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REVIEW

## Beta-blockers and Statins: Role in Portal Hypertension and Beyond

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### ABSTRACT

Clinically significant portal hypertension is a cornerstone in cirrhosis's natural history, significantly impacting these patients' morbidity and mortality. Unless adequate preventive measures are implemented, the recurrence rate of bleeding can reach up to 65% of patients and with mortality of 57%. The goals in portal hypertension treatment focus on reducing the hepatic venous portal gradient, both by reducing portal blood flow and intrahepatic resistance. Nonselective beta-blockers and esophageal varices ligation have been the standard of care in esophageal varices' treatment. Currently, statins and carvedilol role in reducing portal pressure, preventing esophageal variceal bleeding, and other advanced liver disease complications seem to be promising.

**Key words:** Portal hypertension; Variceal bleeding; Nonselective beta-blockers; Carvedilol; Statins

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### INTRODUCTION

There is a consensus that the outcomes of patients with advanced chronic liver disease (ACLD) are consistently related to the success in reducing the hepatic venous pressure gradient (HVPG)<sup>[1,2]</sup>. From a clinical perspective, liver cirrhosis is classified into compensated, decompensated, and further decompensated stages, which have different prognostic implications. Patients in the compensated stage have an average survival of twelve years, while those in the decompensated phase have no more than two years<sup>[3]</sup>.

Current evidence has shown that the most fundamental driving force responsible for migration between stages (compensated to decompensated) is the degree of portal hypertension (PH), which, in practice, can be determined by the measurement of the hepatic venous pressure gradient<sup>[2]</sup>. Regarding pharmacological treatment, drugs that act by causing splanchnic vasoconstriction, such as nonselective beta-blockers (NSBBs; propranolol, nadolol, and carvedilol) are known to reduce HVPG and represent the mainstay in esophageal varices' treatment. However, whether these drugs could have effects beyond those classically described is unknown. Statins have emerged as promising drugs in the improvement of HVPG. The present review aims to address the current state of the art of beta-blockers and statins in portal hypertension management.

### BETA-BLOCKERS AND BLEEDING FROM ESOPHAGEAL VARICES IN CIRRHOSIS

The development of PH is a milestone in the natural history of chronic liver disease. It is responsible for clinical manifestations, such as variceal bleeding, that imposes a remarkable impact on these patients' morbidity and mortality<sup>[4]</sup>. At the time of diagnosis, 30% to 40% of cirrhotic patients have esophageal varices, and the risk of bleeding from small esophageal varices is about 5% a year, increasing to 15% whether it is from large-caliber varices. Esophageal varices

are responsible for 80% of acute upper gastrointestinal bleeding in cirrhotic patients<sup>[4,5]</sup>. Unless adequate preventive measures are implemented, the recurrence rate of bleeding can reach up to 65% of patients, being the mortality rate of this complication still high, around 15% to 20%, increasing to 57% from the second bleeding<sup>[4,6]</sup>.

Studies have shown that increased intrahepatic vascular resistance is the initial determining factor for PH. Functional and structural factors are responsible for the rise in vascular resistance. The development of intrahepatic fibrosis and the presence of regenerative nodules cause the distortion and compression of the venous system, which leads to the increment in the resistance of portal venous flow. The increase in resistance to sinusoidal intrahepatic portal venous flow occurs due to architectural distortion caused by the deposition of extracellular matrix and endothelial dysfunction. As in any vascular territory, according to Ohm's law, portal pressure increment can be caused by the rise in resistance of venous flow or a higher venous flow. In cirrhosis, both changes can occur.

The hepatic fibrogenesis is characterized by excessive deposition of proteins in the extracellular matrix, including type I and III collagen and fibronectin. Liver stellate cells (LSC) are primarily responsible for this process. During liver injury by different agents, quiescent stellate cells acquire an activated phenotype that produces proteins in the extracellular matrix. The transforming growth factor beta-1 (TGF $\beta$ 1), one of the most potent profibrogenic cytokines in the liver, promotes the synthesis of extracellular matrix proteins by LSC. Multiple pathways are involved in transduction via TGF $\beta$ 1.

