Non-selective beta blockers in portal hypertension; Why, When and How?

Anahita Rabiee[1], Guadalupe Garcia-Tsao[1,2], Elliot B. Tapper[3,4]

1. Digestive Diseases Section, Yale School of Medicine, New Haven
2. Digestive Diseases Section, VA-CT Healthcare System, West Haven
3. Division of Gastroenterology and Hepatology, University of Michigan
4. Gastroenterology Section, VA Ann Arbor Healthcare System, Ann Arbor

Emails: etapper@umich.edu, anahita.rabiee@yale.edu, guadalupe.garcia-tsao@yale.edu

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Corresponding author: Anahita Rabiee, anahita.rabiee@yale.edu

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DR. ANAHITA RABIEE (Orcid ID : 0000-0002-8833-3592)

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Introduction

In the past 3 decades, non-selective beta blockers (NSBBs) have been the cornerstone in the management of portal hypertension (PH) in patients with cirrhosis. PH in cirrhosis initially develops as a result of increased hepatic resistance (architectural distortion and intrahepatic vasoconstriction). This initial increase in pressure leads to splanchnic vasodilation resulting in an increased portal venous inflow and a further increase in portal pressure. Additionally, vasodilation leads to decreased effective arterial blood volume, and to compensatory neurohormonal activation resulting in sodium and water retention from the kidneys, plasma volume expansion, and an increase in cardiac output (hyperdynamic circulation). This further augments portal venous inflow and pressure, thereby creating a vicious cycle.(1)(Figure 1)

NSBBs were first shown to reduce portal pressure in patients with variceal hemorrhage in 1980.(2) In contrast to cardioselective beta blockers whose affinity is specific for β1 (located in cardiac muscles), NSBBs such as propranolol or nadolol have a similar affinity for β1 and β2 (located in splanchnic vessels). Blocking β1 results in decreased cardiac output and blocking β2 results in splanchnic vasoconstriction, both of which contribute to decreasing portal pressure. Carvedilol, a newer NSBB, additionally blocks α1 adrenergic receptors which decreases intrahepatic resistance, with a consequent greater reduction in portal pressure.(1)

The effect of NSBBs depends on the stage of cirrhosis and PH. In compensated cirrhosis PH is initially mild with a hepatic venous pressure gradient (HVPG) 6-10 mmHg. With the onset of the hyperdynamic circulation, HVPG increases to >10 mmHg,

a threshold identified as being “clinically significant PH (CSPH)” because it is the main predictor of cirrhosis decompensation.(3) NSBBs play a major role in the treatment of PH in patients in whom hyperdynamic circulation has developed, i.e. those with CSPH and those who have bled from varices.(4)(Figure 2)
We will discuss major indications of NSBBs and future directions.

Primary prophylaxis of variceal hemorrhage:
Currently, guidelines recommend NSBBs or endoscopic variceal ligation (EVL) to prevent first variceal hemorrhage (primary prophylaxis) in patients with high-risk varices. High risk varices are defined as medium/large varices, varices of any size with red wale marks, or varices of any size in Child C patients.(5) Treatment selection is based on patient and provider preference, but guided by data on benefits and risks.

When used for primary prophylaxis, NSBBs have also been shown to decrease decompensation as opposed to EVL which is a local treatment and does not alter the disease progression. NSBBs can additionally decrease intestinal permeability and bacterial translocation.(6–8) Also, once a patient is on NSBBs the risk of bleeding is reduced similarly to eradication of the varices with EVL and thus repeat endoscopy is not required.(9) The risks or drawbacks of each approach, however, are real. Thus, it is important to individualize treatment selection based on contraindications, tolerance, side effect profile and patient preference.(figure 3)

Secondary prophylaxis of variceal hemorrhage:
In patients who have previously bled from varices, combination therapy with NSBBs and EVL is recommended.(5) Multiple trials have demonstrated the benefits of combination therapy over either of these treatments alone. Interestingly, NSBBs have been shown to be the key component of the combination therapy and drive the majority of the benefit.(1)

