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Heterogeneity of treatment response to beta-blockers in the treatment of portal hypertension: A systematic review

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Abstract

Background: It has been suggested that a relevant proportion of patients do not respond to nonselective beta-blockers (NSBB)s, which raises questions regarding the need for individualized therapy. The existence of potential heterogeneity in the treatment response can be assessed using the variability ratio (VR) of the outcome measurement (in this case, HVPG) between the treated and placebo groups. We conducted a systematic review and meta-analysis of randomized controlled trials to assess the potential heterogeneity in the portal pressure response to NSBBs.

Methods: After a systematic search, we quantified the heterogeneity of treatment response with the VR between the treatment and control groups, with VR $>$ 1 indicating potential heterogeneity. We used a similar approach to compare carvedilol with propranolol and statins with placebo.

Results: We identified 18 studies that included 965 patients. A comparison between beta-blockers and placebo showed a pooled VR of 0.99 (95% CI:0.87—1.14), which suggests a homogeneous HVPG response to NSBB at the individual patient level (ie, no evidence to support that some patients responded to beta-blockers and others did not). For the comparison between carvedilol and propranolol, pooled VR was 0.97 (95% CI 0.82–1.14), suggesting that carvedilol achieves a greater average response (rather than an increase in the proportion of responders). There was no evidence of a heterogeneous response to statins.

Conclusion: Our analysis did not support the existence of a heterogeneous patient-by-patient response to NSBBs in cirrhosis. These findings challenge the concept of personalized therapy based on portal pressure response and indicate that routine portal pressure measurement may not be necessary to guide NSBB therapy.

Abbreviations: NSBB, nonselective beta-blockers; RCTs, randomized controlled trials; VR, variability ratio.

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INTRODUCTION

A number of randomized trials have shown that nonselective beta-blockers (NSBBs) improve several clinical outcomes in cirrhosis with portal hypertension.[1] In addition, longitudinal studies have shown that, as a group, those patients who achieve a $>20\%$ reduction in HVPG (or to levels <12 mm Hg) on NSBBs have a much better prognosis than patients not achieving these hemodynamic targets.[2,3] It has been suggested that $>50\%$ of patients treated with conventional NSBBs (nadolol/propranolol) do not achieve these hemodynamic targets and are therefore referred to as "nonresponders to NSBBs."[2] This assumes that there is a clinically relevant and repeatable between-person difference in HVPG response (some patients responding and some nonresponding).

On this basis, it has been suggested that portal pressure measurements, which are done in clinical practice by measuring the HVPG,[4] should be used to guide therapy with NSBBs, as a way to personalize patient care, improving the precision of NSBBs treatment.[4] However, after over 40 years of use of NSBBs for portal hypertension, only 1 trial has compared HVPG-guided with non-HVPG–guided therapy[5] out of over 50 beta-blocker trials in different contexts of portal hypertension. In addition, recent data suggest that the consistency of HVPG measurements might be insufficient to reliably detect, at the individual patient level, relevant changes in portal pressure related to a drug intervention.[6] Finally, from a conceptual point of view, individual patient responses cannot be directly observed, since they would reflect the difference in the outcome (in this case, HVPG) if the patient had been treated as compared to the outcome if the patient had not been treated,[7] and both situations cannot occur at the same time. It is important to note that in other clinical contexts, like the use of statins in primary prevention, in which the readouts of efficacy would be much simpler than HVPG (i.e., LDL cholesterol), there is still no evidence that therapy titrated to target lipid levels improves outcomes *versus* the use of fixed doses.[8]

Recently, it has been suggested that the heterogeneity in the effects of an intervention can be indirectly quantified from randomized parallel trials by assessing the variability in the outcome measurement in the experimental and control groups (when outcomes are a continuous measurement).[9] If the intervention is associated with a heterogeneous response (there are "responders" and "nonresponders"), outcome variability in the intervention group would be greater than in the control group. This concept is illustrated with a simulation in Figure 1 (with details explained in Supplemental Data S1, http://links.lww.com/HC9/A657). An extensive literature review by Cortes et al showed that there was little evidence for heterogeneous effects for medical interventions with quantitative outcomes,[9] meaning that in most cases, the average treatment effect of those interventions could be assumed to reflect the individual patient effect. The same strategy to assess potential patient-to-patient heterogeneity in treatment effects has also been used in the context of pharmacological treatment for hypertension,[10] schizophrenia[11] and depression,[12] or on exercise treatment for weight loss,[13] again suggesting no substantial heterogeneity of treatment effects in those conditions.

Whether the effect of NSBB on portal pressure is heterogeneous in patients with cirrhosis could have relevant implications for personalized medicine (ie, identification of "NSBB responders" vs. "nonresponders," with, eg, additional treatments for "nonresponders"). Therefore, in the present study, we aimed to quantify this heterogeneity by reviewing the results of randomized controlled trials (RCT) comparing the effects of NSBBs with placebo (or no intervention) on portal pressure. We postulated that if there were responders and nonresponders to NSBBs, RCTs would show higher variability in the final HVPGs in the beta-blocker groups than in the placebo groups (Supplemental Data S1, http://links.lww.com/HC9/A657). In addition, carvedilol is increasingly being used as a beta-blocker of choice[14] and has been suggested to increase the number of "responders" compared to propranolol.[15] Thus, to assess if this occurs by achieving a greater effect on portal pressure in most patients or by changing the proportion of responders, we compared the heterogeneity in outcome HVPG in studies comparing carvedilol with propranolol. Finally, we addressed a similar question with statins, which act through a different mechanism of action than beta-blockers and are under evaluation for the treatment of portal hypertension.[16]

METHODS

The study protocol is provided as Supplemental Data S2, http://links.lww.com/HC9/A658. The study was not registered.