Moreover, the increase in vascular resistance leads to an increase in portal venous flow due to splanchnic vasodilation. In advanced liver disease, the imbalance between endothelial vasodilating and vasoconstrictor substances causes systemic vasodilation. Furthermore, neurohumoral systems are activated, leading to a hyperdynamic circulatory state. The persistent increment in portal pressure is further transmitted to the portosystemic anastomosis, with a subsequent deviation of the portal blood flow, forming the so-called portosystemic shunt.

Measures that decrease portal pressure are related to better outcomes, lower the risk of decompensation and mortality. Thus, methods that measure portal pressure are useful as prognostic markers. The measurement of hepatic portal perfusion corresponds to the pressure gradient between the portal vein and the inferior vena cava and varies between 1 to 5 mmHg. An HVPG above 5 mmHg demonstrates portal hypertension, and when it reaches 10 mmHg, it is called clinically significant portal hypertension (CSPH). CSPH is characterized by the occurrence of splenomegaly, thrombocytopenia, portosystemic collaterals, esophageal varices, and increased risk of decompensation and development of hepatocellular carcinoma. The measurement of HVPG is done by invasive technique, limiting its performance to protocols<sup>[7]</sup>.

The rupture of esophageal varices usually occurs when the HVPG is above 12 mmHg, and whether the variceal bleeding occurs in a patient with a gradient above 20 mmHg, there is a higher rate of therapeutic failure, rebleeding, and mortality. Therapeutic measures that reduce portal pressure to values ideally below 12 mmHg or at least a 20% reduction in baseline portal pressure have been shown to reduce the bleeding rate in more advanced cirrhosis stages. With this objective in mind, for almost forty years, the use of NSBBs such as propranolol and nadolol has positively impacted the prophylactic treatment of variceal bleeding thanks to the blockade of  $\beta$ 1 adrenergic receptors, resulting in decreased cardiac output and the blockade of  $\beta$ 2 receptors, generating vasoconstriction in the splanchnic territory.

Recently, carvedilol, a potent NSBB with mild antagonist activity

at alpha-1-adrenergic receptors, has been used in cirrhotic patients with high-risk variceal bleeding. The additional action generates a decrease in intrahepatic vascular resistance, leading to an even more significant drop in the HVPG than propranolol. Studies demonstrate that beta-blockers such as propranolol and nadolol effectively reduce HVPG in only 35% to 40% of treated patients. Conversely, carvedilol, even at a low dose (e.g., 12.5 mg daily), can reduce HVPG to values below 12 mmHg or a 20% reduction in baseline pressure in about 60% of patients<sup>[8]</sup>. Interestingly, in a study using sequential treatment with invasive measurement of HVPG, carvedilol reduced it in 56% of patients who did not respond to propranolol<sup>[9]</sup>. There was no significant difference between pharmacological treatments concerning side effects. In a randomized trial, with cirrhotic patients with low-risk esophageal varices, that evaluate the prevention of progression from small to large caliber varicose veins, the so-called early primary prophylaxis, comparing carvedilol with placebo showed a benefit of non-progression in the treated group (80% versus 64.3%;  $p < 0.04$ ), despite a slight reduction in GPVH (<10%) over a 24-month follow-up period<sup>[4]</sup>. Thus, in the compensated phase of cirrhosis, slight reductions in portal pressure have already been shown to be beneficial during carvedilol use. Other effects of this drug, such as the hepatic antifibrotic effect, have previously been demonstrated and could explain the decrease in ascites development and a reduction in long-term mortality<sup>[10-12]</sup>. This benefit has not been found in studies with traditional beta-blockers.

