Statin therapy: improving survival in patients with hepatocellular carcinoma and portal hypertension is possible?

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Abstract

Statins are generally known for their lipid-lowering properties and protection against cardiovascular events. However, growing evidence suggests that statins are a promising treatment for patients with chronic liver disease. Specifically, there is data supporting their role in reducing portal pressure and having a chemopreventive effect on hepatocellular carcinoma (HCC). Treatment options for HCC remain limited with portal hypertension (PH), thus statins could represent an inexpensive alternative, increasing survival of patients with HCC and PH. These drugs cannot be considered standard of care without a cardiac-metabolic indication to prescription in this patient group, although the potential beneficial effect should be indication for prompt use whenever considered appropriate. Our aim is to review the effects of statins on PH and on HCC, both in the pre-clinical and clinical setting in literature, discussing safety issues and limitations to the current body of evidence.(Acta gastroenterol. belg., **2024,** 87, **395-402**.

Keywords: chemoprevention, hepatic venous portal gradient, cardiovascular events.

List of abbreviations: LT: liver transplantation, MASLD: metabolic dysfunction-associated steatotic liver disease, MACE: major adverse cardiovascular events, HCC: hepatocellular carcinoma, MELD: Model for End-Stage Disease, HVPG: hepatic venous portal gradient, PH: portal hypertension, RCT: Randomized Controlled Trial, RR: risk ratio, TACE: trans-arterial chemoembolization, TAE: trans-arterial embolization, NSSB: non-selective beta-blocker, PCSK9: proprotein convertase subtilisin/kexin type 9.

Introduction

Statins are the most common lipid-lowering drugs by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase and considered a cornerstone treatment in primary and secondary prevention of major adverse cardiovascular events (MACE) (1). It is estimated that about 25% of adults over 40 are prescribed a statin (2). Besides the effect on lipid levels, pleiotropic effects of statins have been reported to be responsible for improving survival in patients with MACE (3), prompting the idea of their possible utility in other chronic diseases. Indeed, growing evidence, both in pre-clinical (4,5) and clinical settings (6,7) have recognized statins as a promising treatment for patients with chronic liver disease. These positive effects range from improved hepatic sinusoidal endothelial function with reduced intrahepatic vascular tone and portal pressure, to decreased fibrogenesis (8). Furthermore, epidemiological studies in large cohorts have shown a protective effect of statins, reducing the rate of development and progression of hepatocellular carcinoma (HCC), resulting in improved survival (9,10). Given that curative options for HCC remain limited and that portal hypertension (PH) may be a possible barrier to their implementation, statins could represent an inexpensive approach to increase the survival of patients with HCC and PH, in patients who are eligible and can tolerate these drugs (11). Despite widespread use of statins, a relatively high rate (around 10%) (12) of discontinuation of therapy has been observed, mainly due to side effects such as muscle symptoms, from muscle pain to rhabdomyolysis, or elevation in liver enzymes. These adverse effects, which are often dose dependent, have frequently caused patients with liver disease to be inadequately treated with these drugs due to safety concerns (13). In this review we analyze the current literature, both in pre-clinical and clinical setting, on the effect of statins on PH and in HCC. Additionally, we discuss safety issues and limitations of current evidence of these drugs in this setting.

Evidence supporting the effects of statins on PH

Some evidence has suggested a beneficial effect of statins in chronic liver disease, mainly attributed to their pleiotropic effects, namely: anti-inflammatory, anti-oxidative, and anti-proliferative properties, responsible for the improvement of endothelial dysfunction, and the promotion of neo-angiogenesis (14,15). The principal mechanisms considered responsible for the beneficial effect of statins on portal hypertension are summarized in Figure 1.