Our inclusion criteria were RCTs including patients with cirrhosis, published in the English language, comparing beta-blockers (nadolol or carvedilol or propranolol or timolol) with placebo, of carvedilol versus propranolol or nadolol, and of statins versus placebo, using HVPG as an outcome measure (either primary or secondary). The studies had to report either the SD, variances, SE, or CIs of the final HVPGs or show graphs with individual data that could be extracted.

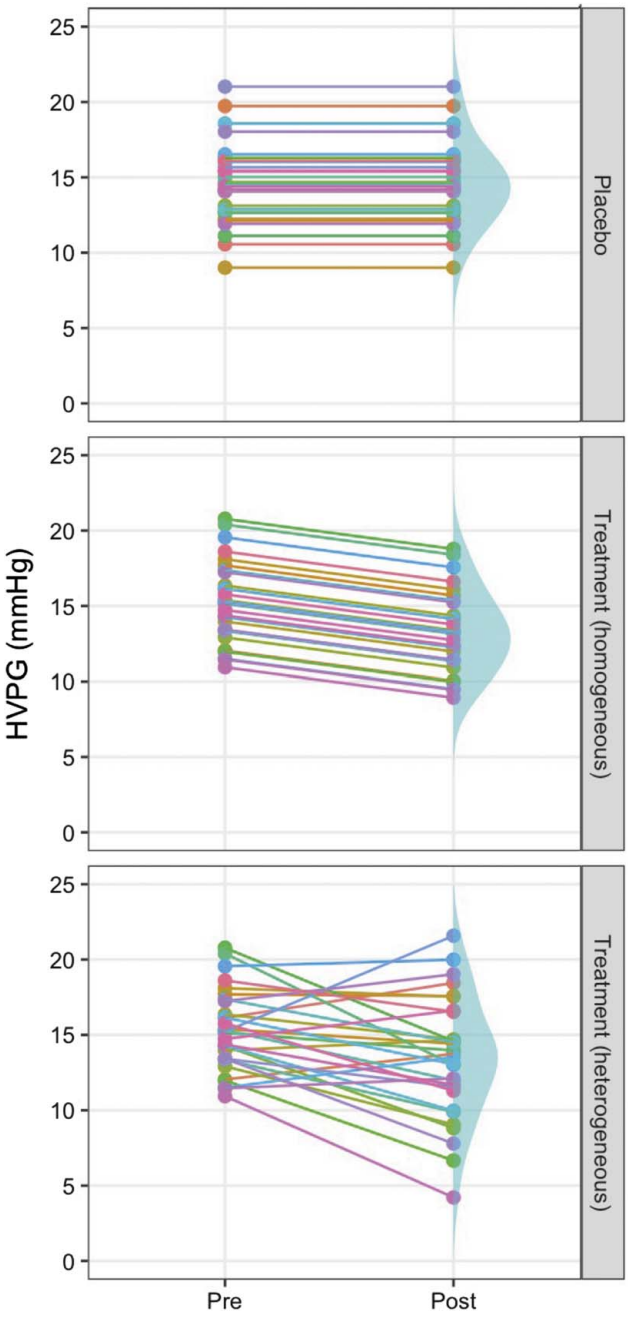

FIGURE 1 Illustration of the concept of increased variability in the outcome measure with a heterogeneous treatment response. A homogeneous effect assumes the same effect occurred in all patients and thus, the lines in the middle panel are parallel. In this case, the HVPG variability at the end of the study (represented by the blue distribution) is comparable between the treatment group and the placebo group. If the treatment induces a heterogeneous response, the lines are no longer parallel (lower panel), and the variability of the HVPG at the end of the study would be greater in the treatment group as compared with the control group. Further details and a more thorough data simulation are provided in Supplemental Data 1, http://links.lww.com/HC9/A657.

Search strategy, study selection, and quality assessment are presented in detail in Supplemental Data S3, http://links.lww.com/HC9/A659.

Statistical analysis

Analysis was conducted in R, with the aid of the metafor package, and based on methods and code reported in Cortes et al[9] and Winkelbeiner et al.[11] Our main analysis compared the HVPG variability between beta-blockers and placebo (or control) arms at the end of the trial. This is referred to as variability ratio (VR) throughout this manuscript, and represents the ratio of the SD of the outcome in the treatment group versus the control group.[17] A VR greater than 1 would support that there is some form of heterogeneity, including individual heterogeneity in treatment response (a different patient-to-patient effect on HVPG or a "patient-by-treatment interaction"), whereas a VR equal to 1 would support the notion that the average decrease in HVPG observed with beta-blockers is the best estimate that we can apply to patients within the defined/used selection criteria. Finally, a VR lower than 1 would suggest that the variability in HVPG at the end of the trial is lower in the treatment group as compared to the control group. This might occur in some situations. For example, in the presence of a "floor effect," patients with high HVPG at baseline show a strong HVPG response, and patients with low HVPG at baseline do not show substantial changes.

For the quantitative meta-analysis, we pooled the VRs of the studies by fitting a random-effects model using the logarithm of the outcome VR at the end of the trial as a response to the study as a random effect. We assessed between-study heterogeneity (ie, to what extent the pooled VR value is applicable to all studies) with the raw value of Cochran's Q, not the corresponding significance test, in accordance with the American Statistical Association statement about *p* values. We investigated the potential influence of different study variables (baseline VRs, baseline HVPG, treatment duration, route of administration, sample size, and type of beta-blocker) on the VRs with moderator analysis by regressing the logarithm of the VR individually on these variables, introduced as fixed effects, with the study as a random effect. A funnel plot showing the ratio of variances as a function of their SE is reported to investigate asymmetries. These analyses were limited to the beta-blockers versus placebo comparisons since the number of studies was low for the other comparisons. The code used for analysis is provided in Supplemental Data S4, http://links.lww.com/HC9/A660.