Several studies have demonstrated the similar effectiveness of NSBB use and esophageal variceal ligation (EVL) in variceal primary prophylaxis of variceal hemorrhage<sup>[13,14]</sup>. Besides that, the advantageous use of beta-blockers due to the lower occurrence of other complications associated with portal hypertension, mainly ascites<sup>[15]</sup>, is associated with the reduction of bacterial translocation and subsequent spontaneous bacterial peritonitis, making it an interestingly choice for primary prophylaxis. Conversely, in the secondary prophylaxis of variceal bleeding, several studies reported that the association of EVL with pharmacological treatment, either propranolol or carvedilol, also improve the response to eradicating varices and reducing the rate of rebleeding<sup>[13]</sup>. Nevertheless, no statistical difference in the rate of side effects, bleeding-related mortality, or overall mortality was observed. The current formal consensus for secondary prophylaxis recommends the association of EVL with propranolol.

It should be noted that the association of EVL with carvedilol in secondary prophylaxis may be harmful in a subgroup of patients with more advanced disease, renal dysfunction, and arterial hypotension<sup>[16]</sup>. Studies are still controversial regarding beta-blockers' effect on renal function in patients with refractory ascites, spontaneous bacterial peritonitis, and other infectious complications. Indeed, in this setting, there is an exacerbation of the hyperdynamic circulatory condition with a drop in mean arterial pressure, forcing the suspension or reduction of the dose of beta-blockers, at least transiently until clinical recovery occurs. New non-invasive methods, especially hepatic elastography and, more recently, splenic elastography for monitoring the hemodynamic response of these patients may facilitate the performance of long-term studies with a larger patient population. Splenic elastography has a higher correlation with portal hypertension than hepatic elastography<sup>[7,17-19]</sup>. It is believed that the measurement of splenic stiffness is directly related to portal hypertension and is highly accurate as a non-invasive method for the diagnosis of esophageal varices, especially in those at high risk of bleeding is more precise to hemodynamic changes in the course of liver disease.

Thus, additional studies are needed to refine decisions such as the best time to introduce drug therapy, which drug would be most recommended, confirmation of the accuracy of non-invasive methods to assess the drug response and its cutoff points for reducing portal pressure, and significant change in the natural history of the cirrhotic patient. Table 1 shows the suggestion for beta-blockers' use to prevent variceal bleeding in portal hypertension due to liver cirrhosis.

## ROLE OF NSBBS: BEYOND ESOPHAGEAL VARICES

The development of CSPH is a cornerstone of cirrhosis's natural history and is strongly related to morbidity and mortality in these patients. An important strategy to reduce the risk of decompensation is the elimination of the offending agent. Studies have demonstrated that patients with HCV cirrhosis treated with a direct-acting antiviral drug (DAA) recover liver function, reduce portal pressure, and get off from the liver transplant list<sup>[20]</sup>. Moreover, patients with alcoholic liver disease who obtain alcohol abstinence can reduce portal pressure and improve liver function<sup>[21]</sup>.

NSBBs are effective drugs in reducing the portal pressure, and their use has been fully established in primary and secondary prophylaxis of variceal bleeding since the 1990s, as previously explained. In patients with CSPH, NSBBs reduce portal pressure by reducing portal blood flow, which is increased due to hyperdynamic circulation in this phase of the disease. This mechanism is not relevant in patients without CSPH, in which the driving force of PH is the increase of vascular resistance.

Since most complications that arise during the natural history of liver cirrhosis occur when the degree of PH reaches clinically significant levels ( $> 10$  mmHg), it is logical to infer that the decrease in HVPG below this critical limits can reduce the onset of all complications related to PH and not only variceal bleeding. Thus, it would be possible to keep the patient compensated and prolong their survival. However, patients with CSPH are not the same concerning the risk of decompensation. Patients with CSPH without varices or small varices have a lower risk of decompensation than those with CSPH and high-risk varices<sup>[22]</sup>. When the measurement of HVPG is not available in clinical practice, transient liver stiffness can identify patients with CSPH. Values below 13.6 kPa rule out CSPH while levels above 20-25 kPa strongly suggest the presence of CSPH and risk of decompensation<sup>[23]</sup>. Although rational, this hypothesis had never been tested in a well-designed trial.