In the early 2000s, pre-clinical studies demonstrated that in endothelial cells of the hepatic sinusoids, simvastatin leads to an up-regulation of endothelial nitric oxide synthase, promoting the production of nitric oxide, which results in a reduction of vascular tone and hepatic resistance both in rat models (4) and in 13 patients

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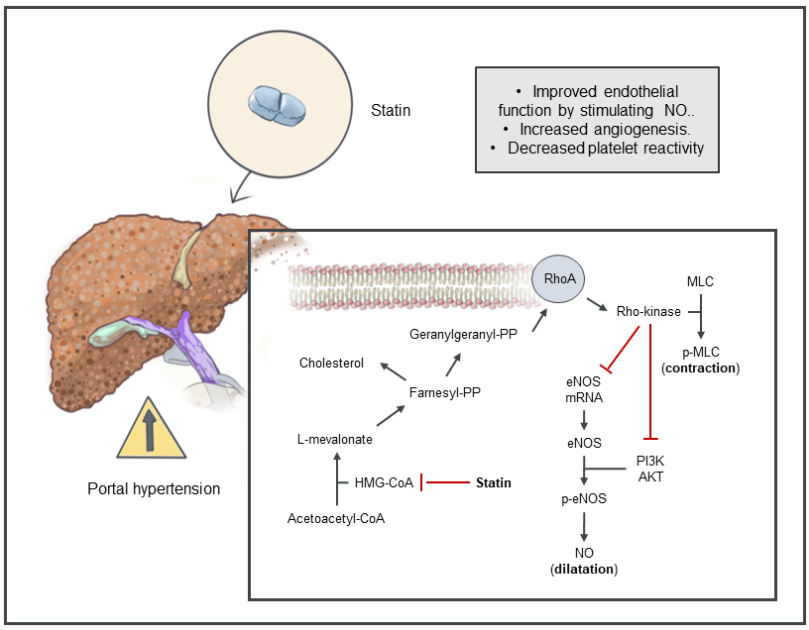


Figure 1. — The mechanism underlined to the pleiotropic effect of statins in chronic liver disease.

with cirrhosis (16). In 2009, these studies provided the foundation for the first proof-of-concept randomized controlled trial (RCT), in which Abraldes *et al.* evaluated the effects of administering simvastatin on hepatic venous pressure gradient (HVPG) and its safety in patients with cirrhosis complicated by PH. In this double-blind randomized study, fifty-nine patients with cirrhosis and PH (HVPG > 12 mmHg) were given either 20 mg/day of simvastatin or placebo for one month. Simvastatin significantly reduced HVPG from 18.5 ± 7.2 to 17.1 ± 4.6 mmHg ($p = 0.003$); in particular, in 32% of subjects, it led to a reduction of HVPG by 20% compared to baseline, or less than 12 mmHg (17). In the following years, further RCTs confirmed these findings. Pollo-Flores *et al.* demonstrated that 55% of patients with cirrhosis and PH, treated with 40 mg/day of simvastatin for three months, achieved a significant reduction in HVPG. Furthermore, they observed a slight improvement in liver function as assessed by the Child-Pugh score (6.6 vs 6.2; $p = 0.08$), although not statistically significant (18). These results prompted the BLEPS trial in 2010, the largest double-blind, multicenter, randomized study conducted in Spain, investigating the protective effects of simvastatin on rebleeding and mortality in patients with cirrhosis after variceal bleeding. One hundred and fifty-eight patients with variceal bleeding were randomly assigned to receive either the standard of care therapy (non-selective beta-blocker [NSBB] and endoscopic variceal ligation) or the standard of care therapy and 20 mg/day of simvastatin. The treatment did not show a reduction in the risk of rebleeding, which occurred in approximately 50% in both groups, nor did it reduce other complications of cirrhosis (infections, progression of liver disease). However, it increased survival in Child-Pugh A and B score, but not in Child-Pugh C score patients (19).

