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# Avatrombopag, a new tool for the management of thrombocytopenia in patients undergoing medical procedures

## Original publication

Terrault N, Chen YC, Izumi N, Kayali Z, Mitrut P, Tak WY et al (2018) Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. Gastroenterology 155(3):705–718 (https://pubmed.ncbi.nlm.nih.gov/29778606/)

In two recent trials including patients with advanced chronic liver disease and severe thrombocytopenia, those receiving avatrombopag in advance showed higher platelet counts and less need for transfusion or rescue therapy on the procedure day compared with placebo recipients. The most frequent side effects were nausea, headache, fever, abdominal pain, fatigue, and edema.

In patients with advanced chronic liver disease (ACLD) complex changes in the hemostatic system occur, including modifications in the synthesis of pro- and anticoagulant proteins, alterations of fibrinolysis, and significant functional changes in platelets, as well as decreased numbers. Thrombocytopenia, i.e., platelet counts below $150 \times 10^9$/l, affects 64–84% of patients with cirrhosis and an estimated 1% of them have platelet counts $< 50 \times 10^9$/l [1, 2]. There is currently no clear evidence for the optimal platelet threshold that reduces the bleeding risk in patients with ACLD who undergo an invasive procedure. Although the clinical practice guidelines of several scientific societies advise ensuring a minimum of $30–50 \times 10^9$/l platelets before at-risk invasive procedures [3–5], other recent recommendations do not include any threshold and support an individualized approach to patients with severe thrombocytopenia before procedures [6]. A procedure is considered high risk if major bleeding is expected in >1.5% of patients or if even minor bleeding is likely to result in permanent organ damage or death (**Table 1**; [6]).

In patients with severe thrombocytopenia, a prudent risk assessment policy advocates taking appropriate measures before high-risk invasive procedures to potentially decrease bleeding and the use of blood-derived products in the peri-procedural period. Prophylactic and therapeutic options include platelet transfusions and exceptionally other measures such as splenic artery embolization, splenectomy, transjugular in-

**Table 1** High-risk procedures for bleeding

| | |
|---|---|
| Percutaneous | Biliary intervention (cholecystostomy or percutaneous biliary drain) |
| | Liver biopsy |
| | Tumor ablation |
| | Non-liver intra-abdominal solid-organ biopsy |
| | Intrathoracic organ biopsy |
| | Nephrostomy tube placement |
| | Central nervous system procedures |
| | Intra-ocular procedures/injections |
| | Intra-articular injections |
| Vascular | Transjugular intrahepatic portosystemic shunt |
| | Angiography or venography with intervention |
| | Transjugular liver biopsy |
| | Transhepatic arterial chemoembolization or radioembolization |
| | Therapeutic coronary angiography |
| Endoscopic | Endoscopic polypectomy |
| | Endoscopic stricture dilation or mucosal resection |
| | Balloon-assisted enteroscopy |
| | Percutaneous endoscopic gastrostomy placement |
| | Endoscopic retrograde cholangiopancreatography with sphincterotomy |
| | Sphincterotomy |
| | Endoscopic ultrasound with fine-needle aspiration |
| | Cysto-gastrostomy |
| | Therapeutic bronchoscopy or diagnostic bronchoscopy with biopsy |

