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## Safety and efficacy of dual antiplatelet therapy after percutaneous coronary interventions in patients with end-stage liver disease

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### Abstract

The prevalence of coronary artery disease (CAD) increases in patients with end-stage liver disease, with part of them receiving the percutaneous coronary intervention (PCI) as a treatment option. Dual antiplatelet therapy (DAPT), a standard of care after PCI, could result in catastrophic consequences in this population. Before PCI and the start of DAPT, it is recommended to assess patient bleeding risk. Based on novel findings, liver cirrhosis does not necessarily lead to a significant increase in bleeding complications. Furthermore, conventional methods, such as the international normalized ratio, might not be appropriate in assessing individual bleeding risk. The highest bleeding risk among cirrhotic patients has a subgroup with severe thrombocytopenia ( $< 50 \times 10^9/L$ ) and elevated portal pressure. Therefore, every effort should be made to maintain thrombocyte count above  $> 50 \times 10^9/L$  and prevent variceal bleeding. There is no solid evidence for DAPT in patients with cirrhosis. However, randomized trials investigating short (one month) DAPT duration after PCI with new drug-eluting stents (DES) in a high bleeding risk patient population can be implemented in patients with cirrhosis. Based on retrospective studies (with older stents and protocols), PCI and DAPT appear to be safe but with a higher risk of bleeding complications with longer DAPT usage. Finally, novel methods in assessing CAD severity should be performed to avoid unnecessary PCI and potential risks associated with DAPT. When indicated, PCI should be performed over radial artery using contemporary DES. Complementary medical therapy, such as proton pump inhibitors and beta-blockers, should be prescribed for lower bleeding risk patients. Novel approaches, such as thromboelastography and "preventive"

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upper endoscopies in PCI circumstances, warn clinical confirmation.

**Key Words:** End-stage liver disease; Cirrhosis; Liver transplantation; Coronary artery disease; Percutaneous coronary intervention; Antiplatelet therapy

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**Core Tip:** Dual antiplatelet therapy (DAPT) is necessary after a percutaneous coronary intervention (PCI). However, it could result in severe consequences in patients with liver cirrhosis. Based on novel findings, liver cirrhosis does not necessarily lead to a significant increase in bleeding complications. Patients with cirrhosis who have the highest bleeding risk are those with severe thrombocytopenia and elevated portal pressure. Despite the lack of solid evidence for DAPT in patients with cirrhosis, trials investigating one month of DAPT duration after PCI can be implemented in cirrhotic patients. Before PCI, functional assessment of coronary artery disease severity should be performed to avoid unnecessary interventions.

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## INTRODUCTION

The prevalence of coronary artery disease (CAD) in patients with liver cirrhosis is estimated from 20% to 26% [1-3]. Furthermore, due to the growing incidence of cirrhosis caused by non-alcoholic fatty liver disease, which has overlapping risk factors with the CAD, an even higher prevalence of CAD in patients with cirrhosis can be expected [4,5]. The presence of both comorbidities can limit treatment options for each. For example, a patient can be rejected for surgical heart revascularization due to high operative risk or for the potential liver transplantation (LT) due to unresolved CAD. Percutaneous coronary intervention (PCI) with stent implantation represents a valid treatment option for CAD [6]. Data from the United States report that 1.2% of patients undergoing PCI have cirrhosis [7]. However, dual antiplatelet therapy (DAPT), a standard of care after stent implantation, can have severe consequences in cirrhotic patients with cirrhosis due to elevated bleeding risk.

This article aims to define; do all patients with liver cirrhosis have the same bleeding risk, the evidence behind DAPT in patients with cirrhosis, and what can be done to lower bleeding risk in such patients.

## ARE ALL PATIENTS WITH CIRRHOSIS AT THE SAME RISK OF BLEEDING?

In the past, all patients with liver cirrhosis were classified as having high bleeding risk (HBR) due to coagulation abnormalities, thrombocytopenia, and elevated portal pressure-related complications. However, these presumptions are changing with growing evidence that, at least, part of patients with cirrhosis might have a high thrombotic risk [8,9]. Complex alterations in the hemostatic system cause so-called rebalanced hemostasis, meaning that impaired protein synthesis leads to a decreased level of procoagulant factors and anticoagulant factors [10,11]. The international normalized ratio (INR) is often used as a parameter for coagulation cascade competence in cirrhosis, although primarily invented for the warfarin dosing and not for the above mentioned [9]. The potential problem arises from the fact that it measures procoagulant factors but not anticoagulant factors such as protein C and S, which are also depleted in patients with liver cirrhosis [9,12]. Furthermore, it does not measure Factor VIII, whose levels are elevated in cirrhosis patients due to its endothelial

production[13]. Finally, studies that tried to "correct" INR using fresh frozen plasma or activated Factor VII, failed to reduce bleeding events[14-17]. Additionally, fibrinogen measurement has been proposed as a potential alternative to INR for assessing bleeding risk, although its clinical usefulness is yet to be confirmed[9].