RESULTS

Beta-blockers versus placebo comparison

We identified 18 studies, including 19 comparisons between beta-blockers and placebo, with data available for a total of 965 patients. The characteristics of these studies are summarized in Table 1, and the full

TABLE 1 Characteristics of the studies comparing beta-blockers versus placebo

References	Comparison (intervention and time of outcome assessment)	Patient characteristics	Child-Pugh Class (A/B/C)/ Score	NSBB Titration method	Mean NSBB dose (mean ± SD; range)	Etiology (%)	Initial number of patients randomized	Number of patients for each comparison	HVPG measurement technique
Lebrec[18]	Propranolol (p.o.) vs. Placebo 1 month	Within 15 d after variceal hemorrhage (with patient stable)	NR	25% reduction in HR	NR	81% alcohol 19% cryptogenic	16 (8 vs. 8)	8 vs. 8	NR
Lebrec[19]	Propranolol (p.o.) *vs.* Placebo 1 h, 1,3,9 mo Only 1 h data included in the present analysis	10–15 d after variceal hemorrhage	NR	25% reduction in HR	158 mg/d	100% alcohol	24 (12 vs. 12)	12 vs. 12 for 1 h comparison	NR
Pomier-Layrargues[20]	Propranolol vs. placebo 10 d	Patients after variceal hemorrhage, within 24 h of control of the bleeding episode	4/10/5	Started at 40 mg twice daily, and subsequent dosing was titrated to produce plasma propranolol concentrations between 50 and 150 ng per mL	102 mg/day[a]	74% alcohol 10% viral 16% cryptogenic	19 (11 vs. 8)	11 vs. 8	Balloon catheter
Groszmann[21]	Propranolol (p.o.) vs. placebo 3,12,24 mo Only data at 3 mo analyzed	Patients with varices without previous bleeding	Mean 8.1 ± 2.1	Increase in dose weekly until one of the following achieved (a) a 25% reduction in HVPG, (b) a decrease in HVPG to 12 mm Hg or less, or (c) a decrease in HR to 55 beats/min or less.	132 ± 78 mg/day[b]	78% alcohol 22% nonalcohol-associated	102 (51 vs. 51)	45 vs. 39 at 3 mo	Balloon catheter
Bendtsen[22]	Propranolol (p.o.) vs. no treatment 12 mo	Patients with varices without previous bleeding	12/9/3	Initial dose 160 mg, adjusted weekly with 80 mg tablets until a decrease in HR of 25% was achieved	NR	88% alcohol-associated 12% nonalcohol-associated	46 (unclear distribution between propranolol vs. placebo)	14 vs. 10	Straight catheter
Bendtsen[23]	Propranolol (i.v.) vs. no treatment (both groups with a test meal) We report measurements after 2 h, when the meal effect is over	Patients with varices without previous bleeding	3/9/1	0.1 mg/kg propranolol i.v. Followed by a constant infusion of 1 mcg/min/kg	14.2 mg (first 2 h)	100% alcohol	13 (6 vs. 7)	6 vs. 7	Straight catheter

Feu[24]	Propranolol (i.v. vs. placebo) 20 min Effects on HVPG and on variceal pressure	All varices 43% previous hemorrhage	Mean 6.3 ± 1.6	Propranolol (0.15 mg/kg), intravenously over 10 min	NR	51% alcohol 27% cryptogenic 22% viral	37 (21 vs. 16)	21 vs. 16	Balloon catheter
Luca[25]	Propranolol (i.v. vs. placebo) 20 min	93% varices 59% previous hemorrhage	Mean 6.9 ± 1.7	Propranolol (0.15 mg/kg), intravenously over 10 min	NR	33% alcohol 58% viral 9% cryptogenic	58 (44 vs. 14) (random-ization 3:1)	44 vs. 14	Balloon catheter
Escorsell[26]	Propranolol (i.v. vs. placebo) 40 min Effects on variceal pressure	All varices 33% previous hemorrhage	Mean 7.8 ± 1.8	Propranolol (0.15 mg/kg), intravenously over 10 min	NR	50% alcohol-associated 50% Nonalcohol-associated	18 (9 vs. 9)	9 vs. 9	NA
Albillos[27]	Propranolol (i.v. vs. placebo) 30 min	All varices 44% previous hemorrhage	Mean 6.7 ± 1.4	Propranolol (0.15 mg/kg), intravenously over 10 min	12.3 ± 11.5 mg	55% alcohol 45% nonalcohol-associated	80 (60 vs. 20)	60 vs. 20	Balloon catheter
Bandi[28]	Propranolol (i.v. vs. placebo) 20 min	All varices. 13% previous hemorrhage	Mean 6.1 ± 0.6	0.15 mg · kg-1 over 15 min followed by a constant infusion of 0.2 mg · h-1.	NR	48% alcohol 52% viral	23 (12 vs. 11)	12 vs. 11	Balloon catheter
Bañares[29]	Carvedilol (p.o.) vs. propranolol (i.v.) vs. placebo after 1 h of administration	All esophageal varices 62% had previous variceal bleed 57% had ascites	13/15/7	Carvedilol (25 mg orally). Propranolol (0.15 mg/kg i.v., followed by a continuous infusion of 0.2 mg/kg)	NA	57% alcohol	35 (14 vs. 14 vs. 7)	35 (14 vs. 14 vs. 7)	Balloon catheter
Merkel[30]	Nadolol vs placebo	All patients small varices 25% ascites	Mean 6.9 ± 1.8	Starting from 40 mg/day with a target of a 25% decrease or a heart rate of 50 bpm	62 ± 25 mg/day	Alcohol 57% Viral 39% others 4%	161 (83 vs. 78)	10 vs. 9	Balloon catheter
Groszmann[31]	Timolol vs placebo 12 mo and yearly thereafter up to 8 y 12 mo data used for analysis	All patients compensated without varices	189/24/0 Mean: 5.4 ± 0.7	Started at 5 mg per day and increased by 5 mg every 3 d until either: HR reduced by 25%, HR < 55, or a maximum of 80 mg was reached	Median: 10.8 (range: 1.25–80) mg/day	Viral 67% Alcohol 24% cryptogenic 5% Others 4%	213 (108 vs. 105)	72 vs. 82	Balloon catheter
Mishra[32]	BB vs. control vs. cyanoacrylate	Patients with cirrhosis with gastric varices of size > 10 mm who have never bled.	29/35/25	Propranolol started at 20 mg bid, increased by 20 mg to achieve a HR of 55/min, or to a maximum of 360 mg/day if SBP > 90 mm Hg	140 (80–240) mg/day	51% alcohol 29% cryptogenic 20% others	89 (30 Cyano-acrylate , 29 BB, 30 no treatment)	89 (30 Cyano-acrylate , 29 BB, 30 no treatment)	Balloon catheter

