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The Impact of Heart Rate Reduction From Individual Baseline With Propranolol for Primary and Secondary Prophylaxis of Variceal Hemorrhage in Cirrhosis

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ABSTRACT

A target heart rate of 55–60 beats per minute is a goal for propranolol in both primary and secondary prophylaxis of variceal hemorrhage (VH). However, dose adjustments are often needed based on baseline heart rates. This study analyzed the effect of heart rate reduction from baseline with propranolol therapy on VH in patients with cirrhosis. A retrospective study was conducted on cirrhotic patients receiving propranolol for primary and secondary prophylaxis, 2008–2023. Patients were categorized as responders or non-responders based on the achievement of a heart rate reduction of ≥ 25% from baseline. The primary outcome was the incidence of VH. A survival analysis with propensity score-inverse probability treatment weighting was performed to associate heart rate reduction and the outcome. Among the 215 patients treated with propranolol for primary prophylaxis, 72 (33.5%) were responders and 143 (66.5%) non-responders. In secondary prophylaxis, 157 patients were included, with 52 (33.1%) classified as responders and 105 (66.9%) as non-responders. The median Child–Pugh score was 6 (range 5–12) for primary and 7 (range 5–12) for secondary prophylaxis. Responders and non-responders showed a similar incidence of VH in both primary (adjusted hazard ratio (HR) 1.70, 95% CI: 0.82–3.49) and secondary prophylaxis (adjusted HR 1.00, 95% CI: 0.34–2.90). Our analysis did not support achieving a heart rate reduction of ≥ 25% from baseline as a response to propranolol for the primary and secondary prophylaxis of VH in cirrhosis.

JEL Classification: Integrity Check

1 | Introduction

Cirrhosis is a condition characterized by chronic inflammatory liver injury, leading to the accumulation of collagen (fibrosis) in the extracellular matrix. This process impedes portal inflow, resulting in portal hypertension [1]. Variceal hemorrhage (VH) in cirrhosis is a consequence of portal hypertension [1]. Propranolol is a standard of care for preventing the first episode of VH in primary prophylaxis and, when combined with band ligation, for reducing recurrent VH in secondary prophylaxis [2]. Propranolol effectively lowers portal pressure by decreasing splanchnic blood flow, achieved through a reduction in cardiac output and splanchnic vasoconstriction, mediated by beta-1 and beta-2 blockade, respectively [3].

Summary

- What is the current knowledge on the topic?
  - For the past decade, achieving a heart rate of 55–60 bpm has been utilized as a key indicator of propranolol efficacy in both primary and secondary prophylaxis of VH.
  - Nonetheless, in clinical practice, propranolol regimens are often adjusted based on individual variations in baseline heart rates.
  - Consequently, some patients may be unable to achieve the target heart rate due to a high baseline heart rate, while others may reach the target with a lower dose of propranolol because of a low baseline heart rate.
  - Thus, heart rate reduction from baseline influences the efficacy of VH prophylaxis with propranolol.
- What question did this study address?
  - This study aimed to analyze the impact of a heart rate reduction of ≥ 25% from each patient's baseline, achieved through propranolol therapy, on VH in primary and secondary prophylaxis of cirrhosis.
  - These findings will help define the appropriate response to propranolol for individual patients and can be generalized to real-world practice, considering the variability in baseline heart rates among patients with cirrhosis.
- What does this study add to our knowledge?
  - Our analysis did not support achieving a heart rate reduction of ≥ 25% from baseline as a response to propranolol for the primary and secondary prophylaxis of VH in cirrhosis.
- How might this change clinical pharmacology?
  - These findings challenge the concept of personalized therapy based on heart rate reduction and indicate that routine heart rate measurement may not be essential for assessing the efficacy of propranolol therapy.

Achieving a reduction in the hepatic venous pressure gradient (HVPG), which reflects portal pressure, by ≥ 20% from baseline in response to propranolol therapy can significantly reduce the risk of VH and other complications compared to patients with lower HVPG reductions [4]. Nonetheless, HVPG is not recommended for regular monitoring, as it lacks the sensitivity to detect minor variations in pressure, which can be influenced by measurement inaccuracies and daily fluctuations [3]. The current recommendations from the American Association for the Study of Liver Diseases practice guidelines suggest a target heart rate of 55–60 beats per minute (bpm) as the efficacy goal for propranolol in both primary and secondary prophylaxis of VH [2].

A target heart rate of 55–60 bpm, regardless of an individual's baseline heart rate, has been used for propranolol dose titration, typically at a median dose of ≥ 80 miligrams (mg) per day, in several clinical studies that demonstrated significant prophylaxis of VH with propranolol treatment [5–8]. However, in clinical practice, dose titration often needs to be adjusted based on each patient's baseline heart rate. Consequently, some patients may be unable to achieve the target heart rate due to a high baseline heart rate, while others may reach the target with a lower dose of propranolol because of a low baseline heart rate. Thus, heart rate reduction from baseline influences the efficacy of VH prophylaxis with propranolol. Additionally, another target—a reduction in heart rate of ≥ 25% from baseline—has been used as a target for propranolol dose adjustment in several studies, though it is less commonly recognized today [5, 7, 9]. Moreover, there is limited evidence linking a heart rate reduction to 55–60 bpm with a corresponding decrease in HVPG to the therapeutic threshold, defined as either < 12 mmHg or a ≥ 20% reduction from baseline. Therefore, the primary objective of this study was to analyze the impact of a heart rate reduction of ≥ 25% from each patient's baseline, achieved through propranolol therapy, on VH in the primary and secondary prophylaxis of cirrhosis. Additionally, the secondary objective was to evaluate the impact of heart rate reduction based on both heart rate reduction of ≥ 25% and/or heart rate at ≤ 60 bpm on VH [2]. These findings will help define the appropriate response to propranolol for individual patients and can be generalized to real-world practice, considering the variability in baseline heart rates among patients with cirrhosis.

