

# Lowering Portal Pressure Improves Outcomes of Patients With Cirrhosis, With or Without Ascites: A Meta-Analysis

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Q9 **BACKGROUND & AIMS:** In unselected patients with cirrhosis, those with reductions in hepatic venous pressure gradient (HVPG) to below a defined threshold (responders) have a reduced risk of variceal hemorrhage (VH) and death. We performed a meta-analysis to compare this effect in patients with vs without ascites.

**METHODS:** We collected data from 15 studies of primary or secondary prophylaxis of VH that reported data on VH and death in responders vs nonresponders. We included studies in which data on ascites at baseline and on other relevant outcomes during follow-up evaluation were available. We performed separate meta-analyses for patients with vs without ascites.

**RESULTS:** Of the 1113 patients included in the studies, 968 patients (87%) had been treated with nonselective  $\beta$ -blockers. In 993 patients (89%), HVPG response was defined as a decrease of more than 20% from baseline (>10% in 11% of patients) or to less than 12 mm Hg. In the 661 patients without ascites, responders (n = 329; 50%) had significantly lower odds of events (ascites, VH, or encephalopathy) than nonresponders (odds ratio [OR], 0.35; 95% CI, 0.22–0.56). Odds of death or liver transplantation were also significantly lower among responders than nonresponders (OR, 0.50, 95% CI, 0.32–0.78). In the 452 patients with ascites, responders (n = 188; 42%) had significantly lower odds of events (VH, refractory ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome) than nonresponders (OR, 0.27; 95% CI, 0.16–0.43). Overall, odds of death or liver transplantation were lower among responders (OR, 0.47; 95% CI, 0.29–0.75). No heterogeneity was observed among studies.

**CONCLUSIONS:**

**In a meta-analysis of clinical trials, we found that patients with cirrhosis with and without ascites who respond to treatment with nonselective  $\beta$ -blockers (based on reductions in HVPG) have a reduced risk of events, death, or liver transplantation.**

*Keywords:* NSBB; Outcome; Portal Hypertension; Hepatic Venous Pressure Gradient.

Cirrhosis is the end stage of any chronic liver disease and, based on a large body of evidence, it now is classified into 2 distinct stages: compensated and decompensated. Each stage differs significantly in the prognosis, predominant pathophysiological mechanisms, and predictors of death.<sup>1-4</sup>

Nonselective  $\beta$ -blockers (NSBBs) have been the mainstay of therapy of portal hypertension since 1981 when Lebrec et al<sup>5</sup> showed the efficacy of propranolol in reducing portal pressure. Since then, many randomized controlled trials have shown that NSBBs are effective in preventing variceal hemorrhage, both first and recurrent, and therefore NSBBs are considered first-line therapy in the primary and secondary prophylaxis of variceal hemorrhage.<sup>6</sup>

Because NSBBs, by reducing portal pressure, may prevent not only variceal hemorrhage but other complications of portal hypertension, many studies have correlated the decrease in portal pressure (as determined by the hepatic venous pressure gradient [HVPG]) with the prevention of all complications of cirrhosis, including death. In a meta-analysis by D'Amico et al<sup>7</sup> that included 12 studies (including 943 patients with cirrhosis), HVPG responders, defined as those with an HVPG reduction to 12 mm Hg or less or 20% or more from baseline had a significantly lower risk of bleeding and death. However, all studies included in the D'Amico et al<sup>7</sup> meta-analysis combined results from patients with both compensated and decompensated cirrhosis.

Because the effect of NSBBs on portal pressure and outcomes may differ in these 2 different stages of cirrhosis<sup>8</sup> and because it has been suggested that NSBBs may be deleterious in patients with refractory ascites,<sup>9,10</sup> we considered it important to update the D'Amico et al<sup>7</sup> meta-analysis by not only adding data from additional recent studies reporting HVPG response and outcomes but, more importantly, to stratify patients by the presence or absence of ascites and to report on clinically relevant outcomes. For this study, we considered ascites as the hallmark of decompensation because it is the most common decompensating event, it is the only one that is continuous (as opposed to variceal hemorrhage and hepatic encephalopathy, which are episodic), and because it is the most likely to be recorded accurately in study databases on which this meta-analysis was based.

## Materials and Methods

### Methods

We performed a meta-analysis to pool data from patients with cirrhosis included in studies (randomized

controlled trials or other) that assessed the difference in clinically relevant outcomes between HVPG responders and nonresponders relating to the 2 main prognostic stages of cirrhosis, compensated or decompensated,<sup>13</sup> which in this study is defined as the absence or presence of ascites, respectively. This meta-analysis was conducted and reported according to the Quality Assessment of Systematic Reviews and Meta-Analyses of the National Institutes of Health, last updated in March 2014.<sup>11</sup>

### Eligibility Criteria

Studies that included patients with cirrhosis and varices undergoing treatment with NSBBs to prevent first or recurrent esophageal variceal hemorrhage were included in this analysis if the following criteria were met: (1) patients included in the study had at least 2 measurements of HVPG performed, at baseline (before therapy) and during therapy; (2) the published report included the number of patients who were HVPG responders vs nonresponders; and (3) information regarding the presence or absence of ascites at baseline and relevant clinical outcomes during follow-up evaluation were available for each of the responder groups.

### Exclusion Criteria

Case reports, editorials, letters, review articles, and guidelines were excluded from the analysis. We also excluded studies in which cirrhosis developed after liver transplantation. The D'Amico et al<sup>7</sup> meta-analysis found the long interval (5.3 mo) between HVPG measurements observed in 1 study<sup>12</sup> to be the main predictor of heterogeneity, therefore this study<sup>12</sup> and any other study with a mean/median interval between HVPG measurements of 5 months or longer were excluded.

### Information Sources and Search

The studies conducted until December 2005 were identified from the D'Amico et al<sup>7</sup> meta-analysis. Studies conducted from January 1, 2006, to November 30, 2015, were identified by searching electronic databases using the terms "hepatic venous pressure gradient" or "HVPG," limiting the search to human studies. This search was performed in MEDLINE via PubMed, Embase using the ScienceDirect interface, and The Cochrane Central Register of Controlled Trials. Publications in personal reference lists and citation sections of the recovered

articles also were reviewed and abstracts presented at meetings of the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver were searched manually.

### *Study Selection and Data Collection Process*

Two authors (L.T. and G.G.-T.) independently assessed titles and abstracts of studies identified in the primary search. If the title and/or abstract showed that the article did not meet inclusion criteria, the study was excluded. If the inclusion criteria could not be assessed from the title/abstract with certitude, the full-text article was evaluated to determine eligibility. Disagreements were resolved by discussion between L.T. and G.G.-T.

Once studies that met inclusion criteria had been selected and because data regarding the presence or absence of ascites and clinical outcomes specific for each of these subgroups and for each of the responder groups (responder vs nonresponder) could not be extracted from published studies, principal investigators of eligible studies were contacted to obtain data for all subgroups in their trials. Specifically, we provided a data collection form divided into HVPG responder vs nonresponder groups (providing the numbers for each group that had been reported in the published article), and the principal investigators then provided data on the presence or absence of ascites and on relevant clinical outcomes (see later) for each responder group separately. Therefore, this was not an individual meta-analysis and the objective was to analyze the development of clinical outcomes separately in HVPG responders vs nonresponders (as defined in each of the studies) stratified by the presence or absence of ascites. To include only unique patients, when the same patient population was used in multiple publications, the authors were asked to provide data from the most recent publication that included all patients (in which case the previous publication would not be considered) or to report only on the additional patients in the newer publication (in which case both publications would be cited). Authors were asked to exclude data from patients with only 1 HVPG measurement. The original data sets were checked for completeness and internal consistency and amended through correspondence with the principal investigators.

### *Data Collected on Outcomes*

Relevant outcomes were defined separately for patients without ascites (compensated) and those with ascites (decompensated), as follows.

For patients without ascites, primary outcomes were the development of ascites, variceal hemorrhage (first in primary prophylaxis studies, recurrent in secondary prophylaxis studies), or encephalopathy. For patients with ascites, primary outcomes were the development of variceal bleeding (first in primary prophylaxis studies,

## **What You Need to Know**

### **Background**

In patients with cirrhosis, lowering portal pressure mostly by treatment with a nonselective  $\beta$ -blocker (NSBB) is associated with lower rates of variceal hemorrhage and death. However, it is not clear if the benefits of this treatment apply to patients with or without ascites.

### **Findings**

In a meta-analysis of 15 studies, we found outcomes (not only variceal hemorrhage) and death to be significantly lower in patients with cirrhosis with a mostly NSBB-induced reduction in portal pressure. This beneficial effect applies to patients with and without ascites.

### **Implications for patient care**

Patients with cirrhosis, with or without ascites, who have reductions in portal pressure mostly after treatment with NSBBs are at reduced risk for adverse events or death. NSBBs should not be avoided in patients with ascites.

recurrent in secondary prophylaxis studies) or refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, or encephalopathy. For patients in both groups, data were collected for both transplant and death. However, because the number of transplanted patients was small ( $n = 76$ ), death or transplant (death/transplant) was used as a secondary end point.

Authors of each of the publications were asked to report on clinical outcome as follows: (1) bleeding or re-bleeding alone (according to whether the patient was in a primary prophylaxis study/group or a secondary prophylaxis study/group; (2) bleeding or re-bleeding plus another outcome; and (3) any other clinical outcome without bleeding or re-bleeding. For the final analysis, all of these outcomes were combined. Careful initial evaluation was performed to ensure completeness of data, and to check the consistency of the results of the primary analyses for each trial with published reports.

