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With Cirrhos	is, With or Without Ascites: A Meta-Analysis
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DAGRANOUND & AIMS.	(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 viriand 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.
DECIII TC.	Of the 1113 nationts included in the studies 968 nationts (87%) had been treated with
NEOULIO.	of the 1115 patients included in the studies, 700 patients (0770) had been treated with
NEGULIG.	nonselective β -blockers. In 993 patients (89%), HVPG response was defined as a decrease of momentum 20% for momentum 20% in the 10% in 11% of activity bursts have then the 12 m.
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NEGULIS:	nonselective β -blockers. In 993 patients (89%), HVPG response was defined as a decrease o 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 henatorenal syndrome) than nonresponders (OR 0.27, 95% CI 0.16-0.43)
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Abbreviations used in this paper: HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; NSBB, nonselective *β*-blocker; OR, odds ratio; RCT, randomized controlled trial; VH, variceal hemorrhage.

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CONCLUSIONS:

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In a meta-analysis of clinical trials, we found that patients with cirrhosis with and without ascites who respond to treatment with nonselective β -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.¹⁻⁴

130 Nonselective β -blockers (NSBBs) have been the main-131 stay of therapy of portal hypertension since 1981 when 132 Lebrec et al⁵ showed the efficacy of propranolol in reducing 133 portal pressure. Since then, many randomized controlled 134 trials have shown that NSBBs are effective in preventing 135 variceal hemorrhage, both first and recurrent, and there-136 fore NSBBs are considered first-line therapy in the primary 137 and secondary prophylaxis of variceal hemorrhage.⁶

138 Because NSBBs, by reducing portal pressure, may pre-139 vent not only variceal hemorrhage but other complications 140 of portal hypertension, many studies have correlated the 141 decrease in portal pressure (as determined by the hepatic 142 venous pressure gradient [HVPG]) with the prevention of all 143 complications of cirrhosis, including death. In a meta-144 analysis by D'Amico et al⁷ that included 12 studies 145 (including 943 patients with cirrhosis), HVPG responders, 146 defined as those with an HVPG reduction to 12 mm Hg or less 147 or 20% or more from baseline had a significantly lower risk 148 of bleeding and death. However, all studies included in the 149 D'Amico et al⁷ meta-analysis combined results from patients 150 with both compensated and decompensated cirrhosis.

151 Because the effect of NSBBs on portal pressure and 152 outcomes may differ in these 2 different stages of 153 cirrhosis⁸ and because it has been suggested that NSBBs 154 may be deleterious in patients with refractory ascites,^{9,10} 155 we considered it important to update the D'Amico et al^7 156 meta-analysis by not only adding data from additional 157 recent studies reporting HVPG response and outcomes 158 but, more importantly, to stratify patients by the pres-159 ence or absence of ascites and to report on clinically 160 relevant outcomes. For this study, we considered ascites 161 as the hallmark of decompensation because it is the most 162 common decompensating event, it is the only one that is 163 continuous (as opposed to variceal hemorrhage and he-164 patic encephalopathy, which are episodic), and because it 165 is the most likely to be recorded accurately in study 166 databases on which this meta-analysis was based. 167

Materials and Methods

Methods

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173 Q12We performed a meta-analysis to pool data from pa-174tients 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, ^{Q13} 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 2014.¹¹

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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 followup 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 al⁷ meta-analysis found the long interval (5.3 mo) between HVPG measurements observed in 1 study¹² to be the main predictor of heterogeneity, therefore this study¹² and any other study with a mean/median interval between HVPG measurements of 5 months or longer were excluded.

Information Sources and Search

223 The studies conducted until December 2005 were identified from the D'Amico et al⁷ meta-analysis. Studies 224 conducted from January 1, 2006, to November 30, 2015, 225 were identified by searching electronic databases using 226 the terms "hepatic venous pressure gradient" or "HVPG," 227 limiting the search to human studies. This search was 228 229 performed in MEDLINE via PubMed, Embase using the 230 ScienceDirect interface, and The Cochrane Central Register of Controlled Trials. Publications in personal 231 reference lists and citation sections of the recovered 232

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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.

248 Once studies that met inclusion criteria had been 249 selected and because data regarding the presence or 250 absence of ascites and clinical outcomes specific for each 251 of these subgroups and for each of the responder groups 252 (responder vs nonresponder) could not be extracted 253 from published studies, principal investigators of eligible 254 studies were contacted to obtain data for all subgroups 255 in their trials. Specifically, we provided a data collection 256 form divided into HVPG responder vs nonresponder 257 groups (providing the numbers for each group that had 258 been reported in the published article), and the principal 259 investigators then provided data on the presence or 260 absence of ascites and on relevant clinical outcomes (see 261 later) for each responder group separately. Therefore, 262 this was not an individual meta-analysis and the objec-263 tive was to analyze the development of clinical outcomes 264 separately in HVPG responders vs nonresponders (as 265 defined in each of the studies) stratified by the presence 266 or absence of ascites. To include only unique patients, 267 when the same patient population was used in multiple 268 publications, the authors were asked to provide data 269 from the most recent publication that included all pa-270 tients (in which case the previous publication would not 271 be considered) or to report only on the additional pa-272 tients in the newer publication (in which case both 273 publications would be cited). Authors were asked to 274 exclude data from patients with only 1 HVPG measure-275 ment. The original data sets were checked for 276 completeness and internal consistency and amended 277 through correspondence with the principal investigators. 278

Data Collected on Outcomes

282 Relevant outcomes were defined separately for pa283 tients without ascites (compensated) and those with
284 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 β -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 rebleeding 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 pa-
tients without ascites and for those with ascites, and also
was performed separately for patients enrolled in pri-
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mary prophylaxis studies and those enrolled in second-
ary prophylaxis studies. Because the results of each
study had dichotomous frequency data, a meta-analysis
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study had dichotomous frequency data, a meta-analysis
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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 on339
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the magnitude of the effect, we chose to pool data and compare it using a random-effects model.¹³ A *P* value less than .05 was considered significant. Statistical heterogeneity was calculated by the I^2 . Values less than 30%, 30% to 59%, 60% to 75%, and greater than 75% were classified as low, moderate, substantial, and considerable heterogeneity, respectively.¹⁴ All analyses were performed using the software Review Manager (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

362 A total of 459 unique citations were identified using 363 our search criteria (Supplementary Figure 1). After 364 excluding 420 studies because they did not report data on 365 follow-up HVPG, 30 studies because they did not report on 366 outcomes, and 1 study¹⁵ because the median time be-367 tween the baseline and follow-up HVPG was longer than 5 368 months (13 months in compensated patients and 8 369 months in decompensated patients), 8 studies published 370 between January 2006 and November 2015 met our in-371 clusion criteria. These 8 studies were added to 12 studies 372 published before December 2005 as identified by D'Amico 373 et al⁷ (Supplementary Figure 1). We could not identify any 374 eligible study published in abstract form that was not 375 subsequently published in full. 376

Additional data on the outcomes of patients with and 377 without ascites (separately) were requested from the 378 authors of the 20 eligible studies. Original data were no 379 longer available for 4 of them (including the study from 380 McCormick et al^{12}), and data from 1 publication¹⁶ was 381 duplicated in a second publication¹⁷ and therefore was 382 excluded. Therefore, the meta-analysis includes data 383 from 15 studies^{17–31} (Supplementary Figure 1). 384

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.

391 Overall, the 15 selected studies included 1341 pa-392 tients, of whom 228 were excluded (124 patients did not 393 have a second HVPG performed, 72 patients had been 394 reported in other studies, and 32 patients were tested 395 after a single intravenous dose of propranolol). There-396 fore, data from 1113 unique patients were analyzed. Of 397 these, 452 (40.6%) had ascites. Notably, and as expected, 398 the mean HVPG levels were higher in patients with as-399 cites than in those without ascites (Table 2).

400Table 3 shows the different outcomes including401death/liver transplant rates by the presence or absence402of ascites, according to the HVPG response category403(responders vs nonresponders), as defined in each of the404studies. Except for 2 studies^{19,25} (all patients taking405NSBBs for primary prophylaxis) defining HVPG406

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407 responders as those patients achieving a reduction of more than 10% or a decrease to less than 12 mm Hg, the Q14 408 remaining 13 studies defined HVPG response as a 409 decrease to less than 12 mm Hg or a reduction of more 410 than 20% from baseline. Notably, raw data were avail- Q15 411 able for a study in which the original publication had 412 defined only HVPG response as a decrease in HVPG to 413 less than 12 mm Hg²⁰ so that response could be rede-414 fined as a decrease greater than 20% or a decrease less 415 than 12 mm Hg to be consistent with the majority of 416 studies. Table 3 also shows the specific pharmacologic 417 therapy. Notably, of 1113 unique patients, only 145 418 (13%) were not on active pharmacologic treatment (39 419 420 were on placebo and 106 received endoscopic treatment only) (Table 3). Supplementary Table 1 shows the HVPG 421 methodology used in each study. 422

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^{19,25} 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 1*A*), 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 1*A*)

Death/transplant rates also were significantly lower among responders (OR, 0.50; 95% CI, 0.32–0.78) (Figure 1*B*) 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 1*B*).