2 | Methodology

2.1 | Study Design and Patient Characteristics

A retrospective cohort study was conducted among patients with cirrhosis at a university hospital in Thailand from 2008 to 2023. The protocol was approved by the research ethics committee (EC approval number AF/04-009/02.0 No. 049/2024). We included patients who met the following criteria: (1) aged 18 years or older; (2) diagnosed with cirrhosis, initially identified using the International Classification of Diseases, 10th Edition (ICD-10) codes, including K70.2 (alcoholic fibrosis and sclerosis of liver), K70.3 (alcoholic cirrhosis), K70.4 (alcoholic hepatic failure), K70.9 (alcoholic liver disease, unspecified), K74.3 (primary biliary cirrhosis), K74.4 (secondary biliary cirrhosis), K74.5 (biliary cirrhosis, unspecified), K76.6 (portal hypertension), and K76.9 (liver disease, unspecified), and diagnosis confirmed by the treating physician's documentation in the electronic medical records; (3) patients receiving propranolol for either primary or secondary prophylaxis of VH. For primary prophylaxis, patients had no prior history of VH and met at least one of the following criteria: moderate to large varices or small varices with red wale marks observed on esophagogastroduodenoscopy (EGD), or classification as Child-Pugh class C. For secondary prophylaxis, patients had cirrhosis with a history of VH. We excluded patients based on the following criteria: (1) those who had undergone liver transplantation; (2) patients who received propranolol < 1 month; (3) absence of baseline heart rate data; (4) baseline heart rate < 60 bpm.

2.2 | Subject Classification

Patients who met the inclusion and exclusion criteria were divided into two groups based on their ≥ 25 percentage of heart rate reduction (25-HRR) achieved. 25-HRR represented the percentage of heart rate measurements showing a reduction of ≥ 25% from baseline.

$$25-\mathrm{HRR}=\frac{\text{Total number of heart rate measurements at OPD that showed a reduction of}\geq 25\%\text{ from the baseline}*}{\text{Total number of heart rate measurements at OPD during the follow}-\text{up period}}\times 100$$

* Heart rate measurement after propranolol administration.

25-HRR was calculated using the equation above. Baseline heart rate was defined as the average of three heart rate measurements at the outpatient department (OPD) within 1 year prior to propranolol administration. Patients with a 25-HRR ≥ 50% were categorized into the responder group, indicating patients with a heart rate reduction of ≥ 25% from baseline after propranolol administration. While those with a 25-HRR < 50% were placed in the non-responder group, indicating patients with a heart rate reduction of < 25% from baseline after propranolol administration.

Example: A patient had a baseline heart rate of 80 bpm, so a reduction in heart rate of ≥ 25% after propranolol administration corresponded to ≤ 60 bpm. During the total follow-up period, heart rate measurements were taken at OPD 20 times, with the heart rate being ≤ 60 bpm on 10 times. Therefore, 25-HRR = (10/20) × 100 = 50%, and the patient was classified into the responder group.

2.3 | Data Collection

All the clinical data were extracted from a hospital database. Baseline characteristics were collected on the first day of initiating propranolol for primary or secondary prophylaxis of VH, including age, gender, weight, etiology of cirrhosis, presence of hepatocellular carcinoma (HCC), hypertension, thyroid disorders, and vital signs recorded at OPD prior to propranolol initiation (heart rate and mean arterial pressure). Additionally, cirrhosis complications (ascites, hepatic encephalopathy, and spontaneous bacterial peritonitis) and laboratory values (aspartate aminotransferase, alanine transaminase, total bilirubin, international normalized ratio, prothrombin time, albumin, platelets, serum sodium, serum creatinine, and estimated glomerular filtration) were documented. The Child–Pugh score and Model for End-Stage Liver Disease Sodium (MELD-Na) score were also calculated.

Moreover, all heart rate measurements were taken during OPD for calculating 25-HRR, where patients with cirrhosis were being followed. Moreover, if there was more than one heart rate measurement at the same OPD visit, we did not use the mean HR but instead used the lowest HR. Similarly, all doses of propranolol were assessed to determine the starting and maximum doses. The primary outcome was the incidence of VH defined as active bleeding from varices observed during EGD. The outcome was monitored until the occurrence of the VH, liver transplantation, discontinuation of propranolol, loss to follow-up, or up to 5 years after enrollment.