The second risk factor for bleeding in patients with cirrhosis is thrombocytopenia, occurring in 64%-84% of patients with cirrhosis or fibrosis[18]. Its cause is multifactorial, with the most important being decreased production due to depressed thrombopoietin levels, splenic sequestration, and increased destruction[9,19-21]. However, a platelet count of  $> 50 \times 10^9/L$  has been shown to be sufficient to maintain thrombin generation in *in vitro* studies[8,21-23]. This cut level has been recognized by McCarthy *et al*[24] in their opinion paper on management of DAPT in patients with thrombocytopenia, where they advise avoiding PCI in case of thrombocyte count  $< 50 \times 10^9/L$ . Furthermore, in cirrhotic patients, platelet-induced anticoagulation changes are counterbalanced with the higher activity of endothelium-derived von Willebrand factor[8,9,25].

The third risk factor for bleeding in patients with cirrhosis are complications arising from portal hypertension, primarily esophageal varices[26,27]. The risk of variceal hemorrhage is related to variceal size, the severity of liver dysfunction (Child-Pugh B/C), and the presence of red wale marks on varices[28]. This issue had been recognized in a consensus document from Academic Research Consortium for High Bleeding Risk, in which they defined patients with cirrhosis and portal hypertension as having HBR after PCI[29]. Of note, in the same document, patients with thrombocytopenia (defined as  $< 100 \times 10^9/L$ ), irrespective of etiology, and those with chronic bleeding diathesis are likewise defined as having HBR. Finally, it is essential to emphasize there is no valid bleeding risk score for patients with liver cirrhosis. Most used Child-Pugh and Mayo End-Stage Liver Disease criteria are developed for predicting mortality and not bleeding events, despite having INR as an integrative part of both[30-32]. In summary, based on presented data, patients with the highest bleeding risk are those with severe thrombocytopenia ( $< 50 \times 10^9/L$ ) and those with portal hypertension.

## WHAT IS THE CURRENT EVIDENCE REGARDING DAPT AFTER PCI IN PATIENTS WITH CIRRHOSIS?

Historically, due to the concerns for late stent thrombosis after drug-eluting stent (DES) implantation, DAPT was recommended for 12 mo after such procedures. Thus, patients with HBR, including those with liver disease, were excluded from most modern DES trials[29]. Therefore, implantation of a bare-metal stent (BMS) followed by one month of DAPT was recommended in those cases[29]. However, with DES technology advancements and stent thrombosis reduction, randomized trials in HBR patients have been performed. In the LEADERS FREE trial, almost 2500 patients were allocated to modern DES or BMS, followed by one month of DAPT. After one year of follow-up, DES implantation was superior to BMS concerning primary safety endpoint [a composite of cardiac death, myocardial infarction (MI), or stent thrombosis] [9.4% *vs* 12.9%; hazard ratio, 0.71; 95% confidence interval (CI): 0.56-0.91;  $P < 0.001$  for noninferiority and  $P = 0.005$  for superiority] with the lower incidence of clinically driven target lesion revascularization (5.1% *vs* 9.8%; hazard ratio, 0.50; 95%CI: 0.37-0.69;  $P < 0.001$ )[33]. Similarly, in ONYX ONE trial, which included 1996 patients, DES implantation was non-inferior to BMS (both with one month of DAPT) after one year of follow-up[34]. Even though both trials investigated patients with HBR, the prevalence of patients with liver disease/cirrhosis was  $< 1\%$ , too small to extract conclusions in this patient population[33,34].

Several retrospective studies described and investigated outcomes after PCI in patients with liver cirrhosis compared to different patient populations, with only one of them more focused on antiplatelet management[4,7,35-38]. The largest of them was conducted by Wu *et al*[35], which included 914 cirrhotic patients who underwent PCI due to MI and compared them to a four times larger propensity-matched group of patients without cirrhosis. The cirrhosis group had significantly higher 1-year mortality (32.7% *vs* 23.7%, 95%CI: 1.28-1.74) but less recurrent MIs (6.0% *vs* 8.7%, 95%CI: 0.54-0.92). Importantly, cirrhosis group had non-significant increase in major bleeding (3.7% *vs* 2.9%, 95%CI: 0.87-1.23) and significantly increased gastrointestinal bleeding (28.0% *vs* 20.2%, 95%CI: 1.31-1.70). A sub-analysis showed significantly lower mortality and non-significant decreases in recurrent MI in the DAPT subgroup (duration of DAPT had to be  $> 3$  mo) compared to cirrhotic patients on a single