Patients With Ascites (n = 452)

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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 study25 in459whom response was defined as an HVPG decrease of460more than 10% or a reduction to less than 12 mm Hg (all461patients were on NSBBs for primary prophylaxis), in the462remaining 417 (92.3%) patients, HVPG response was463464

Table 1. Characteristics of the 15 Included Studies

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	Study	Study type	Study population (inclusion criteria)	Exclusion criteria	Patient recruitment period	Age, y	Sex, % male	Main etiology, %
Q24	Groszmann et al, ²⁰ 1990 Gastroenterology	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, ¹⁹ 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, ²¹ 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, ²² 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, ²³ 2009 <i>Aliment Pharmacol Ther</i>	Case series	Cirrhosis, medium–large esophageal varices \pm 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, ²⁴ 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, ²⁵ 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, ¹⁸ 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, ¹⁷ 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 o endoscopic variceal obliteration, contraindications to NSBB or ISMN, advanced HCC, severe comorbidity, PVT, HVPG <10 mm Hg	2001–2010	54	78	Alcohol, 50 c

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Table 1. Continued

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Study	Study type	Study population (inclusion criteria)	Exclusion criteria	Patient recruitment period	Age, y	Sex, % male	Main etiology, %
García-Pagán et al, ²⁶ 2009 Gut	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 ²⁷ N Engl J Med	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, ²⁸ 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, ²⁹ 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, ³⁰ 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, ³¹ 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 legation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; ISMN, isosorbide mononitrate; NA, not available; NSBB, nonselective β-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

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

^aData not in original publication, provided by authors.

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^bOne month in responders to propranolol; 2 months for nonresponders to propranolol in whom isosorbide mononitrate was added.

^cOf 105 patients in the study, 32 were excluded because only the HVPG response to a single intravenous dose of propranolol was evaluated.

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

											Outcomes		Surviv	al
Study	Unique patients included, n	Therapy	Unique patients on placebo or endoscopic treatment only, n	Mean follow- up period, <i>m</i> o	Definition of responder	No ascites/ ascites	N	R/NR	Ν	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, ²⁰	84	Propranolol vs	39	16	HVPG \leq 12 mm Hg or	No ascites	43	R	15	0	NA	NA	NA	1
1990 Castroenterology		placebo	Placebo		HVPG decrease	Ascitos	11	NK R	28 15	3	NA NA	NA NA	NA	4
Gastroenterology					<u>~</u> 20%	ASCILES	41	NR	26	2	NA	NA	NA	5
Hernandez-Gea	47	Nadolol	0	53	HVPG decrease >10%	No ascites	47	R	20	0	1	7	0	4
et al, ¹⁹ 2012 <i>Am J</i>								NR	27	0	8	16	1	12
Gastroenterol						Ascites	NA	R	NA	NA	NA	NA	NA	NA
Madada at 21 0000	10		0	00		NI	07	NR	NA	NA	NA	NA	NA	NA
Merkel et al, 2000	49	Nadolol or	0	36	$HVPG \leq 12 \text{ mm Hg or}$	INO ascites	27	K NR	17	0	1	1	1	2
Пераююду		ISMN			>20%	Ascites	22	B	13	2	0	4	0	4
					<u>-</u> 2070		_	NR	9	2	2	1	1	3
Reiberger et al, ²²	104	Propranolol or	29	19	HVPG <12 mm Hg or	No ascites	93	R	68	3	2	13	5	4
2013 Gut		carvedilol	EVL		HVPG decrease			NR	25	2	3	7	2	6
		vs EVL			≥20%	Ascites	11	R	7	1	1	4	1	5
Observes at al ²³ 0000	50	Duanuanalal	0	0.4			00	NR	4	2	0	2	1	3
Aliment	50	Propranoioi \pm	0	24	$HVPG \leq 12 \text{ mm Hg or}$	INO ASCITES	29	K NR	12	1	1	1	0	1
Pharmacol Ther					>20%	Ascites	27	B	15		0	0	0	0
								NR	12	2	Ő	0	0	1
Turnes et al, ²⁴ 2006	71	Propranolol \pm	0	68	HVPG \leq 12 mm Hg or	No ascites	46	R	16	1	1	8	3	6
Am J		ISMN			HVPG decrease			NR	30	4	6	8	1	13
Gastroenterol					<u>≥</u> 20%	Ascites	25	R	9	0	0	4	0	3
V(11-1-1-25	70	N	0	05		NI	00	NR	16	1	3	8	3	5
villanueva et al,	73	INACOIOI	0	25	HVPG <12 mm Hg or	NO ascites	38	K ND	26	1	0	6	0	2
Gastroenterology					>10%	Ascites	35	B	21	0	4	12	4	4
addiroontorology					<u>></u> 1070	71001100	00	NR	14	1	7	6	0	2
Secondary prophylaxi	s													
Abraldes et al, ¹⁸	73	Propranolol \pm	0	70	HVPG ${\leq}12$ mm Hg or	No ascites	50	R	19	3	2	3	4	1
2003 Hepatology		ISMN			HVPG decrease			NR	31	6	9	4	3	8
					≥20%	Ascites	23	R	9	0	1	4	0	0
Augustin et al ¹⁷	90	Nadolol –	0	48	HVPG <12 mm Ha or	No ascites	57	INK R	14 32	і 8	4	ა ვ	U 3	ю 7
2012 Henatology	30	ISMN + FVI	0	40	HVPG decrease	NU asciles	57	NR	25	0	3	11	4	9
_0, _ , iopatology					>20%	Ascites	33	R	16	3	0	4	2	4
					-		-	NR	17	1	1	8	5	5
	000	0000	0000	000		• • • • • • • •	$\infty \infty$	$\infty \infty$	$\infty \infty$	$\infty \propto \infty \propto \infty$	$\infty \infty \infty \infty$	$\infty \propto \infty \propto \infty$	$\infty \infty \infty \infty c$	$\infty \infty \infty$

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980 981 982 983 984 985 985	978 979	973 974 975 976	967 968 970 971	965 966	958 959 960 961 962 963	954 955 956	952 953	950 951	948 949	944 945 946 947	940 941 942 943	936 937 938 939	932 932 933 934 935	929 930 931	
García-Pagán	135	Nadolol +	00	15	HVPG ≤12 mm Hg or	No ascites	94	R	36 58	3 11	2	5	2	4	1
Gut		nadolol +	Л		≥20%	Ascites	41	R	12	0	1	3	0	2	9
Villanueva et al, ²⁷	62	Nadolol \pm	31	18	HVPG <12 mm Hg or	No ascites	35	R	29 14	1	0	3	1	2	
Med		sclerothera	Scierotherapy		\geq 20%	Ascites	27	R	5	0	4	2	2	1	
Villanueva et al, ²⁸	95	Nadolol \pm	46	24	HVPG <12 mm Hg or	No ascites	32	NR R	22 13	4 1	8 0	4 0	2 0	3 1	
2001 N Engl J Med		ISMN vs EVL	EVL		HVPG decrease >20%	Ascites	63	NR R	19 18	6 1	5 3	1 3	0 2	8 2	

NR

NR

NR

NR

34 R

57 R

15 R

Pharmacol Ther		nadolol +			>20%	Ascites	34	R	17	1	1	7	4	
		ISMN vs						NR	17	1	6	8	2	
		nadolol +												
		EVL												
Primary and secondary	prophyla	kis												
Bureau et al, ³¹ 2002	34	Propranolol \pm	0	28	HVPG <12 mm Hg or									
Hepatology		ISMN			HVPG decrease	No ascites	9	R	8	0	NA	NA	0	
Bureau, ³¹ 2002,		ISMN			>20%			NR	1	1	NA	NA	0	
Hepatology						Ascites	11	R	6	0	NA	NA	0	
								NR	5	1	NA	NA	0	
						No ascites	12	R	5	1	NA	NA	0	
								NR	7	6	NA	NA	0	
						Ascites	2	R	1	1	NA	NA	0	
								NR	1	1	NA	NA	0	

HVPG \leq 12 mm Hg or No ascites

HVPG <12 mm Hg or No ascites

Ascites

HVPG decrease

HVPG decrease

>20%

EVL, endoscopic variceal ligation; HVPG, hepatic venous pressure gradient; ISMN, isosorbide mononitrate; NA, not available; NR, nonresponder; R, responder.

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Villanueva et al,29

Villanueva et al,30

2009 Aliment

2004 J Hepatol

Nadolol ±

ISMN

Nadolol +

prazosin or

10 Turco et al

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Outcome: Any Clinical Event*