Groszmann *et al.* failed to demonstrate a reduced risk of varices bleeding in 79 cirrhotic patients without CSPH (HVPG between 5 and 10 mmHg) who used timolol. Probably, the low risk of decompensation in this group and the primary mechanism of portal hypertension in this phase of the disease, not susceptible to the NSBB's action, justifies the failure<sup>[24]</sup>. Hernandez-Gea, in 2012 included 83 patients without previous decompensation, with large esophageal varices and HVPG  $\geq 12$  mmHg and treated with nadolol after hemodynamic evaluation. During 53 months of follow-up, decompensation occurred in 62%, being ascites present in 81% of these cases. Patients with an HVPG decrease  $\geq 10\%$  had a lower probability of developing ascites (19% vs. 57% at 3 years,  $p < 0.001$ ), refractory ascites ( $p = 0.007$ ), and hepatorenal syndrome ( $p = 0.027$ )<sup>[25]</sup>.

The recently published PRESDECI study included patients with compensated liver cirrhosis to verify whether long-term use of NSBBs can prevent disease progression toward clinical decompensation and death. This multicenter, randomized, placebo-controlled, and double-

blind study included patients with compensated cirrhosis without high-risk varices (absence of varices or small-caliber varices without red spots) and CSPH proved by a hemodynamic study<sup>[15]</sup>. Responders to intravenous propranolol administration (reduction greater than 10% on HVPG) were randomized to receive either propranolol (40 to 160 mg twice daily) or placebo, and non-responders to intravenous propranolol received either carvedilol (maximum dose of 25 mg/day) or placebo. The primary outcomes evaluated were the development of decompensation (ascites development, gastrointestinal bleeding related to portal hypertension and hepatic encephalopathy) or death analyzed in the first and third months after randomization and then every six months. After 631 patients were initially selected, 101 were included in the placebo arm, and 100 received NSBBs (67 propranolol and 33 carvedilol). The mean follow-up time was 37 months, and decompensation or death was observed in 27% and 16% of patients in the placebo and NSBBs group, respectively (hazard ratio [HR] 0.51; 95% CI 0.26-0.97;  $p = 0.041$ ). The reduction in decompensation was mainly due to the decrease in ascites onset that occurred in 20% of patients in the placebo group and 9% of NSBBs users. The NSBB did not prevent progression to high-risk varices. In a post hoc analysis, the cumulative incidence of decompensation or death was lower in the group in which the HVPG reduction was greater than 10% compared to baseline values or reached values lower than 10mmHg at the end of one year. Furthermore, patients with acute hemodynamic response before treatment achieved the better results with lower decompensation rate (9% vs 29% at 1 year; hazard ratio [HR] 0.32; 95% CI 0.13-0.75;  $p = 0.0077$ ).

In the PREDESCI study, the reduction in portal pressure with carvedilol was higher than that with propranolol, and the prevention of primary outcomes was also higher in the carvedilol group. A possible explanation is that in compensated liver cirrhosis, the intrahepatic vascular resistance is a crucial mechanism of portal hypertension and carvedilol due to its intrinsic vasodilator action and increased release of nitric oxide on intrahepatic circulation seems to be more effective than propranolol. In patients with cirrhosis and CSPH with high-risk varices, a recent meta-analysis has shown that patients on primary prophylaxis with NSBB for variceal bleeding had lower all-cause mortality compared to patients undergoing EVL, suggesting that NSBBs are the drugs of choice in this group of patients<sup>[26]</sup>. Other studies have shown that patients with hemodynamic responses to NSBB (acute or chronic) prevent not only variceal bleeding but also reduce intestinal permeability and bacterial translocation, consequent SBP and, need for transplantation with improvement in survival<sup>[27,28]</sup>.