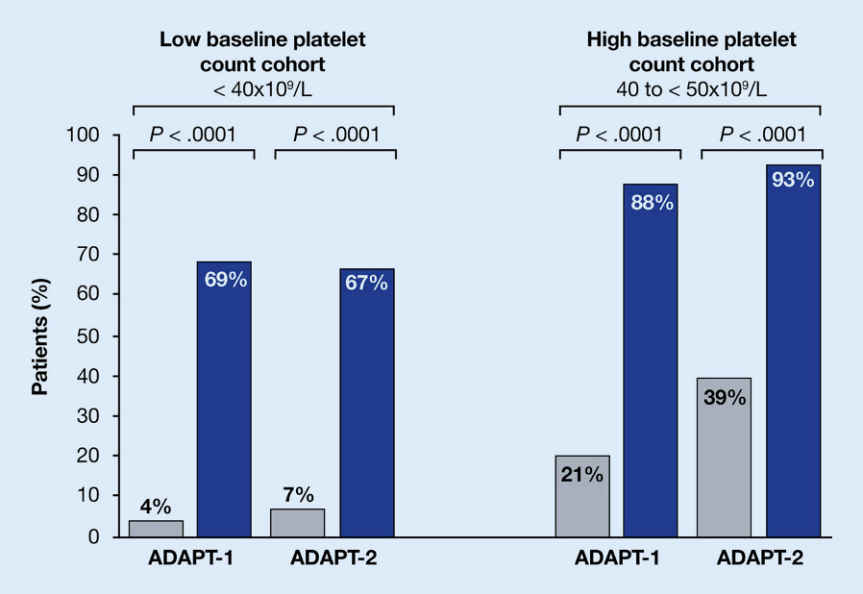


**Fig. 1** ▲ Proportion of patients not requiring a platelet transfusion or any rescue procedure for bleeding. (Reprinted from Terrault et al. [10], with permission from Elsevier. This figure is not included under the Creative Commons CC BY license of this publication.)

trahepatic portosystemic shunts, or medical treatments that may be prothrombotic such as recombinant activated factor VII or prothrombin complex concentrates.

Platelet transfusion has until recently been considered the treatment of choice to increase platelet number in patients with ACLD and severe thrombocytopenia undergoing high-risk procedures. Up to 10% of platelet concentrate recipients develop transfusion-related complications including fever, allergic reactions, transfusion purpura, infections, volume overload, and acute transfusion-associated lung injury. In patients with ACLD, the number of platelets at 10 min after transfusion increases by an average of only $12 \times 10^9$/l, in comparison with $30 \times 10^9$/l in non-cirrhotic patients. Moreover, the transfused platelets are eliminated much more rapidly, so that their hemostatic effect is marginal and lasts no more than 12 h [7]. As the volume of a platelet transfusion unit is around 250–300 ml and each 100 ml of plasma increases the portal pressure by an estimated 1.4 mm Hg in patients with cirrhosis, the transfusion of more than two platelet units could increase the circulating volume and portal pressure by more than 7 mm Hg, significantly increasing the risk of bleeding [8]. In addition to hemodilution, increased platelet destruction and splenic sequestration, in patients with ACLD, reduced hepatic synthesis of thrombopoietin, the main regulator of platelet production by megakaryocytes, also plays a relevant role in the pathophysiology of thrombocytopenia [9]. Therefore, owing to the limitations of platelet transfusion, the risks involved, and the relative scarcity of this component as a therapeutic resource, alternative options for procedural prophylaxis of thrombocytopenia in patients with ACLD are greatly needed.

Thrombopoietin receptor agonists (TPO-RA), including romiplostim, eltrombopag, avatrombopag, and lusutrombopag, promote the growth and differentiation of megakaryocytes and their precursors by mimicking the action of TPO.

The ADAPT-1 and ADAPT-2 trials examined avatrombopag versus placebo in a total of 435 patients with thrombocytopenia (platelets $\leq 50 \times 10^9$/l) and ACLD undergoing invasive procedures with a bleeding risk that would require a platelet transfusion [10]. The primary endpoint was the proportion of patients who did not require a platelet transfusion or rescue procedure for bleeding after randomization, and up to 7 days following the scheduled procedure. Patients were randomized 2:1 into two cohorts to receive avatrombopag or placebo according to their mean platelet count at baseline. Those with platelets $< 40 \times 10^9$/l received 60 mg avatrombopag once daily orally for 5 days, whereas patients with platelets 40 to $< 50 \times 10^9$/l received 40 mg for the same period. Platelet counts increased with a peak effect between days 10 and 13 and returned to baseline levels by day 35. The main results were that 67% of patients in the low baseline platelet count group and 88% of those in the high basal platelet count group achieved the primary endpoint, compared with 29% and 36% with placebo (**Fig. 1**). As a consequence of the personalized dosing scheme, only 1.1% of avatrombopag-treated patients achieved platelet counts $> 200 \times 10^9$/l, thereby avoiding the risk of thrombosis. Indeed, only one avatrombopag-treated patient (with a maximum platelet count below $100 \times 10^9$/l) developed portal vein thrombosis and two placebo-treated patients developed thromboembolic events. The overall safety profile was similar for avatrombopag and placebo and main side effects included abdominal pain, dyspepsia, nausea, pyrexia, dizziness, and headache. The design of these studies limited the ability to show a difference in the rates of bleeding between the avatrombopag and placebo treatment groups, because patients in both treatment arms were eligible to receive platelet transfusions. However, despite several limitations due to the number of patients included, these studies consistently show the efficacy and safety of avatrombopag in increasing the proportion of patients with thrombocytopenia associated with ACLD undergoing a procedure who did not require a platelet transfusion or rescue procedure for bleeding.