	Respor	nder	Non Respo	nder		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight M	-H, Random, 95% CI		M-H, Random, 95% Cl
2.1.1 Primary Prophylaxis		-						
Bureau, 2002 Hepatology	0	8	1	1	1.2%	0.02 [0.00, 1.43]	• •	
Groszmann, 1990 Gastroenterology	0	15	3	28	2.2%	0.24 [0.01, 4.86]		
Hernandez-Gea, 2012 Am J Gastr	8	20	24	27	6.8%	0.08 [0.02, 0.37]		
Reiberger 2012 Cut	19	17	5	10	4.7%	0.13 [0.02, 0.92]		•
Sharma 2009 APT	10	12	12	17	3.0%	0.59 [0.15, 1.01]		
Turnes 2006 Am Castro	10	16	18	30	8.6%	1 11 [0 32 3 87]		
Villanueva 2009 Gastroenterology	7	26	8	12	6.9%	0 18 [0 04 0 81]		
Subtotal (95% CI)		182	Ū.	150	45.0%	0.28 [0.13, 0.58]		
Total events	46		73					
Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 1$	0.41, df =	7 (P =	.17); l ² = 33%	6				
Test for overall effect: $Z = 3.40$ ($P = 3.40$	0007)							
2.1.2 Secondary Prophylaxis								
Abraldes 2003 Hepatol	8	19	19	31	9.4%	0.46 [0.14, 1.47]		
Augustin, 2012 Hepatology	16	32	14	25	10.4%	0.79 [0.27, 2.25]		
Bureau, 2002 Hepatology	1	5	6	7	2.2%	0.04 [0.00, 0.88]	•	
Garcia-Pagan, 2009 Gut	10	36	23	58	12.1%	0.59 [0.24, 1.44]		
Villanueva, 1996 NEJM	4	14	12	21	7.2%	0.30 [0.07, 1.27]		
Villanueva, 2001 NEJM	1	13	12	19	3.7%	0.05 [0.01, 0.46]	•	·
Villanueva, 2004 J Hepatology	2	18	5	10	7.2%	1.10 [0.26, 4.65]		
Subtotal (95% CI)	5	147	4	182	55.0%	0.41 [0.22, 0.78]		
Total events	49		95					•
Heterogeneity: $Tau^2 = 0.27$: $Chi^2 = 1$	0.57. df =	7 (P =	.16): l ² = 34%	6				
Test for overall effect: $Z = 2.73$ ($P = 1$	006)	,	,,					
Total (95% CI)		329		332	100.0%	0.35 [0.22, 0.56]		◆
Total events	95		168					
Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 2$	2.21, df =	= 15 (P	= .10); I ² = 32	%			0.01	
Test for overall effect: $Z = 4.37$ ($P <$	0001)						0.01	Favours Responder Favours Non Responder
Test for subgroup differences: Chi ² =	• 0.64, df	= 1 (P =	= .42); l ² = 0%	Ď				
* Defined as any of the following	na: vario	oal he	morrhade	(first	in nrimar	v prophylaxis stud	ies recu	rrent in secondary prophylaxis studies)
Defined as any of the following	ig. valio	curre	monnaye	, (in st	in primar	piopingiaxis stud	ics, recu	rient in secondary propriyiaxis studies),

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Outcome: Death OR Transplant

1075										1133
1076	Study or Subgroup	Respor	nder Total	Non Resp	onder	Weight	Odds Ratio	Odds Ratio		1134
1077	2.1.1 Primary Prophylaxis	Lvents	Total	Lvents	Total	weight	-1, Kandoni, 55% Cr		-	113
1079	Bureau, 2002 Hepatology	0	8	1	1	1.0%	0.02 [0.00, 1.43]	←		1124
10/8	Groszmann, 1990 Gastroenterology	1	15	4	28	3.5%	0.43 [0.04, 4.22]			1130
1079	Hernandez-Gea, 2012 Am J Gastr	4	20	13	27	8.8%	0.27 [0.07, 1.02]			113'
1080	Merkel, 2000 Hepatology	3	17	2	10	4.5%	0.86 [0.12, 6.26]			1139
1000	Reiberger, 2013 Gut	9	68	8	25	11.8%	0.32 [0.11, 0.97]			1120
1081	Sharma, 2009 API	1	12	0	17	1.8%	4.57 [0.17, 122.05]			1139
1082	Turnes, 2006 Am J Gastro	9	16	14	30	10.1%	1.47 [0.43, 4.98]			1140
1092	Subtotal (95% CI)	2	182	2	150	46.5%	0.12 [0.02, 0.74]			114
1085	Total events	29	101	47	190	1015/0	0111 [0120, 0150]			114
1084	Heterogeneity: $Tau^2 = 0.43$: $Chi^2 = 1$	10.96. df =	7 (P =	.14): l ² = 36	%					1142
1085	Test for overall effect: $Z = 2.02$ ($P =$.04)	, (, _							1143
1086	2.1.2 Secondary Prophylaxis									1144
1087	Abraldes 2003 Hepatol	5	19	11	31	9.6%	0.65 [0.18, 2.29]			1144
1007	Augustin, 2012 Hepatology	10	32	13	25	12.0%	0.42 [0.14, 1.24]			114.
1088	Bureau, 2002 Hepatology	1	5	2	7	2.5%	0.63 [0.04, 9.65]			1146
1089	Garcia-Pagan, 2009 Gut	6	36	9	58	11.3%	1.09 [0.35, 3.37]			114
1000	Villanueva, 1996 NEJM	3	14	3	21	5.5%	1.64 [0.28, 9.58]			1140
1090	Villanueva, 2001 NEJM	1	13	8	19	3.6%	0.11 [0.01, 1.07]	· · · · · ·		1148
1091	Villanueva, 2004 J Hepatology	2	18	6	16	5.4%	0.21 [0.03, 1.24]			1149
1002	Villanueva, 2009 APT	3	10	3	5	3.6%	0.29 [0.03, 2.69]			1150
1092	Subtotal (95% CI)		147		182	53.5%	0.55 [0.32, 0.95]	-		1130
1093	Laterogeneity $T_{2}u^{2} = 0.00$, $Chi^{2} = 4$	31	7 (D	101/12 00/						1151
1094	Heterogeneity: $Tau^2 = 0.00$; $Chl^2 = 0$	0.56, ar = 0.02	7 (P = .2)	$(18); 1^{\circ} = 0\%$						115
1007	Test for overall effect. $Z = 2.14$ (P =	.03)								11.52
1095	Total (95% CI)		329		332	100.0%	0.50 [0.32, 0.78]	◆		115.
1096	Total events	60		102						1154
1097	Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 1$	L7.74, df =	: 15 (P :	= .28); l ² = 1	5%			0.01 0.1 1 10 100		115:
1098	Test for subgroup differences: $Ch^2 = -2.08$.002) = 0.20. df	= 1 (P =	$= .65$): $I^2 = 0$	%			Favours Responder Favours Non Responder		1156
1099	Eiguro 1 Dationt	o with o	ut 00	oitoo (A) Out-		a dinical avent	(P) Outcome: dooth or transplant	022	115
1100	rigure 1. Patient	s witho	ut as	cites. (A		ome: ar	iy clinical event.	(D) Outcome: death or transplant.	422	115
1100										1150
1101										1159

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Lowering Portal Pressure in Cirrhosis 11

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

1163 Overall, responders (41.6%) had a significantly lower 1164 rate of clinical events (variceal hemorrhage, refractory as-1165 cites, spontaneous bacterial peritonitis, hepatorenal syn-1166 drome, or encephalopathy) than nonresponders (OR, 0.27; 1167 95% CI, 0.16–0.43) (Figure 2A), both in patients included in 1168 primary (OR, 0.38; 95% CI, 0.16-0.89) and in secondary 1169 prophylaxis studies (OR, 0.24; 95% CI, 0.12-0.48) without 1170 significant heterogeneity (P = .40) (Figure 2A).

1171Death/transplantrateswereloweramongre-1172sponders (OR, 0.47; 95% CI, 0.29-0.75) (Figure 2B) both1173in patients in primary (OR, 0.74; 95% CI, 0.34-1.63) or1174secondary prophylaxis (OR, 0.36; 95% CI, 0.20-0.65)1175without significant heterogeneity (P = .69) (Figure 2B).1176However, the difference was not statistically significant1177in patients receiving primary prophylaxis (P = .46).

1178 Of note, the mean reduction in HVPG observed in pa-1179 tients with ascites (from 19.9 mm Hg at baseline to 17.2 1180 mm Hg at follow-up evaluation, a decrease of 14%) was 1181 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 1182 1183 HVPG responders was significantly lower in patients with 1184 ascites compared with those without ascites (42% vs 50%, 1185 respectively; P = .0085). The highest HVPG response rate 1186 was observed in patients without ascites or variceal hem-1187 orrhage (VH) (50%), and the lowest HVPG response rate 1188 was in patients with ascites and prior VH (36%). 1189

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

1216This study shows that a reduction in portal pressure,1217as determined by predefined threshold reductions in1218HVPG, 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 al⁷ 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.¹⁸ 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.¹⁹

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.¹⁻³ These 2 stages differ not only in terms of prognosis, but also in terms of the underlying pathophysiological drivers of disease progression^{4,32} 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.³³ 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).³⁴ It is note- Q18 worthy 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 RCT³⁴ 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.^{4,32} 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.