Therefore, in patients with compensated cirrhosis and CSPH without high-risk varices, the NSBBs increase decompensation-free survival, primarily by preventing ascites' onset. Although with a lower grade of evidence, this also seems to be true for patients with compensated cirrhosis and high-risk varices. In clinical practice, these relevant findings may, in a short time, represent a new indication for the use of NSBBs in cirrhotic patients, and possibly the carvedilol is the preferred drug in this scenario.

## STATINS AND PORTAL HYPERTENSION: HIGHLIGHTS FOR POTENTIAL USE

The pharmacological therapeutic options currently used in the treatment of PH, based on the use of beta-blockers, achieve the target hemodynamic response, *i.e.*, the reduction of HVPG, in little more than 50% of patients. Also, 15% of patients may have contraindications, and 15% do not tolerate NSBBs<sup>[29]</sup>. Therefore, it

is opportune to search for therapeutic alternatives that can improve the therapeutic efficacy in reducing HVPG and, consequently, the outcomes of patients with cirrhosis. Statins have emerged as a promising therapy, from studies demonstrating their role in hepatic microcirculation and the dynamic component of portal hypertension, besides possibly acting on inflammation and hepatic fibrosis<sup>[30]</sup>. One of the first experimental evidence in cirrhotic rats demonstrated that simvastatin improved hepatic endothelial dysfunction<sup>[31]</sup>. Based on this evidence, several studies have focused on evaluating the role of statins on PH.

The significant increase in hepatic vascular tone is an important and determining component of PH. This dynamic component of PH results from the imbalance secondary from the reduction of the concentration of vasodilator factors, mainly nitric oxide (NO), and an increase in vasoconstrictor factors, such as  $\alpha$ -adrenergic, endothelin-1, thromboxane A2 and renin-angiotensin system, in endothelial cells and Kupffer cells<sup>[30]</sup>. Statins seem to act on hepatic microcirculation, increasing the expression of nitric oxide synthetase (eNOS) and, consequently, the production of NO reducing vascular tone, the tendency to thrombosis and angiogenesis<sup>[31,32]</sup>. There is evidence that statins have antithrombotic effects and reduce oxidative stress and inflammation in the wall of intra-hepatic vessels<sup>[33]</sup>. Additionally, experimental studies in rats have documented that statins can deactivate hepatic stellate cells (HSCs), reducing fibrogenesis and, consequently, hepatic fibrosis. In liver cells, simvastatin is the most effective statin upregulating factor Kruppel-like factor 2 (KLF2) and promotes the deactivation of HSCs and the improvement in endothelial cells functionality<sup>[34,35]</sup> (Table 2).

The first prospective controlled randomized phase II study on the effects of statins in the PH of ACLD patients was conducted by Abraldes and colleagues. Oral simvastatin was used for 30 days at a 20 mg dose, progressing to 40 mg/d according to tolerance<sup>[36]</sup>. The results showed that simvastatin led to a significant reduction in HVPG compared to the placebo group, with no reduction in hepatic blood flow, suggesting that simvastatin acts by reducing hepatic vascular resistance. There was a significant increase in indocyanine green clearance, suggesting that simvastatin increases effective liver perfusion and improves liver function. (Table 3). The group that used simvastatin showed an average reduction of 8.3% in HVPG, an effect of moderate magnitude, but independent of concomitant use of NSBBs. It was verified that a greater number of patients in the treatment group reached the target hemodynamic response, which would be the reduction in HVPG of at least 20% of baseline values. Noteworthy, no effects on systemic hemodynamics nor increased adverse events were observed in the group treated with simvastatin, demonstrating that it was well tolerated. In another clinical study, with prolonged use of simvastatin for three months, it also was demonstrated a reduction in HVPG mainly in patients with previous variceal bleeding and medium/large varices<sup>[37]</sup>.