### *Statistical Analysis*

Meta-analyses were performed separately for patients without ascites and for those with ascites, and also was performed separately for patients enrolled in primary prophylaxis studies and those enrolled in secondary prophylaxis studies. Because the results of each study had dichotomous frequency data, a meta-analysis was performed by calculating odds ratios (ORs) and 95% CIs. Because the differences in the patients enrolled, the way the intervention was administered, and the way the outcome was measured may have had an impact on

the magnitude of the effect, we chose to pool data and compare it using a random-effects model.<sup>13</sup> A *P* value less than .05 was considered significant. Statistical heterogeneity was calculated by the *I*<sup>2</sup>. Values less than 30%, 30% to 59%, 60% to 75%, and greater than 75% were classified as low, moderate, substantial, and considerable heterogeneity, respectively.<sup>14</sup> All analyses were performed using the software Review Manager (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

## Results

A total of 459 unique citations were identified using our search criteria (Supplementary Figure 1). After excluding 420 studies because they did not report data on follow-up HVPG, 30 studies because they did not report on outcomes, and 1 study<sup>15</sup> because the median time between the baseline and follow-up HVPG was longer than 5 months (13 months in compensated patients and 8 months in decompensated patients), 8 studies published between January 2006 and November 2015 met our inclusion criteria. These 8 studies were added to 12 studies published before December 2005 as identified by D'Amico et al<sup>7</sup> (Supplementary Figure 1). We could not identify any eligible study published in abstract form that was not subsequently published in full.

Additional data on the outcomes of patients with and without ascites (separately) were requested from the authors of the 20 eligible studies. Original data were no longer available for 4 of them (including the study from McCormick et al<sup>12</sup>), and data from 1 publication<sup>16</sup> was duplicated in a second publication<sup>17</sup> and therefore was excluded. Therefore, the meta-analysis includes data from 15 studies<sup>17-31</sup> (Supplementary Figure 1).

**Characteristics of studies and patients.** The characteristics of the 15 studies are shown in Table 1. Ten studies were case-series and 5 were randomized controlled trials (RCT), and alcohol was the main etiology of cirrhosis in most studies.

Overall, the 15 selected studies included 1341 patients, of whom 228 were excluded (124 patients did not have a second HVPG performed, 72 patients had been reported in other studies, and 32 patients were tested after a single intravenous dose of propranolol). Therefore, data from 1113 unique patients were analyzed. Of these, 452 (40.6%) had ascites. Notably, and as expected, the mean HVPG levels were higher in patients with ascites than in those without ascites (Table 2).

Table 3 shows the different outcomes including death/liver transplant rates by the presence or absence of ascites, according to the HVPG response category (responders vs nonresponders), as defined in each of the studies. Except for 2 studies<sup>19,25</sup> (all patients taking NSBBs for primary prophylaxis) defining HVPG

responders as those patients achieving a reduction of more than 10% or a decrease to less than 12 mm Hg, the remaining 13 studies defined HVPG response as a decrease to less than 12 mm Hg or a reduction of more than 20% from baseline. Notably, raw data were available for a study in which the original publication had defined only HVPG response as a decrease in HVPG to less than 12 mm Hg<sup>20</sup> so that response could be redefined as a decrease greater than 20% or a decrease less than 12 mm Hg to be consistent with the majority of studies. Table 3 also shows the specific pharmacologic therapy. Notably, of 1113 unique patients, only 145 (13%) were not on active pharmacologic treatment (39 were on placebo and 106 received endoscopic treatment only) (Table 3). Supplementary Table 1 shows the HVPG methodology used in each study.

### Patients Without Ascites (*n* = 661)

Of 661 patients without ascites, 332 did not have a history of variceal hemorrhage (included in primary prophylaxis studies) and 329 had a history of variceal hemorrhage (included in secondary prophylaxis studies).

Except for 85 patients (12.9%) analyzed in 2 studies<sup>19,25</sup> in whom response was defined as an HVPG decrease of more than 10% or a decrease to less than 12 mm Hg (all patients taking NSBBs for primary prophylaxis), in the remaining 576 (87.1%) patients, HVPG response was defined as a decrease to less than 12 mm Hg or more than a 20% reduction from baseline.

Overall, responders (49.8%) had a significantly lower rate of clinical events (variceal hemorrhage, ascites, or encephalopathy) than nonresponders (OR, 0.35; 95% CI, 0.22–0.56) (Figure 1A), both in patients included in primary prophylaxis studies (OR, 0.28; 95% CI, 0.13–0.58) and in secondary prophylaxis studies (OR, 0.41; 95% CI, 0.22–0.78) without significant heterogeneity (*P* = .10) (Figure 1A).

Death/transplant rates also were significantly lower among responders (OR, 0.50; 95% CI, 0.32–0.78) (Figure 1B) in both patients in primary (OR, 0.44; 95% CI, 0.20–0.98) or secondary prophylaxis (OR, 0.55; 95% CI, 0.32–0.95) studies without significant heterogeneity (*P* = .28) (Figure 1B).

### Patients With Ascites (*n* = 452)

Of the 452 patients with ascites, 172 did not have a history of variceal hemorrhage (included in primary prophylaxis studies) and 280 had a history of variceal hemorrhage (included in secondary prophylaxis studies).

Except for 35 patients (7.7%) analyzed in 1 study<sup>25</sup> in whom response was defined as an HVPG decrease of more than 10% or a reduction to less than 12 mm Hg (all patients were on NSBBs for primary prophylaxis), in the remaining 417 (92.3%) patients, HVPG response was

**Table 1.** Characteristics of the 15 Included Studies

Study	Study type	Study population (inclusion criteria)	Exclusion criteria	Patient recruitment period	Age, y	Sex, % male	Main etiology, %
Groszmann et al, <sup>20</sup> 1990 <i>Gastroenterology</i>	Randomized controlled trial	Cirrhosis, esophageal varices, no previous variceal bleeding	Severe hepatic disease, known neoplasms Severe nonhepatic disorders	1982–1986	54	72	Alcohol, 78
Hernandez-Gea et al, <sup>19</sup> 2012 <i>Am J Gastroenterol</i>	Case series	Cirrhosis, large esophageal varices, no previous variceal bleeding, ascites, jaundice, or encephalopathy	Age <18 or >80 y, Child score >10, HCC, splanchnic venous thrombosis, treatment with diuretics or vasoactive drugs, contraindications to NSBB, comorbidity with life expectancy <1 y	2001–2008	62	49	HCV, 62
Merkel et al, <sup>21</sup> 2000 <i>Hepatology</i>	Case series	Cirrhosis, medium–large esophageal varices or small varices with RWM, no previous variceal bleeding, no previous treatment for PH	NA	NA	60	70	Alcohol, 37; virus-related, 37
Reiberger et al, <sup>22</sup> 2013 <i>Gut</i>	Case series	Cirrhosis, esophageal varices, no previous bleeding, HVPG >12 mm Hg	Age <18 y, HCC or other malignancy, prehepatic or posthepatic causes of portal hypertension, severe liver failure, uncontrolled HE, alcohol or intravenous drug abuse, renal failure, contraindications to NSBB	2008–2012	53	77	Alcohol, 55
Sharma et al, <sup>23</sup> 2009 <i>Aliment Pharmacol Ther</i>	Case series	Cirrhosis, medium–large esophageal varices ± RWM, no previous variceal bleeding	Age <18 or >70 y, previous varices endoscopic treatment, use of NSBB in previous 3 mo, history of surgery for portal hypertension, PVT, Child score >13, cardiopulmonary or renal failure, any neoplasm, contraindications to NSBB, concomitant treatment for HBV or HCV	2004–2005	47	79	Virus-related, 61
Turnes et al, <sup>24</sup> 2006 <i>Am J Gastroenterol</i>	Case series	Cirrhosis, esophageal varices, no previous variceal bleeding, HVPG >12 mm Hg	HCC, PVT, contraindications to NSBB, cholestatic liver disease	1994–2000	58	67	NA
Villanueva et al, <sup>25</sup> 2009 <i>Gastroenterology</i>	Case series	Cirrhosis, large esophageal varices, no previous variceal bleeding	Age <18 or >80 y, HCC, Child score >13, PVT, contraindications to NSBB, previous treatment for portal hypertension, comorbidity with life expectancy <1 y	1999–2005	62	57	HCV, 42; alcohol, 34
Abraldes et al, <sup>18</sup> 2003 <i>Hepatology</i>	Case series	Cirrhosis, variceal bleeding, HVPG >12 mm Hg	HCC, PVT, contraindications to NSBB, cholestatic liver disease	NA	54	66	Alcohol, 51
Augustin et al, <sup>17</sup> 2012 <i>Hepatology</i>	Case series	Cirrhosis, variceal bleeding	Age >80 y, Child score >13, failure to control the index bleeding, current active therapy with NSBB and ISMN or endoscopic variceal obliteration, contraindications to NSBB or ISMN, advanced HCC, severe comorbidity, PVT, HVPG <10 mm Hg	2001–2010	54	78	Alcohol, 50