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Α

Outcome: Any Clinical Event**

1279	· · · · · · · · · · · · · · · · · · ·	Pasno	ndor	Non Pern	ndor		Odds Patio		Odds Patio	
1280	Study or Subgroup	Events	Total	Events	Total	Weight I	M-H, Random, 95% Cl		M–H, Random, 95% Cl	
1281	2.1.1 Primary Prophylaxis									
1201	Bureau, 2002 Hepatology	0	6	1	5	2.0%	0.23 [0.01, 7.05]	←	· · · · · · · · · · · · · · · · · · ·	
1282	Groszmann, 1990 Gastroenterology	2	15	3	26	6.3%	1.18 [0.17, 8.00]			
1283	Merkel, 2000 Hepatology	5	13	5	9	7.6%	0.50 [0.09, 2.81]			
1284	Reiberger, 2013 Gut	6	7	4	4	2.0%	0.48 [0.02, 14.70]			
1207	Sharma, 2009 API	1	15	2	12	3.6%	0.36 [0.03, 4.50]			
1285	Villanuova 2000 Castroenterology	4	21	12	16	7.6%	0.27 [0.05, 1.51]	-		
1286	Subtotal (95% CI)	12	86	14	86	31.8%	0.38 [0.16, 0.89]	•		
287	Total events	30		41						
1288	Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3$	3.85, df =	6 (P = .	70); l ² = 0%						
1200	Test for overall effect. $z = 2.22$ (P =	.03)								
1289	2.1.2 Secondary Prophylaxis									
1290	Abraldes 2003 Hepatol	3	9	8	14	7.5%	0.38 [0.07, 2.14]			
201	Augustin, 2012 Hepatology	7	16	10	17	11.6%	0.54 [0.14, 2.17]			
291	Bureau, 2002 Hepatology	1	1	1	1		Not estimable			
292	Garcia-Pagan, 2009 Gut	4	12	17	29	11.2%	0.35 [0.09, 1.44]			
293	Villanueva, 1996 NEJM	4	5	16	22	4.1%	1.50 [0.14, 16.27]			
204	Villanueva, 2001 NEJM	7	19	39	44	12.7%	0.07 [0.02, 0.28]			
294	Villanueva, 2004 J Hepatology	9	23	29	34	13.7%	0.11 [0.03, 0.39]			
295	Villanueva, 2009 APT	9	17	15	17	7.4%	0.15 [0.03, 0.87]	-		
296	Subtotal (95% CI)		102	105	178	68.2%	0.24 [0.12, 0.48]			
207	lotal events Heterogeneity: $T_{2}u^{2} = 0.20$; $Chi^{2} = 3$	44 - 202 df	6 (D -	135						
297	Test for overall effect: $7 = 4.01$ (P <	0001)	0 (10), 1 = 32 70						
298		.0001)								
299	Total (95% CI)		188		264	100.0%	0.27 [0.16, 0.43]		◆	
200	Total events	74		176						
300	Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1$	13.58, df =	= 13 (P	= .40); l ² = 4%	6			0.01	01 1 10 1	
301	Test for overall effect: $Z = 5.31$ ($P < $.00001)						0.01	Favours Responder Favours Non Responder	
302	Test for subgroup differences: Chi ² =	= 0.73, df	= 1 (P)	= .39); I ² = 0%	0					
202	** Any clinical event in patient	e with as	cites	wara defir	ned ac	any of th	e following: devel	nmen	t of variceal bemorrhage (first in primary	
303	prophylaxic studios, requirent	in cooor	adany	nronhylay	ieu do	lioc) or ro	fractory assisted of	pinen		
1304	propriyatis studies, recurrent	in secor	luary	рюрнувах	is sidu		asches, s	Jonan	eous paolenai pentonitis, nepatorenai	

syndrome or encephalopathy.

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Outcome: Death OR Transplant

1308		Respon	nder	Non Respo	nder		Odds Ratio	Odds Ratio		1366
1309	Study or Subgroup	Events	Total	Events	Total	Weight I	M-H, Random, 95% Cl	I M-H, Random, 95% CI		1367
1210	2.1.1 Primary Prophylaxis									1269
1310	Bureau, 2002 Hepatology	1	6	2	5	2.8%	0.30 [0.02, 4.91]]		1308
1311	Groszmann, 1990 Gastroenterology	2	15	5	26	7.0%	0.65 [0.11, 3.83]			1369
1312	Merkel, 2000 Hepatology	4	13	4	9	7.1%	0.56 [0.10, 3.25]			1370
1212	Sharma 2009 APT	0	15	4	12	2.0%	0.48 [0.02, 14.70]	1		1271
1313	Turnes, 2006 Am I Gastro	3	9	8	16	7.7%	0.50 [0.09, 2.73]	· · · · · · · · · · · · · · · · · · ·		13/1
1314	Villanueva, 2009 Gastroenterology	8	21	2	14	7.3%	3.69 [0.65, 20.97]			1372
1315	Subtotal (95% CI)		86		86	35.8%	0.74 [0.34, 1.63]			1373
1210	Total events	24		26						1274
1316	Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4$	l.52, df =	6 (P = .6	61); I ² = 0%						13/4
1317	Test for overall effect: $Z = 0.74$ ($P = 1$.46)								1375
1318	2.1.2 Secondary Prophylaxis									1376
1319	Abraldes 2003 Hepatol	0	9	6	14	2.4%	0.07 [0.00, 1.41]] ←		1377
1220	Augustin, 2012 Hepatology	6	16	10	17	11.3%	0.42 [0.10, 1.70]]		1270
1320	Bureau, 2002 Hepatology	1	1	0	1	1.1%	9.00 [0.10, 831.78]]		13/8
1321	Garcia-Pagan, 2009 Gut	2	12	7	29	7.3%	0.63 [0.11, 3.58]]		1379
1322	Villanueva, 1996 NEJM	1	5	5	22	3.8%	0.85 [0.08, 9.44]			1380
1322	Villanueva, 2001 NEJM	4	19	22	44	14.1%	0.27 [0.08, 0.93]			1300
1323	Villanueva, 2004 J Hepatology	5	23	16	34	15.4%	0.31 [0.09, 1.04]			1381
1324	Subtotal (95% CI)	10	102	14	178	64.2%	0.36 [0.20, 0.65]			1382
1325	Total events	29		80			• • • • •			1383
1326	Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4$	1.34, df =	7 (P = .7	74); I ² = 0%						1384
1327	Test for overall effect. $Z = 3.38 (P = 1)$.0007)								1385
1327	Total (95% CI)		188		264	100.0%	0.47 [0.29, 0.75]	1 🔶		1305
1328	Total events	53		106						1386
1329	Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1$	0.89, df =	= 14 (P :	= .69); l ² = 0%	5					1387
1330	Test for overall effect: $Z = 3.15$ ($P =$.002)						Favours Responder Favours Non Responder		1388
1221	lest for subgroup differences: Chi* =	= 2.04, df	= 1 (P =	= .15); l ² = 51.	1%					1200
1222	Figure 2. Patie	nts with	n asci	ites. (A) C	Outco	me: any	clinical event. (E	B) Outcome: death or transplant.	Q23	1209
1332										1390
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1393 Results of this study in the subgroup of patients with 1394 ascites (ie, with decompensation) are particularly rele-1395 vant in light of recent concerns about potential deleterious effects of NSBBs on renal function and a potential 1396 risk for increased mortality in patients with ascites.^{9,10} 1397 Even though, as previously shown,^{4,8} HVPG was higher 1398 1399 at baseline in these patients and the rate of HVPG re-1400 sponders was lower than in patients without ascites, we 1401 could show that portal pressure reduction achieved by 1402 pharmacologic treatment was associated not only with a 1403 lower rate of further decompensation (defined as the 1404 development of VH, refractory ascites, spontaneous 1405 bacterial peritonitis, HRS), but also with a decrease in 1406 death/transplant in the overall group of patients with 1407 ascites. The decrease in death/transplant was significant 1408 in patients with a history of variceal hemorrhage (sec-1409 ondary prophylaxis studies), who likely represent a 1410 sicker patient population. Although we did not observe a 1411 significant benefit on the death/transplant rate in pa-1412 tients included in primary prophylaxis studies, there was 1413 no indication of a higher mortality rate in this group 1414 because the subgroup difference testing was not signifi-1415 cant (Figure 2B). This lack of effect on survival already 1416 had been noted in previous meta-analyses^{7,35} and, in our study, this could have been because this was the smallest 1417 1418 subgroup and rates of death/transplant were lower than 1419 expected based on other studies. In addition, although in 1420 patients with ascites who have bled from varices the 1421 main driver of mortality is the severity of portal hyper-1422 tension (and therefore is affected by hemodynamic 1423 response), in patients without variceal hemorrhage 1424 confounders such as hepatocellular carcinoma, not 1425 directly related to hemodynamic changes, may 1426 contribute to overall mortality. We chose to analyze 1427 deaths/transplant jointly because of the multinational 1428 nature of the publications with different availability/ 1429 criteria for transplant and the timespan of the studies 1430 (with the earliest in 1990 when transplant rarely was 1431 performed). The number of transplants in the whole 1432 series was only 76, representing 23% of the combined

1433 death/transplant outcome. 1434 NSBB (propranolol, nadolol) were used in 87% of 1435 patients included in the meta-analysis and the remaining 1436 13% were on a therapy without an effect on portal 1437 pressure (placebo or endoscopic therapy). A sensitivity 1438 analysis that excluded the 4 studies with patients on 1439 inactive therapy yielded the same results on outcomes 1440 and death/transplant rates (data shown in 1441 Supplementary Table 2).

1442 Our meta-analysis is unique in that not only did we 1443 explore outcomes other than variceal hemorrhage and 1444 death, but we explored outcomes relevant to each prog-1445 nostic stage. In addition, because data were requested from 1446 the original authors, we could ensure that duplicate pa-1447 tients were excluded and, therefore, unlike other meta-1448 analyses that extracted data from publications that had 1449 duplicate patients, we report data on unique patients with 1450 cirrhosis.

Limitations of the study were those inherent to the 1451 collection of retrospective selected data from prospective 1452 studies. In addition, some important variables such as 1453 comorbidities, hepatocellular carcinoma, Child-Pugh 1454 score, and model for end-stage liver disease, were not 1455 1456 collected uniformly, therefore we were not able to explore the impact of these predictive scores on out-1457 comes. Notably, although the second most common eti-1458 1459 ology was viral, all studies were performed before the advent of effective antiviral therapy and such therapy 1460 therefore would not represent a confounder. A potential 1461 confounder was the use (or not) of alcohol during the 1462 study. Although alcohol was the etiology in fewer than 1463 half of the patients (n = 516), 9 of 15 studies reported on 1464 alcohol abstinence during the follow-up evaluation. Of 1465 these, 2 studies^{20,22} reported that all patients had been 1466 abstinent during the study, 5 studies^{18,19,25,27,31} showed 1467 no significant differences between alcohol abstinence/ 1468 nonabstinence and HVPG response/nonresponse, and 1469 only 2 studies^{17,29} comprising only 110 patients found a 1470 higher percentage of alcohol abstinence among HVPG 1471 responders compared with nonresponders. Therefore, it 1472 is unlikely that better outcomes in HVPG responders 1473 observed in this meta-analysis could have been ascribed 1474 1475 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 described³⁶), but data on individual data were not requested from the original authors ⁽¹⁹⁾ (only data on responders vs nonresponders), and therefore such analysis could not be performed.