Despite their proven efficacy, there is hesitancy in using NSBBs in patients with decompensated cirrhosis with ascites, because retrospective studies have shown

increased mortality in these patients.(10) Despite initial concerns, recent meta-analyses showed an overall survival benefit with appropriate dosing of NSSBs in subgroup analyses of patients with ascites or even refractory ascites.(11) NSBBs should be used cautiously in patients with refractory ascites as it is in these patients that NSBBs can lead to a decrease in renal perfusion pressure and acute kidney injury.(12) It is important that mean arterial pressure is maintained above 65 mmHg in patients with ascites as this will not only prevent kidney injury but it is the threshold pressure that has been associated with an improved survival.(13) Additionally, it should be noted that the maximal recommended doses of NSBBs are lower compared to patients without ascites (Table 1).(5)

Preventing clinical decompensation:

NSBBs have been used for many years for variceal bleeding prophylaxis. Previous studies have shown that the benefits of NSBBs are mainly observed in hemodynamic responders (defined as patients with HVPG reduction of >20% or HVPG <12 mmHg), but only 50% of patients respond to traditional NSBBs.(figure 4)(14) Traditional NSBB dose is often titrated to a goal heart rate (HR). However, this dogma has been challenged. First, patients at goal HR are just as likely to have reduced HVPG as they are not to on follow-up HVPG measurements.(15) Second, each given point estimate of HVPG has wide confidence intervals owing to measurement error and patient factors, particularly among those with decompensated cirrhosis, which can result in significant day-to-day changes in HVPG. Accordingly, HVPG measurement is insensitive to detect changes in pressures that are <30%.(16) Third, using carvedilol in patients who do not respond to traditional NSBB increases the proportion of responders to 75%.(17) Given these difficulties in identification of responders, an alternative approach could be to use carvedilol first-line.

As the pathophysiology of portal HTN is better clarified, there has been an increased interest in extending the indications for NSBBs to earlier stages. In this backdrop, the PREDESCI trial evaluated the role of NSBBs in patients with CSPH with no or small varices.(18) Patients were randomized to propranolol (or carvedilol in cases where

HVPG did not fall by 10% on propranolol) or placebo. The primary outcome was a composite of decompensation (ascites, variceal hemorrhage or encephalopathy) or death. Notably, although the decision to use carvedilol was made for those lacking hemodynamic response to propranolol, HVPG response was not assessed after starting it. The cumulative incidence of decompensation or death was significantly lower in the NSBB group compared with placebo (HR 0.51, 95% CI 0.26–0.97). The number needed to treat (NNT) to prevent one decompensation was 9 (3 year follow up). This difference was largely due to a lower appearance of ascites in this group compared to placebo (9% vs 20%).

Features of this study, however, limit generalizability. First, HVPG assessment is not part of usual care. It is unclear if identification of CSPH via non-invasive methods (i.e. using liver stiffness values) would provide similar results. Second, there is uncertainty about the utility of measurement of hemodynamic response to NSBBs in clinical practice outside of expert centers.

This landmark study could shift the paradigm of how we treat CSPH and compensated cirrhosis with the goal of changing the natural history of the disease rather than just preventing variceal bleeding. More studies are needed to show feasibility, benefit and lastly uptake in real-world clinical practice where comorbidities such a diastolic dysfunction and kidney disease may influence effects.

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Figures were created with BioRender.com

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Tables and figures:

Table1: Non-selective beta blockers used in portal hypertension

NSBB	Frequency	Starting dose (mg)		Therapy goal		Maximum dose (mg)	
		No ascites	With ascites	with or without ascites		No ascites	With ascites
Propranolol	Twice a day	20-40	10-20	HR: 55-60	Maintain SBP > 90	320	160
Nadolol	Daily	10-20	10-20			160	80
Carvedilol	Daily	6.25-12.5	NA	No HR goal		12.5-25 *	NA