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Table 1. Continued

Study	Study type	Study population (inclusion criteria)	Exclusion criteria	Patient recruitment period	Age, y	Sex, % male	Main etiology, %
García-Pagán et al, <sup>26</sup> 2009 <i>Gut</i>	Randomized controlled trial	Cirrhosis, recent bleeding successfully treated with vasoactive drugs, antibiotics, and endoscopy	Age <18 or >75 y, pregnancy; Child score >13, HCC, renal failure, comorbidity with reduced life expectancy, contraindications to NSBB or ISMN, PVT, previous treatment to prevent rebleeding, treatment with EVL in the 3 months before, bleeding from isolated gastric or ectopic varices	2003–2005	56	75	Alcohol, 51
Villanueva et al, 1996 <sup>27</sup> <i>N Engl J Med</i>	Randomized controlled trial	Cirrhosis, variceal bleeding	Age <18 y, Child score >12, advanced HCC, other cancer, previous sclerotherapy, failure of medical therapy to control the bleeding	1991–1994	59	67	Alcohol, 57
Villanueva et al, <sup>28</sup> 2001 <i>N Engl J Med</i>	Randomized controlled trial	Cirrhosis, variceal bleeding	Age <18 y, Child score >12, advanced HCC, previous variceal endoscopic treatment, history of surgery for portal hypertension, previous treatment with NSBB and ISMN, failure of medical therapy to control the bleeding, comorbidity with life expectancy <6 mo	1994–1999	59	61	Alcohol, 44; virus-related, 35
Villanueva et al, <sup>29</sup> 2004 <i>J Hepatol</i>	Case series	Cirrhosis, variceal bleeding	Age <18 y, Child score >12, advanced HCC, previous variceal endoscopic treatment, history of surgery for portal hypertension, previous treatment with NSBB and ISMN, failure of medical therapy to control the bleeding, comorbidity with life expectancy <6 mo	1999–2001	58	67	Alcohol, 46; virus-related, 28
Villanueva et al, <sup>30</sup> 2009 <i>Aliment Pharmacol Ther</i>	Randomized controlled trial	Cirrhosis, variceal bleeding	Child score >12, advanced HCC, previous variceal endoscopic treatment, previous treatment with NSBB and ISMN	2000–2002	63	64	Alcohol, 39; virus-related, 34
Bureau et al, <sup>31</sup> 2002 <i>Hepatology</i>	Case series	Cirrhosis, medium–large esophageal varices	Age <18 or >75 y, HCC, PVT, previous treatment or contraindication to NSBB and ISMN, history of surgery for portal hypertension	1997–2000	53	62	Alcohol, 76

EVL, endoscopic varices ligation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HVP, hepatic venous pressure gradient; ISMN, isosorbide mononitrate; NA, not available; NSBB, nonselective  $\beta$ -blockers; PH, portal hypertension; PVT, portal vein thrombosis; RWM, red weal marks.

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**Table 2.** Characteristics of Patients Included in Each Study

Study	Total patients, n	Patients with repeated HVPG during follow-up evaluation, n	Unique patients included, n	Unique patients without/with ascites, n	Mean time $\pm$ SD between baseline and follow-up HVPG, mo <sup>a</sup>	Mean HVPG $\pm$ SD in unique patients without ascites, mm Hg <sup>a</sup>		Mean HVPG $\pm$ SD in unique patients with ascites, mm Hg <sup>a</sup>	
						Baseline	Follow-up evaluation	Baseline	Follow-up evaluation
Primary prophylaxis									
Groszmann et al, <sup>20</sup> 1990 <i>Gastroenterology</i>	102	84	84	43/41	3	17.4 $\pm$ 3.6	15.4 $\pm$ 3.8	19.9 $\pm$ 5.2	17.6 $\pm$ 4.9
Hernandez-Gea et al, <sup>19</sup> 2012 <i>Am J Gastroenterol</i>	78	78	47	47/0	2.4 $\pm$ 1.1	16.9 $\pm$ 3	15.7 $\pm$ 3	NA	
Merkel et al, <sup>21</sup> 2000 <i>Hepatology</i>	49	49	49	27/22	1.5	17.4	14.3	20.2	16.2
Reiberger et al, <sup>22</sup> 2013 <i>Gut</i>	104	104	104	93/11	1.7 $\pm$ 0.6	20.3 $\pm$ 4.1	16.0 $\pm$ 3.7	22.3 $\pm$ 4.3	17.9 $\pm$ 2.6
Sharma et al, <sup>23</sup> 2009 <i>Aliment Pharmacol Ther</i>	56	56	56	29/27	1 or 2 <sup>b</sup>	17.8	16.3	18.2	16.1
Turnes et al, <sup>24</sup> 2006 <i>Am J Gastroenterol</i>	71	71	71	46/25	5	17.8	15.6	19.6	17.0
Villanueva et al, <sup>25</sup> 2009 <i>Gastroenterology</i>	73 <sup>c</sup>	73	73	38/35	3.1 $\pm$ 1.1	17.5 $\pm$ 3	15.6 $\pm$ 4	19.1 $\pm$ 3	16.9 $\pm$ 4
Secondary prophylaxis									
Abraldes et al, <sup>18</sup> 2003 <i>Hepatology</i>	73	73	73	50/23	4.1	18.7	16.1	18.1	15.4
Augustin et al, <sup>17</sup> 2012 <i>Hepatology</i>	90	90	90	57/33	0.25	17.3	14.1	19.6	16.2
García-Pagán et al, <sup>26</sup> 2009 <i>Gut</i>	158	135	135	94/41	1	20	17	21	18
Villanueva et al, <sup>27</sup> 1996 <i>N Engl J Med</i>	86	62	62	35/27	3.5	16.8 $\pm$ 3	14.9 $\pm$ 4	17.4 $\pm$ 4	16.6 $\pm$ 4
Villanueva et al, <sup>28</sup> 2001 <i>N Engl J Med</i>	144	95	95	32/63	2.3 $\pm$ 1	18.9 $\pm$ 4	16.4 $\pm$ 4	20.6 $\pm$ 4	18.2 $\pm$ 3
Villanueva et al, <sup>29</sup> 2004 <i>J Hepatol</i>	132	132	91	34/57	2.5	18.3 $\pm$ 3	14.5 $\pm$ 3	20.7 $\pm$ 4	17.5 $\pm$ 4
Villanueva et al, <sup>30</sup> 2009 <i>Aliment Pharmacol Ther</i>	59	49	49	15/34	2.2 $\pm$ 1.2	16.9 $\pm$ 4	14.3 $\pm$ 3	21.7 $\pm$ 5	18.4 $\pm$ 5
Primary and secondary prophylaxis									
Bureau et al, <sup>31</sup> 2002 <i>Hepatology</i>	20 (primary prophylaxis)	20	20	9/11	0.6	16.8	11.4	17.8	14.8
	14 (secondary prophylaxis)	14	14	12/2	1	22.2	18.6	22.5	16.5

HVPG, hepatic venous pressure gradient; NA, not applicable.

<sup>a</sup>Data not in original publication, provided by authors.

<sup>b</sup>One month in responders to propranolol; 2 months for nonresponders to propranolol in whom isosorbide mononitrate was added.

<sup>c</sup>Of 105 patients in the study, 32 were excluded because only the HVPG response to a single intravenous dose of propranolol was evaluated.

**Table 3.** Outcomes According to Ascites Group (Absent or Present) and HVPG Group

Study	Unique patients included, n	Therapy	Unique patients on placebo or endoscopic treatment only, n	Mean follow-up period, mo	Definition of responder	No ascites/ascites	N	R/NR	N	Outcomes			Survival	
										Bleeding/re-bleeding only, n	Bleeding/re-bleeding plus another outcome, n	Another clinical outcome without bleeding/re-bleeding, n	Transplant, n	Died, n
Primary prophylaxis Groszmann et al, <sup>20</sup> 1990 <i>Gastroenterology</i>	84	Propranolol vs placebo	39 Placebo	16	HVPG $\leq$ 12 mm Hg or HVPG decrease $\geq$ 20%	No ascites	43	R	15	0	NA	NA	NA	1
								NR	28	3	NA	NA	NA	4
						Ascites	41	R	15	2	NA	NA	NA	2
Hernandez-Gea et al, <sup>19</sup> 2012 <i>Am J Gastroenterol</i>	47	Nadolol	0	53	HVPG decrease $\geq$ 10%	No ascites	47	R	20	0	1	7	0	4
								NR	27	0	8	16	1	12
						Ascites	NA	R	NA	NA	NA	NA	NA	NA
Merkel et al, <sup>21</sup> 2000 <i>Hepatology</i>	49	Nadolol or nadolol $\pm$ ISMN	0	36	HVPG $\leq$ 12 mm Hg or HVPG decrease $\geq$ 20%	No ascites	27	R	17	0	1	1	1	2
								NR	10	2	0	3	0	2
						Ascites	22	R	13	1	0	4	0	4
Reiberger et al, <sup>22</sup> 2013 <i>Gut</i>	104	Propranolol or carvedilol vs EVL	29 EVL	19	HVPG $<$ 12 mm Hg or HVPG decrease $\geq$ 20%	No ascites	93	R	68	3	2	13	5	4
								NR	25	2	3	7	2	6
						Ascites	11	R	7	1	1	4	1	5
Sharma et al <sup>23</sup> 2009 <i>Aliment Pharmacol Ther</i>	56	Propranolol $\pm$ ISMN	0	24	HVPG $\leq$ 12 mm Hg or HVPG decrease $\geq$ 20%	No ascites	29	R	12	0	0	1	0	1
								NR	17	1	0	0	0	0
						Ascites	27	R	15	1	0	0	0	0
Turnes et al, <sup>24</sup> 2006 <i>Am J Gastroenterol</i>	71	Propranolol $\pm$ ISMN	0	68	HVPG $\leq$ 12 mm Hg or HVPG decrease $\geq$ 20%	No ascites	46	R	16	1	1	8	3	6
								NR	30	4	6	8	1	13
						Ascites	25	R	9	0	0	4	0	3
Villanueva et al, <sup>25</sup> 2009 <i>Gastroenterology</i>	73	Nadolol	0	25	HVPG $<$ 12 mm Hg or HVPG decrease $\geq$ 10%	No ascites	38	R	26	1	0	6	0	2
								NR	12	0	4	4	0	5
						Ascites	35	R	21	0	0	12	4	4
Secondary prophylaxis Abraldes et al, <sup>18</sup> 2003 <i>Hepatology</i>	73	Propranolol $\pm$ ISMN	0	70	HVPG $\leq$ 12 mm Hg or HVPG decrease $\geq$ 20%	No ascites	50	R	19	3	2	3	4	1
								NR	31	6	9	4	3	8
						Ascites	23	R	9	0	1	4	0	0
Augustin et al, <sup>17</sup> 2012 <i>Hepatology</i>	90	Nadolol + ISMN + EVL	0	48	HVPG $\leq$ 12 mm Hg or HVPG decrease $\geq$ 20%	No ascites	57	R	32	8	5	3	3	7
								NR	25	0	3	11	4	9
						Ascites	33	R	16	3	0	4	2	4
							NR	17	1	1	8	5	5	