2.4 | Statistical Analysis

Categorical data were expressed as frequency distributions, and the Chi-square or Fisher's exact tests were used to assess a significant difference among groups. Continuous variables were presented as mean ± standard deviation or median and range, depending on their distribution. The normality of distributions was assessed by the Kolmogorov–Smirnov test. Continuous variables were compared by the Student's *t*-test or the Mann–Whitney *U*-test, as appropriate. The primary objective was to analyze the impact of a heart rate reduction of ≥ 25% from each patient's baseline, achieved through propranolol therapy, on VH in the primary and secondary prophylaxis of cirrhosis. The primary outcome was the incidence of VH, evaluated as the time to the first event, expressed as an adjusted hazard ratio (HR) with 95% confidence intervals (CIs). A survival analysis with propensity score (PS)–inverse probability treatment weighting (IPTW) was performed to associate heart rate reduction and the primary outcome. First, the PS was calculated based on the following factors: (1) baseline characteristics such as age and gender; (2) clinical factors associated with the development of VH, including the presence of HCC, ascites, MELD-Na score, and Child–Pugh score [10, 11], and (3) factors influencing heart rate reduction with propranolol therapy, such as baseline heart rate, achieving a heart rate of ≤ 60 bpm for ≥ 50% of the total measurements after receiving propranolol, and receiving a propranolol dosage of ≥ 80 mg per day. Second, individual weights were determined as the inverse of the probability of their assigned exposure level, defined as the degree of heart rate reduction. Applying these weights to the study population generated a pseudopopulation in which measured confounders were balanced across groups. In time-to-event analyses, inverse probability of censoring weights were used to address informative censoring by up-weighting individuals remaining in the study who shared similar characteristics with those who were censored [12, 13].

Additionally, our secondary objective was to assess the impact of heart rate reduction following current recommendations [2] on VH in the primary and secondary prophylaxis of cirrhosis. A responder was defined based on the following heart rate reduction criteria: (1) achieving a heart rate of ≤ 60 bpm, (2) a reduction of ≥ 25% from each patient's baseline and achieving a heart rate of ≤ 60 bpm, and (3) a reduction of ≥ 25% from each patient's baseline or achieving a heart rate of ≤ 60 bpm. Achieving a heart rate of ≤ 60 bpm was defined as having ≥ 50% of heart rate measurements at ≤ 60 bpm, as calculated using the equation in Appendix S1. The incidence of VH was evaluated HR with 95% CIs. A survival analysis with PS-IPTW was performed to associate heart rate reduction and the incidence of VH, as detailed in Appendix S2.

Moreover, subgroup analysis of VH based on the maximum dose of propranolol and responses with a heart rate reduction of ≥ 12.5%, 50%, and 75% from each patient's baseline was conducted. In primary prophylaxis, our study requires a sample size of 233 patients per group, while in secondary prophylaxis, a sample size of 39 patients per group is needed to achieve a power of 80% [7, 14, 15]. A two-tailed probability value of $p < 0.05$ was considered statistically significant. All statistical analyses in this study were performed using STATA version 14.

3 | Results

3.1 | Patient Characteristics According to Response With A Reduction of ≥25% From Baseline

Between 2008 and 2023, 484 patients with cirrhosis receiving propranolol for either primary or secondary prophylaxis were screened. A total of 112 patients were excluded for the following reasons: underwent liver transplantation ($n=3$), received propranolol for <1 month ($n=50$), absence of baseline heart rate data ($n=57$), and baseline heart rate <60 bpm ($n=2$). A total of 215 patients treated with propranolol for primary prophylaxis were included, categorized into a responder group of 72 (33.5%) patients with a median 25-HRR of 68% (range 50%–100%) and a non-responder group of 143 (66.5%) patients with a median 25-HRR of 22% (range 6%–47%). The median length of follow-up was 19.7 months (range 0.4–64.3) (Table 1). Additionally, 157 patients receiving propranolol for secondary prophylaxis were analyzed, with a median follow-up period of 11.4 months (range 0.5–67.6). Of these, 52 (33.1%) were classified as responders (median 25-HRR 73%, range 50%–100%) and 105 (66.9%) as non-responders (median 25-HRR 25%, range 5%–45%) (Table 1).

The most common etiology was alcoholic cirrhosis, accounting for 33.5% in the primary prophylaxis and 52.9% in the secondary prophylaxis. The median Child–Pugh score was 6 (range 5–12) for primary prophylaxis and 7 (range 5–12) for secondary prophylaxis. The most common complication of cirrhosis was ascites grade 2, identified by moderate abdominal distension on physical examination, occurring in 31.2% of patients with primary prophylaxis and 28.7% of those with secondary prophylaxis (Table 1).

3.2 | Heart Rate Measurement and Propranolol Administration According to Response With A Reduction of ≥25% From Baseline

In both primary and secondary prophylaxis, the responder group had a higher baseline heart rate than the non-responder group. For example, in primary prophylaxis, the responder group had a median heart rate of 88.5 bpm (range 69–132) compared to 81 bpm (range 62–114) in the non-responder group ($p<0.001$) (Table 1). In contrast, after receiving propranolol for the prophylaxis of VH, the minimum and maximum heart rates in the responder group were lower than those in the non-responder group across both indications (Table 2). Furthermore, the responder group had a higher number of patients with a heart rate of ≤60 bpm for more than 50% of the total measurements across both indications (Table 2). In primary prophylaxis, 43% of patients in the responder group had a heart rate of ≤60 bpm for more than 50% of the measurements, compared to 16.8% in the non-responder group ($p<0.001$). The frequency of heart rate measurements and the time intervals between measurements were comparable in both groups for both primary and secondary prophylaxis (Table 2). Additionally, there was no significant difference in the starting and maximum dose of propranolol and the number of patients receiving the maximum dose of propranolol ≥80 mg/day between the two groups (Table 2).