HR: Heart Rate; SBP: Systolic Blood Pressure; NA: Not Applicable

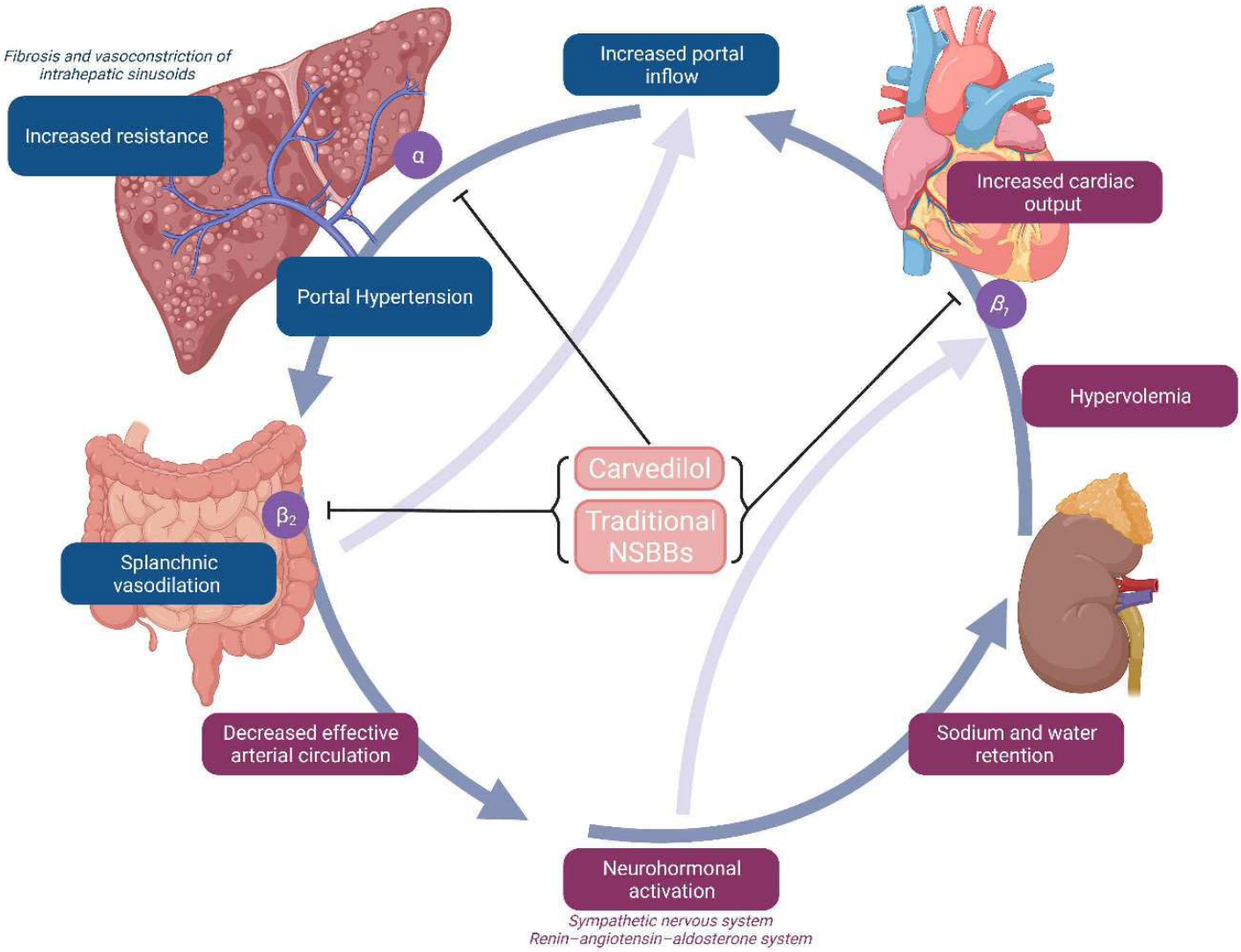
**Maximum dose used in PREDECSI was 25 mg*

Figure 1: Pathophysiology of portal hypertension

Figure 2: Stages of compensated cirrhosis and hemodynamic characteristics

Figure 3: Pros and cons of Non Selective Beta Blockers (NSBB) versus Endoscopic Variceal Ligation (EVL) for primary prophylaxis

Figure 4: Response to Non Selective Beta Blockers (NSBB) and prevention of variceal bleed



