKCC2, sodium-potassium-chloride cotransporter 2; SGLT2, sodium-glucose cotransporter-2; RAAS, renin-angiotensin-aldosterone system; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; MRAs, mineralocorticoid receptor antagonists; SGLT2i, SGLT2 inhibitor; TIPS, transjugular intrahepatic portosystemic shunt. Adapted from Saffo S, *et al.* Clin Liver Dis (Hoboken) 2018;11:141-144, with permission from Wolters Kluwer Health, Inc.[44]

on the small arteries would be a strong stimulus to RAAS through the feedback-activated pathways and overwhelm its direct influence on RAAS. To date, attempts to manage cirrhotic ascites with ACEIs have been unsuccessful.

2. Nonselective β-blockers

Nonselective β-blockers are established as a cornerstone of pharmacotherapy for patients with compensated cirrhosis, as demonstrated by multiple trials. These agents not only reduce portal pressure but also inhibit renin expression and secretion,[45,46] effectively preventing decompensation occurrence among cirrhosis patients with clinically significant portal hypertension.[47] A meta-analysis showed that long-term carvedilol therapy could reduce the risk of progression to decompensated stage and improve survival in patients with cirrhosis, primarily by reducing ascites.[48] Despite their success in compensated cirrhosis, β-blockers have shown very limited effects on lowering portal pressure or suppressing RAAS once the disease progresses to decompensated stage.[5] In particular, for patients with advanced liver cirrhosis and compromised cardiac output function, the negative inotropic effects of nonselective β-blockers significantly worsen the hemodynamic condition, contributing to elevated mortality rates in those awaiting a liver transplant.[5]

We conducted a systematic review to comprehensively evaluate the impact of drugs that act directly or indirectly on the RAAS in patients with decompensated cirrhosis, summarizing our finding in Table 1.[6,40-44,49-92] The search process and inclusion-exclusion criteria for literature are detailed in the Supplementary Tables 1, 2 and Supplementary Fig. 1. Our review revealed that although these drugs inhibit the overactivated RAAS, most studies observed a decrease in urinary sodium or a reduction in urine volume, a characteristic inherent to ACEI/ARB or nonselective β-blockers. This suggests that successful modulating RAAS may be challenging without simultaneous improvements in urinary sodium and urine volume.

3. Albumin: RAAS modulator rather than plasma expansion

Albumin comprises about three-quarters of the oncotic pressure and is often classed as a plasma expander in patients with cirrhosis. As a plasma expander, albumin effectively mitigates relative hypovolemia,[93] and corrects hyponatremia by increasing free water clearance in cirrhosis.[94] Clinical trials have demonstrated that the combination of albumin and loop diuretics is more effective than loop diuretics alone in controlling ascites,[95,96] and considerably improve survival in cirrhotic patients with ascites.[97,98] Moreover, unlike other artificial colloids, albumin uniquely prevents circulatory deterioration following large-volume paracentesis.[99] Current guidelines therefore recommend administering 8 g of albumin after each liter of ascites removal.[1] Albumin infusion could restore blood pressure, increase blood volume and improve cardiac index in patients with cirrhosis.[6,100,101] The circulatory benefits of albumin in cirrhosis patients cannot be solely attributed to its volume-expanding function. If the primary function of albumin were to expand volume, its initial administration as a plasma expander should lead to a decrease in plasma sodium concentrations (5% albumin solution and 25% solution contain 130 to 160 mEq/L sodium and are considered isotonic with plasma). Stated in another way, there should be a decline in plasma sodium concentration upon albumin infusion at initial stage. However, the results from the ATTIRE study, which evaluated albumin administration in hospitalized decompensated cirrhotic patients, challenged this perception. The study's appendix indicated that serum sodium levels started to increase within 24 hours among patients in albumin group, with a significant difference in serum sodium levels between the two study groups observed within 48 hours and this difference maintained throughout the trial.[102] In the ANSWER study, long-term albumin infusion was proved to bring about prolonged overall survival with the concurrent improvement of hyponatremia in patients with decompensated cirrhosis.[98] Intriguingly, if albumin was regarded solely as a plasma expander, it would be difficult to rationalize why transfusion of other blood products increases portal pressure,[103] whereas the incidence of or gastro-esophageal variceal bleeding was not increased in albumin group in the ANSWER study.[98] Another study highlighted albumin's dose-dependent effect on reducing cytokine plasma concentrations and alleviating cardiocirculatory dysfunction without significant increase in portal pressure.[104] The evidence supports the view that albumin's role far extends beyond that of a plasma expander, further exploration of its pleiotropic effects apart from its oncotic properties is needed.