Lipophilic statins, such as simvastatin and atorvastatin, are the mainly studied in cirrhosis, since their beneficial effect has been demonstrated to be cumulative with NSBB (15, 20). In a small RCT, Bishnu *et al.* found that treatment with atorvastatin for one month in addition to propranolol, compared to propranolol alone, resulted in a greater reduction in HVPG. The hemodynamic target of a 20% decrease in HVPG from the baseline or less than 12 mmHg was achieved in up to 90% of patients, which is higher than the percentages reported by Abraldes *et al*. However, no significant differences were observed in cirrhosis complications and mortality at one-year follow-up (21). In contrast to this data, in the prospective randomized study by Vijayaraghavan *et al*, three-month therapy with simvastatin and carvedilol did not lead to a greater reduction in HVPG in patients with cirrhosis and PH, and no correlation with a lower risk of variceal bleeding (22). This is the only trial that fails to demonstrate the effectiveness of statins in reducing PH, which might be related to the use of the combination of simvastatin with carvedilol, which is a more potent beta-blocker in reducing HVPG. Interestingly, a trial in India involving one hundred and two patients investigated the sequential use of simvastatin in patients with cirrhosis and PH who did not respond to carvedilol evaluated by a reduction in the HVPG. Sixty-four patients (63%) were carvedilol-responders, while the remaining patients received simvastatin for one month, resulting in a reduction of HVPG in 16 subjects. This led to an overall response to carvedilol plus statin of 79% vs. 63% with carvedilol alone (23).

In conclusion, statins have been proven to be effective in reducing portal pressure in patients with cirrhosis, as evidenced by the majority of RCTs conducted to date (Table 1), including the meta-analyses (23,24). Therefore,

Table 1. — **Summary of the studies evaluating the effect of statins in patients with PH**

Author	Year	Comparison groups	Number of patients	Endpoint	Outcome
Abraldes et al. (17)	2009	Simvastatin vs. placebo	27 vs. 28	Change in HVPG	HVPG decreased in simvastatin group from 18.5 ± 7.2 to 17.1 ± 4.6 mmHg; p = 0.003.
Pollo-Flores et al. (18)	2015	Simvastatin vs. placebo	14 vs. 20	Change in HVPG	HVPG decreased in simvastatin vs placebo: -2 vs 0 mmHg; p = 0.02.
Abraldes et al. (19)	2016	Simvastatin vs. placebo	69 vs.78	Composite endpoint (rebleeding or death), death	Non-significant decrease in risk of rebleeding or death. Simvastatin decreased mortality HR = 0.39; p = 0.030
Wani et al (23)	2017	Carvedilol vs. Carvedilol + Simvastatin (in carvedilol non-responders)	101 vs. 35	Change in HVPG	HVPG decreased 62% in carvedilol and 16% in carvedilol + simvastatin (carvedilol non responders)
Bishnu et al. (21)	2018	Atorvastatin + Propanolol vs. Propanolol	11 vs. 12	Change in HVPG	HVPG decreased in atorvastatin + propranolol vs. propanolol: 4.81±2.82 vs. 2.58±1.88 mmHg; p = 0.041.
Vijayaraghavan et al. (22)	2020	Carvedilol vs. Carvedilol + Simvastatin	110 vs. 110	Change in HVPG	HVPG decreased in carvedilol vs. carvedilol + simvastatin: 2.95 vs. 3.15 mmHg; p = 0.98.

Abbreviations: HVPG: Hepatic venous pressure gradient; HR: Hazard ratio.

Table 2. — **Summary of the studies evaluating the effect of statins in patients with HCC**

Author	Year	Comparison groups	Number of patients	Endpoint	Outcome
Graf et al. (39)	2008	TACE + pravastatin vs. TACE	131 vs. 53	OS	Median OS improved in pravastatin group (20.9 vs 12 months; p = 0.003)
Kawata et al. (40)	2001	Pravastatin vs. placebo after TAE + 5-FU	41 vs.42	Death	Median OS was 18 months in the pravastatin group vs 9 months in controls (p = 0.006)
Jouve et al. (41)	2019	Pravastatin + sorafenib vs. sorafenib in Child-Pugh A cirrhosis	162 vs. 161	OS	Median OS was no different in the two groups (10.7 *vs* 10.5 months; p = 0.975)
Blanc et al. (42)	2020	Sorafenib vs. pravastatin vs. pravastatin + sorafenib vs. best supportive care in Chid-Pugh B cirrhosis	41 vs. 40 vs. 40 vs. 39	TTP and OS	Median TTP was no different in the four groups (3.5 vs 2.8 vs 2.0 vs 2.2 months). No difference in the median OS (3.8 vs 3.1 vs 4.0 vs 3.5 months).
Riano et al. (43)	2020	Sorafenib + pravastin vs. sorafenib	15 vs.17	TTP and OS	Median OS was no different in the two groups (12.4 vs 11.6 months; p = 0.967). Median TTP was longer in the sorafenib + pravastatin group (9.9 vs 3.2 months; p = 0.008)