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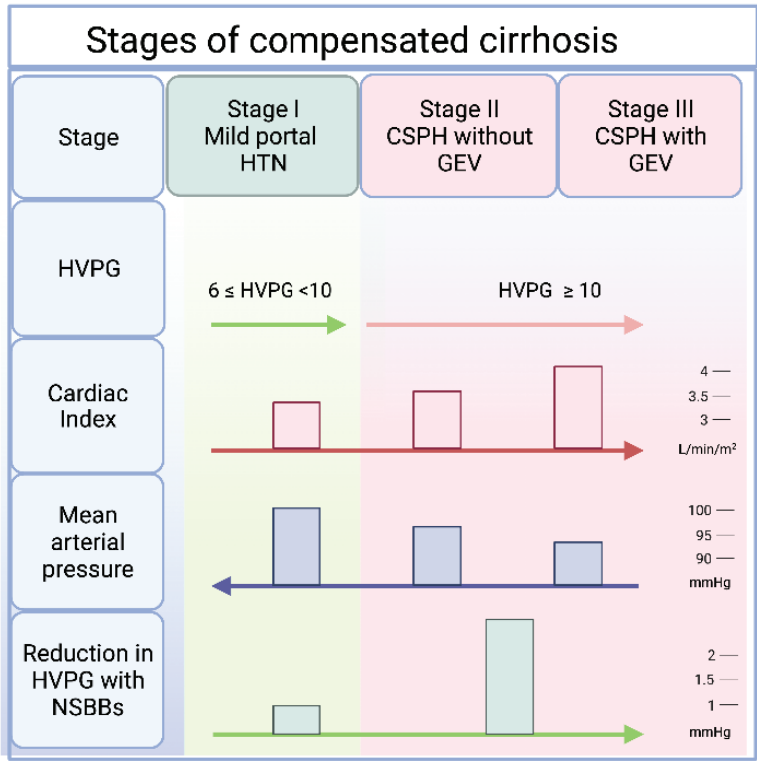

CSPH: Clinically Significant Portal Hypertension; GEV: Gastroesophageal Varices; HVPG: Hepatic Venous Pressure Gradient; NSBB: Non Selective Beta Blockers
**Units on the right are just an approximation to better illustrate the difference*

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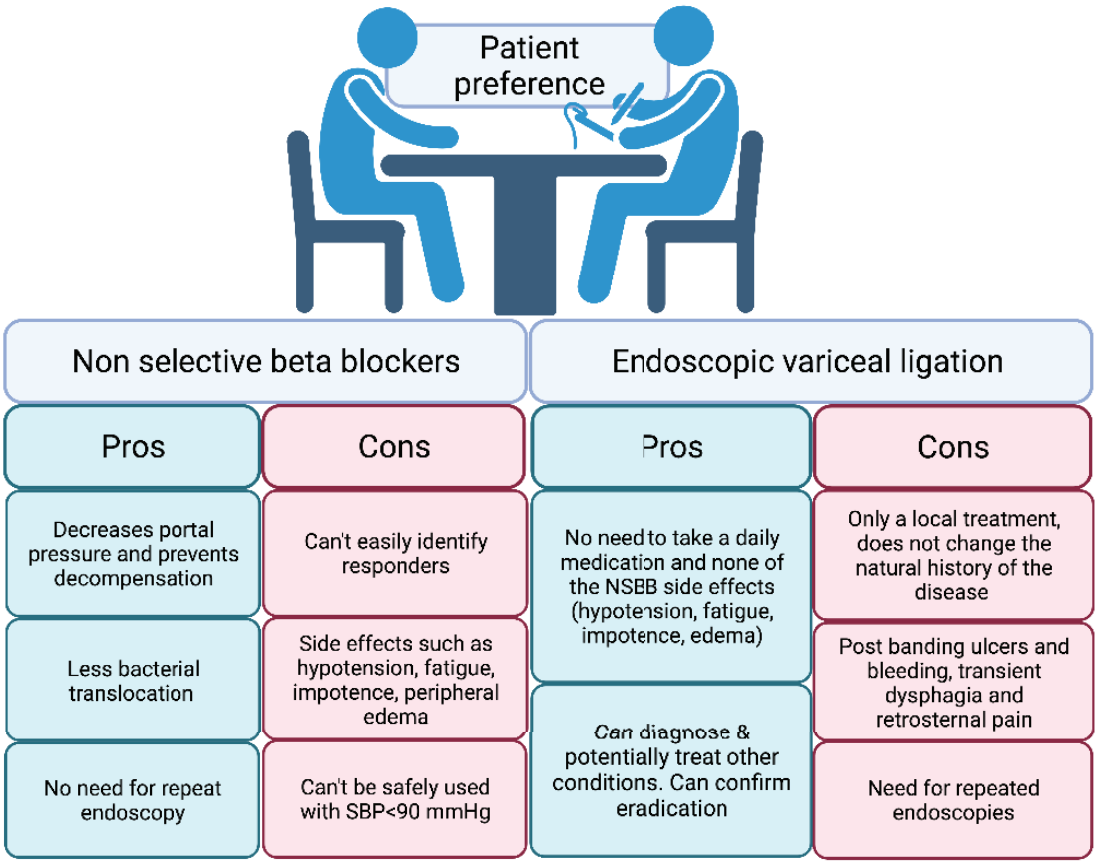