3.3 | The Effect of Propranolol on VH Through Achieving Heart Rate Reduction ≥25% From Baseline

Table S1 showed the baseline characteristics for both groups after adjustment with inverse probability of treatment weighting. Table 3 demonstrated the incidences of first VH in primary prophylaxis and recurrent VH in secondary prophylaxis. The responder group with achieving heart rate reduction ≥25% from baseline had a similar incidence of VH compared to the non-responder group in both primary and secondary prophylaxis, with an unadjusted HR of 1.73 (95% CI: 0.85–3.50) and adjusted HR of 1.70 (95% CI: 0.82–3.49) for primary prophylaxis and an unadjusted HR of 1.20 (95% CI: 0.62–2.32) and adjusted HR of 1.00 (95% CI: 0.34–2.90) for secondary prophylaxis. A comparison of the cumulative adjusted hazard of VH for the two groups is shown in Figure 1 (primary prophylaxis) and Figure 2 (secondary prophylaxis). Moreover, a subgroup analysis of VH based on the maximum dose of propranolol and responses with a heart rate reduction of ≥12.5%, 50%, and 75% from each patient's baseline is presented in Tables S2 and S3.

3.4 | The Effect of Propranolol on VH Through Achieving Heart Rate Reduction Based on Current Recommendation

Tables S4–S9 showed baseline characteristics for responders and non-responders, defined as follows: (1) response in achieving a heart rate of ≤60 bpm, (2) response with a reduction of ≥25% from each patient's baseline and achieving a heart rate of ≤60 bpm, and (3) response with a reduction of ≥25% from each patient's baseline or achieving a heart rate of ≤60 bpm. Table 4 showed the impact of VH in primary and secondary prophylaxis based on these heart rate reductions. Responders, as defined by these heart rate reductions, had similar incidences of VH compared to non-responders in both primary and secondary prophylaxis. The cumulative hazard curve for variceal hemorrhage prophylaxis based on these heart rate reductions is shown in Figures S1–S3.

4 | Discussion

For the past decade, achieving a heart rate of 55–60 bpm has been utilized as a key indicator of propranolol efficacy in both primary and secondary prophylaxis of VH [2]. Nonetheless, in clinical practice, propranolol regimens are often adjusted based on individual variations in baseline heart rates. This study aimed to evaluate the impact of a heart rate reduction of ≥25% from baseline through propranolol therapy to determine the most appropriate heart rate target for individual patients. Interestingly, our results revealed that patients who achieved a heart rate reduction of ≥25% (the responder group) exhibited a similar incidence of VH compared to those who did not achieve this target (the non-responder group) in both primary and secondary prophylaxis.

Propranolol provides prophylaxis against VH by reducing portal pressure [3]. Achieving a reduction in HVPG (referring

TABLE 1 | Baseline characteristics according to propranolol indication for variceal hemorrhage prophylaxis, categorized by response with a reduction of ≥25% from each patient's baseline.

	Primary prophylaxis				Secondary prophylaxis			
	All ($n=215$)	Responder ($n=72$)	Non-responder ($n=143$)	p	All ($n=157$)	Responder ($n=52$)	Non-responder ($n=105$)	p
25-HRR, %	22 (6–100)	68 (50–100)	22 (6–47)	<0.001	25 (5–100)	73 (50–100)	25 (5–45)	<0.001
Duration of follow-up (months), median (range)	19.7 (0.4–64.3)	21.3 (1.0–62.3)	17.1 (0.4–64.3)	0.35	11.4 (0.5–67.6)	11.3 (0.6–67.6)	11.4 (0.5–66.5)	0.62
Male, *n* (%)	167 (77.7)	55 (76.4)	112 (78.3)	0.75	130 (82.8)	47 (90.4)	83 (79.1)	0.11
Age, mean (SD)	56.1 (10.9)	56.4 (9.9)	56.0 (11.4)	0.80	54.3 (10.9)	53.8 (9.5)	54.6 (11.6)	0.69
Weight, kg, median (range)	61 (38–105)	60 (40–99)	62 (38–105)	0.17	62 (38–110)	65 (50–105)	60 (38–110)	0.002
Etiology, *n* (%)				0.86				0.63
Alcoholic	72 (33.5)	23 (31.9)	49 (34.0)		83 (52.9)	32 (61.5)	51 (48.6)	
HBV	47 (21.9)	15 (20.8)	32 (22.2)		32 (20.4)	10 (19.2)	22 (21.0)	
HCV	52 (24.2)	20 (27.8)	32 (22.2)		21 (13.4)	5 (9.6)	16 (15.2)	
NASH	13 (6.1)	3 (4.2)	10 (6.9)		6 (3.8)	1 (1.9)	5 (4.8)	
Others	31 (14.4)	11 (15.3)	20 (14.0)		15 (9.6)	4 (7.7)	11 (10.5)	
HCC, *n* (%)	64 (29.7)	25 (34.7)	39 (27.3)	0.26	29 (18.5)	12 (23.1)	17 (16.2)	0.38
Hypertension, *n* (%)	43 (20.0)	12 (16.7)	31 (21.7)	0.47	30 (19.1)	12 (23.1)	18 (17.1)	0.37
Thyroid disorder, *n* (%)	3 (1.4)	1 (1.4)	2 (1.4)	1.00	1 (0.6)	1 (1.9)	0	—
Child-Pugh score, median (range)	6 (5–12)	6 (5–12)	6 (5–12)	0.31	7 (5–12)	7 (5–12)	7 (5–11)	0.09
Child–Pugh group, *n* (%)				0.88				0.12
A	116 (54.0)	37 (51.4)	79 (55.2)		69 (44.0)	18 (34.6)	51 (48.6)	
B	80 (37.2)	28 (38.9)	52 (36.4)		77 (49.0)	28 (53.9)	49 (46.7)	
C	19 (8.8)	7 (9.7)	12 (8.4)		11 (7.0)	6 (11.5)	5 (4.8)	
MELD-Na score, median (range)	14 (6–36)	14 (7–32)	13 (6–36)	0.73	14 (6–29)	16 (6–29)	14 (7–25)	0.24
Ascites[a], *n* (%)				0.31				0.20
Grade 1 mild	1 (0.5)	0	1 (0.7)		2 (1.3)	2 (3.9)	0	
Grade 2 moderate	67 (31.2)	27 (37.5)	40 (28.0)		45 (28.7)	14 (26.9)	31 (29.5)	
Grade 3 severe	8 (3.8)	1 (1.4)	7 (4.9)		4 (2.6)	2 (3.9)	2 (1.9)	