Abbreviations: OS: overall survival; TTP: time to progression; TACE: transarterial chemo-emobolization; TAE: transarterial chemo-emobolization; 5-FU: 5-fluoruracil.

statins may represent a promising disease-modifying agent in cirrhosis, particularly in the compensated stage of the disease (25). Statin use is certainly well-established in the metabolic dysfunction-associated steatotic liver disease (MASLD), as the treatment of dyslipidemia represents a key aspect in controlling metabolic risk factors (26), whereas the effect may be more nuanced in presence of other etiologies. However, there seems to be room for statin treatment regardless of the etiology of cirrhosis in patients with PH, as also suggested by the recent Baveno VII guidelines (27).

Evidence supporting the effects of statins on HCC

HCC is a leading cause of tumor-related morbidity and mortality worldwide, and its incidence has increased in the last decades (28,29). Statins have often been advocated as a potential chemo-preventive agent. This was attributed to a dual mechanism. First, through the reduction of LDL cholesterol, which is necessary for the synthesis of the neoplastic cell membrane and therefore tumor proliferation (30), but, more importantly, because of their pleiotropic effects. By inhibiting the mevalonate pathway and the prenylation of proteins such as Ras and RhoA GTPases, statins exert apoptotic, antiangiogenic, anti-inflammatory, and antimetastatic properties (31). Statins can also modulate the tumor micro-environment by promoting the activity of natural killer cells and inducing a shift from M2 to M1 macrophages. Tumor-associated macrophages are also influenced by statin treatment (31).

The use of statins in chemoprevention

From a clinical perspective, several retrospective studies have investigated the impact of statin exposure in preventing HCC occurrence. An observational case-control study conducted on a large cohort of patients with diabetes and HCC demonstrated that exposure to any type of statins is associated with a 25% reduction in the risk of HCC in adjusted analyses (32). In a large cohort of veterans with chronic hepatitis C undergoing Peg-interferon based treatment, the addition of statins correlated with a significant reduction in the progression of liver fibrosis to cirrhosis and a decrease in the incidence of HCC (33). Notably, atorvastatin and fluvastatin were associated with the most significant antifibrotic effects, compared with other statins (10). Similarly, the incidence of HCC was reduced by up to 32% in hepatitis B positive patients taking statins in the Asian population study by Hsiang *et al*., and this incidence was further reduced when statins were taken in conjunction with nucleoside analogs (34). This data is confirmed by several meta-analyses (35-38), suggesting the beneficial role of statins, especially lipophilic ones, in preventing HCC and improving outcomes. However, these studies have several limitations, as they are retrospective studies characterized by a wide heterogeneity of the cohort, etiology and different stages of liver disease, with limited information regarding any antiviral drugs taken, making them difficult for objective comparison.