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In summary, our results show that HVPG re-1484 1485 sponders to NSBB-based pharmacologic therapy, mainly defined as a reduction in HVPG to less than 12 1486 1487 mm Hg or a more than 20% reduction from baseline, have a significantly lower risk of developing clinically 1488 relevant outcomes in both patients with and without 1489 ascites. In patients without ascites but with varices, 1490 1491 lowering portal pressure significantly reduces the risk 1492 of any clinical decompensation (not only variceal bleeding but also ascites and encephalopathy) and 1493 1494 improves survival. In patients with ascites (decompensated) with or without variceal hemorrhage, a 1495 reduction in portal pressure lowers the risk of further 1496 1497 decompensation (variceal hemorrhage, refractory ascites, spontaneous bacterial peritonitis, or encepha-1498 1499 lopathy). Importantly, achieving an HVPG response improves survival in patients with ascites and a pre-1500 vious episode of bleeding who are notoriously those 1501 patients with the poorest survival rate. By showing 1502 that reductions in portal pressure induced by NSBB-1503 based pharmacologic therapy improve outcomes and 1504 decrease mortality, our study supports the use of 1505 NSBB in all clinical settings (primary or secondary 1506 prophylaxis) and in both patients with or without 1507 ascites. 1508

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Supplementary Material

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

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Reprint requests

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Conflicts of interest

The authors disclose no conflicts.

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transplant.