TABLE 1. (*continued*)

References	Comparison (intervention and time of outcome assessment)	Patient characteristics	Child-Pugh Class (A/B/C)/ Score	NSBB Titration method	Mean NSBB dose (mean ± SD; range)	Etiology (%)	Initial number of patients randomized	Number of patients for each comparison	HVPG measurement technique
Sarin[33]	Propranolol (p.o) vs. placebo 12 mo	Small varices without previous bleeding	Mean 7.5 ± 2.1	Target HR of 55/min or to maximal dose of 360 mg/day	Median dose 120 (range 40–360)	54% viral 35% alcohol 11% Others	150 (77 vs. 73)	25 vs. 24 (random sample of one-third of the total sample)	Balloon catheter
Bhardwaj[34]	Carvedilol (p.o.) vs. placebo 12 mo	Small varices and no history of bleeding	Mean 6.9 ± 1.8	Start dose of 3.125 mg BID, increased up to a maximum of 12.5 mg BID if SBP > 100 mm Hg and heart rate > 55 bpm	12 ± 1.67 mg/ day	44% cryptogenic 25% viral 24% alcohol 7% others	140 (70 vs 70)	52 vs 48	Balloon catheter
Villanueva[35]	Propranolol or carvedilol (according to acute HVPG response) Versus placebo. 67% received propranolol and 33% received carvedilol. HVPG at 12 mo and yearly up to 24 mo Only 12 mo data used for analysis	All patients compensated with HVPG >= 10 mm Hg and no large varices	161/40/0 Mean 5.8 ± 0.9	HVPG acute responders: propranolol 40 mg BID increased up to 160 mg BID. Nonresponders: carvedilol, starting with 6.25 mg/ day increased up to 25 mg/day, keeping HR > 55 and SBP > 90 mm Hg	95 ± 78 mg/ day	56% viral 16% alcohol 13% others 9% alcohol/ viral 6% MASLD	201 (100 vs. 101)	78 vs. 78	Balloon catheter

Note: In those studies in which response is assessed at different time points, the earlier assessment of response time point was used for analysis (the reason is that over time the population is increasingly selected (dropouts and patients with terminal events).

[a]Mean dose extracted from Villeneuve et al (clinical report of the trial)[36]

[b]Mean dose extracted from Conn et al (clinical report of the trial)[37]

[c]Mean HVPG/SD at 1 year was extracted from Figure 2B of the manuscript.

Abbreviations: BID, twice daily; MASLD, metabolic-associated steatotic liver disease; NA, not applicable; NR, not reported; NSBB, nonselective beta-blockers ; SBP, systolic blood pressure.