The use of statin in patients diagnosed with HCC

Data regarding the use of statins in patients diagnosed with HCC seems less favorable. In 2008, an RCT conducted by Graf *et al*. demonstrated that trans-arterial chemoembolization (TACE) combined with pravastatin improves survival in patients with unresectable HCC. One hundred and eighty-three HCC patients were randomized to receive TACE alone or TACE combined with pravastatin (20-40 mg/day). The 5-year survival rate was 23% in the group treated with TACE alone and 36% in the group treated with TACE and pravastatin, showing a significant improvement in the overall survival (39). These results are similar to those of a previous Japanese RCT, where pravastatin was shown to increase survival in patients with advanced HCC undergoing trans-arterial embolization (TAE), followed by oral 5-fluoruacil for two months, and then randomized to receive pravastatin or placebo (40). Three RCTs have studied the use of statin in combination with sorafenib in advanced HCC. In the PRODIGE-11 trial, the authors compared Child-Pugh A naive to systemic treatment, patients receiving sorafenib plus pravastatin vs. patients receiving sorafenib alone. Following a median follow-up of 35 months no difference in median overall survival between the two arms was observed (hazard ratio 1.00; p = 0.975) (41). These results were also confirmed by the PRODIGE-21 trial conducted in HCC patients with Child-Pugh B cirrhosis (42). In patients not eligible for LT, four study arms were compared, sorafenib; pravastatin; sorafenib-pravastatin combination; palliative care, with primary endpoint considered being time to progression. No difference was found among the four arms, but accounting for the fact that half of patient deceased without radiological progression. The authors had to conclude that neither sorafenib nor pravastatin provided benefit to patients in Child-Pugh B class (42). Riano *et al.* studied the efficacy and safety of the combination of sorafenib and pravastatin in advanced HCC in 31 patients. Overall survival was similar in the two groups, with 12.4 months survival in the sorafenib combined with pravastatin group versus 11.6 months in the sorafenib group (p=0.967). The first group had a longer time to progression (43). Considering retrospective studies, in a metanalysis including nine studies, statin use was associated with a reduced all-cause mortality in patients with HCC (risk ratio (RR): 0.81, 95% CI: 0.74-0.88, $P < 0.001$; $I^2 = 63\%$). This was accurate for patients with intermediate stage of HCC and following palliative care (RR: 0.83, $P < 0.01$ and RR: 0.80, $P < 0.001$, respectively), but not following curative treatment (RR: 0.92, $P = 0.20$). However, in patients exposed to statins after curative therapies the RR for HCC recurrence was 0.55 ($p < 0.001$) (38). The studies available on statins in patients with HCC are summarized in Table 2.

Considering the changing in HCC treatment with immunotherapy (44), the association with statins will probably deserve evaluation in prospective studies. Indeed, a recent viewpoint article published in 2022 postulated that statins may improve the efficacy of immune checkpoint inhibitor therapy in patients with cancer, based on preclinical evidence (45) and evidence coming from the field of lung cancer seems to suggest that statin use positively correlates with performance status and overall survival in lung cancer patient treated with immunotherapy (46). Another study in renal cell cancer treated with Nivolumab found an overall clinical benefit in statin users than non-users (71% versus 54%, p = 0.030) (47). However, to our knowledge, there are no studies regarding the use of statins in combination with chemo-immunotherapeutics or other therapeutic approaches in HCC.

In the scenario of best supportive care, an interesting retrospective study including 20.200 HCC patients deemed for palliative care, the administration of statins was associated with lower HCC-specific death rates in all HCC-stages (relative risk (RR) = 0.763 (p = 0.0001), 0.775 (p=0.0002), 0.839 (p=0.0012), and 0.718 (p=0.0002), for stages I to IV, respectively) (11).

The potential benefit of statin use has been demonstrated in other important hepatology settings. Although data is not always consistent, statins use in the post-LT setting has been associated with a reduced risk of post-LT HCC recurrence (48,49) and cancer-related mortality (50).

In summary, the available data suggest that statin therapy is associated with reduced incidence of HCC and may reap benefits also in patients that already have the disease, and possibly even in the advanced stages. However, most of the positive results related to retrospective studies. Therefore, calibrated prospective randomized data is needed.