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Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 NO ASCILES Rureau 2002 Henatology	0	0	1	1	1 70/	0 02 [0 00 1 42]	←
Groszmann, 1990 Gastroenterology	0	0 15	3	28	2.4%	0.24 [0.01, 4.86]	· · · · · · · · · · · · · · · · · · ·
Hernandez-Gea, 2012 Am J Gastr	8	20	24	27	9.7%	0.08 [0.02, 0.37]	
Merkel, 2000 Hepatology	2	17	5	10	6.0%	0.13 [0.02, 0.92]	
Reiberger, 2013 Gut	18	68	12	25	22.8%	0.39 [0.15, 1.01]	
Sharma, 2009 APT Turnes, 2009 Am I Gastro	10	12	18	30	3.5% 13.8%	0.68 [0.05, 8.50]	
Villanueva, 2009 Gastroenterology	7	26	8	12	9.9%	0.18 [0.04, 0.81]	
Subtotal (95% CI)		182		150	69.4%	0.28 [0.13, 0.58]	◆
Total events	46		73				
Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 10$	0.41, df = 0.007	7 (P =	$(0.17); I^2 =$	33%			
Test for overall effect. $z = 3.40$ (r = 0).0007)						
1.1.2 Ascites							
Bureau, 2002 Hepatology	0	6	1	5	1.9%	0.23 [0.01, 7.05]	· · · · ·
Groszmann, 1990 Gastroenterology	2	15	3	26	6.0%	1.18 [0.17, 8.00]	
Reiberger 2013 Cut	5	13	5	9	7.4% 1.9%	0.50 [0.09, 2.81]	
Sharma, 2009 APT	1	15	2	12	3.5%	0.36 [0.03, 4.50]	
Turnes, 2009 Am J Gastro	4	9	12	16	7.3%	0.27 [0.05, 1.51]	
Villanueva, 2009 Gastroenterology	12	21	14	14	2.6%	0.05 [0.00, 0.86]	
Subtotal (95% CI)	20	86	41	86	30.6%	0.38 [0.16, 0.89]	
Heterogeneity: $Tau^2 = 0.00$. $Chi^2 = 3$	30 85. df = ۴	5 (P = 0	$^{41}_{(,70): 1^2 = 0}$	0%			
Test for overall effect: $Z = 2.22$ (P = 0).03)			- / -			
Total (95% CI)	70	268		236	100.0%	0.33 [0.20, 0.52]	◆
Heterogeneity: $Tau^2 = 0.02$ · Chi ² - 1	76 434 df -	14 (P -	$114 = 0.42 \cdot 1^2$	= 2%			· · · · · · · · · · · · · · · · · · ·
Test for overall effect: $Z = 4.63$ (P < 0	0.00001)	11(1	- 0.12), 1	- 270			0.01 0.1 1 10 10
Test for subgroup differences: Chi ² =	0.31, df =	= 1 (P =	= 0.58), l ²	= 0%			Responder Non Responder
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2, Patie	the fol perito	llowi nitis	ng: firs , hepa	st var toren	iceal h al syn	drome or ence	efractory ascites, ephalopathy.
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie	the fol perito	llowi nitis	ng: firs , hepa n studies	toren of prin	iceal h al syn	emorrhage, re drome or ence ohylaxis of variceal l	efractory ascites, ephalopathy. hemorrhage. Outcome: any clinical eve
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie	the fol perito nts inclu	llowi nitis Ided ii	ng: firs , hepa n studies	st var toren of prim	iceal h al syn	emorrhage, re drome or ence ohylaxis of variceal l	phalopathy. hemorrhage. Outcome: any clinical eve
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie	the fol perito nts inclu Respond Events	llowi nitis Ided in der Total	ng: firs , hepa n studies Non Resp Events	onder Total	iceal h al syn nary prop	I patients <u>with</u> Iemorrhage, re drome or ence ohylaxis of variceal I Odds Ratio M-H, Random, 95% Cl	Practory ascites, ephalopathy. hemorrhage. Outcome: any clinical eve Odds Ratio M-H, Random, 95% Cl
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie	the fol perito nts inclu Respond Events	llowi nitis ded in der Total	ng: firs , hepa n studies Non Resp Events	onder Total	iceal h al syn nary prop	Demorrhage, re drome or ence ohylaxis of variceal l Odds Ratio M-H, Random, 95% Cl	Practory ascites, ephalopathy. hemorrhage. Outcome: any clinical eve Odds Ratio М-Н, Random, 95% СІ
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> 1.1.1 No Ascites Bureau, 2002 Hepatology	the fol perito nts inclu Respond Events	llowi nitis ded in der Total	ng: firs , hepa n studies Non Resp Events	onder Total	iceal h al syn nary prop <u>Weight 1</u> 1.5%	odds Ratio 0.02 [0.00, 1.43]	Practory ascites, ephalopathy. hemorrhage. Outcome: any clinical eve Odds Ratio M-H, Random, 95% CI
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> 1.1.1 No Ascites Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology	ascites the fol perito nts inclu Respond Events	der Total	ng: firs , hepa n studies Non Resp Events	of prim	Weight 1 1.5% 4.7%	Odds Ratio 0.02 [0.00, 1.43] 0.43 [0.04, 4.22]	Practory ascites, ephalopathy. hemorrhage. Outcome: any clinical eve Odds Ratio M-H, Random, 95% CI
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel 2000 Hepatology	ASCITES the fol perito nts inclu Respon Events	Ilowi nitis Ided in der Total 8 15 20 17	ng: firs , hepa n studies Non Resp <u>Events</u>	onder Total	weight 1 1.5% 4.7% 11.6% 6.1%	Odds Ratio 0.02 [0.00, 1.43] 0.43 [0.04, 4.22] 0.27 [0.07, 1.02] 0.86 [0.12, 6.25]	Control of the second of the s
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut	ASCITES the fol perito nts inclu Respon Events 0 1 4 3 9	der Total	ng: firs , hepa n studies Non Resp <u>Events</u>	onder Total	Weight 1 1.5% 4.7% 11.6% 6.1% 15.3% 15.3%	Odds Ratio 0.02 [0.00, 1.43] 0.43 [0.04, 4.22] 0.66 [0.12, 6.26] 0.86 [0.12, 6.26] 0.32 [0.11, 0.97]	Control of the second of the s
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT	ASCITES the fol perito nts inclu Respon Events 0 1 4 3 9 1	der Total 8 15 20 17 68 12	ng: firs , hepa n studies Non Resp <u>Events</u>	onder Total	Weight 1 1.5% 4.7% 11.6% 6.1% 15.3% 2.4%	Odds Ratio 0.02 [0.00, 1.43] 0.43 [0.04, 4.22] 0.66 [0.12, 6.26] 0.32 [0.11, 0.97] 4.57 [0.17, 122.05]	Control of the second of the s
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro	ASCITES the fol perito nts inclu Respond Events 0 1 4 3 9 1 9	der Total 8 15 20 17 68 12 16	Non Resp Events	onder Total	Weight 1 1.5% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 2.6%	Odds Ratio 0.02 [0.00, 1.43] 0.43 [0.04, 4.22] 0.27 [0.07, 1.02] 0.86 [0.12, 6.26] 0.32 [0.11, 0.97] 4.57 [0.17, 122.05] 1.47 [0.43, 4.98]	Control of the second of the s
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% CI)	ASCITES the fol perito nts inclu Respon Events 0 1 4 3 9 1 9 2	der Total 8 15 20 17 68 12 16 22 16 22	ng: firs , hepa n studies Non Resp <u>Events</u> 1 4 13 2 8 0 14 5	onder Total	Weight 1 1.5% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9%	Odds Ratio 0.02 [0.00, 1.43] 0.43 [0.04, 4.22] 0.66 [0.12, 6.26] 0.86 [0.12, 6.26] 0.86 [0.12, 6.26] 0.86 [0.12, 6.26] 0.86 [0.12, 6.26] 0.86 [0.12, 0.74] 1.47 [0.43, 4.98] 0.12 [0.02, 0.74] 0.48 [0.20, 0.98]	Control of the second of the s
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% CI) Total events	ASCITES the fol perito nts inclu Respon Events 0 1 4 3 9 1 9 2 2 29	der Total 8 15 20 17 68 12 16 26 182	ng: firs , hepa n studies Non Resp <u>Events</u> 1 4 13 2 8 0 14 5 47	onder Total	Weight 1 1.5% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9% 61.8% 1.8%	Odds Ratio 0.02 [0.00, 1.43] 0.43 [0.04, 4.22] 0.27 [0.07, 1.02] 0.86 [0.12, 6.26] 0.32 [0.11, 0.97] 4.57 [0.17, 122.05] 1.47 [0.43, 4.98] 0.12 [0.02, 0.74] 0.44 [0.20, 0.98]	Control of the second of the s
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.43; Chi ² = 10	ASCITES the fol perito nts inclu Respond Events 0 1 4 3 9 1 9 2 2 29 0.96, df =	der Total 8 15 20 17 68 12 16 26 182 7 (P =	ng: firs , hepa n studies <u>Non Resp</u> <u>Events</u> 1 4 13 2 8 0 14 5 0 14 5 47 0.14); ² =	of prin of prin 0 f prin 1 28 27 10 25 17 30 12 150 36%	Weight 1 1.5% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9% 61.8% 6.18%	Odds Ratio 0.02 [0.00, 1.43] 0.43 [0.04, 4.22] 0.27 [0.07, 1.02] 0.86 [0.12, 6.26] 0.32 [0.11, 0.97] 4.57 [0.17, 122.05] 1.47 [0.43, 4.98] 0.12 [0.02, 0.74] 0.44 [0.20, 0.98]	Concest, any chined event effactory ascites, ephalopathy. hemorrhage. Outcome: any clinical eve Odds Ratio M-H, Random, 95% CI
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variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.43; Chi ² = 10 Test for overall effect: Z = 2.02 (P = C	ASCITES the fol perito nts inclu Respon Events 0 1 4 3 9 1 9 2 29 0.96, df = .04)	der Total 8 15 20 17 68 12 16 26 182 7 (P =	ng: firs , hepa n studies <u>Non Resp</u> <u>Events</u> 1 4 13 2 8 0 14 5 47 0.14); l ² =	of prim of prim of prim 1 28 27 10 25 17 30 12 150 36%	Weight 1 1.5% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9% 61.8% 61.8%	Odds Ratio 0.02 [0.00, 1.43] 0.43 [0.04, 4.22] 0.27 [0.07, 1.02] 0.86 [0.12, 6.26] 0.32 [0.11, 0.97] 4.57 [0.17, 122.05] 1.47 [0.43, 4.98] 0.12 [0.02, 0.74] 0.44 [0.20, 0.98]	Control of the second of the s
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variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.43; Chi ² = 10 Test for overall effect: Z = 2.02 (P = C) 1.1.2 Ascites Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology	ASCITES the fol perito nts inclu Respon Events 0 1 4 3 9 1 9 2 29 0.96, df = .04) 1 2	Bot of the second sec	ng: firs , hepa n studies Non Resp <u>Events</u> 1 4 13 2 8 0 14 5 47 0.14); l ² =	onder Total 1 28 27 10 25 17 30 12 150 36% 5 26	Weight 1 1.5% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9% 61.8% 3.3% 7.3% 7.3%	Odds Ratio 0.02 [0.00, 1.43] 0.43 [0.04, 4.22] 0.27 [0.07, 1.02] 0.86 [0.12, 6.26] 0.32 [0.11, 0.97] 4.57 [0.17, 122.05] 1.47 [0.43, 4.98] 0.12 [0.02, 0.74] 0.44 [0.20, 0.98]	Concess, any chinedic event efractory ascites, ephalopathy. hemorrhage. Outcome: any clinical eve Odds Ratio M-H, Random, 95% CI
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variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> 1.1.1 No Ascites Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.43; Chi ² = 10 Test for overall effect: Z = 2.02 (P = C) 1.1.2 Ascites Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am L Gastro	ASCITES the fol perito nts inclu Respond Events 0 1 4 3 9 2 29 0.96, df = .04) 1 2 4 6 0 3	Bot of the second sec	ng: firs , hepa n studies Non Resp <u>Events</u> 1 4 13 2 8 0 14 5 47 0.14); l ² =	onder Total 1 28 27 10 25 17 30 12 150 36% 5 26 9 4 12 150 36%	Weight I 1.5% 4.7% 11.5% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9% 61.8% 3.3% 7.4% 2.2% 2.4% 7.9%	Odds Ratio 0-H, Random, 95% CI 0.02 [0.00, 1.43] 0.43 [0.04, 4.22] 0.27 [0.07, 1.02] 0.86 [0.12, 6.26] 0.32 [0.11, 0.97] 4.57 [0.17, 122.05] 1.47 [0.43, 4.98] 0.12 [0.02, 0.74] 0.44 [0.20, 0.98] 0.30 [0.02, 4.91] 0.65 [0.11, 3.83] 0.56 [0.10, 3.25] 0.48 [0.02, 14.70] 0.25 [0.01, 6.64] 0.50 [0.02, 273]	Concess, any chinedic event effractory ascites, ephalopathy. hemorrhage. Outcome: any clinical eve Odds Ratio M-H, Random, 95% CI
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.43; Chi ² = 10 Test for overall effect: Z = 2.02 (P = C 1.1.2 Ascites Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology	ASCITES the fol perito nts inclu Respond Events 0 1 4 3 9 2 29 0.96, df = .04) 1 2 4 6 0 3 8	Bot of the second sec	ng: firs , hepa n studies Non Resp <u>Events</u> 1 4 13 2 8 0 14 5 47 0.14); l ² =	onder Total 1 28 27 10 25 17 30 12 150 36% 5 26 9 4 12 150 36%	Weight I 1.5% 4.7% 11.5% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9% 61.8% 3.3% 7.4% 2.2% 2.4% 7.9% 7.6% 7.6%	Odds Ratio 0-H, Random, 95% CI 0.02 [0.00, 1.43] 0.43 [0.04, 4.22] 0.27 [0.07, 1.02] 0.86 [0.12, 6.26] 0.32 [0.11, 0.97] 4.57 [0.17, 122.05] 1.47 [0.43, 4.98] 0.12 [0.02, 0.74] 0.44 [0.20, 0.98] 0.30 [0.02, 4.91] 0.65 [0.11, 3.83] 0.56 [0.10, 3.25] 0.48 [0.02, 14.70] 0.25 [0.01, 6.64] 0.50 [0.09, 2.73] 3.69 [0.65, 20.97]	And the second s
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.43; Chi ² = 10 Test for overall effect: Z = 2.02 (P = C <u>1.1.2 Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% CI)	ASCITES the fol perito nts inclu Respond Events 0 1 4 3 9 2 29 0.96, df = .04) 1 2 4 6 0 3 8	Bot of the second sec	ng: firs , hepa n studies <u>Non Resp</u> <u>Events</u> 1 4 13 2 8 0 14 5 0 14 5 0 14 5 0 14 5 47 0.14); l ² =	onder Total 1 28 27 10 25 17 30 12 150 36% 5 26 9 4 12 160	Weight I 1.5% 4.7% 11.5% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9% 61.8% 3.3% 7.4% 2.2% 2.4% 7.9% 7.6% 38.2%	Odds Ratio 0-H, Random, 95% CI 0.02 [0.00, 1.43] 0.43 [0.04, 4.22] 0.27 [0.07, 1.02] 0.86 [0.12, 6.26] 0.32 [0.11, 0.97] 4.57 [0.17, 122.05] 1.47 [0.43, 4.98] 0.12 [0.02, 0.74] 0.44 [0.20, 0.98] 0.30 [0.02, 4.91] 0.65 [0.11, 3.83] 0.56 [0.10, 3.25] 0.48 [0.02, 14.70] 0.25 [0.01, 6.64] 0.50 [0.09, 2.73] 3.69 [0.65, 20.97] 0.74 [0.34, 1.63]	All y chinical event efractory ascites, ephalopathy. hemorrhage. Outcome: any clinical eve Odds Ratio M-H, Random, 95% CI
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> 1.1.1 No Ascites Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.43; Chi ² = 10 Test for overall effect: Z = 2.02 (P = C 1.1.2 Ascites Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Merkel, 2000 Gastroenterology Subtotal (95% CI) Total events	ascrites the fol perito nts inclu Respon- Events 0 1 4 3 9 1 9 2 29 0.96, df = 0.04) 1 2 29 0.96, df = 0.04)	Bit Ion in the second	ng: firs , hepa n studies Non Resp <u>Events</u> 1 4 13 2 8 0 14 5 47 0.14); I ² = 2 5 4 4 1 8 2 2 5 4 4 1 8 2 2 5	onder Total 1 28 27 10 25 17 30 12 150 36% 5 26 9 4 12 160	Weight I 1.5% 4.7% 11.6% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9% 61.8% 3.3% 7.4% 2.2% 2.4% 7.9% 7.6% 38.2%	0.30 [0.02, 4.91] 0.30 [0.02, 4.91] 0.65 [0.11, 3.83] 0.56 [0.10, 3.25] 0.43 [0.02, 14.70] 0.7 [0.7, 102] 0.86 [0.12, 6.26] 0.30 [0.02, 4.91] 0.65 [0.11, 3.83] 0.56 [0.10, 3.25] 0.48 [0.02, 14.70] 0.25 [0.01, 6.64] 0.56 [0.12, 3.25] 0.48 [0.02, 14.70] 0.25 [0.01, 6.64] 0.50 [0.02, 2.73] 3.69 [0.65, 2.097] 0.74 [0.34, 1.63]	And the second s
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.43; Chi ² = 10 Test for overall effect: Z = 2.02 (P = C <u>1.1.2 Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 Gastroenterology Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 4. Tast for overall affect: Z = 0.74 (b. chi	ASCITES the fol perito nts inclu Respon- Events 0 1 4 3 9 2 29 0.96, df = 0.04) 1 2 4 6 0 3 8 24 52, df = 6 0 1 24 52, df = 6 1 24 52 46 52 52 52 52 52 52 52 52 52 52	der der Total 8 15 200 17 68 12 16 216 26 182 7 (P = 6 15 9 21 86 (P = 0	ng: firs , hepa n studies Non Resp <u>Events</u> 1 4 13 2 8 0 14 5 0.14 ; $1^2 =$ 2 5 4 4 1 8 2 25 4 4 1 8 2 25 4 4 1 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 2 25 4 4 1 1 2 25 4 4 1 1 2 25 4 4 1 1 2 26 5 4 4 1 1 2 26 5 4 4 1 1 2 26 5 4 4 1 1 2 26 5 4 4 1 1 2 26 5 4 4 1 1 26 26 1 1 1 26 1 26 1 1 26 1 1 26 1 1 26 1 1 26 1 1 26 1 1 26 1 1 26 1 1 26 1 1 26 1 1 26 1 1 26 1 1 26 1 1 26 1 1 26 1 1 26 1 1 1 26 1 1 1 26 1 1 1 26 1 1 1 26 1 1 1 26 1 1 1 1 26 1 1 1 1 26 1 1 1 1 26 1 1 1 26 1 1 1 1 1 26 1 1 1 26 1 1 26 1 1 1 1 1 1 1 26 1 1 1 26 1 1 1 1 1 26 1 1 1 1 1 1 1 26 1 1 1 1 1 1 1 1 1 1	St var toren of prin of prin 1 28 27 10 25 17 30 12 150 36% 5 26 9 4 12 16 14 86 %	Weight I 1.5% 4.7% 11.6% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9% 61.8% 3.3% 7.4% 2.2% 2.4% 3.8% 7.4% 2.8% 3.8.2%	0.30 [0.02, 4.91] 0.30 [0.02, 4.91] 0.30 [0.02, 4.91] 0.44 [0.20, 0.98]	And the second s
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie <u>Study or Subgroup</u> <u>1.1.1 No Ascites</u> Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.43; Chi ² = 10 Test for overall effect: Z = 2.02 (P = Cl) 1.1.2 Ascites Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 4. Test for overall effect: Z = 0.74 (P = Cl)	ASCITES ASC	der der Total 8 15 200 17 68 12 16 216 26 182 7 (P = 6 15 9 21 86 (P = 0	ng: firs , hepa n studies Non Resp <u>Events</u> 1 4 13 2 8 0 14 5 0.14 ; $1^2 =$ 2 5 4 4 1 8 2 25 4 4 1 8 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 2 25 4 4 1 1 2 25 4 4 1 1 2 25 4 4 1 1 2 25 4 4 1 1 2 26 1 2 26 1 26 1 $1^{2} = 0$ 1 $1^{2} = 0$	St var toren of prin 0 1 28 27 10 25 17 30 12 150 36% 5 26 9 4 12 16 14 86 %	Weight I 1.5% 4.7% 11.6% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9% 61.8% 3.3% 7.4% 2.2% 2.4% 3.8% 7.6% 38.2%	0.30 [0.02, 4.91] 0.30 [0.02, 4.91] 0.30 [0.02, 4.91] 0.44 [0.20, 0.98]	All y chinical event efractory ascites, ephalopathy. hemorrhage. Outcome: any clinical eve Odds Ratio M-H, Random, 95% CI
variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie i.1.1 No Ascites Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.43; Chi ² = 10 Test for overall effect: Z = 2.02 (P = C 1.1.2 Ascites Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 4. Test for overall effect: Z = 0.74 (P = C	ASCITES the fol perito nts inclu Respond Events 0 1 4 3 9 1 9 2 29 0.96, df = 0.04) 1 2 4 6 0 3 8 24 52, df = 6 0 1	Bot of the second sec	ng: firs , hepa n studies Non Resp <u>Events</u> 1 4 13 2 8 0 14 5 0.14 ; $1^2 =$ 2 5 4 4 1 8 2 25 4 4 1 8 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 1 2 25 4 4 1 1 $1^2 = 0$ 1^2 $1^2 = 0$ $1^2 = 0$	onder Total 1 28 27 10 25 17 30 12 150 36% 5 26 9 4 12 16 14 86 1% 236	unity: iceal h al syn al syn hary prop unity: 1.5% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9% 61.8% 3.3% 7.3% 7.4% 2.2% 2.4% 3.8.2% 38.2% 1000.0% 100.0%	0.30 [0.02, 4.91] 0.30 [0.02, 4.91] 0.65 [0.11, 3.83] 0.54 [0.32, 0.92]	All y chinical event efractory ascites, ephalopathy. hemorrhage. Outcome: any clinical eve Odds Ratio M-H, Random, 95% CI
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variceal hemorrhage, a was defined as any of spontaneous bacterial Supplementary Figure 2. Patie i.1.1 No Ascites Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Hernandez-Gea, 2012 Am J Gastr Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.43; Chi ² = 10 Test for overall effect: Z = 2.02 (P = C 1.1.2 Ascites Bureau, 2002 Hepatology Groszmann, 1990 Gastroenterology Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Merkel, 2000 Hepatology Reiberger, 2013 Gut Sharma, 2009 APT Turnes, 2006 Am J Gastro Villanueva, 2009 Gastroenterology Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 4. Test for overall effect: Z = 0.74 (P = C Total (95% Cl) Total events Heterogeneity: Tau ² = 0.16; Chi ² = 16 Tast for overall effect: Z = 0.79 (P = C)	ASCITES the fol perito nts inclu Respond Events 0 1 4 3 9 2 29 0.96, df = 0.04) 1 2 4 6 0 3 8 24 52, df = 6 0 3 8 24 52, df = 6 0 3 8 24 53 547, df = 6 0 1 2 2 2 2 2 2 3 3 8 2 4 5 3 8 1 2 2 5 5 3 8 2 4 5 5 5 5 5 5 5 5 5 5 5 5 5	Bot of a constraint of	ng: firs , hepa n studies Non Resp Events 1 4 13 2 8 0 14 5 0.14 ; $1^2 =$ 2 5 4 47 0.14 ; $1^2 =$ 2 5 4 4 1 8 2 6 -61 ; $1^2 = 0$ -73 $= 0.29$; $1^2 =$	ander toren of prin of prin 1 28 27 10 25 17 30 12 150 36% 5 26 9 4 12 16 14 86 % 236 = 15%	unity: iceal h al syn hary prop Weight 1 1.5% 1.5% 4.7% 11.6% 6.1% 15.3% 2.4% 13.2% 6.9% 61.8% 3.3% 7.3% 7.4% 2.2% 2.4% 38.2% 100.0%	0.27 0.002	Odds Ratio M-H, Random, 95% CI

