We thus believe that the minor differences between the *Trim24*$^{ex4-/-}$ and *Trim24*$^{ex1-/-}$ mouse models are more likely accounted for by differences in genetic backgrounds of the mice and the ages at which gene expression was analyzed rather than the existence of Trim24 isoforms arising from the *Trim24*$^{ex4-/-}$ allele that were overlooked in our previous studies and for which we find no evidence.

Conflict of interest

The authors who have taken part in this letter to the editor declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Coagulation and fibrosis: A potential non-negligible target of statins in chronic hepatitis

To the Editor:

We read with interest the paper by Simon and colleagues demonstrating a reduced rate of fibrosis progression in HCV positive patients receiving a chronic treatment with statins [1]. This observation could be clinically relevant in a scenario where we have not effective antifibrotic drugs. It emerges alongside the growing agreement on the safety of statins in patients with liver disease, including cirrhosis [2]. Statins inhibit 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase and interfere with the "mevalonate pathway". As a result, they exert a complex modulation of anti-inflammatory and anti-proliferative properties of the endothelium. This also occurs at sinusoidal level where endothelial cells regulate the activation of hepatic stellate cells (HSCs) toward a myo-fibroblast phenotype [3]. The clinical results of Simon stimulated us to speculate on the mechanisms behind the antifibrotic effect of statins in chronic liver disease along with their ability to preserve the endothelial function.

Among the pleiotropic effects of statins, their anti-inflammatory properties have often been considered potentially useful in chronic liver diseases [4]. However, Simon unexpectedly showed that in his series statins reduced the rate of fibrosis independently from the reduction of the inflammatory activity index. As a consequence, the authors suggested that the effect of statins on liver histology was due to the ability of this class of drugs to improve the endothelial function rather than to reduce inflammation. In line with this hypothesis, Maieron *et al.* demonstrated that liver fibrosis at different stages of chronic HCV infection correlates with the plasma levels of von Willebrand factor (vWF), a marker of endothelial dysfunction involved in hemostasis [5]. Interestingly, some clinical studies observed that statins may reduce the plasma levels of vWF (Table 1). Unfortunately, the study by Simon *et al.* did not include the dosage of vWF, an assessment that would have been useful to confirm any interrelationships between endothelial dysfunction and fibrosis progression. In our opinion, the complex interaction between endothelium and HSCs could also be affected by the impairment of the coagulation function in patients with liver disease as suggested by different experimental observations [6]. First, thrombin *per se* can activate HSCs via PAR-1 and PAR-4 (protease-activated receptor) receptors promoting a myo-fibroblast phenotype. Second, the occurrence of micro-thrombi in small hepatic and portal venules can lead to sinusoidal ischemic injury and hepatocyte apoptosis, as proposed by the "parenchymal extinction theory". Third, antifibrotic effects have been obtained by anticoagulation in animal models and humans, with encouraging results. Statins can interfere with several of the mentioned mechanisms. First, they can decrease the expression of tissue factor, reducing thrombin formation [7]. Second, they can increase endothelial expression of thrombomodulin that converts thrombin into an anticoagulant enzyme through the activation of

Table 1. Clinical studies observed that statins may reduce the plasma levels of von Willebrand factor (vWF).

Reference	Type of study	Treatments	Time of treatment	Number of patients (pathology)	VWF pre treatment (%)	VWF post treatment (%)
Krysiak, 2010	OS	Simvastatin 20 mg/day	90 days	28 (IGT)	145.2 ± 9.7	104.2 ± 8.6
				28 (IH)	147.1 ± 10.1	103.1 ± 8.7
		Controls		28 (IH)	110.2 ± 8.3	106.4 ± 9.6
Joukhadar, 2000	RCT	Atorvastatin 10 mg/simvastatin 40 mg/pravastatin 40 mg	90 days	99 (IH)	124 ± 35	111 ± 40
Krysiak, 2011	RCT	Simvastatin 40 mg/day	90 days	24 (IH)	147.6 ± 11.2	106.0 ± 6.5
		Placebo		24 (IH)	145.3 ± 10.7	147.3 ± 9.1

RCT, randomized controlled study; OS, observational study; IGT, impaired glucose tolerance; IH, isolated hypercholesterolemia.

protein C anticoagulant system [7]. Third, plasma from patients treated with statins have a reduced ability to generate thrombin as demonstrated by Tripodi *et al.* in 51 patients suffering from hypercholesterolemia [8]. Interestingly, patients with non-alcoholic fatty liver disease, the liver expression of the metabolic syndrome, show a procoagulant imbalance when compared with healthy subjects [9]. Noteworthy, in this study, Simon included a significant proportion of patients with histologically proven steatosis. Therefore, a positive effect of statins on a procoagulant imbalance can be postulated also for most of the patients in this study.

In conclusion, coagulation can play a key role in the hepatic process of fibrogenesis as well as inflammation and necrosis. In this context, the statins' ability to modulate the coagulation cascade and the interplay between endothelium and HSCs could justify a significant antifibrotic effect. Accordingly, future studies should define more precisely the statins effects on coagulation in patients with chronic liver disease. We hope that statins, if not a remedy of all seasons [10], will represent a spring in the field of antifibrotic drugs.

Conflict of interest

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Authors' contributions

Concept and design: VLM; Drafting of the manuscript NB, VLM; Critical revision of the manuscript for major intellectual content: FS, AT; Supervision: VLM.

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