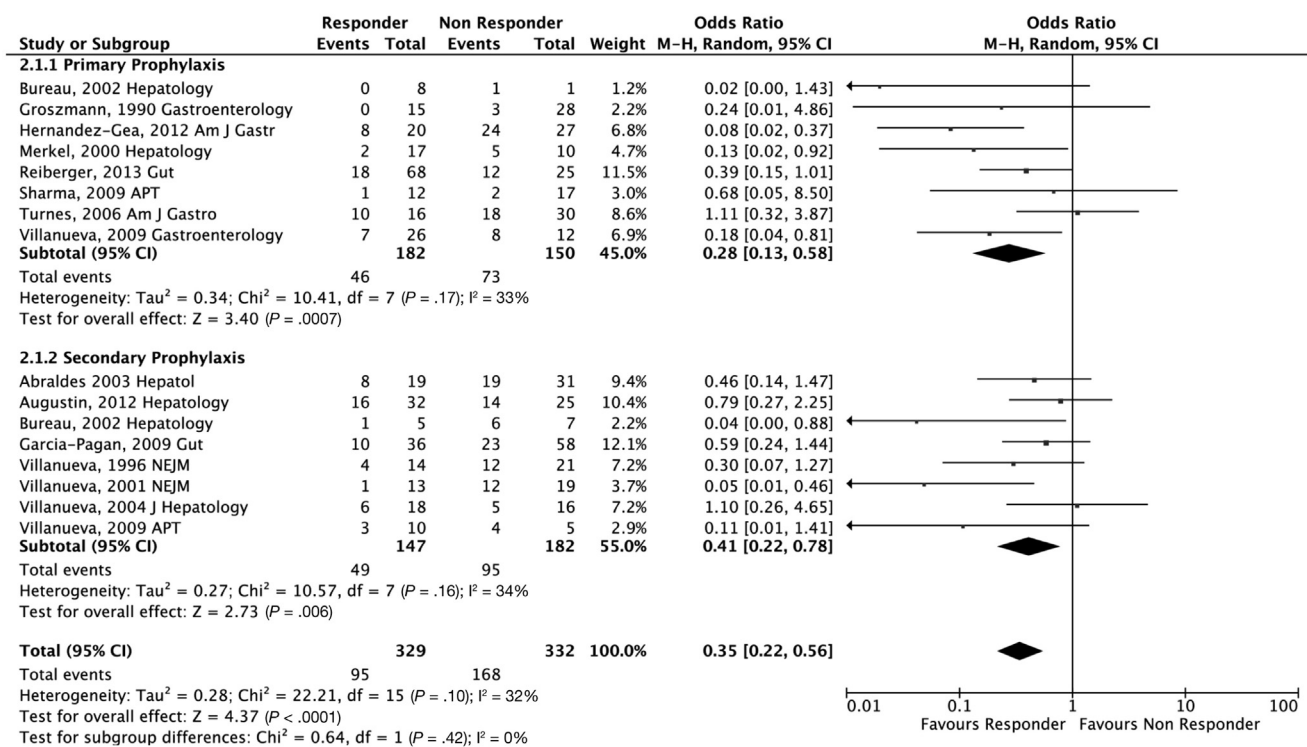
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## A

### Outcome: Any Clinical Event\*



\* Defined as any of the following: variceal hemorrhage (first in primary prophylaxis studies, recurrent in secondary prophylaxis studies), development of ascites or encephalopathy

## B

### Outcome: Death OR Transplant

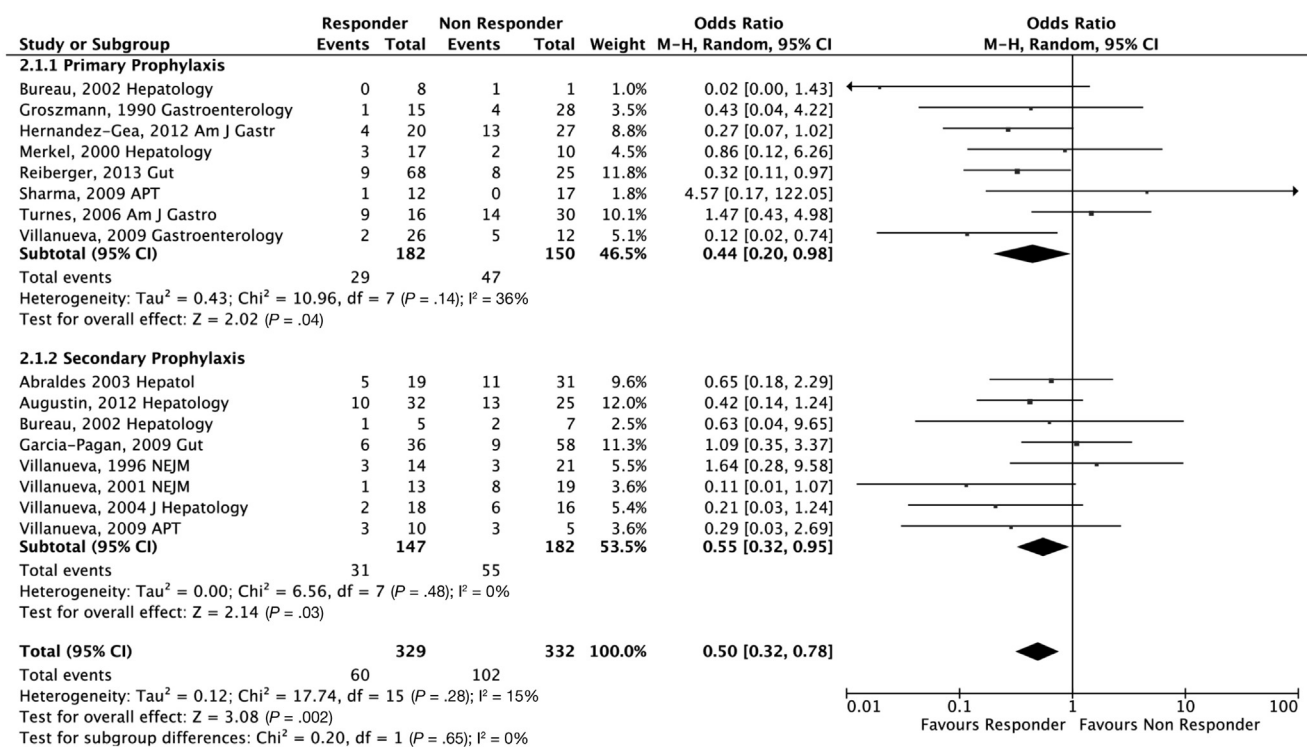


Figure 1. Patients without ascites. (A) Outcome: any clinical event. (B) Outcome: death or transplant.

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defined as a decrease to less than 12 mm Hg or a more than 20% reduction from baseline.

Overall, responders (41.6%) had a significantly lower rate of clinical events (variceal hemorrhage, refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, or encephalopathy) than nonresponders (OR, 0.27; 95% CI, 0.16–0.43) (Figure 2A), both in patients included in primary (OR, 0.38; 95% CI, 0.16–0.89) and in secondary prophylaxis studies (OR, 0.24; 95% CI, 0.12–0.48) without significant heterogeneity ( $P = .40$ ) (Figure 2A).

Death/transplant rates were lower among responders (OR, 0.47; 95% CI, 0.29–0.75) (Figure 2B) both in patients in primary (OR, 0.74; 95% CI, 0.34–1.63) or secondary prophylaxis (OR, 0.36; 95% CI, 0.20–0.65) without significant heterogeneity ( $P = .69$ ) (Figure 2B). However, the difference was not statistically significant in patients receiving primary prophylaxis ( $P = .46$ ).