Approximately one-third of the body's total albumin resides in the vascular bed, with the remainder distributed within the extravascular and interstitial space. Albumin constantly exchanges between the intravascular and extravascular compartments, with approximately 4% to 5% of total albumin per hour traversing the capillary endothelium to the interstitial space before, then returning to the veins via lymphatics system.[92] The plasma volume expansion effect of 5% albumin infusion only lasts only 4 to 6 hours, which is significantly weaker than that provided by other artificial colloids.[105] This suggests that the principle of the therapeutic benefits derived from albumin should not primarily be attributed to its volume expansion

Table 1. The Summary of ACEI/ARB or Nonselective β-Blockers in the Treatment of Liver Cirrhosis

Author (year)	Study type	No. of participants	Intervention	Result
Tergast *et al.* (2023)[49]	Propensity scored matching study	123 vs 41	RAS-inhibitors	RAS-Inhibitor is associated with lower incidences of grade III AKI.
Danielsen *et al.* (2023)[50]	Cross-over study	39	Propranolol infusion	Renal artery blood flow fell by –5%.
Nabilou *et al.* (2022)[51]	Prospective study	38	Propranolol infusion	Effect of β-blockade on cardiac index is less potent in advanced cirrhosis.
Singh *et al.* (2022)[52]	Prospective study	160	Propranolol vs endoscopic variceal ligation	PPL is associated with lower survival, poor control of ascites, and increased risk of AKI when compared with EVL.
Chen *et al.* (20220)[53]	Propensity scored matching study	1,788 vs 1,788	Propranolol user vs not used	Propranolol was associated with reduced mortality in patients with cirrhosis and ascites.
Tapper *et al.* (2022)[54]	Population survey study	63,364	NSBB	The risk of ascites was higher for persons taking any NSBB.
Kang *et al.* (2021)[55]	Retrospective study	740	NSBB user vs not used	NSBB therapy was associated with longer survival in prophylactic treatment of esophageal varices.
Sasso *et al.* (2021)[56]	Retrospective study	2,165	NSBB user vs not used	Use of NSBB for patients with cirrhosis was associated with fewer infection-related admissions.
McDowell *et al.* (2021)[57]	Retrospective study	152	Carvedilol vs variceal band ligation	carvedilol offers a longer survival benefit than patients receiving EVL.
Kalambokis *et al.* (2021)[58]	Prospective study	32 vs 64	Continued use propranolol vs switch to carvedilol	In patients with cirrhosis and nonrefractory ascites, as carvedilol improves renal perfusion and clinical outcomes.
Téllez *et al.* (2020)[59]	Clinical trial	20 vs 18	NSBB	NSBB impair global circulatory homeostasis and renal function in cirrhotic patients with refractory ascites.
Alvarado-Tapias *et al.* (2020)[60]	Comparative study	403	NSBB	The short-term effect of β-blockers on cardiac output may adversely influence survival in patients with decompensated cirrhosis.
Yoo *et al.* (2020)[61]	Retrospective study	271	EVL vs propranolol +EVL	EVL alone is a more appropriate treatment option for prophylaxis of esophageal varices than propranolol combination therapy in cirrhotic ascites patients.
Ngwa *et al.* (2020)[62]	Retrospective study	65 vs 105	NSBB user vs not used	NSBB use was associated with lower 90-day mortality.
Giannelli *et al.* (2020)[6]	Retrospective study	584	NSBB	NSBB use in cirrhotic patients with compromised cardiac performance increase the mortality before liver transplant.
Tergast *et al.* (2019)[63]	Retrospective study	624	NSBB	Treatment with NSBB was associated with a higher 28-day transplant-free survival, but no benefit in mean arterial blood pressure <65 mm Hg group.
Chen *et al.* (2019)[64]	Clinical trial	60 vs 61	GVO + carvedilol vs GVO	carvedilol + GVO did not decrease recurrence of EGVB, no impact on survival time, but produced more adverse events.
Giannitrapani *et al.* (2018)[65]	Retrospective study	230	NSBB user vs not used	The use of NSBB indicated a higher risk of PVT.
Zampino *et al.* (2018)[66]	Retrospective study	130	NSBB	NSBB treatment were independent risk factors of PVT.
Pfisterer *et al.* (2018)[67]	Retrospective study	766	NSBB	NSBB do not increase efficacy of band ligation in primary prophylaxis, but they improve survival in secondary prophylaxis of variceal bleeding.
Onali *et al.* (2017)[68]	Retrospective study	316	NSBB	Patients with ascites on NSBB did not have impaired survival compared to those not receiving NSSB.
Sinha *et al.* (2017)[69]	Retrospective study	325	Carvedilol	Low dose, chronic treatment with carvedilol in patients with liver cirrhosis and ascites is not detrimental.
Kim *et al.* (2017)[70]	Retrospective study	2,361	NSBB	NSBB in patients with ascites significantly increased the risk of AKI.
Bossen *et al.* (2016)[71]	Retrospective study	1,198	NSBB	Use of NSBBs in cirrhosis patients with ascites did not increase mortality.
Mookerjee *et al.* (2016)[72]	Prospective observational study	349	NSBB	NSBBs in cirrhotic patients is safe and reduces the mortality if they develop ACLF.