Abraldes and colleagues, based on previous evidence that simvastatin reduces portal pressure and improves hepatocellular function, assessed whether adding simvastatin to standard therapy could reduce rebleeding and death after variceal bleeding in cirrhotic patients<sup>[38]</sup>. The researchers then performed a multicenter, double-blind trial of 158 patients with cirrhosis receiving standard prophylaxis to prevent rebleeding (a beta-blocker and band ligation). The primary endpoint was a combination of death and rebleeding, while the secondary endpoint was these two components separately. The intention-to-treat analysis included 78 patients in the standard prophylaxis and 69 patients in the standard prophylaxis plus simvastatin arm (20 mg/day the first 15 days, 40 mg/day after that).

**Table 1** Indication of beta-blockers in the prophylaxis of variceal bleeding in cirrhosis.

	Early primary prophylaxis *	Primary prophylaxis	Secondary prophylaxis
Objective: reduction in HGPV	10% of baseline		20% of baseline or < 12 mmHg
Treatment	Carvedilol	Carvedilol or Propranolol or Endoscopic variceal ligation	Propranolol and endoscopic variceal ligation

\*Early primary prophylaxis defined as prophylaxis in patients with small varices. Initial dose of carvedilol: 6.25 mg per day. Maximum dose: 12.5 mg per day. Initial dose of propranolol: 20 mg twice a day. Maximum dose 320mg per day.

**Table 2** Potential benefits of statins in portal hypertension in cirrhosis.

Hepatic microcirculation	↑Hepatic endothelial function
	↓ Hepatic vascular tonus
	↓ Thrombogenesis
Liver function	↑ Hepatic blood flow
	↓ Inflammation
	↓ Oxidative stress
Fibrosis	↓ Hepatic fibrogenesis

**Table 3** Evidence for the effects of simvastatin in cirrhotic patients' with portal hypertension.

	Placebo (n=29)			Simvastatin (20→40 mg/dia) (n=30)		
	Baseline	4 weeks	p *	Baseline	4 weeks	p *
HVPG † (mmHg)	19.8 ± 3.8	19.4 ± 4.4	0.473	18.5 ± 7.2	17.1 ± 4.6	0.003
HBF ‡ (L/min)	939 ± 458	830 ± 339	0.109	1124 ± 548	1216 ± 676	0.44
ICG § clearance	237 ± 148	222 ± 129	0.436	221 ± 104	276 ± 182	0.017

† hepatic venous pressure gradient, ‡ hepatic blood flow, § Indocyanine green, \* p-value. Abraldes, Albillos *et al.*, Gastroenterology 2009; 136:1651-8.

No difference was observed either on the primary endpoint (38% versus 32%) or in rebleeding (28% versus 25%), after a mean follow-up period of 382 days in the standard group and 371 days in patients receiving simvastatin. Conversely, significantly lower mortality was observed in the simvastatin group (17/78 or 22% versus 6/69 or 9%,  $p = 0.03$ ), mostly in patients Child A and B. Of note, 2 patients with advanced cirrhosis (Child C) developed rhabdomyolysis, raising some concerns about the safety of statins in decompensated cirrhotic patients. This reduction in mortality is impressive because it occurred despite the lack of an expected rebleeding risk reduction. Because survival was not the study's primary endpoint, these results would require further validation in additional randomized controlled trials.