Of note, the mean reduction in HVPG observed in patients with ascites (from 19.9 mm Hg at baseline to 17.2 mm Hg at follow-up evaluation, a decrease of 14%) was lower than that observed in patients without ascites (from 18.4 to 14.9 mm Hg, a decrease of 19%). In fact, the rate of HVPG responders was significantly lower in patients with ascites compared with those without ascites (42% vs 50%, respectively;  $P = .0085$ ). The highest HVPG response rate was observed in patients without ascites or variceal hemorrhage (VH) (50%), and the lowest HVPG response rate was in patients with ascites and prior VH (36%).

#### *Patients Without Ascites Vs Patients With Ascites*

Subgroup (no ascites vs ascites) difference testing in patients enrolled in primary and secondary prophylaxis studies was performed to assess whether the effects within each subgroup deviated significantly from the overall effect (Supplementary Figures 2–5).

**Primary prophylaxis studies.** Subgroup difference testing showed no significant differences between patients with or without ascites when looking at HVPG response and the development of any clinical event ( $\chi^2 = 0.31$ ;  $df = 1$ ;  $P = .58$ ;  $I^2 = 0\%$ ) (Supplementary Figure 2) or the death/transplant rate ( $\chi^2 = 0.82$ ;  $df = 1$ ;  $P = .37$ ;  $I^2 = 0\%$ ) (Supplementary Figure 3).

**Secondary prophylaxis studies.** Subgroup difference testing showed no significant differences between patients with or without ascites when looking at HVPG response and the development of any clinical event ( $\chi^2 = 1.33$ ;  $df = 1$ ;  $P = .25$ ;  $I^2 = 25\%$ ) (Supplementary Figure 4) or the death/transplant rate ( $\chi^2 = 1.07$ ,  $df = 1$ ;  $P = .30$ ;  $I^2 = 6.8\%$ ) (Supplementary Figure 5).

## Discussion

This study shows that a reduction in portal pressure, as determined by predefined threshold reductions in HVPG, is associated with a lower rate of relevant

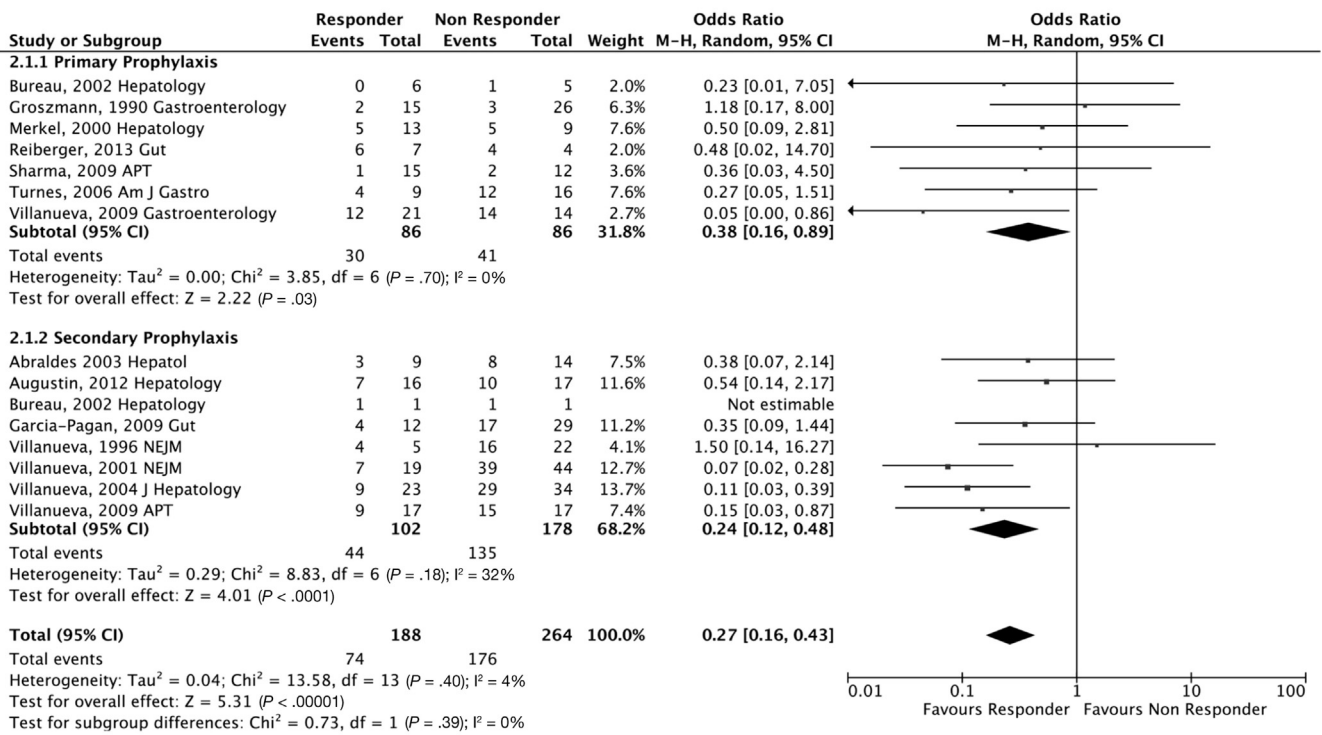
outcomes both in patients with and without ascites. Because ascites is the hallmark of cirrhosis decompensation, our study shows that decreases in portal pressure are associated with better outcomes in both patients with compensated and decompensated cirrhosis and is proof that portal hypertension is a major mechanism in the development of both decompensation and further decompensation.

D'Amico et al<sup>7</sup> had already shown an association between a reduction in HVPG to levels less than 12 mm Hg or more than a 20% reduction from baseline and a reduced risk of variceal hemorrhage and death. Other studies also have shown that achievement of these hemodynamic targets leads to a reduced risk of developing ascites, spontaneous bacterial peritonitis, hepatorenal syndrome (HRS), and hepatic encephalopathy.<sup>18</sup> In patients with compensated cirrhosis who have never bled, it has been suggested that even a target HVPG reduction of more than 10% is associated with a reduced risk of developing ascites, variceal bleeding, refractory ascites, or HRS.<sup>19</sup>

However, since the publication of these studies it has become clear that cirrhosis cannot be described as a single-stage disease and, with decompensation being the main determinant of prognosis, research on outcomes has to be analyzed separately by considering the 2 main prognostic stages of cirrhosis: compensated vs decompensated.<sup>1–3</sup> These 2 stages differ not only in terms of prognosis, but also in terms of the underlying pathophysiological drivers of disease progression<sup>4,32</sup> and in terms of clinically relevant outcomes. The most important outcome in compensated patients is the development of decompensation and, in decompensated patients, the main outcome is mortality.<sup>33</sup> Therefore, in this meta-analysis we not only stratified patients by the absence or presence of ascites (as the surrogate for decompensation), but relevant clinical events were defined differently in each of the groups.

In the subgroup of patients without ascites (ie, compensated) we showed that decompensation (defined as development of ascites, VH, or encephalopathy) was reduced significantly in HVPG responders. This is not surprising in light of a recent double-blind RCT showing that NSBBs, compared with placebo, are associated with a lower rate of ascites development and are associated with a decrease in HVPG (PREDESCI RCT).<sup>34</sup> It is noteworthy to mention that all patients without ascites included in the studies analyzed in our meta-analysis had varices needing treatment and, therefore, by definition, had clinically significant portal hypertension similar to patients included in the PREDESCI RCT<sup>34</sup> but with more advanced portal hypertension. These are patients in whom hyperdynamic circulation already is present and the NSBB effect on HVPG is more pronounced.<sup>4,32</sup> Importantly, HVPG response to NSBBs in our study was associated not only with a reduced risk of decompensation, but also with a reduced risk for death/liver transplantation in patients without ascites.

**A**  
Outcome: Any Clinical Event\*\*



\*\* Any clinical event in patients with ascites were defined as any of the following: development of variceal hemorrhage (first in primary prophylaxis studies, recurrent in secondary prophylaxis studies) or refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome or encephalopathy.