Table 1. Continued

Author (year)	Study type	No. of participants	Intervention	Result
Mandorfer *et al.* (2014)[73]	Retrospective study	607	NSBB	NSBBs increase the risks for hepatorenal syndrome, acute kidney injury and reduce transplant-free survival.
Sersté *et al.* (2011)[74]	Clinical trial	10	NSBB	NSBB might be associated with a high risk of paracentesis-induced circulatory dysfunction.
Sersté *et al.* (2010)[75]	Observational prospective study	151	NSBB	The use of NSBB was associated with poor survival in patients with refractory ascites.
Therapondos *et al.* (2006)[76]	Before-and-after control study	10	Losartan	Low dose losartan did not ameliorate erect posture-induced sodium retention in post-TIPS ascites-free patients.
Cholongitas *et al.* (2006)[77]	Retrospective study	134	Propranolol	Propranolol was not associated with a lower risk for SBP.
Groszmann *et al.* (2005)[78]	Clinical trial	213	NSBB	NSBB was ineffective in preventing varices in unselected patients with cirrhosis.
Abecasis *et al.* (2003)[79]	Clinical trial	100	Nadolol + placebo vs Nadolol + spironolactone	Nadolol plus spironolactone effectively reduced the incidence of both portal-hypertensive complications.
Sen *et al.* (2002)[80]	Clinical trial	20	spironolactone, alone or with propranolol	Spironolactone in combination with propranolol achieved adequate reduction in HVPG in propranolol-resistant portal hypertension.
Wong *et al.* (2002)[81]	Clinical trial	10	Losartan	beneficial natriuretic effects of low-dose losartan on erect posture-induced sodium retention.
De *et al.* (2002)[82]	Clinical trial	36	Carvedilol vs propranolol	Carvedilol reduced portal pressure in both acutely and over 7 days, but not superior to propranolol.
Lee *et al.* (2000)[83]	Before-and-after control study	25	Carvedilol	Single dose of captopril decreased glomerular filtration rate and increased plasma renin activity.
Forrest *et al.* (1996)[84]	Comparative study	16	Carvedilol	Carvedilol did not compromise renal perfusion but increase the risk of hypotension in ascitic patients.
Tsai *et al.* (1996)[43]	Clinical trial	50	Captopril	Captopril did not improve sodium and water retention in cirrhotic patients with ascites.
Amarapurkar *et al.* (1994)[85]	Comparative study	68	Enalapril	Enalapril improved creatinine clearance in patients with liver cirrhosis.
Ohnishi *et al.* (1994)[40]	Before-and-after control study	10	Enalapril	Enalapril slightly increased daily urinary volume and sodium excretion.
Gentilini *et al.* (1993)[41]	Double-blind, cross-over clinical trial	NA	Captopril	Low dose of captopril decreased glomerular filtration rate and sodium excretion in ascitic patients.
van Vliet *et al.* (1992)[86]	Before-and-after control study	8	Captopril	Among diuretic resistance patients, half of them increases urine sodium after low-dose captopril administered.
Ibarra *et al.* (1992)[87]	Before-and-after control study	9	Captopril	7 of 9 showed enhanced natriuresis after captopril administered.
Poynard *et al.* (1991)[88]	Clinical trial	589	NSBB	Propranolol and nadolol were effective in preventing first bleeding and reducing the mortality rate.
Group (1989)[89]	Clinical trial	174	Propranolol	Propranolol prevented first gastrointestinal bleeding in cirrhotic patients.
Daskalopoulos *et al.* (1987)[42]	Before-and-after control study	11	Captopril	Urinary volume was reduced and natriuretic effect of furosemide was blunted.
Pariente *et al.* (1985)[90]	Before-and-after control study	6	Captopril	Captopril decreased mean arterial pressure and glomerular filtration.
Rector *et al.* (1984)[91]	Before-and-after control study	13	Propranolol	Propranolol induced an anti-natriuretic effect.
Lebrec *et al.* (1984)[92]	Clinical trial	74	Propranolol	Propranolol increased the survival rate in cirrhotic patients.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; RAS, renin-angiotensin system; AKI, acute kidney injury; PPL, propranolol; EVL, endoscopic variceal ligation; NSBB, nonselective beta-blocker; GVO, gastroesophageal variceal obliteration; EGVB, esophagogastric variceal bleeding; PVT, portal vein thrombosis; ACLF, acute-on-chronic liver failure; TIPS, transjugular intrahepatic portosystemic shunt; SBP, spontaneous bacterial peritonitis; HVPG, hepatic venous pressure gradient.