The effects of atorvastatin on PH have also been studied. Uschner *et al.* investigated atorvastatin's role in cirrhotic and noncirrhotic PH in an experimental study in rats. The investigators found that atorvastatin reduced portal pressure in cirrhotic rats attributable to significant decreased hepatic vascular resistance. Interestingly, the opposite effect on portal pressure was observed in noncirrhotic PH rats, leading to aggravating PH<sup>[39]</sup>. Supported in the hypothesis that statins potentially have beneficial effects on patients' outcomes, survival, and PH bleeding prevention<sup>[38,39]</sup>, Kimer and colleagues performed a two-center, randomized, double-blind placebo-controlled clinical trial with atorvastatin 10-20 mg daily<sup>[40]</sup>. This trial, which is still ongoing, was designed to include 18 months of treatment and up to 5 years of follow-up and investigate clinical endpoints of survival, hospitalizations, decompensation of liver cirrhosis, and time to decompensation, as also safety. Perspectives are that beneficial effects of atorvastatin on clinical outcomes in preventing disease progression and decompensation of cirrhosis will provide cost-benefit



and effective treatment for cirrhosis, inflammation, and fibrogenesis and not just symptom relief in decompensated liver disease<sup>[40]</sup>. The results are being awaited and may contribute to validate the findings of Abralde and colleagues.

It is essential to highlight that, in other clinical studies, although not prospective and/or controlled, statins have demonstrated beneficial effects in reducing fibrosis and progression to cirrhosis in patients with hepatitis C and sustained virological response after treatment. Likewise, in patients with compensated cirrhosis, statins have reduced the risk of decompensation and mortality<sup>[41,42]</sup>. Also, we cannot underestimate other possible desirable and protective effects, reduce steatosis and inflammation, and reduce cardiovascular risk, as additional therapy in patients with Non-Alcoholic Fatty Liver Disease (NAFLD)<sup>[43]</sup>. Moreover, statin has been associated with improved outcomes of patients with primary sclerosing cholangitis<sup>[44]</sup>. There are also scientific publications that, although the various effect concerning the etiology of cirrhosis may be considered, have shown a reduction in hepatic decompensation, including a reduction in the risk of developing hepatocarcinoma. (HCC)<sup>[45]</sup>. A systematic review of existing data on statin use and the risk of cirrhosis development as well as the occurrence of cirrhosis-related complications in patients with the chronic liver disease showed that there is a possible association between statin use and a lower risk of hepatic decompensation and mortality and that statins might reduce PH in these patients<sup>[46]</sup>.

After reviewing and understanding the evolution of evidence on statins in patients with cirrhosis, it is appropriate to check the leading international guidelines' statements. Baveno VI Consensus Conference states that statins' clinical use is promising and should be evaluated in other phases III studies<sup>[23]</sup>. Indeed, the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines for the management of patients with decompensated cirrhosis recommends that strategies based on decreasing inflammation (i.e., statins) and portal hypertension (i.e., beta-blockers) have shown potential benefit in reducing cirrhosis progression. However, further clinical research is needed to confirm if those strategies are safe and their potential benefits as therapeutic approaches for preventing cirrhosis progression in decompensated patients<sup>[47]</sup>. Finally, the American Association for the Study of Liver Diseases (AASLD) "Practice Guidance on Portal Hypertensive Bleeding in Cirrhosis" makes a point about that a conceptually more appealing approach to improving the functional component of PH is to use drugs that will reduce portal pressure by improving endothelial dysfunction, such as statins. The intrahepatic vasodilation caused by simvastatin can improve both hepatic blood flow and liver function. Besides, it also has antifibrotic properties. Use should be indicated mainly in patients in the earliest stage of compensated cirrhosis (patients with mild PH) when the treatment objective is to prevent the development of CSPH or decompensation. Although statins appear to have a beneficial effect at all cirrhosis stages, the specific phase associated with maximal benefit from statins remains to be determined. Then, AASLD suggests that it is necessary for future research<sup>[29]</sup>. Therefore, currently, there is no strong enough evidence for recommending statins for cirrhosis treatment<sup>[48]</sup>.

To date, it is essential to pay attention, during clinical consultation and evaluation of the patient with compensated chronic liver disease, about the prescription of statins when their use is indicated to treat metabolic or cardiovascular diseases. Future studies should focus on finding answers in critical points of statins' role in the treatment of portal hypertension and liver cirrhosis, given the promising horizons of their use.

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