Safety issues and limitations

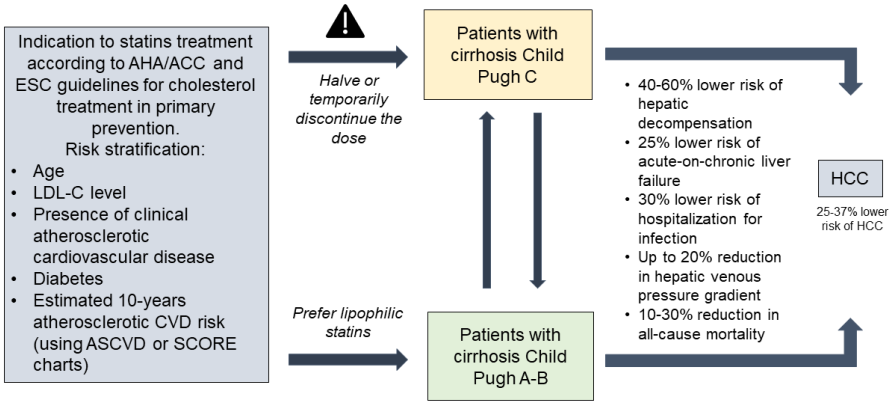
Despite the body of evidence supporting the beneficial effects of statins in PH and HCC, these drugs are still under-prescribed in this target population.

In the majority of countries statin prescription status is associated to cardiovascular and metabolic diseases, and the leaflet for those medications still places an alert on their use in patients with liver disease. This probably discourages their prescription in patients with cirrhosis even when indicated. It is estimated that among the patients evaluating for LT with coronary artery disease, only 23% were receiving statin therapy (13).

Despite the fact that there is probably an increased plasma concentration of statin in patients with cirrhosis Child-Pugh A and B compared to patients without (51), not a higher rate of liver-related side effects due to statins are reported. Safety data comes from the trials conducted by Munoz *et al.* (52) and the LIVERHOPE-SAFETY TRIAL (53). According to both studies, the use of 40 mg/day of simvastatin is more strongly associated with adverse effects like muscle damage and, in rare cases, rhabdomyolysis in decompensated cirrhotic patients with a Child-Pugh C score. However, there is no observed increased hepatotoxicity.

Another relevant issue is the interpretation of survival data from retrospective cohorts of oncology patients taking statins. Immortal-time bias and selection bias are advocated as possible explanations for the survival benefit derived from retrospective studies on cancer and statin exposure. In fact, when emulation trial analysis is adopted, the results obtained do not suggest a survival benefit (54). Hence, there is a need for clinical trials in the field. On the other hand, their design presents several challenges that need to be considered: sample size calculation, patient characteristics, statin type, dose, duration of exposure, and treatment discontinuation. While these aspects are less relevant when considering PH, in HCC they are a priority.

A new scenario has opened up in recent years regarding the treatment of HCC with the advent of immunotherapy in hepatology (55). However, these new therapies must contend with advancing liver disease and particularly PH, which may hinder access to curative or more effective treatment options. In the IMbrave 150 study, PH-bleeding events were more frequently observed with the combination bevacizumab/atezolizumab than with sorafenib (2.4% vs. 0.6%) (56), as shown by other studies (57,58), therefore targeting PH at the highest level is now considered a goal to start this combination therapy. Although there are no studies demonstrating statins can



Abbreviation: AHA: American Heart Association; ACC: American College of Cardiology; LDL-C: low-density lipid cholesterol; CVD: cardiovascular disease; ASCVD: atherosclerotic cardiovascular disease; HCC: hepatocellular carcinoma;

Figure 2. — Algorithm about the indications of the use of statins in patients with PH and HCC with reference to the AHA/ACC (2018) and ESC (2019) guidelines on treatment of dyslipidemia.

be considered disease modifiers so some patients with PH may fall within the eligibility criteria for systemic treatment, the added benefit conferred by this drug to patients with HCC cannot be excluded and statin use should be favored when indicated.