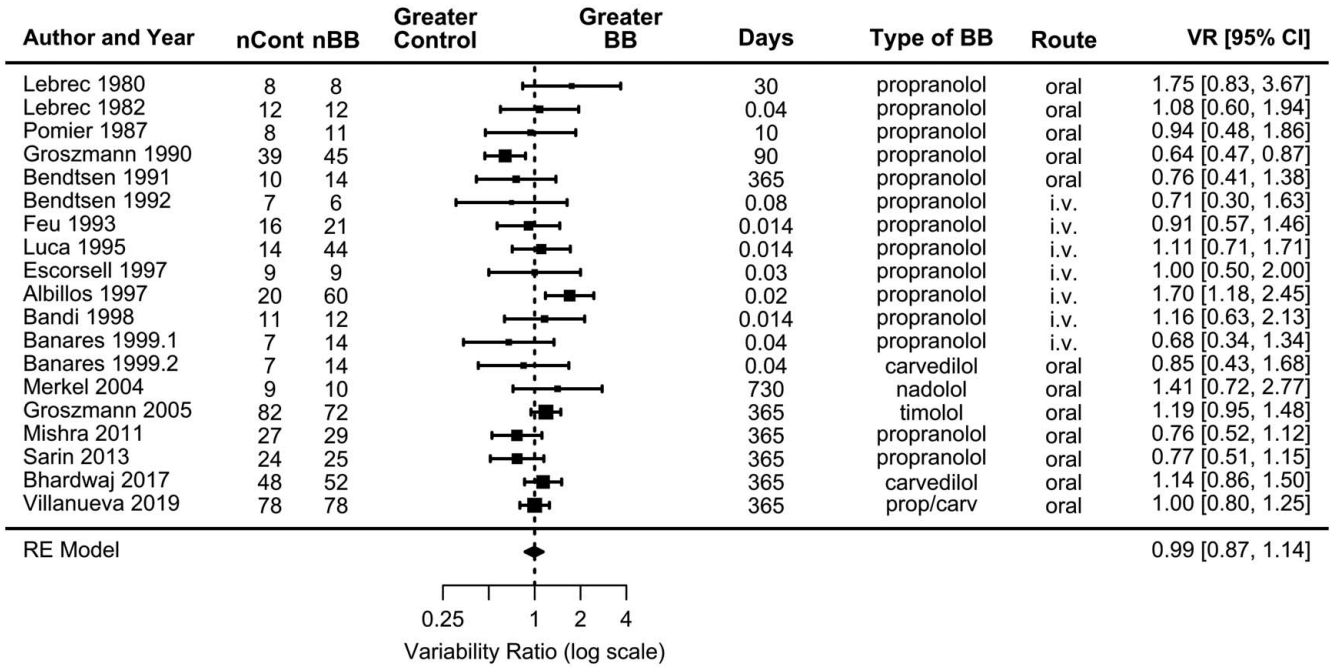

FIGURE 2 Forest plot showing VR of the 19 study arms (in 18 studies) comparing the effects of beta-blockers versus placebo (or control) on portal pressure. Studies are summarized in Table 1. Values of VR below 1 indicate a greater variability in the final HVPG in the control than in the treatment group. Values over 1 indicate a greater variability in the final HVPG in the treatment group. A VR significantly greater than 1 would support that beta-blocker treatment has a heterogeneous patient-to-patient effect on HVPG (a patient-by-treatment interaction), whereas a VR not significantly different from 1 (as found in the present study) would support the notion that the average decrease in HVPG observed with beta-blockers can be assumed to apply to all patients. Abbreviation: BB, beta-blockers; nCont, number of patients assessed in the control group; nBB, number of patients assessed in the beta-blocker group; Days, duration of treatment in days; Route, route of administration; VR, variability ratio.

database used for the analysis is provided as Supplemental Data S5, http://links.lww.com/HC9/A661. In studies with follow-up HVPG measurements at more than 1 time point, we used the earliest assessment since this was the one associated with less dropouts. Fourteen studies used propranolol, 7 of them assessing acute HVPG response after i.v. administration. In one study, both propranolol and carvedilol were used in the beta-blockers arm (selected according to the i.v. response of propranolol.[35] Titration strategies and beta-blocker doses were variable and are summarized in Table 1.

Figure 2 shows a forest plot with the meta-analysis of the VR in the final HVPG. Pooled VR was 0.99 (95% CI 0.87–1.14). This indicates a homogeneous HVPG response between NSBB and the placebo group at the individual patient level (ie, there is no evidence to support that some patients responded to beta-blockers and others did not).

There was significant heterogeneity in the estimate of the pooled VR (Q test ($df = 18$) = 29.56). The heterogeneity was explained by 2 outlier studies with high baseline VR, which had a carried-over effect on the final VR: Groszmann[21] et al showed a lower baseline variability in the NSBB group, while Albillos et al showed a greater variability in the NSBB group.[27] Indeed, adjusting the model by the baseline VR (log-transformed) completely abrogated the heterogeneity in the estimation of the pooled VR (adjusted VR 1.01 (95% CI: 0.92–1.11; Q test for residual heterogeneity ($df = 17$) = 13.99).

We further assessed if the baseline HVPG, route of administration, type of beta-blocker, and treatment duration (until HVPG assessment) had any impact on the VRs. None of these variables had explanatory value for the final VRs, indicating that they did not have a role in making the effects of beta-blockers more or less heterogeneous (Supplemental Data 6, http://links.lww.com/HC9/A662).

Finally, Figure 3 shows a funnel plot representing the association between VRs and the precision of the studies. Distribution was symmetrical, suggesting that the study-to-study variation in the VRs occurred by chance.

Comparison between carvedilol versus propranolol

Six studies (n = 295) contributed data to the comparison between carvedilol and propranolol (Table 2 and Figure 4). No studies were identified comparing carvedilol and nadolol; all studies used the oral route for carvedilol.

The pooled VR was 0.97 (95% CI 0.82–1.14), suggesting no differences in the variability of the final HVPG between carvedilol and propranolol, with no heterogeneity (Q test ($df = 5$) = 2.83, p-val = 0.7261).

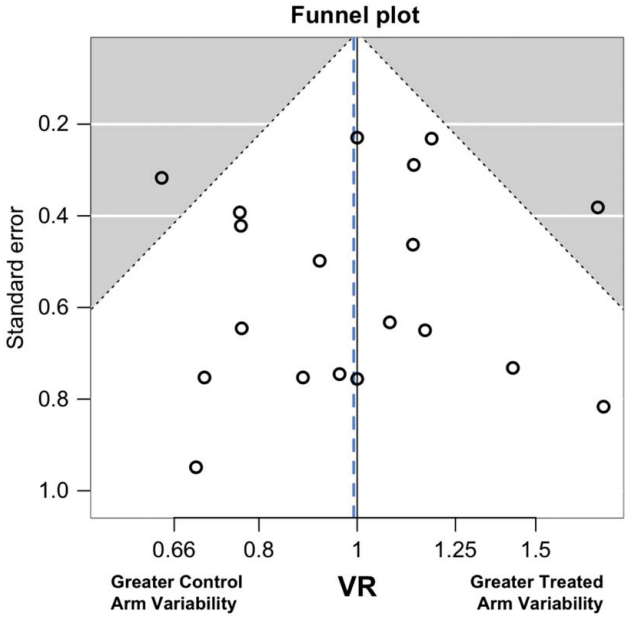

FIGURE 3 Funnel plot showing the VR at outcome between treatment and control arms with the 19 comparisons. Vertical axis indicates the precision of the estimate of the VR (estimated by the SE), with points inside the triangle indicating the 95% most probable. The 2 points outside of the triangle correspond to the 2 studies identified in the text as being outliers.[19,20] Points on the right indicate higher outcome variability for the treated individuals, as expected if there is heterogeneity in treatment effects. Points on the left correspond to lower variability in the treatment arm, which implies a more homogenous response after treatment. The vertical dashed line corresponds to the pooled VR. The distribution of the studies was symmetrical, suggesting that the study-to-study variation in the VRs occurred by chance. Abbreviation: VR, variability ratio.

This supports the notion that, even if carvedilol has been shown to be more effective than propranolol for the treatment of portal hypertension, this does not occur through achieving a different proportion of patients responding (or not responding) to treatment. Rather, the data suggest that this occurs through a greater average decrease in HVPG with carvedilol than with propranolol.

Comparison statins versus placebo

Only 3 studies provided data to estimate the VRs at the end of the study with statins (Figure 5). These included 199 patients (Table 3). The pooled VR was 0.88 (95% CI: 0.72–1.07), indicating that overall final HVPG variability was numerically lower in the treatment groups than in the control groups, though the wide CI makes any conclusion uncertain. Again, this suggests no treatment-by-patient interaction with statins in portal hypertension.