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1973		Responde	r	Non Respo	onder		Odds Ratio	Odds	Ratio	203
974	Study or Subgroup	Events To	otal	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	lom, 95% Cl	2032
975	Abraldes 2003 Hepatol	Q	10	10	21	0.1%	0.46 [0.14, 1.47]			2033
976	Augustin, 2012 Hepatology	16	32	19	25	10.0%	0.79 [0.27, 2.25]		<u> </u>	2034
977	Bureau, 2002 Hepatology	1	5	6	7	2.3%	0.04 [0.00, 0.88]	← .		2034
1070	Garcia-Pagan, 2009 Gut	10	36	23	58	11.4%	0.59 [0.24, 1.44]		+	205
1978	Villanueva, 1996 NEJM	4	14	12	21	7.2%	0.30 [0.07, 1.27]		Ť	2030
19/9	Villanueva, 2001 NEJM Villanueva, 2004 Henatology	1	13 18	12	19	3.9%	0.05 [0.01, 0.46]	· ·		203
1980	Villanueva, 2009 APT	3	10	4	5	3.1%	0.11 [0.01, 1.41]	· · ·	<u></u>	2038
1981	Subtotal (95% CI)	1	147		182	54.1%	0.41 [0.22, 0.78]	•		2039
1982	Total events	49		95	.2					2040
1983	Heterogeneity: $Iau^2 = 0.27$; Chi Test for overall effect: $7 - 2.73$	$I^{2} = 10.57, d$	f = 7	P = 0.16	; $I^2 = 34$	1%				2041
1984		(1 - 0.000)								2042
985	1.1.2 Ascites									2043
1986	Abraldes 2003 Hepatol	3	9	8	14	5.6%	0.38 [0.07, 2.14]	<u> </u>	<u> </u>	2012
1007	Augustin, 2012 Hepatology	7	16	10	17	7.6%	0.54 [0.14, 2.17]		<u> </u>	204-
1987	Bureau, 2002 Hepatology Garcia-Pagan, 2009 Gut	1	12	17	29	7 4%	0 35 [0 09 1 44]		L	2043
1988	Villanueva, 1996 NEJM	4	5	16	22	3.5%	1.50 [0.14, 16.27]			2046
1989	Villanueva, 2001 NEJM	7	19	39	44	8.0%	0.07 [0.02, 0.28]			2047
1990	Villanueva, 2004 J Hepatology	9	23	29	34	8.3%	0.11 [0.03, 0.39]			2048
1991	Villanueva, 2009 APT Subtotal (95% CI)	9	17	15	17 178	5.6%	0.15 [0.03, 0.87]			2049
1992	Total events	44		135	1/0	10.070	0.24 [0.12, 0.40]			2050
1993	Heterogeneity: $Tau^2 = 0.29$; Chi	i ² = 8.83, df	= 6 ((P = 0.18);	$I^2 = 32\%$	6				205
1994	Test for overall effect: $Z = 4.01$	(P < 0.0001))							2051
1005		-	240		260	100.0%	0 22 [0 10 0 52]			2052
1995	Total events	93	249	230	500	100.0%	0.32 [0.19, 0.32]	•		2053
1990	Heterogeneity: $Tau^2 = 0.35$; Chi	i ² = 23.05, d	f = 1	.4 (P = 0.06)	5); $I^2 = 3$	39%				2052
1997	Test for overall effect: $Z = 4.55$	(P < 0.0000	1)					0.01 0.1 Responder	I IU Non Responder	100 2053
1998	Test for subgroup differences: 0	$Chi^2 = 1.33,$	df =	1 (P = 0.25)	5), $I^2 = 2$	5.0%				2056
1999	* In potiopto without	anaitan				vont v	an defined on a	ony of the fello	vina: roourro	2057
2000	in patients without	ascilles	, ai		care	vent w	as utilited as a	any of the follow	ving. recure	2058
2001	variceal hemorrhage	e, ascite	es c	or ence	phalo	opathy	[,] In patients <u>wr</u>	<u>th ascites,</u> any	clinical even	t 2059
2002	was defined as any	of the fo	ollo	wina: r	ecuri	rent va	ariceal hemorrh	age, refractory	ascites, spo	n- 2060
2003	taneous bacterial n	aritonitie	h h	onator	anala	syndro	me or encenha	alonathy	, I	2061
2002	taneous bacterial po	Shiohila	, 11	epatore	snar s	synarc	ine or enceptic	alopatity.		2061
2004	Supplementary Figure 4. P	Patients inc	clude	ed in stud	dies of	second	ary prophylaxis of v	ariceal hemorrhage.	Outcome: any c	linical 2002
2005	event.									Q27 2003
2006										2064
2007										2065
2008										2066
2009										2067
2010										2068
2011										2069
2012										207(
2013										2070
2015										2071
2014										20/2
2015										2073
2016										2074
2017										2075
2018										2076
2019										207
2020										2079
2020										2070
0021										2073
2022										2080
2023										208]
2024										2082
2025										2083
2026										2084
2027										208
2028										2080
2020										2000
2029										2007
2030										2088