Perspectives and future research

Further clinical trials are essential to better delineate the optimal dosing, safety profile, and long-term effects of statin therapy in patients with chronic liver disease. These studies should also consider the potential statins side effects, such as liver and muscle-related toxicity. In this regard, certain polymorphisms in genes encoding enzymes involved in drug metabolism (such as CYP3A4 or SLCO1B1) can influence the plasma concentration of statins, potentially leading to differences in efficacy and risk of adverse effects (59). In patients who are intolerant to statins antibodies against proprotein convertase

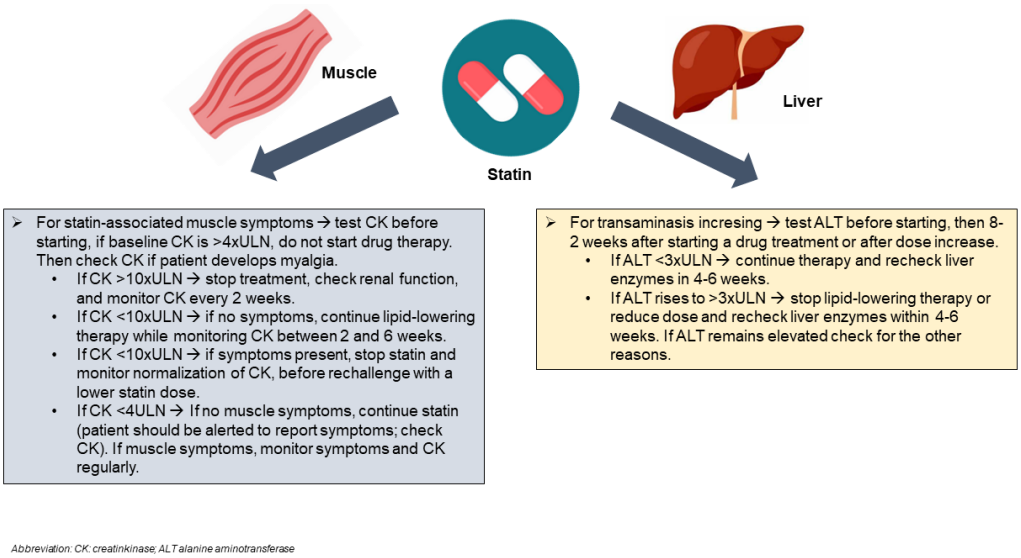


Figure 3. — Algorithm about monitoring for side effects while introducing statins therapy in patients with PH and HCC with reference to the AHA/ACC (2018) and ESC (2019) guidelines on treatment of dyslipidemia.

subtilisin/kexin type 9 (PCSK9) has been recognized as a potential therapeutic option to treat dyslipidemia. However, the pleoiotropic effect of this drug is still to demonstrate. Preclinical studies have demonstrated that PCSK9 expression increased in liver fibrosis and that anti-PCSK9 can alleviated liver injury (60,61). Nevertheless, a specific role in PH and chemoprevention has not yet been observed.

Also, it is of fundamental importance to examine the effects of statins in different subgroups of cirrhotic patients, such as those with different etiologies, stages of liver disease, and the presence of coexisting metabolic diseases. Additionally, further longitudinal studies are necessary to evaluate the long-term outcomes of statin use in cirrhotic patients, including overall survival, progression of liver disease, and quality of life.

Target PH in advanced HCC is of paramount importance in order to offer patients a therapeutic option. Allaire *et al.* recently demonstrated the unsuitability of Baveno VII criteria to rule out clinically significant PH in patients with HCC (62,63), posing additionally question on the non-invasive monitoring on candidates to immunotherapy. Recently, the first-line immune-based regimen of tremelimumab plus durvalumab, integrated in the American Association for the Study of Liver Diseases guidance document (64) has shown particular potential for patients with a high risk of gastrointestinal bleeding. Therefore, the potential synergistic effects of statins with other treatments for HCC, such as immunotherapies is a promising topic of research to be investigated further.

Conclusion

Statin use has demonstrated to confer promising beneficial effects in reducing portal pressure and as chemoprevention for HCC. Statins displayed a safety profile in cirrhosis, although a cautionary approach should be employed in patients with Child-Pugh C cirrhosis. It is premature to empirically recommend statins in this precise setting, given the lack of robust evidence. However, encouraging their use, as proposed by figure 2, whenever possible could have potentially positive effects overall (Figure 3).

Conflict of interest: none

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