(Continues)

TABLE 1 | (Continued)

	Primary prophylaxis				Secondary prophylaxis			
	All (*n* = 215)	**Responder (*n* = 72)**	**Non-responder (*n* = 143)**	***p***	**All (*n* = 157)**	**Responder (*n* = 52)**	**Non-responder (*n* = 105)**	***p***
HE, *n* (%)	7 (3.3)	2 (2.8)	5 (3.5)	1.00	2 (1.3)	0	2 (1.9)	—
SBP, *n* (%)	0	0	0	—	2 (1.3)	0	2 (1.9)	—
HR baseline[b], bpm, median (range)	83 (62–132)	88.5 (69–132)	81 (62–114)	<0.001	86 (61–120)	92.5 (70–120)	81 (61–120)	<0.001
MAP baseline[b], mmHg, median (range)	98 (64–156)	96.5 (64–142)	99 (68–156)	0.61	93 (59–134)	95 (77–134)	91 (59–130)	0.02
AST, U/L, median (range)	59 (14–339)	74.5 (14–339)	55 (20–294)	0.002	59 (19–574)	76.5 (21–481)	56 (19–574)	0.009
ALT, U/L, median (range)	37 (9–489)	41.5 (13–298)	35 (9–489)	0.11	34 (3–368)	41.5 (10–368)	31 (3–297)	0.06
Total bilirubin, mg/dL, median (range)	1.4 (0.3–24)	1.5 (0.3–18)	1.3 (0.3–24)	0.13	1.7 (0.3–13.3)	2.1 (0.6–13.3)	1.5 (0.3–13.3)	1.00
INR, median (range)	1.2 (0.9–4.6)	1.2 (0.9–4.6)	1.2 (0.9–3)	0.33	1.3 (0.9–2.6)	1.4 (1–2.6)	1.3 (0.9–2.1)	0.15
PT, sec, median (range)	13.4 (9.9–49.8)	13.7 (10.6–49.8)	13.2 (9.9–32.4)	0.28	14.4 (10.6–30.7)	14.9 (10.8–30.7)	14.1 (10.6–22.9)	0.07
Albumin, mg/dL, median (range)	3.4 (1.4–5.6)	3.3 (1.4–5.6)	3.5 (1.8–4.6)	0.13	3.1 (1.7–4.8)	3.1 (1.8–4.2)	3.2 (1.7–4.8)	0.31
Platelet, 10^3/L, median (range)	90 (22–401)	91 (22–359)	89 (24–401)	0.69	97 (18–331)	97.5 (40–331)	97 (18–327)	0.75
Serum sodium, mEq/L, median (range)	137 (121–145)	137 (124–145)	137 (121–145)	0.77	137 (123–154)	137 (123–147)	137 (127–154)	0.56
Serum creatinine, mg/dL, median (range)	0.9 (0.4–5.8)	0.9 (0.5–5.8)	0.9 (0.4–3)	0.16	0.9 (0.3–2.9)	0.9 (0.5–2)	0.9 (0.3–2.9)	0.94
eGFR, mL/min/1.73 m^2, median (range)	92.2 (9.7–161.4)	95.2 (9.7–135.1)	90.3 (26.4–161.4)	0.38	92.7 (19–202.1)	90.4 (38.9–202.1)	93.8 (19–137.1)	0.99

Abbreviations: 25-HRR, ≥25 percentage of heart rate reduction; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bpm, beat per minus; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HR, heart rate; INR, International Normalized Ratio; MAP, mean arterial pressure; MELD-Na, model for end-stage liver disease sodium; mg, milligram; NASH, non-alcoholic steatohepatitis; PT, prothrombin time; SBP, spontaneous bacterial peritonitis.

[a]Ascites Grade 1 = only detected by ultrasound, Grade 2 = moderate systemic distension of the abdomen, Grade 3 = marked distension of the abdomen (refractory ascites).

[b]Before propranolol administration.

TABLE 2 | Heart rate measurement after propranolol administration, categorized by response with a reduction of ≥25% from each patient's baseline.