DISCUSSION

In this study, we challenge the concept that the portal pressure response to beta-blockers is heterogeneous, that is, there are patients who respond and patients who do not respond to treatment (in terms of reduction of portal pressure). Rather, the data presented here suggest that, when treating a patient with beta-blockers, it is reasonable to expect that the average decrease in portal pressure described in RCTs applies to individual patients.

Interpretation in the context of other evidence

The causative role of portal hypertension in cirrhosis complications is well established,[2,3,21,44,45] and the concept that decreasing portal pressure with beta-blockers improves prognosis has been unequivocally proven in randomized trials.[14] However, the notion that only a proportion of patients treated with beta-blockers benefit from the treatment has been a contentious issue. Longitudinal studies showed that the greater the decrease in portal pressure, the greater the clinical benefit of beta-blockers,[3] leading to the subsequent definition of "response" criteria. This substantiated the concept that some patients do not respond to beta-blockers, which has been used, in some settings, to support the use of alternative therapies, such as endoscopy when portal pressure measurements are not available, ignoring the fact that the totality of clinical evidence supporting the use of beta-blockers was obtained without guiding treatment based on portal pressure response. The availability of new approaches to measure portal pressure, such as direct portal pressure measurements through endoscopic ultrasound,[46] has renewed the interest in assessing the hemodynamic response to beta-blockers, but without clear evidence to support such need in routine clinical practice.

The assessment of portal pressure responses has additional issues. A recent study by our group[6] showed that the variability of HVPG measurements, which may result from physiological variations, measurement error due to inadequate technique, or random measurement error, might introduce enough noise to question its validity as a tool to guide therapy in an individual patient.[47] While the technique is perfectly valid for drug development of treatments based on portal pressure reductions, in which the response of the treatment arm (as a group) is compared with the placebo arm, getting an accurate estimate of the individual patient response would require repeated measurements on and off treatment,[48] which is not feasible.

These issues led us to further investigate the evidence to support the existence, or lack thereof, of a heterogeneous patient-by-patient response to beta-blockers in the context of cirrhosis. The gold standard to address this question would be trials with more than 1 crossover sequence,[48] which are not available. In this study, we adopted the indirect approach suggested by Cortes et al[9] and others:[11,49] if the response to a treatment has patient-to-patient variation, randomized

TABLE 2 Characteristics of the studies comparing carvedilol vs propranolol

References	Comparison (intervention and time of outcome assessment)	Patient characteristics	Child-Pugh Class (A/B/C)/ Score	NSBB Titration method	Mean NSBB dose (mean ± SD; range)	Etiology	Initial number of patients	Number of patients for each comparison	HVPG measurement technique
Bañares[29]	Carvedilol (p.o.) vs Propranolol (i.v.) vs Placebo 1 h of administration	All esophageal varices 62% previous variceal bleed	13/15/7	Carvedilol 25 mg Propranolol (0.15 mg/kg intravenously, followed by a continuous infusion of 0.2 mg/kg)	NR	57% alcohol 43% Nonalcohol	35 (14 vs. 14 vs. 7)	14 vs. 14 vs. 7	Balloon catheter
De[38]	Carvedilol (p.o.) vs Propranolol (p.o.). 90 minutes and 7 d Only 7 d comparison used	Esophageal varices with no previous bleeds, or who had bleeding 7-10 d prior to inclusion.	5/22/9 Mean: 8.6 ± 1.8	Acute study: 80 mg propranolol and 25 mg carvedilol. 7-day study: propranolol 40 mg twice daily and carvedilol 6.25 mg twice daily	NA	42% alcohol 39% viral	36 (18 vs. 18)	18 vs. 18	Balloon catheter
Bañares[15]	Carvedilol vs Propranolol (p.o) 11.1 +/- 4.1 wk	Esophageal varices without previous bleed	Carvedilol (13/10/3) Propranolol (15/6/4)	Propranolol started at 10 mg twice daily and Carvedilol at 6.25 mg once daily. Both drugs increased every 4 d until heart rate reduced by 25% or to less than 55 provided that systolic pressure was greater than 85 mm Hg	Propranolol 73 +/- 10 mg/d (range, 10–160) Carvedilol 31 +/- 4 mg/d (range,12.5–50)	29% alcohol 67% viral 4% others	51 (26 vs. 25)	24 vs. 22	Balloon catheter
Hobolth[39]	Carvedilol (p.o.) vs. Propranolol (p.o.) 3 mo	Patients with clinical and endoscopic signs of portal hypertension.	5/16/8	Carvedilol started at 3.125 mg BID and Propranolol 40 mg BID. Titrated weekly, to a 25% HR reduction, with HR > 55 and SBP > 90 Max dose Carvedilol: 25 mg/day; Propranolol 320 mg/day	Carvedilol:14 ± 7 mg Propranolol: 122 ± 64 mg	NR	33 (18 vs. 15)	16 vs. 13	NR

TABLE 2. (*continued*)

References	Comparison (intervention and time of outcome assessment)	Patient characteristics	Child-Pugh Class (A/B/C)/ Score	NSBB Titration method	Mean NSBB dose (mean ± SD; range)	Etiology	Initial number of patients	Number of patients for each comparison	HVPG measurement technique
Kim[40]	Carvedilol vs Propranolol (p.o.). 6 wk	All Esophageal varices	Median: 7	Carvedilol 6.25 mg daily and propranolol 20 mg twice daily Carvedilol increased to 12.5 mg and propranolol to 320 mg until HR decreased > 25% from baseline or to 55, with SBP > 90 mm Hg	Carvedilol Median (IQR): 12.5 (12.5–12.5) mg/day Propranolol Median (IQR): 160 (80–175) mg/day	61% alcohol 35% viral 4% others	110 (55 vs. 55)	47 vs. 43	Balloon catheter
Gupta[41]	Carvedilol vs Propranolol 4 wk	All esophageal varices with the first episode of variceal bleed	14/39/6	Carvedilol initial dose 3.125 mg BID, increased up to a dose of 25 mg/day to achieve a target HR 55-60 Propranolol initial dose 40 mg OD, increased to achieve HR between 55-60, or maximum dose of 320 mg/day	Carvedilol Median: 6.25 (6.25–12.5) mg/day Propranolol Median: 40 (40–80) mg/day	47% alcohol 29% viral 7% MASLD 2% AIH 15% cryptogenic	59 (30 vs. 29)	29 vs. 28	NR