**B**  
Outcome: Death OR Transplant

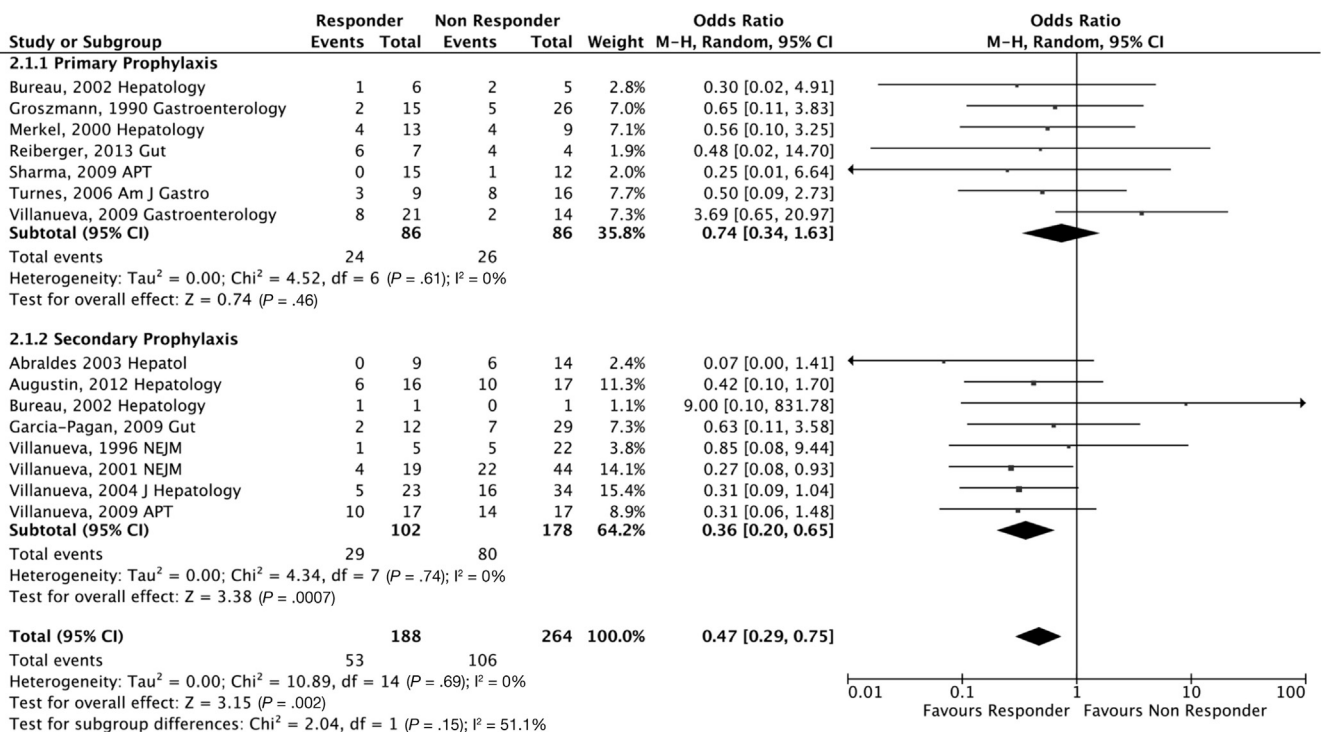


Figure 2. Patients with ascites. (A) Outcome: any clinical event. (B) Outcome: death or transplant.

Results of this study in the subgroup of patients with ascites (ie, with decompensation) are particularly relevant in light of recent concerns about potential deleterious effects of NSBBs on renal function and a potential risk for increased mortality in patients with ascites.<sup>9,10</sup> Even though, as previously shown,<sup>4,8</sup> HVPG was higher at baseline in these patients and the rate of HVPG responders was lower than in patients without ascites, we could show that portal pressure reduction achieved by pharmacologic treatment was associated not only with a lower rate of further decompensation (defined as the development of VH, refractory ascites, spontaneous bacterial peritonitis, HRS), but also with a decrease in death/transplant in the overall group of patients with ascites. The decrease in death/transplant was significant in patients with a history of variceal hemorrhage (secondary prophylaxis studies), who likely represent a sicker patient population. Although we did not observe a significant benefit on the death/transplant rate in patients included in primary prophylaxis studies, there was no indication of a higher mortality rate in this group because the subgroup difference testing was not significant (Figure 2B). This lack of effect on survival already had been noted in previous meta-analyses<sup>7,35</sup> and, in our study, this could have been because this was the smallest subgroup and rates of death/transplant were lower than expected based on other studies. In addition, although in patients with ascites who have bled from varices the main driver of mortality is the severity of portal hypertension (and therefore is affected by hemodynamic response), in patients without variceal hemorrhage confounders such as hepatocellular carcinoma, not directly related to hemodynamic changes, may contribute to overall mortality. We chose to analyze deaths/transplant jointly because of the multinational nature of the publications with different availability/criteria for transplant and the timespan of the studies (with the earliest in 1990 when transplant rarely was performed). The number of transplants in the whole series was only 76, representing 23% of the combined death/transplant outcome.

NSBB (propranolol, nadolol) were used in 87% of patients included in the meta-analysis and the remaining 13% were on a therapy without an effect on portal pressure (placebo or endoscopic therapy). A sensitivity analysis that excluded the 4 studies with patients on inactive therapy yielded the same results on outcomes and death/transplant rates (data shown in Supplementary Table 2).

Our meta-analysis is unique in that not only did we explore outcomes other than variceal hemorrhage and death, but we explored outcomes relevant to each prognostic stage. In addition, because data were requested from the original authors, we could ensure that duplicate patients were excluded and, therefore, unlike other meta-analyses that extracted data from publications that had duplicate patients, we report data on unique patients with cirrhosis.

Limitations of the study were those inherent to the collection of retrospective selected data from prospective studies. In addition, some important variables such as comorbidities, hepatocellular carcinoma, Child-Pugh score, and model for end-stage liver disease, were not collected uniformly, therefore we were not able to explore the impact of these predictive scores on outcomes. Notably, although the second most common etiology was viral, all studies were performed before the advent of effective antiviral therapy and such therapy therefore would not represent a confounder. A potential confounder was the use (or not) of alcohol during the study. Although alcohol was the etiology in fewer than half of the patients ( $n = 516$ ), 9 of 15 studies reported on alcohol abstinence during the follow-up evaluation. Of these, 2 studies<sup>20,22</sup> reported that all patients had been abstinent during the study, 5 studies<sup>18,19,25,27,31</sup> showed no significant differences between alcohol abstinence/nonabstinence and HVPG response/nonresponse, and only 2 studies<sup>17,29</sup> comprising only 110 patients found a higher percentage of alcohol abstinence among HVPG responders compared with nonresponders. Therefore, it is unlikely that better outcomes in HVPG responders observed in this meta-analysis could have been ascribed to alcohol abstinence.

Reductions in HVPG all were described as threshold reductions (responders vs nonresponders) in the studies included in this meta-analysis. It may well be that analysis of absolute changes in mm Hg could provide more granularity (as recently described<sup>36</sup>), but data on individual data were not requested from the original authors (only data on responders vs nonresponders), and therefore such analysis could not be performed.

In summary, our results show that HVPG responders to NSBB-based pharmacologic therapy, mainly defined as a reduction in HVPG to less than 12 mm Hg or a more than 20% reduction from baseline, have a significantly lower risk of developing clinically relevant outcomes in both patients with and without ascites. In patients without ascites but with varices, lowering portal pressure significantly reduces the risk of any clinical decompensation (not only variceal bleeding but also ascites and encephalopathy) and improves survival. In patients with ascites (decompensated) with or without variceal hemorrhage, a reduction in portal pressure lowers the risk of further decompensation (variceal hemorrhage, refractory ascites, spontaneous bacterial peritonitis, or encephalopathy). Importantly, achieving an HVPG response improves survival in patients with ascites and a previous episode of bleeding who are notoriously those patients with the poorest survival rate. By showing that reductions in portal pressure induced by NSBB-based pharmacologic therapy improve outcomes and decrease mortality, our study supports the use of NSBB in all clinical settings (primary or secondary prophylaxis) and in both patients with or without ascites.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org), and at <https://doi.org/10.1016/j.cgh.2019.05.050>.

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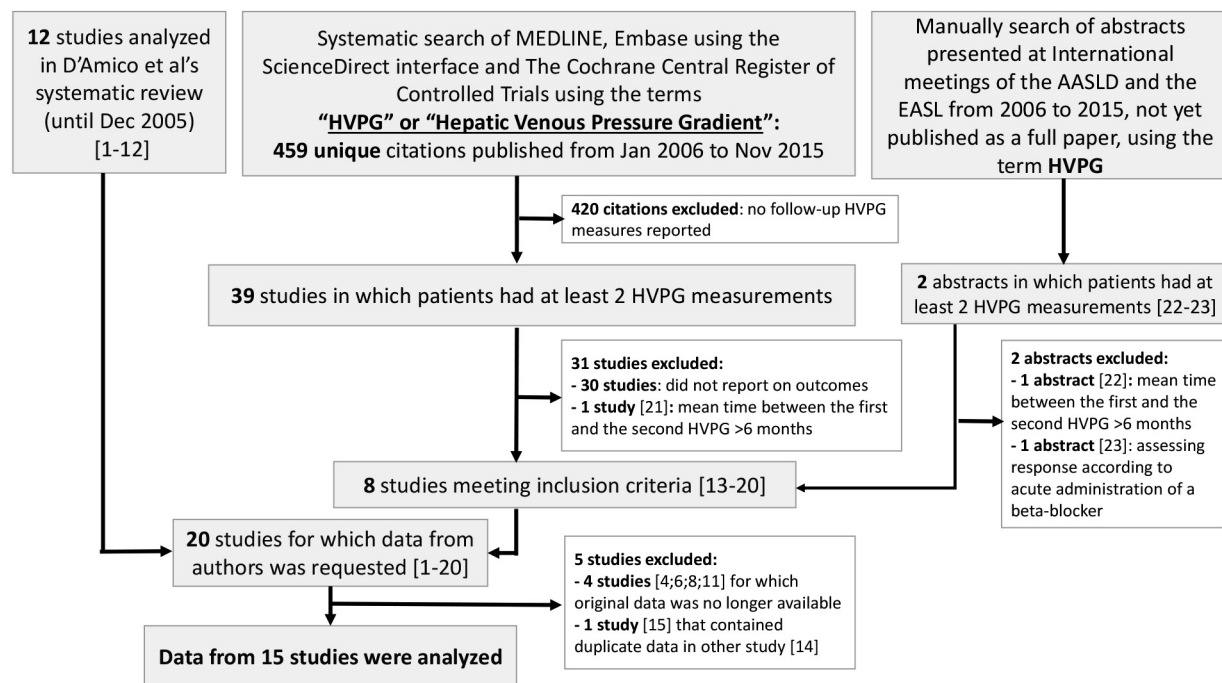
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**Conflicts of interest**

The authors disclose no conflicts.