Avatrombopag has been recently approved in Switzerland for ACLD patients with severe thrombocytopenia undergoing invasive procedures [11]. It does not require dietary restrictions and has not been associated with portal vein thrombosis, with apparently insignificant drug interactions. Moreover, avatrombopag is expected to be cost-saving while reducing the need for prophylactic platelet transfusions [12].

In conclusion, although more real-life data will be required to confirm the findings from these studies, the availability of avatrombopag will likely promote the adoption of new clinical practice standards to optimize the care of thrombocytopenic patients with ACLD undergoing a scheduled invasive procedure.

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## References

1. Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F et al (2008) Thrombocytopenia associated with chronic liver disease. J Hepatol 48(6):1000–1007 (https://pubmed.ncbi.nlm.nih.gov/18433919/)
2. Ware J, Corken A, Khetpal R (2013) Platelet function beyond hemostasis and thrombosis. Curr Opin Hematol 20(5):451–456 (https://pubmed.ncbi.nlm.nih.gov/23839296/)
3. Estcourt LJ, Birchall J, Allard S, Bassey SJ, Hersey P, Kerr JP et al (2017) Guidelines for the use of platelet transfusions. Br J Haematol 176(3):365–394 (https://pubmed.ncbi.nlm.nih.gov/28009056/)
4. Patel IJ, Rahim S, Davidson JC, Hanks SE, Tam AL, Walker TG et al (2019) Society of Interventional radiology consensus guidelines for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided interventions-part II: recommendations: endorsed by the Canadian association for Interventional radiology and the cardiovascular and Interventional radiological society of Europe. J Vasc Interv Radiol 30(8):1168–1184.e1 (https://pubmed.ncbi.nlm.nih.gov/31229333/)
5. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH (2019) AGA clinical practice update: coagulation in cirrhosis. Gastroenterology 157(1):34–43.e1 (https://pubmed.ncbi.nlm.nih.gov/30986390/)
6. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN et al (2021) Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American association for the study of liver diseases. Hepatology 73(1):366–413 (https://pubmed.ncbi.nlm.nih.gov/33219529/)
7. Seeff LB, Everson GT, Morgan TR, Curto TM, Lee WM, Ghany MG et al (2010) Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol 8(10):877–883 (https://pubmed.ncbi.nlm.nih.gov/20362695/)
8. Tripodi A, Primignani M, Chantarangkul V, Lemma L, Jovani M, Rebulla P et al (2013) Global hemostasis tests in patients with cirrhosis before and after prophylactic platelet transfusion. Liver Int 33(3):362–367 (https://pubmed.ncbi.nlm.nih.gov/23231699/)
9. Moore AH (2019) Thrombocytopenia in Cirrhosis: A Review of Pathophysiology and Management Options. Clin Liver Dis 14(5):183–186 (https://onlinelibrary.wiley.com/doi/full/10.1002/cld.860)
10. Terrault N, Chen YC, Izumi N, Kayali Z, Mitrut P, Tak WY et al (2018) Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. Gastroenterology 155(3):705–718 (https://pubmed.ncbi.nlm.nih.gov/29778606/)
11. Doptelet, Filmtabletten (Avatrombopagum). https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/new-medicines/doptelet-filmtabletten.html. Accessed 26 Feb 2022
12. Mladsi D, Barnett C, Aggarwal K, Vredenburg M, Dieterich D, Kim R (2020) Cost-effectiveness of avatrombopag for the treatment of thrombocytopenia in patients with chronic liver disease. Clinicoecon Outcomes Res 12:515–526 (https://pubmed.ncbi.nlm.nih.gov/32982341/)