effect. Decompensated cirrhosis is characterized by systemic pro-oxidant and pro-inflammatory environments. Furthermore, gut microbiota dysbiosis and translocation lead to the release of pro-inflammatory mediators, which can increase the release of vasodilatory molecules and exacerbate the overactivation of RAAS. In patients with decompensated cirrhosis, it is not only the quantity of albumin that is insufficient; the pleiotropic non-oncotic properties of albumin, including antioxidant capacity, free radical scavenging, immune regulation, and endothelial protection function are also impaired,[93] resulting in a significant deficiency in "effective" albumin. In patients with decompensated cirrhosis, the levels of interleukin 6 (IL-6) and vascular endothelial growth factor (VEGF) are significantly elevated. It has been confirmed in other diseases that IL-6 can stimulate the secretion of renin, thereby affecting the expression of angiotensin II and potentially impacting RAAS components.[106] Moreover, IL-6 can influence VEGF production, which enhances angiogenesis and alters vascular structure, thus affecting the vascular response to angiotensin II and indirectly influencing RAAS activity.[107] In the Pilot-PRECIOSA and INFECIR-2 study, large-volume albumin transfusions increased body albumin level and reduced the levels of IL-6 and VEGF, thereby regulating RAAS activity through both direct and indirect pathways.[104,108] In addition, albumin is capable of indirectly modulating the RAAS system by restoring left ventricular function, compensating for relative hypovolemia in patients with liver cirrhosis,[100,109] a property is not fully reliant upon changes in preload,[110] however, other artificial colloids do not provide similar benefits on this aspect of circulatory function.[111] Additionally, albumin corrects molecule profile abnormalities by reducing endogenous NO production, which in turn restores peripheral vessel resistance,[112,113] improves vascular endothelial function, counteracts endotoxin-induced inflammation and oxidative stress,[114] and diminishes systemic inflammation.[113] These effects ultimately improve circulatory blood volume. Therefore, it can be inferred that albumin acts as a RAAS modulator in the treatment of cirrhotic ascites.