	Primary prophylaxis			Secondary prophylaxis		
	Responder ($n=72$)	Non-responder ($n=143$)	p	Responder ($n=52$)	Non-responder ($n=105$)	p
Minimum HR, bpm, median (range)	57 (42–76)	62 (43–115)	0.001	58 (43–77)	63 (40–97)	0.002
Maximum HR, bpm, median (range)	80.5 (50–119)	86 (51–118)	0.004	81.5 (52–114)	85 (56–125)	0.04
Number of patients with a heart rate of ≤60 bpm for ≥50% of the total measurements, *n* (%)	31 (43.1)	24 (16.8)	<0.001	22 (42.3)	14 (13.3)	<0.001
Frequency of heart rate measurement, *n* (%)	9.5 (1–29)	7 (1–32)	0.36	5 (1–24)	5 (1–22)	0.54
Time difference between heart rate measurements, day, median (range)	77 (10–188)	71 (17–168)	0.24	57.5 (11–161)	67 (13–141)	0.19
Starting dose of propranolol, mg/day, median (range)	40 (20–120)	40 (20–120)	0.48	40 (10–160)	40 (10–80)	0.84
Maximum dose of propranolol, mg/day, median (range)	80 (20–240)	80 (20–320)	0.60	80 (10–240)	80 (20–400)	0.68
Number of patients receiving maximum dose of propranolol ≥80 mg/day, *n* (%)	44 (61.1)	95 (66.4)	0.44	32 (61.5)	68 (64.8)	0.73

Abbreviations: bpm, beat per minus; HR, heart rate; mg, milligram.

TABLE 3 | The effect of propranolol on variceal hemorrhage through achieving heart rate reduction ≥25% with inverse probability of treatment weighting (primary objective).

Variceal hemorrhage							
Indication	All[a]	Responder[a]	Non-responder[a]	Hazard ratio (95% CI)	p	Adjusted hazard ratio[b] (95% CI)	p
Primary prophylaxis	31/215 (14.4)	15/72 (20.8)	16/143 (11.2)	1.73 (0.85–3.50)	0.13	1.70 (0.82–3.49)	0.15
Secondary prophylaxis	38/157 (24.2)	14/52 (26.9)	24/105 (22.9)	1.20 (0.62–2.32)	0.60	1.00 (0.34–2.90)	0.99

[a]Values are the number of patients with VH/total number (%).
[b]Adjusted hazard ratio obtained from inverse probability of treatment-weighted analysis.

to portal pressure) to the therapeutic threshold, either to <12 mmHg or by ≥20% from baseline, has been shown to significantly decrease the risk of VH and other complications compared to patients with smaller HVPG reductions (HR 3.88, 95% CI 1.64–9.19, $p=0.002$) [4]. However, HVPG measurement is not routinely recommended for clinical monitoring due to its limited sensitivity in detecting minor pressure variations, which may be influenced by measurement inaccuracies and physiological daily fluctuations [3]. Additionally, it is a less practical method owing to its invasive nature. According to these limitations, our study aimed to evaluate the impact of a less invasive method, specifically a heart rate reduction of ≥25% from baseline, as an alternative indicator of propranolol response. We selected a heart rate reduction of ≥25% from baseline for several reasons. First, dose adjustment of propranolol depends on individual variations in baseline heart rates. Therefore, comparing heart rate reduction from baseline is more appropriate than using a fixed target of 55–60 bpm,

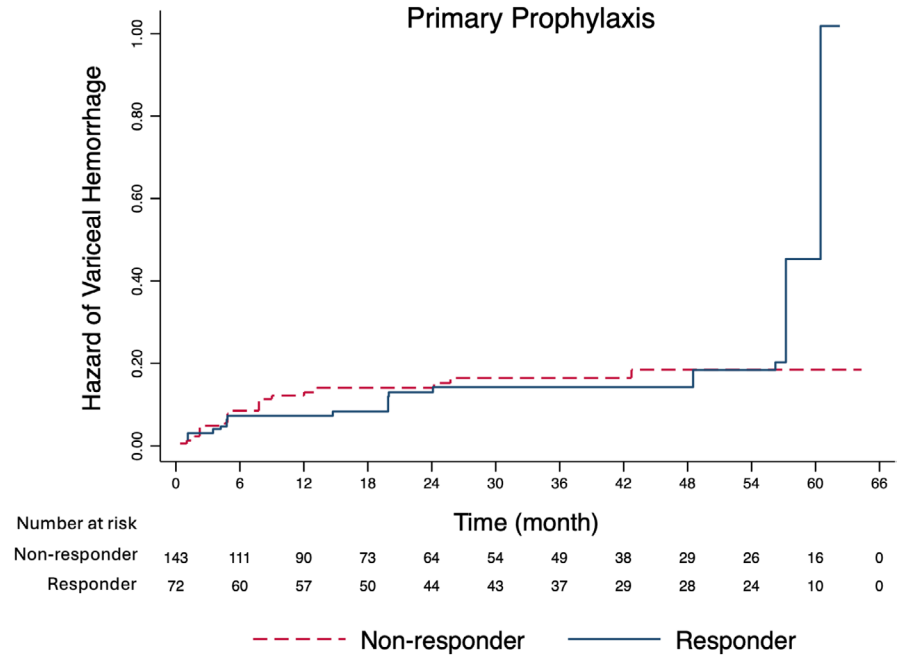

FIGURE 1 | Cumulative hazard curve for variceal hemorrhage based on response with a reduction of ≥ 25% from baseline in primary prophylaxis with propranolol, the primary outcome. Adjusted hazard ratio: 1.70 [0.82–3.49], $p = 0.15$.