antiplatelet agent. However, patients with a single antiplatelet agent were significantly older with significantly more severe comorbidities (such as heart failure and history of gastrointestinal bleeding), so direct comparison is questionable[35]. After PCI in patients with cirrhosis, worse in-hospital mortality than a historic non-cirrhotic group has also been described by Singh *et al*[7]. In the same study, patients with cirrhosis had worse outcomes if they received BMS instead of DES[7].

The two studies comparing PCI and medical therapy in CAD patients with cirrhosis found no difference in 1-year mortality and a higher bleeding rate[36,37]. Importantly, Krill *et al*[36] described a temporal change in bleeding events. The difference in bleeding was non-significantly different at 30- and 90-d follow-up (although higher in the PCI group) but become significant after 1 and 2 years. That might be associated with higher and extended use of DAPT in the PCI group (63% of patients had DAPT 1 year after PCI)[36]. Similarly, Russo *et al*[4] and Azarbal *et al*[38] described no significant difference in bleeding after PCI than medical therapy, although higher in the PCI group, in shorter follow up of 11 and 1 mo, respectively.

Finally, it is essential to emphasize that the studies mentioned above-included patients up to 2015, with consequent high use of BMS or old generation DES without new DAPT duration protocols.

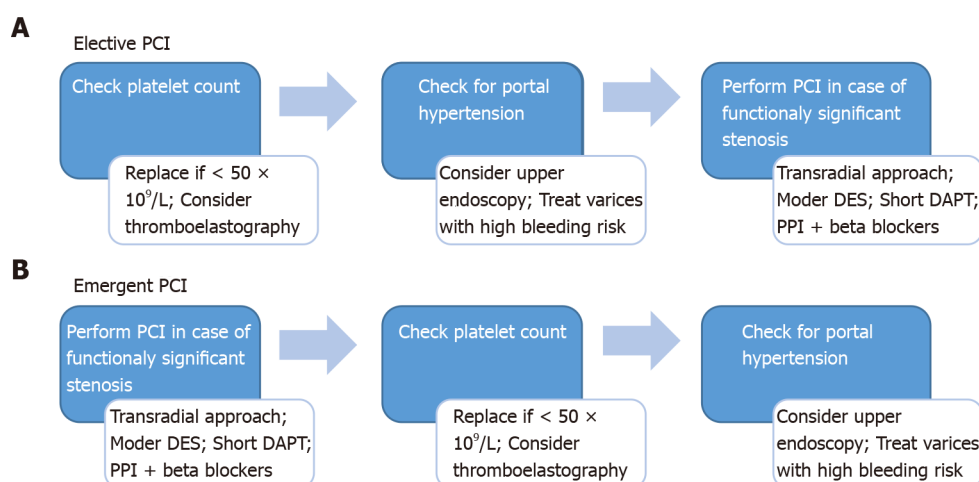
In conclusion, "hard" evidence for DAPT in patients with liver cirrhosis is scarce. Based on retrospective studies (with older stents and protocols), PCI and DAPT appear to be safe but with a higher risk of bleeding complications with longer DAPT usage.