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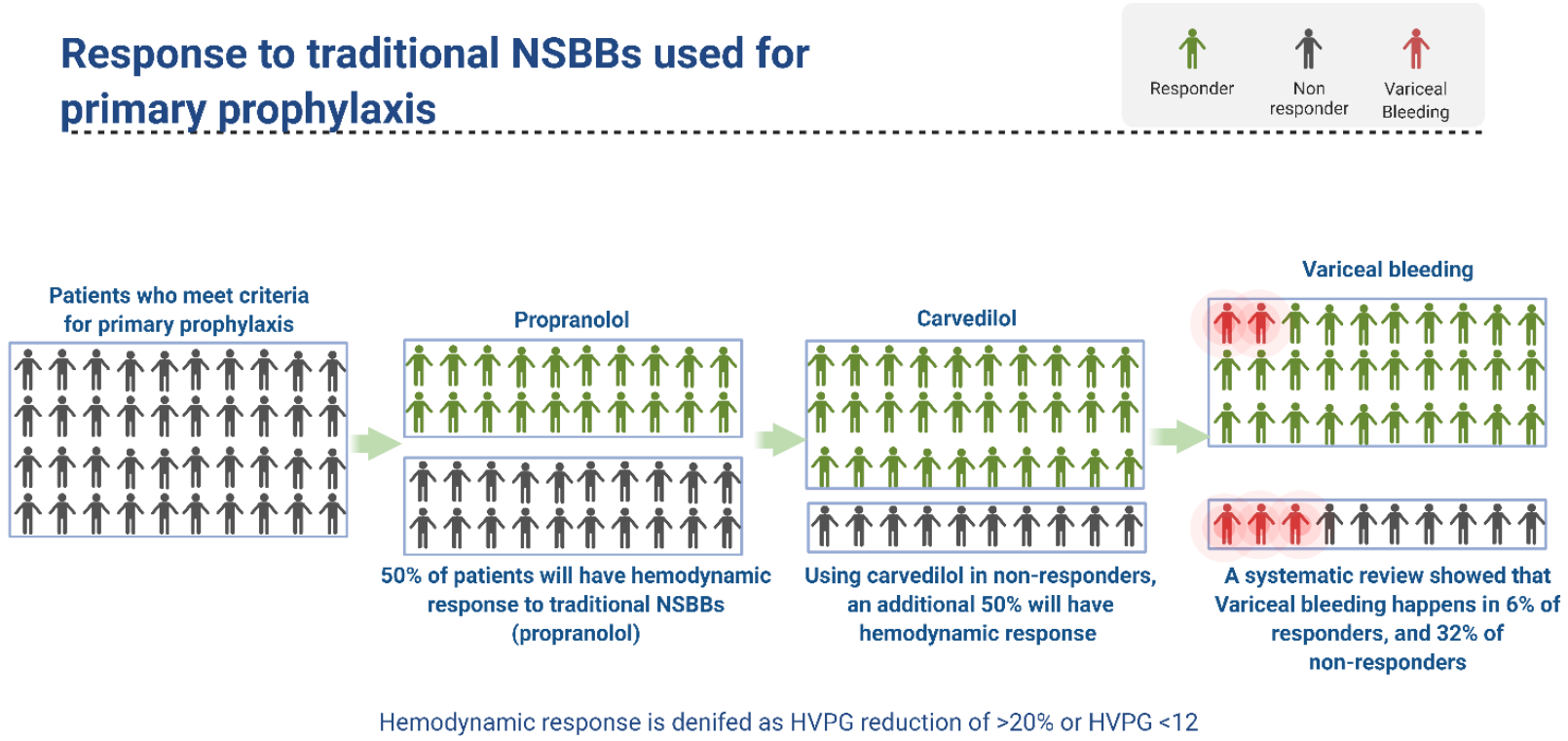

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