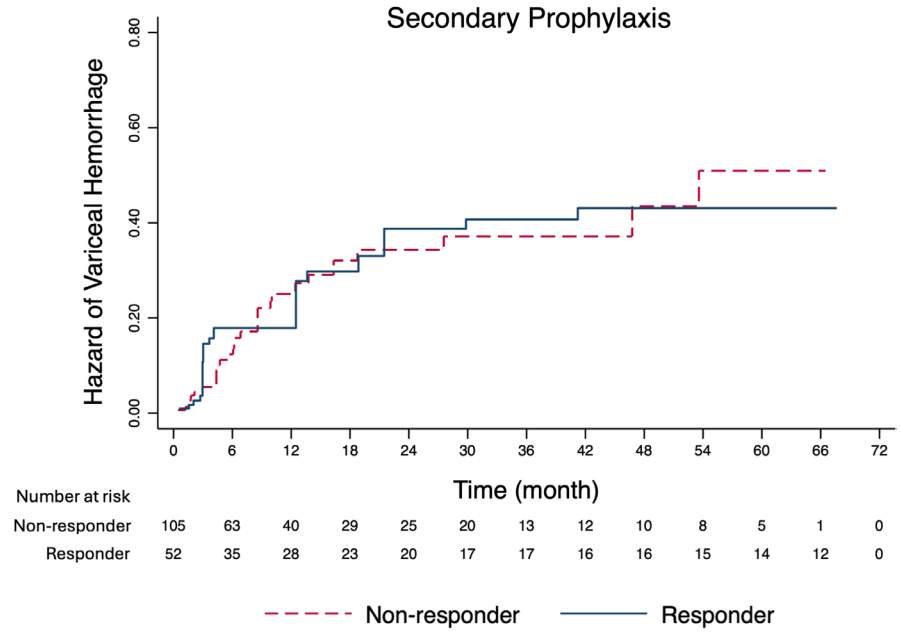

FIGURE 2 | Cumulative hazard curve for variceal hemorrhage based on response with a reduction of ≥ 25% from baseline in secondary prophylaxis with propranolol, the primary outcome. Adjusted hazard ratio: 1.00 [0.34–2.90], $p = 0.99$.

irrespective of the baseline rate. Moreover, a heart rate reduction of ≥ 25% from baseline has been used as a target for increasing propranolol dosage in VH in several clinical studies, which confirmed that the responder group achieved a therapeutic threshold by reducing HVPG [5, 7, 9]. However, our results demonstrated that the responder group, defined by a heart rate reduction of ≥ 25% from baseline, did not show a prophylactic effect on the incidence of VH compared to the non-responder group in both primary and secondary prophylaxis. Moreover, our secondary objective was to assess the incidence of VH based on the current recommendation of heart rate reduction to 55–60 bpm [2] and in combination with and/or a heart rate reduction of ≥ 25% from baseline. The results showed no difference in the incidence of VH between responders, as defined by these heart rate reductions, and non-responders. These findings reflect real-world clinical practice, where physicians monitor the heart rate of patients with cirrhosis to adjust propranolol dosages accordingly. Therefore, a heart rate reduction of ≥ 25% from baseline may not represent the efficacy threshold for VH prophylaxis in propranolol therapy.

TABLE 4 | The effect of propranolol on variceal hemorrhage through achieving heart rate reduction based on current recommendations with inverse probability of treatment weighting (secondary objective).

Indication	Responder[a]	Non-responder[a]	Hazard ratio (95% CI)	*p*	Adjusted hazard ratio[b] (95% CI)	*p*
Response with achieving a heart rate of ≤ 60 bpm						
Primary prophylaxis	6/55 (10.9)	25/160 (15.6)	0.64 (0.26–1.56)	0.30	0.76 (0.29–1.98)	0.58
Secondary prophylaxis	5/36 (13.9)	33/121 (27.3)	0.43 (0.17–1.11)	0.06	0.83 (0.29–2.37)	0.72
Response with a reduction of ≥ 25% from each patient's baseline and achieving a heart rate of ≤ 60 bpm						
Primary prophylaxis	6/31 (19.4)	25/184 (13.6)	1.41 (0.58–3.46)	0.47	1.41 (0.53–3.75)	0.49
Secondary prophylaxis	5/22 (22.7)	33/135 (24.4)	0.76 (0.29–1.95)	0.55	0.75 (0.25–2.27)	0.62
Response with a reduction of ≥ 25% from each patient's baseline or achieving a heart rate of ≤ 60 bpm						
Primary prophylaxis	15/96 (15.6)	16/119 (13.5)	1.02 (0.50–2.06)	0.96	0.96 (0.46–1.97)	0.90
Secondary prophylaxis	14/66 (21.1)	24/91 (26.4)	0.81 (0.42–1.56)	0.52	0.64 (0.31–1.33)	0.23

[a]Values are the number of patients with VH/total number (%).
[b]Adjusted hazard ratio obtained from inverse probability of treatment-weighted analysis.