Abbreviations: AIH, autoimmune hepatitis; BID, twice daily; IQR, interquartile range; MASLD, metabolic-associated steatotic liver disease; NA, not applicable; NR, not reported; NSBB, nonselective beta-blockers; OD, once daily.

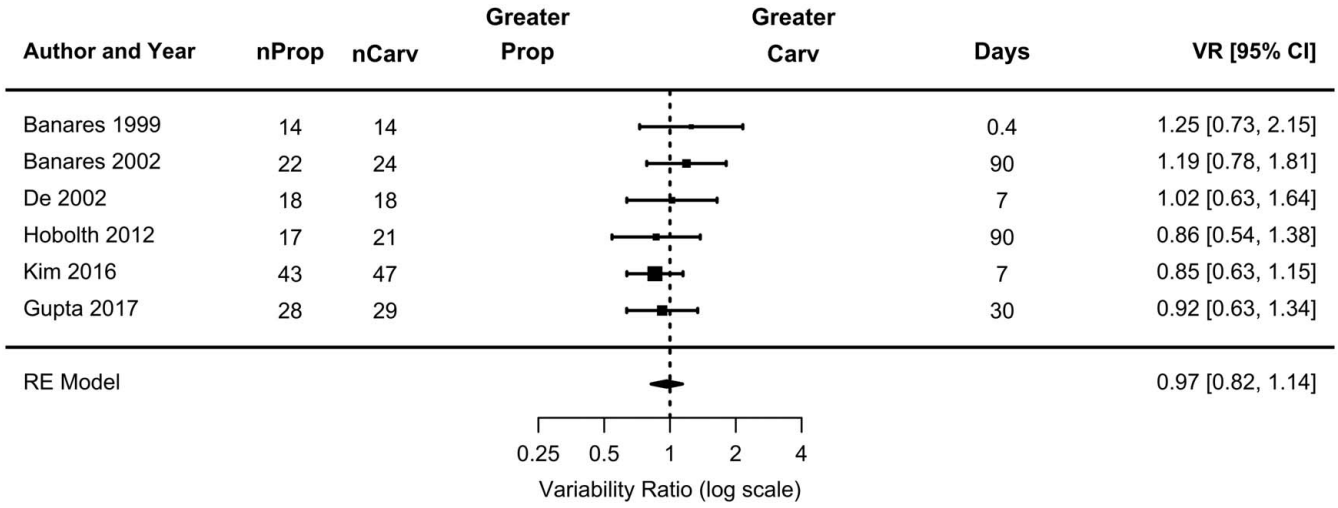

FIGURE 4 Forest plot showing VR of the 6 studies outlined in Table 2 comparing carvedilol and propranolol. Values of VR below 1 indicate a greater variability in the final HVPG in the propranolol than in the carvedilol group. Values over 1 indicate a greater variability in the final HVPG in the carvedilol group. There was no evidence of different variabilities in the final HVPG between the groups. nProp, number of patients in the propranolol group. Abbreviation: nCarv, number of patients assessed in the carvedilol group; Days, duration of treatment; VR, variability ratio.

trials would demonstrate a higher outcome variability in the treated group than the control group (Figure 1 and Supplemental Data S1, http://links.lww.com/HC9/A657). We found in the present study that the VRs between the treatment and placebo group were close to 1. The simplest explanation for this finding is that the effects of beta-blockers are homogeneous (for most patients), and that there is no evidence to support that some patients respond and some do not.

We then addressed whether the response to carvedilol was more homogeneous than the response to propranolol. It is well established that carvedilol induces, in the mean, a greater decrease in portal pressure than propranolol.[14] This could theoretically occur by either increasing the proportion of patients achieving a "HVPG response," or by achieving a greater average decrease in HVPG in every patient. The former, that is, increasing the rate of responders from 40% to 80%, would result in lower variability in the final HVPG in the carvedilol group since most patients would be responders, whereas the latter would result in no differences in final variabilities in HVPG. Our data suggest that the greater average effect of carvedilol is likely related to a greater effect in every patient. Finally, we showed no evidence of heterogeneity of treatment effect with statins that, distinct from beta-blockers, decrease portal pressure by decreasing hepatic resistance.

Study limitations

There are limitations to our approach. The sample size in many studies was low, and the studies were