4. Sodium-glucose cotransporter type 2 inhibitors in cirrhotic ascites treatment

In the setting of RAAS overactivation in decompensated cirrhosis, sodium reabsorption markedly increases at the proximal tubular,[115] the sodium concentration in tubule fluid flow to distal nephron therefore reduced. In this case, the diuretic effect of both conventional MRAs and loop diuretics would be blunted, given that they act at the ionic channel in the distal nephron. Additionally, proximal tubular sodium reabsorption is commonly involved in long-standing or refractory ascites.[115,116] In order to intervene in the process of excessive sodium reabsorption in the proximal tubules, it is imperative to introduce novel approaches.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors belong to a class of oral medications for treating type 2 diabetes.[117] By inhibiting SGLT2, the agents significantly reduce the reabsorption of sodium and glucose in the proximal convoluted tubule. The increased sodium concentration in tubule fluid senses by the macula densa would in turn inhibit the renin release from the juxtaglomerular cells, then the increased sodium concentration in tubular fluid is a stimulus for tubuloglomerular feedback and causing vasoconstriction of the afferent arteriole.[118] In spite of slightly reduced glomerular filtration, the osmotic diuresis caused by increased sodium concentration in the tubule fluid maintains the adequate amount of urine.[119] The complementarity in mechanism suggests that SGLT2 inhibitors could exert a synergistic effect with loop diuretics and mitigate the braking phenomenon (Fig. 3).[120] Their characteristics on promoting urinary excretion of solutes have been recently applied to treat advanced heart failure regardless of preexistence of diabetes.[121,122] Given that advanced heart failure and decompensated liver cirrhosis share common pathophysiological features, it is reasonable to infer that SGLT2 inhibitors might be a candidate for treating cirrhotic ascites as well.[123]

Encouragingly, several case reports have observed regression of ascites after adding SGLT2 inhibitors to the treatment for patients with decompensated cirrhosis and comorbid diabetes, without appreciable adverse events.[124,125] Interestingly, the correction of hyponatremia observed in these cases might also suggest potential capacity on tempering RAAS with these drugs.[125-127] An interesting parallel finding in heart failure treatment, in DAPA-HF trial, dapagliflozin increased urine volume and free water clearance persistently for several weeks, the correction of hyponatremia is along with the improvement of clinical outcomes.[128] A mechanism-based explanation had been proposed from the editorial comment,[129] SGLT2 inhibitors probably alleviate the water and sodium retention without further stimulate the RAAS activation as well as sympathetic nervous system. This class of agents therefore has potential to become a promising complement to the current pharmacologic treatments for ascitic patients. Moreover, the clinical benefits of SGLT2 inhibitors among patients with advanced heart failure do not rely on the existence of glycemia,[121,122] it merits further investigation on ascitic patients regardless of comorbid diabetes.

Before repurposing SGLT2 inhibitors for cirrhotic ascites in a clinical setting, it is imperative to evaluate whether SGLT2 expression increases in the late-stage cirrhotic