Our results reflect long-term clinical practice in the prophylaxis of VH through propranolol therapy. A prospective cohort study on cirrhotic patients receiving non-selective beta blockers for primary prophylaxis demonstrated that a heart rate reduction of > 25% at 3 months was one of the most significant predictors of a positive response, evidenced by stable or downstaging variceal grading on EGD [16]. In contrast, this study assessed the development of VH in relation to heart rate reduction, based on all measurements obtained during OPD visits over the entire long-term follow-up period. The median follow-up duration was 19.7 months for primary prophylaxis and 11.4 months for secondary prophylaxis. Moreover, we collected all measurements of heart rate to account for fluctuations and measurement errors arising from the time series of physiological variables that fluctuate nonlinearly in response to multiple stimuli from various sources [17]. Heart rate variability, which is influenced by autonomic nervous system alterations, correlates with increased portal hypertension as cirrhosis severity progresses [18]. Measurement errors and heart rate variability may limit the reliability of heart rate reduction as a consistent indicator of propranolol efficacy, given its high sensitivity to fluctuations influenced by various factors.

Heart rate reduction reflects the blockade of beta-1 receptors, which is one of the two mechanisms by which propranolol reduces portal pressure [3]. However, it does not indicate the blockade of beta-2 receptors, which mediate splanchnic vasoconstriction. Propranolol, a nonselective beta-blocker that is a cornerstone in the prophylaxis of VH in cirrhosis, reduces portal pressure by blocking both beta-1 and beta-2 receptors. Consequently, only nonselective beta-blockers, rather than selective beta-1 blockers, are recommended for the reduction of portal hypertension [2]. Notably, the measurement of heart rate reduction does not fully account for the decrease in portal pressure mediated by propranolol. Moreover, there is limited evidence supporting a direct relationship between heart rate reduction and HVPG reduction, which reflects portal pressure. Our findings suggest that propranolol exerts beneficial effects on VH rates that might be independent of heart rate reduction. Specifically, our study demonstrated that all responder groups, defined by (1) a reduction of ≥ 25% from each patient's baseline, (2) achieving a heart rate of ≤ 60 bpm, or (3) a reduction of ≥ 25% from baseline and/or achieving a heart rate of ≤ 60 bpm, had a similar incidence of VH compared to non-responder groups. Moreover, the overall incidence of VH among patients receiving propranolol in our study was lower than the reported incidence among patients who did not receive propranolol in previous studies [15, 19]. These findings suggest that the prophylactic effect of propranolol on VH is likely not dependent on heart rate reduction.

The efficacy of propranolol in VH prophylaxis increases with higher doses, particularly when the dose exceeds the starting dose by approximately 1.5–2 times [10]. The adjusted HR for the risk of VH, compared to lower doses, is 0.64 (95% CI, 0.51–0.81) [10]. Moreover, dose titration of propranolol, typically at a median dose of ≥ 80 mg/day, demonstrated significant prophylaxis of VH with propranolol treatment in several clinical studies [5–8]. Our study showed that the median maximum dose of propranolol, 80 mg/day, and the number of patients receiving a maximum dose of propranolol ≥ 80 mg/day were similar in both the responder and non-responder groups across primary and secondary prophylaxis. Therefore, there was a similar incidence of VH in both groups because most patients in both the responder and non-responder groups received a similar dose of propranolol for VH prophylaxis. The dose of propranolol plays a critical role in

determining the efficacy of VH prophylaxis. Therefore, a survival analysis using PS-IPTW, based on receiving propranolol at a dose of ≥80 mg/day, was performed to assess the association between heart rate reduction and the development of VH in this study.

The main limitations of our study should be noted. First, heart rate measurements may not have been taken during sufficient resting conditions, but they reflect the real-world practice of treating patients with cirrhosis. Moreover, we collected heart rate data exclusively from OPD visits to minimize the influence of acute conditions that could interfere with measurements obtained during hospital stays. Additionally, the responder group had a higher baseline heart rate than the non-responder group, which might have influenced the total daily dose of propranolol received. This suggests the presence of confounding by indication, which is why baseline heart rate was included in the calculation of PS-IPTW. Although the confidence intervals are quite wide and the total number of patients in our study was smaller than expected, the incidence of VH in our study was similar to that reported in previous studies. In primary prophylaxis, our results showed an overall incidence of VH of 14.4%, which aligns with previous studies that combined two randomized controlled trials evaluating the effect of propranolol, reporting an incidence of VH between 16% and 19% among 203 patients receiving propranolol and 27%–32% among 201 patients receiving placebo [15]. In secondary prophylaxis, the overall incidence of VH was 24.2%, which is consistent with previous randomized controlled trials, reporting an incidence of VH of 24% among 37 patients receiving propranolol combined with variceal band ligation and 32% among 40 patients receiving variceal band ligation alone [19]. Moreover, our study included all patients with cirrhosis who received propranolol and met the inclusion criteria over a retrospective 15-year period at a single center. However, further investigations into the impact of heart rate reduction on variceal hemorrhage in a multicenter setting are needed. Lastly, due to the retrospective design of the study, we were unable to assess patient compliance with propranolol therapy.

In conclusion, our analysis did not support achieving a heart rate reduction of ≥25% from baseline as a response to propranolol for the primary and secondary prophylaxis of VH in cirrhosis. These findings challenge the concept of personalized therapy based on heart rate reduction and indicate that routine heart rate measurement may not be essential for assessing the efficacy of propranolol therapy.

Author Contributions

W.M. and P.D. wrote the manuscript; W.M. and P.D. designed the research; W.M., W.S., M.N., and T.P. performed the research; W.M. and P.D. analyzed the data.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.