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## Abstract

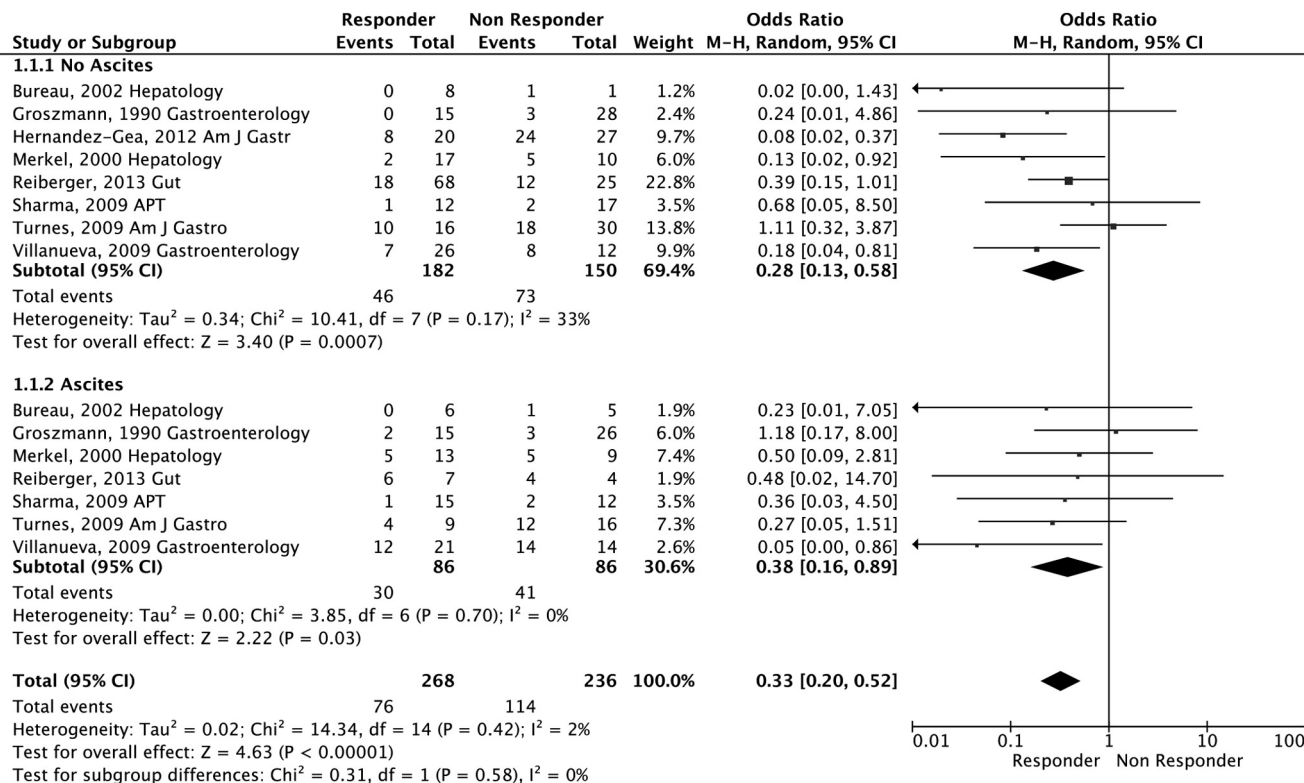
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**Supplementary Figure 1.** Flowchart. AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; HVPG, hepatic venous pressure gradient.



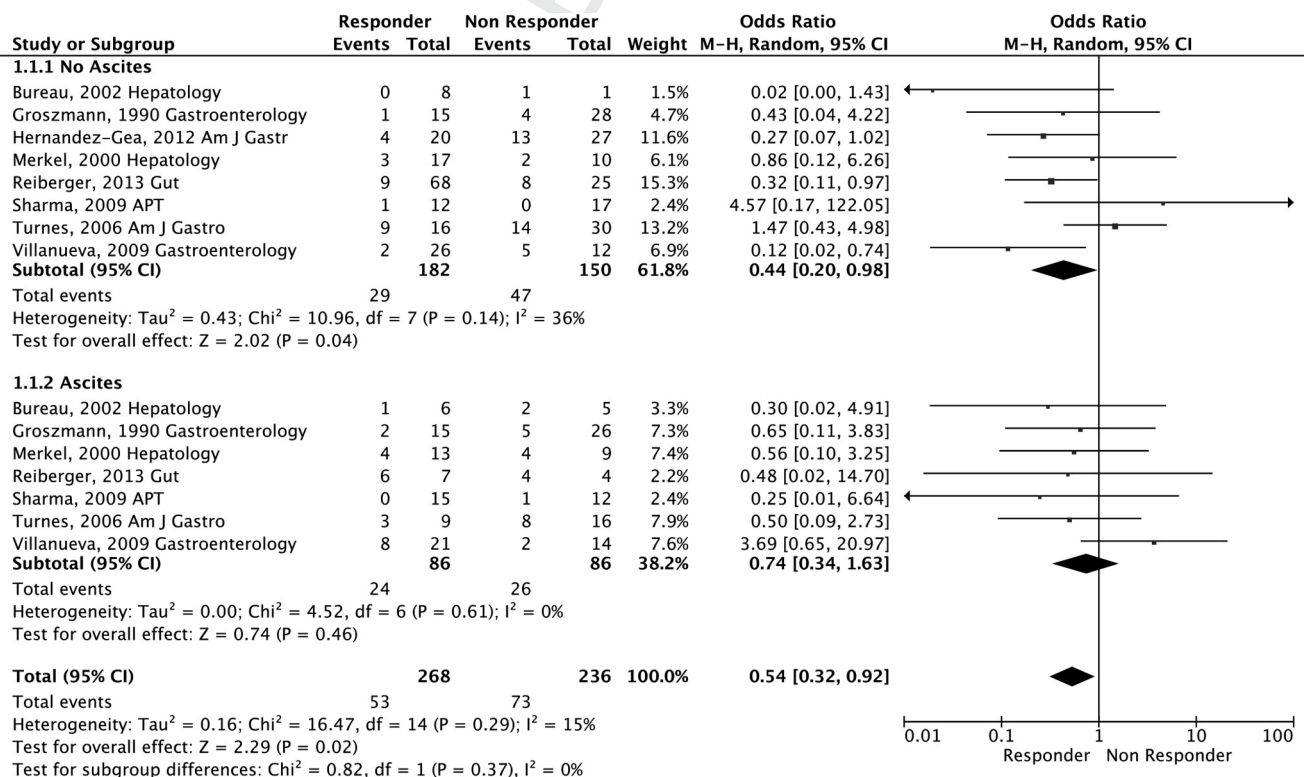
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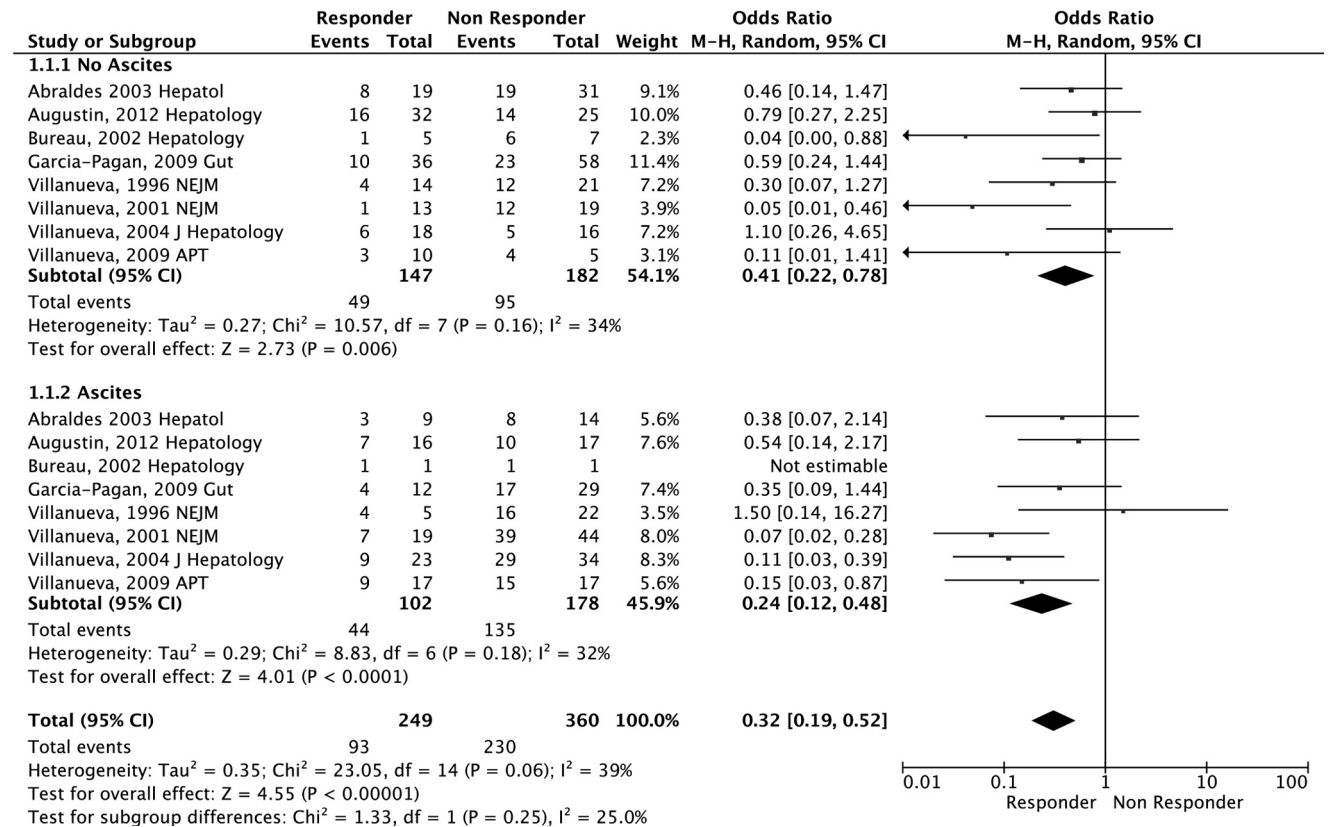


\* In patients without ascites, any clinical event was defined as any of the following: first variceal hemorrhage, ascites or encephalopathy. In patients with ascites, any clinical event was defined as any of the following: first variceal hemorrhage, refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome or encephalopathy.