## WHAT ARE POTENTIAL TOOLS THAT COULD BE USED TO ASSESS AND LOWER BLEEDING RISK?

Based on the aforementioned retrospective studies, PCI's usefulness in patients with liver cirrhosis regarding mortality is questionable due to high non-cardiovascular related mortality[36,37,39]. Therefore, appropriate triage of such patients before PCI, and consequent DAPT related bleeding risk, is mandatory. Based on data in the general population, PCI affects prognosis in patients presenting with MI and selected scenarios of a chronic coronary syndrome such as left main or proximal left anterior descending artery disease, a multi-vessel disease with impaired left ventricular systolic function, and a large area of myocardium at risk[6]. In our opinion, PCI is indicated in a patient with cirrhosis who presents with one of the mentioned scenarios if life expectancy, from the hepatological point of view, is reasonably long (one year) or other treatment modalities, such as LT are available. Except for the scenarios mentioned above, PCI of all significant coronary artery stenosis might be indicated before LT. This conclusion is based on retrospective studies that showed worse outcomes after LT in patients with CAD and increased mortality in multi-vessel CAD cases[40-42]. On the other hand, data from several studies indicate no impact of CAD on post-LT survival if CAD is treated appropriately, including PCI when indicated[43, 44]. All presented studies described CAD using plain angiography as the percentage of coronary artery stenosis (usually over 50%). Although this method is valid for CAD definition, more novel and precise methods, such as functional assessment of stenosis, should be done before PCI, especially in borderline stenosis and HBR patients[6]. Therefore, we advise the usage of instantaneous wave-free ratio or a similar method for confirmation of stenosis significance for all coronary artery stenosis estimated to be between 50%-90% as it not only affects prognosis but reduces the number of stents implanted compared to angiogram alone[6,45-47]. In the cases where PCI is indicated, it should be done with third generation DES, preferably with one tested for the short need for DAPT of only one month[6,33,34,48]. Another off-label option would be PCI using drug-coated balloons which has comparable results with modern DES primarily in small CAD (diameter  $\leq$  2.8 mm) and in HBR patients due to theoretical shorter usage of DAPT and lower risk for thrombosis as no foreign material remains in the artery[49-52]. We advise using the radial artery approach as default vascular access for all left heart catheterization due to better outcomes and lower bleeding risk than transfemoral access[6,53,54]. It also appears to be a safe option in patients with end-stage liver disease based on a single available study[55].

After the PCI, DAPT duration should be shortened in HBR patients, as advised by the guidelines, to three months after elective PCI or six months after PCI in acute coronary syndrome[56]. We also encourage clopidogrel usage compared to more potent P2Y<sub>12</sub> inhibitors due to its lower bleeding risk[24,57,58]. A potential drawback of clopidogrel is that it requires activation in the liver[59]. However, a recent study





**Figure 1** Proposed scheme with the main recommendations of how to approach a patient with cirrhosis undergoing percutaneous coronary intervention in elective and emergent settings. A and B: In case of elective percutaneous coronary intervention (PCI) (A), platelet count and portal hypertension work up should be performed (and treated) before the PCI. However, in emergent settings (B) above mentioned work up should be performed after the PCI. PCI: Percutaneous coronary intervention; DAPT: Dual antiplatelet therapy; DES: Drug eluting stent; PPI: Proton pump inhibitor.

described appropriately reduced platelet function after clopidogrel using thromboelastography (TEG), TEG-based platelet mapping, and impedance platelet aggregometry in patients with decompensated cirrhosis[60]. Importantly, no platelet function test has been studied for guiding DAPT in a patient with cirrhosis. On the other hand, TEG has been used to guide blood product use in various scenarios in patients with cirrhosis and impaired coagulation assessed using conventional methods (INR and platelet count)[61]. In randomized trials, TEG compared to conventional methods led to lower blood products use without an increase in bleeding complications in patients with bleeding varices and before invasive procedures[62,63]. Based on mentioned, TEG can theoretically be used to assess hemostatic pathways before administration of DAPT, with more freely DAPT usage in case of preserved hemostasis. However, these presumptions are supposed to be tested in clinical studies before widespread utilization.

Regarding medical therapy for preventing bleeding complications during DAPT, a proton pump inhibitor should be prescribed as it reduces upper gastrointestinal bleeding in patients with cirrhosis[36,64]. It is also most important to administer a maximally tolerated dose of beta-adrenergic blocking agents due to their positive effect on portal hypertension and CAD[28,65]. Lastly, we encourage repeat upper endoscopy in patients with liver cirrhosis before elective PCI or early after urgent PCI to manage varices according to recommendations for primary and secondary prophylaxis of variceal bleeding, as previously proposed[4,28].

In summary, PCI in patients with cirrhosis should be done over trans-radial artery access, using novel DES (with proved safety in short DAPT protocols), in cases when PCI is proved to affect patient prognosis. Along with DAPT, concomitant medical therapy that reduces the risk of bleeding should be administered. Novel approaches, such as TEG or "preventive" upper endoscopies, although promising, warn clinical conformation. Proposed scheme with the main recommendations of how to approach a patient with cirrhosis undergoing percutaneous coronary intervention in elective and emergent settings is presented in Figure 1.

## CONCLUSION

The highest bleeding risk among patients with liver cirrhosis is present in a subgroup of patients with severe thrombocytopenia and elevated portal pressure. Therefore, every effort should be made to maintain thrombocyte count above  $> 50 \times 10^9/L$  and prevent variceal bleeding. Despite the lack of solid evidence for DAPT in patients with cirrhosis, results from trials investigating shorter DAPT duration after PCI in HBR patient population can be implemented in patients with cirrhosis. Finally, novel methods in the assessment of CAD severity should be performed to avoid unnecessary PCI.

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