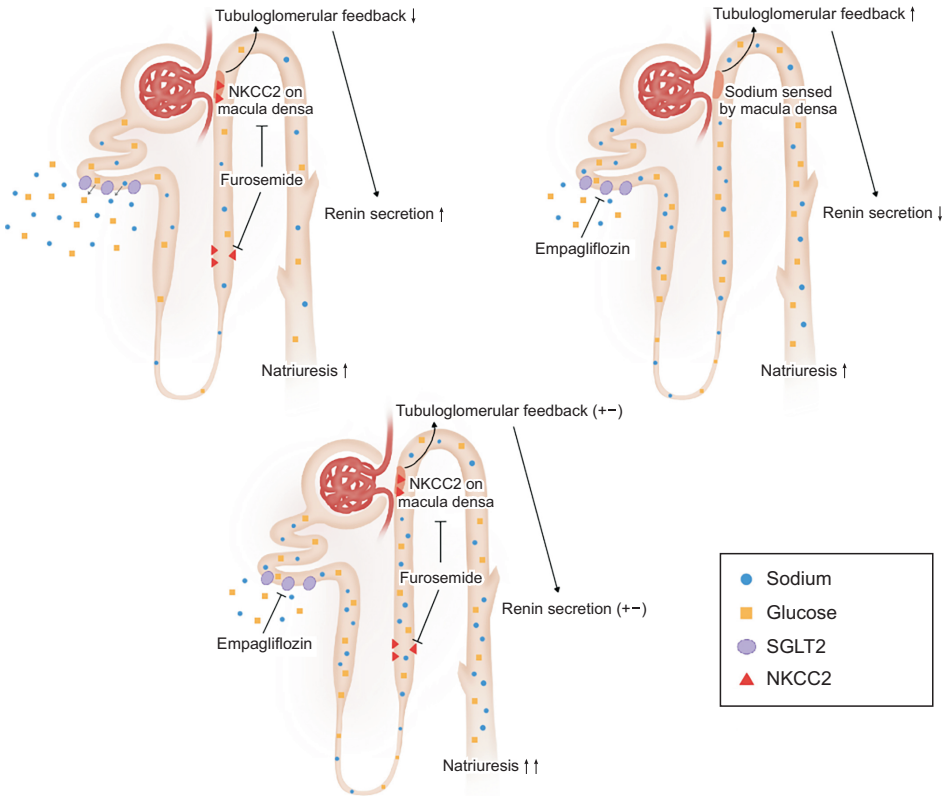

Fig. 3. The individual and synergistic effect of furosemide and empagliflozin on urinary sodium excretion and tubuloglomerular feedback. When furosemide inhibits NKCC2 in the macula densa, it reduces the ability to sense sodium and chloride levels, leading to an increased release of renin. This process suppresses the tubuloglomerular feedback. SGLT2 inhibitors increase the sodium concentration in the tubular fluid, which in turn raises the sodium and chloride levels passing through the macula densa. This increase in ion concentration is detected by the osmoreceptors in the macula densa, subsequently activating the tubuloglomerular feedback. Thus, these two drugs synergistically optimize fluid management in patients with cirrhotic ascites by balancing renin release and maintaining sodium levels. RAAS, renin-angiotensin-aldosterone system; NKCC2, sodium-potassiumchloride cotransporter 2; SGLT2, sodium-glucose cotransporter-2.

model and whether the proximal tubular sodium reabsorption increase is mediated by SGLT2. Additionally, it is essential to determine whether RAAS activity regulates the upregulation of SGLT2 expression in liver cirrhosis. It is probable that the renal pathological changes in progressive cirrhosis resemble those found in heart failure models.[130]

Hepatic glycogen capacity is impaired in patients with decompensated liver cirrhosis, predisposing them to hypoglycemia.[131] However, the impact of SGLT2 inhibitors on blood glucose levels is not dependent on the level of insulin, the magnitude of blood glucose reduction is dependent on plasma glucose level among diabetic population,[132] and less likely to induce a hypoglycemic event. Data from two phase III trials suggest SGLT2 inhibitors showed a comparable incidence with placebo in regard to liver dysfunction or clinical hypoglycemia regardless of diabetes existence.[133] Moreover, hepatic dysfunction does not significantly affect the pharmacokinetics of SGLT2 inhibitors.[134-136] An initial dip of estimated glomerular filtration rate and mild blood pressure drop (systolic and diastolic blood pressures decreased by 4 to 6 and 1 to 2 mm Hg respectively[137]) observed with SGLT2 inhibitors may raise worries about hepato-renal syndrome, but in practice, such change does not irritate RAAS components,[134-136,138,139] it appears unlikely that SGLT2 inhibitors would cause hepato-renal syndrome in absence of an aggravation of RAAS status.

By far, the potential value of SGLT2 inhibitors in this field has begun to be gradually recognized,[140] it is also encouraging to explore this new avenue of therapeutic approach (NCT05014594, NCT05013502, NCT05430243, NCT05726032).

CONCLUSION

In conclusion, despite decades of established medication therapy for cirrhotic ascites, significant therapeutic benefits remain elusive. However, growing understanding of the pathophysiological mechanisms underlying RAAS offers promise prospect for repurposing novel MRAs and

SGLT2 inhibitors in ascites treatment. These efforts may pave the way toward more effective management of the complication of decompensated liver cirrhosis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl240038.

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