Supplementary Figure 2. Patients included in studies of primary prophylaxis of variceal hemorrhage. Outcome: any clinical event. Q26



Supplementary Figure 3. Patients included in studies of primary prophylaxis of variceal hemorrhage. Outcome: death or transplant.



\* In patients without ascites, any clinical event was defined as any of the following: recurrent variceal hemorrhage, ascites or encephalopathy. In patients with ascites, any clinical event was defined as any of the following: recurrent variceal hemorrhage, refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome or encephalopathy.

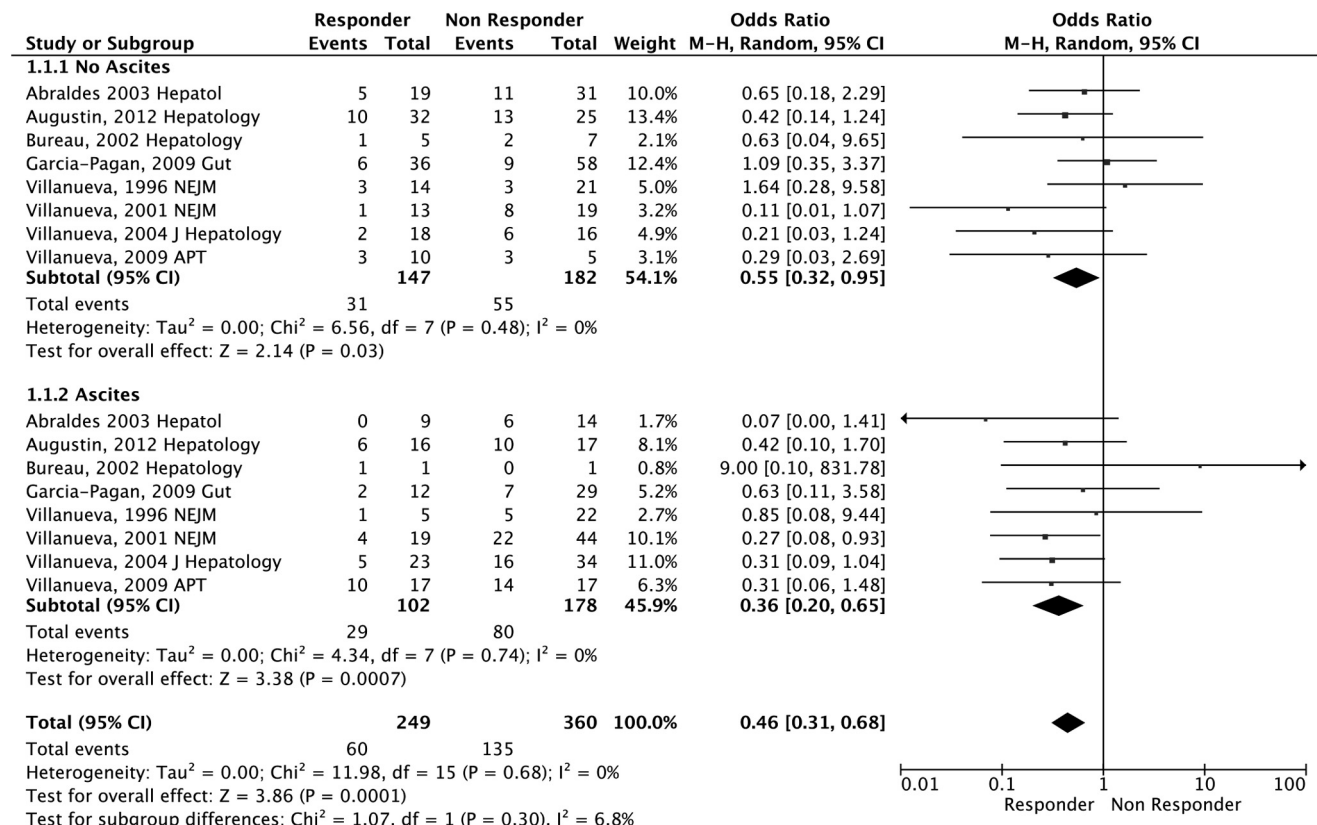
Supplementary Figure 4. Patients included in studies of secondary prophylaxis of variceal hemorrhage. Outcome: any clinical event.

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**Supplementary Figure 5.** Patients included in studies of primary prophylaxis of variceal hemorrhage. Outcome: death or transplant.

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Supplementary Table 1. HVPG Methodology

Study	Details on positioning of external zero and transducer calibration	Use of balloon catheter	Measurements, n	Permanent tracing obtained	Sedation during HVPG	Positioning and sufficient wedge position checked by radiograph/ confirmed by dye injection
Groszmann et al, <sup>20</sup> 1990 <i>Gastroenterology</i>	Yes	Yes	≥2	Yes	NR	Yes
Hernandez-Gea et al, <sup>19</sup> 2012 <i>Am J Gastroenterol</i>	Yes	Yes	3	Yes	NR	Yes
Merkel et al, <sup>21</sup> 2000 <i>Hepatology</i>	NR	Yes	≥3	Yes	NR	Yes
Reiberger et al, <sup>22</sup> 2013 <i>Gut</i>	NR	Yes	≥3	Yes	NR	Yes
Sharma et al, <sup>23</sup> 2009 <i>Aliment Pharmacol Ther</i>	Yes	Yes	3	NR	NR	Yes
Turnes et al, <sup>24</sup> 2006 <i>Am J Gastroenterol</i>	NR	Yes	3	Yes	NR	Yes
Villanueva et al, <sup>25</sup> 2009 <i>Gastroenterology</i>	Yes	Yes	3	Yes	NR	Yes
Abraldes et al, <sup>18</sup> 2003 <i>Hepatology</i>	NR	Yes	NR	NR	NR	NR
Augustin et al, <sup>17</sup> 2012 <i>Hepatology</i>	NR	Yes	3	Yes	NR	NR
García-Pagán et al, <sup>26</sup> 2009 <i>Gut</i>	NR	Yes	≥2	Yes	Yes	Yes
Villanueva et al, <sup>27</sup> 1996 <i>N Engl J Med</i>	Yes	Yes	3	NR	NR	NR
Villanueva et al, <sup>28</sup> 2001 <i>N Engl J Med</i>	Yes	Yes	3	NR	NR	NR
Villanueva et al, <sup>29</sup> 2004 <i>J Hepatol</i>	Yes	Yes	3	NR	NR	Yes
Villanueva et al, <sup>30</sup> 2009 <i>Aliment Pharmacol Ther</i>	Yes	Yes	3	Yes	NR	Yes
Bureau et al, <sup>31</sup> 2002 <i>Hepatology</i>	Yes	NR	≥3	NR	NR	NR

HVPG, hepatic venous pressure gradient; NR, not reported.

Supplementary Table 2. Outcomes of Patients on Active Pharmacologic Therapy

	Benefit of responders vs nonresponders									
	Any clinical event <sup>a</sup>					Death/transplant				
	Overall effect	P	Primary vs secondary prophylaxis	P	Heterogeneity	Overall effect	P	Primary vs secondary prophylaxis	P	Heterogeneity
Patients without ascites (n = 458)	OR, 0.35 (0.22–0.56)	<.0001	Primary (n = 196) OR, 0.28 (0.13–0.58) Secondary (n = 262) OR, 0.41 (0.22–0.78)	.0007  .006	0.10	OR, 0.50 (0.32–0.78)	.0002	Primary OR, 0.44 (0.20–0.98) Secondary OR, 0.55 (0.32–0.95)	.04  .03	0.28
Patients with ascites (n = 310)	OR, 0.27 (0.16–0.43)	<.0001	Primary (n = 120) OR, 0.38 (0.16–0.89) Secondary (n = 190) OR, 0.24 (0.12–0.48)	.03  <.0001	0.40	OR, 0.47 (0.29–0.75)	.0002	Primary OR, 0.74 (0.34–1.63) Secondary OR, 0.36 (0.20–0.75)	.46  .0007	0.69

NOTE. n = 768. Numbers in parentheses represent 95% CI.

<sup>a</sup>In patients without ascites: variceal bleeding (first in primary prophylaxis studies, recurrent in secondary prophylaxis studies), development of ascites or encephalopathy. In patients with ascites: development of variceal bleeding (first in primary prophylaxis studies, recurrent in secondary prophylaxis studies) or refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, or encephalopathy.

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