Editorial

The association between nonselective beta-blockers and portal venous thrombosis in cirrhotic patients: More questions on the horizon

Portal venous thrombosis (PVT) is a common complication of cirrhosis, and is associated with increased mortality in pre- and post-liver transplant patients.[1-3] Reductions in portal venous velocities have been shown to the increase the risk of PVT.[4-6] The use of nonselective beta-blockers (NSBBs) for primary or secondary prevention of esophageal variceal bleeding (EVB) has been hypothesized to increase the risk of PVT by decreasing portal venous velocity.[7] However, reduction in portal venous velocity ultimately decreases portal pressures, thereby reducing the risk of bleeding in patients with esophageal varices. NSBBs have shown to be effective in reducing the incidence of variceal bleeding and improving survival in cirrhotic patients.[8,9] In addition, NSBBs may prevent the development of spontaneous bacterial peritonitis in cirrhotic patients by reducing bacterial translocation, regardless of hemodynamic response.[10] Currently, the standard of care is to use NSBBs for primary prophylaxis in cirrhotic patients with medium or large esophageal varices and to use it in combination with esophageal variceal ligation (EVL) for secondary prophylaxis.[11]

In this issue of the Journal, Zampino *et al.* performed a retrospective, single-center study evaluating the risk factors and clinical features of the first event of PVT in 130 patients with cirrhosis.[12] Patients with PVT (n = 19) were matched with controls (n = 111) based on Child–Turcotte–Pugh (CTP) only. The authors observed that there is a higher rate of PVT (15%) in the study population. However, the study was not designed to evaluate the frequency of PVT in all cirrhotic patients. Therefore, such a statement is not accurate. In addition, the prevalence of PVT among cirrhotic patient varies from 5% to 26%.[13] Therefore, the presence of PVT in 15% of the study population in Zampino's study is within the acceptable range of PVT prevalence. Nevertheless, it was observed that esophageal varices and NSBBs were significantly more frequent in the PVT group compared to controls. These data are in line with the previous retrospective analysis of 56 cirrhotic patients by Pellicelli *et al.* who reported significant increases in PVT in patients treated with NSBBs.[5] In addition, Pellicelli *et al.* reported a significant reduction in portal venous velocity in patients with PVT.[5] The current study may add evidence to the theory that NSBB use will increase PVT rates in cirrhotic patients, while also raising more important questions for future research.

Most importantly, what is the overall risk and benefit of NSBB use when increases in PVT risk are considered? PVT clearly increases the overall mortality risk in cirrhotic patients.[2-3] NSBBs may contribute to increases in PVT risk. At the same time, without preventative measures, 1-year rebleeding rates following EVB are over 60%.[14] In a recent meta-analysis by Albillos *et al.*, when compared to EVL alone, EVL and NSBB combined showed significant mortality and rebleeding rate reductions in CTP B and C patients and significant reductions in rebleeding in CTP class A patients, without a significant mortality benefit.[15] Therefore, there is clear benefit to the use of NSBBs in EVB prevention, but it may not be without risks. The degree to which NSBBs cause an increase in risk has not yet been fully understood. In addition, both the presence of esophageal varices and NSBBs use were risk factors for PVT in the Zampino study.[12] Most patients with varices would be treated with NSBB. Therefore, their use may not be the primary culprit of PVT and patients treated with NSBBs have significant portal hypertension already, which may instead be the primary cause of PVT. In a cross-sectional analysis by Violi *et al.*, there was no significant increase in PVT prevalence among patients who were treated with NSBBs. However, the prevalence of PVT was higher in patients with CTP class B and C, hepatocellular carcinoma, and previous upper gastrointestinal bleeding.[16] Furthermore, patients in the current study were only treated with propranolol.[12] The American Association for the study of liver diseases (AASLD) expanded the recommended beta-blockers for EVB prevention to include carvedilol

along with propranolol and nadolol.[11] It is possible that different beta blockers may confer an increased or lesser risk of PVT. Finally, patients in the current study were mostly CTP class A.[12] Understanding differences in PVT risk across CTP classes would be helpful in future patient selection for NSBB treatment.