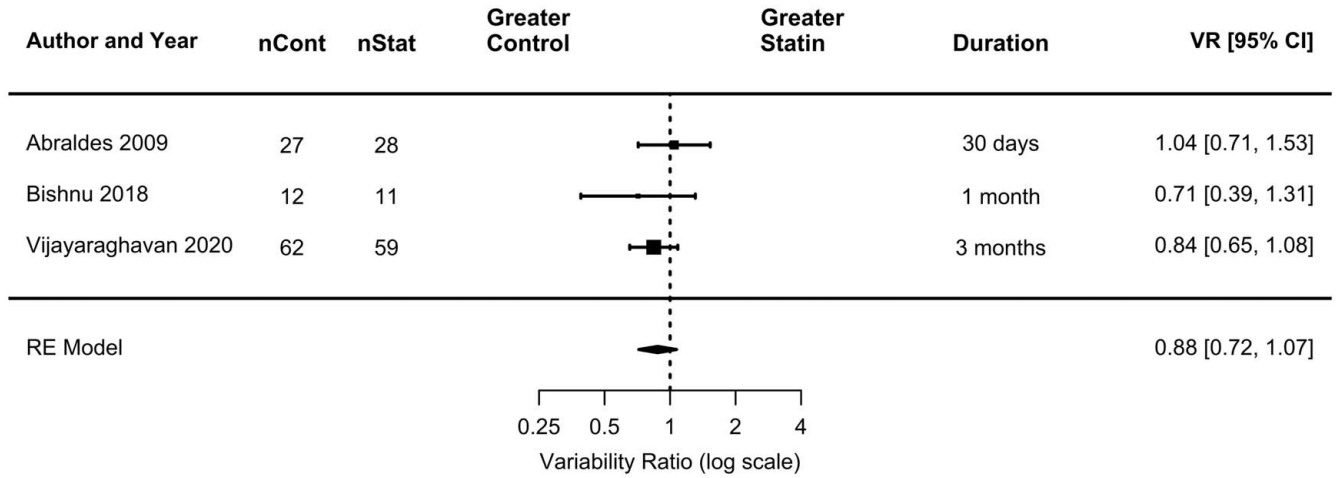

FIGURE 5 Forest plot showing VR of the 3 studies comparing the effects of statins versus placebo on portal pressure. Studies are summarized in Table 3. As shown in the plot, there was no evidence of greater variability in the statins group, which argues against a treatment-by-patient interaction. Abbreviation: VR, variability ratio.

TABLE 3 Characteristics of the studies comparing statins versus placebo

References	Comparison (intervention and time of outcome assessment)	Patient characteristics	Child-Pugh Class (A/B/C)/ Score, mean (± SD)	Statin Titration method	Mean statin dose (mean ± SD; range)	Etiology	Initial number of patients	Number of patients for each comparison	HVPG measurement technique
Abraldes[16]	Simvastatin vs. Placebo 30 d	Patients with cirrhosis and portal hypertension (HVPG ≥ 12 mm Hg)	34/18/3 Placebo: 6.9 ± 1.9 Statin: 6.2 ± 1.3	Initial dose 20 mg for 15 d, increased to 40 mg if no safety issues	Simvastatin 40 mg	49% HCV 42% alcohol 4% HBV 5% other	59 (30 vs. 29)	28 vs. 27	Balloon catheter
Vijayaraghavan[42]	Carvedilol +Simvastatin vs. Carvedilol 3 mo	Patients with cirrhosis with esophageal varices and HVPG > 12	NR	Initial dose 20 mg for 15 d, increased to 40 mg if no safety issues	Maximum Simvastatin dose: 40 (IQR: 20–40) mg/day	40% MASLD 38% alcohol 8% HBV 9% HCV 5% cryptogenic	220 (110 vs. 110)	81 vs. 82	Balloon catheter
Bishnu[43]	Propranolol vs. propranolol+ atorvastatin 1 month	Patients with cirrhosis with evidence of portal hypertension	Median Child-Pugh 6–6.5	20 mg	Atorvastatin 20 mg	43% alcohol 39% cryptogenic 4.5% MALSD 4.5% HBV 4.5% autoimmune 4.5% Wilson	23 (12 vs. 11)	12 vs. 11	NR

Abbreviations: IQR, interquartile range; MASLD, metabolic-associated steatotic liver disease; NR, not reported.

heterogeneous in terms of titration protocols, route of administration, and duration of therapy. However, we did not observe differences in VR according to these factors. In addition, in the studies with longer duration, there were patients who did not reach the second HVPG measurement (both due to loss of follow-up or to the development of a clinical event). This might have selected a more homogeneous sample of patients. Still, results in long-term studies were not different from studies evaluating the acute (i.v.) response, in which all patients reach the second measurement. We could not assess if the VR varies with etiology since HVPG response was rarely reported for individual etiologies. Alternative explanations for the lack of differences in variability are possible.[9] If patients with higher HVPG exhibit a greater treatment response than patients with lower HVPG, then that would reduce the range of final HVPGs in the treatment group. That would tend to decrease the final variability of the treated group and could potentially offset some degree of heterogeneity in the treatment response. This would mean otherwise that most patients achieved a decrease in HVPG, even of different grades, and would have minimal implications for treatment personalization. Finally, our study question addressed the heterogeneity in the hemodynamic effects of beta-blockers, since this is what has been used to classify patients as responders and nonresponders. We have not, however, addressed the potential heterogeneity of effects in clinical outcomes. This is many times addressed with subgroup analysis that can roughly estimate if groups of patients sharing a given characteristic have a distinct effect on the treatment under assessment. More refined approaches have been recently proposed in the PATH statement,[50] which requires large databases based on individual patient data from randomized trials, and was beyond the scope of this study.

Implications for clinical practice and research

Our results question the need to measure portal pressure response to guide therapy with beta-blockers. This further supports the evidence from randomized trials in which (in the vast majority of cases) portal pressure measurements were not used to guide therapy. If the average effect of NSBBs can be assumed to apply to most patients, this facilitates the implementation of current guidelines that have expanded the pool of people with cirrhosis treated with NSBBs.[14] This will also help to define the adequate context for the use of new techniques to measure portal pressure. From a research perspective, our results might contribute to a more efficient allocation of research resources, limiting potentially futile studies aimed at identifying hemodynamic responders to beta-blockers.

CONCLUSION

In conclusion, the analysis of RCTs comparing the HVPG response of beta-blockers with placebo in patients with cirrhosis does not suggest a heterogeneous hemodynamic response to beta-blockers. This further supports the concept that there is no need to measure portal pressure (or perform alternative noninvasive measurements) to guide treatment with beta-blockers.

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CONFLICTS OF INTEREST

Juan G. Abraldes: consulting AstraZeneca, Boehringer Ingelheim, 89bio, Inventiva. Grants from Cook and Gilead (paid to the University of Alberta). Yu Jun Wong: speakers' bureau for Gilead and AbbVie. The remaining authors have no conflicts to report.

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