The data presented in this issue of the Journal represents an interesting starting point which should be explored in detail by future researchers. Perhaps more refined criteria are required for which patients ought to be selected for NSBBs for primary and secondary prevention of EVB with all risks and benefits taken into account.

Nicholas Bartell, Bandar Al-Judaibi

Department of Medicine, University of Rochester, Rochester, New York, USA

Address for correspondence: Dr. Nicholas Bartell, Department of Medicine, University of Rochester, Rochester, New York, USA.
E-mail: nicholas_bartell@urmc.rochester.edu

REFERENCES

1. Kinjo N, Kawanaka H, Akahoshi T, Matsumoto Y, Kamori M, Nagao Y, *et al.* Portal vein thrombosis in liver cirrhosis. World J Hepatol 2014;6:64-71.
2. Englesbe MJ, Kubus J, Muhammad W, Sonnenday CJ, Welling T, Punch JD, *et al.* Portal vein thrombosis and survival in patients with cirrhosis. Liver Transpl 2010;16:83-90.
3. Ghabril M, Agarwal S, Lacerda M, Chalasani N, Kwo, P, Tector AJ. Portal Vein Thrombosis is a risk factor for poor early outcomes after liver transplantation: Analysis of risk factors and outcomes for portal vein thrombosis in waitlisted patients. Transplantation 2016;100:126-33.
4. Zocco, MA, Di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani F, *et al.* Thrombotic risk factors in patients with liver cirrhosis: Correlation with MELD scoring system and portal vein thrombosis development. J Hepatol 2009;51:682-89.
5. Pellicelli AM, D'Ambrosio C, Barbaro G, Villani R, Guarascio P, Fondacaro A, *et al.* Clinical and genetic factors associated to development of portal vein thrombosis in cirrhotic patients without hepatocellular carcinoma. J Hepatol 2011;54:S77.
6. Bosch J, Garcia-Pagan JC. Complications of cirrhosis. I. Portal hypertension. J Hepatol 2000;32:141-56.
7. Qi XS, Bai M, Fan DM. Nonselective β-blockers may induce development of portal vein thrombosis in cirrhosis. World J Gastroenterol 2014;20:11463-66.
8. Lebrec D, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: A controlled study. N Engl J Med 1981;305:1371-4.
9. Bernard B, Lebrec D, Mathurin P, Opolon P, Poynard T. Beta-adrenergic antagonists in the prevention of gastrointestinal rebleeding in patients with cirrhosis: A meta-analysis. Hepatology 1997;25:63-70.
10. Senzolo M, Cholongitas E, Burra P, Leandro G, Thalheimer U, Patch D, *et al.* Beta-blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: A meta-analysis. Liver Int 2009;29:1189-93.
11. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidelines by the American Association for the study of liver diseases. Hepatology 2017;65:310-35.
12. Zampino R, Lebano R, Coppola N, Macera M, Grandone A, Rinaldi L, *et al.* The use of nonselective beta blockers is a risk factor for portal vein thrombosis in cirrhotic patients. Saudi J Gastroenterol 2018;24:25-9.
13. Karvellas CJ, Cardoso FS, Senzolo M, Wells M, Alghanem MG, Handou F, *et al.* Clinical Impact of Portal Vein Thrombosis Prior to Liver Transplantation: A Retrospective Cohort Study. Ann Hepatol 2017;16:236-436.
14. Bosch J, Garcia-Pagan JC. Prevention of variceal rebleeding. Lancet 2003;361:952-4.
15. Albillos A, Zamora J, Martinez J, Arroyo D, Ahmad I, De-la-Peña J, *et al.* Stratifying risk in the prevention of recurrent variceal hemorrhage: Results of an individual patient meta-analysis. Hepatology 2017;66:1219-31.
16. Violi F, Corazza RG, Caldwell SH, Perticone F, Gatta A, Angelico M, *et al.* Portal vein thrombosis relevance on liver cirrhosis: Italian Venous Thrombotic Events Registry. Intern Emerg Med 2016;11:1059-66.

Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.SJG_588_17

How to cite this article: Bartell N, Al-Judaibi B. The association between nonselective beta-blockers and portal venous thrombosis in cirrhotic patients: More questions on the horizon. Saudi J Gastroenterol 2018;24:3-4.