2019

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2089		Responder	Non	Responde	r	Odds Ratio	Odds Ratio	2147
2090	Study or Subgroup	Events To	tal Evei	nts To	al Weig	nt M-H, Random, 95% Cl	M-H, Random, 95% Cl	2148
2091	I.I.I NO ASCITES	-	10	11	21 10 (2149
2092	Augustin, 2012 Hepatology	5 10	32	13	25 134	% 0.42 [0.14, 2.29] % 0.42 [0.14, 1.24]		2150
2002	Bureau, 2002 Hepatology	1	5	2	7 2.1	% 0.63 [0.04, 9.65]	· · · · · · · · · · · · · · · · · · ·	2150
2095	Garcia-Pagan, 2009 Gut	6	36	9	58 12.4	% 1.09 [0.35, 3.37]	i — — — — — — — — — — — — — — — — — — —	2151
2094	Villanueva, 1996 NEJM	3	14	3	21 5.0	% 1.64 [0.28, 9.58]		2152
2095	Villanueva, 2001 NEJM	1	13	8	19 3.2	% 0.11 [0.01, 1.07]		2153
2096	Villanueva, 2004 J Hepatology Villanueva, 2009 APT	2	10	3	5 3.1	% 0.29 [0.03, 2.69]	· · · · · · · · · · · · · · · · · · ·	2154
2097	Subtotal (95% CI)	1	47	1	32 54.1	% 0.55 [0.32, 0.95]	▲	2155
2098	Total events	31		55				2156
2099	Heterogeneity: $Tau^2 = 0.00$; Chi	$f^2 = 6.56, df = 0.02$	= 7 (P = 0	$(.48); I^2 = ($	0%			2157
2100	Test for overall effect: $Z = 2.14$	(P = 0.03)						2158
2100	1.1.2 Ascites							2150
2101	Abraldes 2003 Hepatol	0	9	6	14 1.7	0.07 [0.00, 1.41]	· · · · · · · · · · · · · · · · · · ·	2157
2102	Augustin, 2012 Hepatology	6	16	10	17 8.1	% 0.42 [0.10, 1.70]	· · · · · · · · · · · · · · · · · · ·	2100
2103	Bureau, 2002 Hepatology	1	1	0		% 9.00 [0.10, 831.78]		2161
2104	Villanueva, 1996 NFIM	2	5	5	29 5.2	% 0.85 [0.11, 5.58]		2162
2105	Villanueva, 2001 NEJM	4	19	22	44 10.1	% 0.27 [0.08, 0.93]		2163
2106	Villanueva, 2004 J Hepatology	5	23	16	34 11.0	% 0.31 [0.09, 1.04]		2164
2107	Villanueva, 2009 APT	10	17	14	17 6.3	% 0.31 [0.06, 1.48]		2165
2108	Total events	20	02	80	40.5	/0 0.50 [0.20, 0.65]		2166
2109	Heterogeneity: $Tau^2 = 0.00$: Chi	$i^2 = 4.34. df =$	= 7 (P = 0	$(.74); I^2 = ($	0%			2167
2107	Test for overall effect: $Z = 3.38$	(P = 0.0007)						210/
2110								2108
2111	Total (95% CI)	60 Z	49	30	50 100.0	% 0.46 [0.31, 0.68]	•	2169
2112	Heterogeneity: $Tau^2 = 0.00$: Chi	$^{2} = 11.98$. df	$^{1} = 15 (P =$.55 = 0.68): l ²	= 0%			2170
2113	Test for overall effect: $Z = 3.86$	(P = 0.0001)	15 (1	0.00), 1	0/0		0.01 0.1 1 10 100 Responder Non Perponder	2171
2114	Test for subgroup differences: 0	$Chi^2 = 1.07, d$	lf = 1 (P =	= 0.30), l ² :	= 6.8%		Responder Non Responder	2172
2115	Supplementary Figure 5.	Patients in	cluded	in studie	es of pr	imary prophylaxis of	variceal hemorrhage. Outcome: death or	2173
2116	transplant.						Ũ	2174
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21 <i>33</i> 21 <i>26</i>								2173
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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. ²⁰ 1990	Yes	Yes	>2	Yes	NB	Yes	-
Gastroenterology						100	
Hernandez-Gea et al, ¹⁹ 2012 Am J Gastroenterol	Yes	Yes	3	Yes	NR	Yes	
Merkel et al, ²¹ 2000 <i>Hepatology</i>	NR	Yes	≥3	Yes	NR	Yes	
Reiberger et al, ²² 2013	NR	Yes	≥3	Yes	NR	Yes	
Gut Sharma at al ²³ 2000	Voo	Vaa	0			Vee	
Aliment Pharmacol Ther	Tes	Tes	3			Tes	
Turnes et al, ²⁴ 2006	NR	Yes	3	Yes	NR	Yes	
Am J Gastroenterol	X					X	
Villanueva et al, ²⁰ 2009 Gastroenterology	Yes	Yes	3	Yes	NR	Yes	
Abraldes et al, ¹⁸ 2003	NR	Yes	NR	NR	NR	NR	
Hepatology							
Augustin et al," 2012	NR	Yes	3	Yes	NR	NR	
García-Pagán et al. ²⁶ 2009	NR	Yes	>2	Yes	Yes	Yes	
Gut			_				
Villanueva et al, ²⁷ 1996	Yes	Yes	3	NR	NR	NR	
Villanueva et al. ²⁸ 2001	Yes	Yes	3	NR	NR	NR	
N Engl J Med							
Villanueva et al, ²⁹ 2004	Yes	Yes	3	NR	NR	Yes	
<i>J Hepatol</i> Villanueva et al ³⁰ 2009	Yes	Yes	3	Yes	NB	Ves	
Aliment Pharmacol Ther	100	103	0	100		100	
Bureau et al, ³¹ 2002	Yes	NR	≥3	NR	NR	NR	
Hepatology							

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

Supplementary Table 2. Outcomes of Patients on Active Pharmacologic Therapy

				Benefit	nonresponders						
			Any clinical event ^a	Death/transplant							
	Overall effect	Р	Primary vs secondary prophylaxis	Р	Heterogeneity	Overall effect	Р	Primary vs secondary prophylaxis	Р	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)	.0007 .006	0.10	OR, 0.50 (0.32–0.78)	.0002	Primary OR, 0.44 (0.20–0.98) Secondary	.04 .03	4 0.28 3	
			OR, 0.41 (0.22–0.78)					OR, 0.55 (0.32–0.95)			
Patients with ascites (n = 310)	OR, 0.27 (0.16–0.43)	<.0001	Primary (n = 120) OR, 0.38 (0.16–0.89)	.03	0.40	OR, 0.47 (0.29–0.75)	.0002	Primary OR, 0.74 (0.34–1.63)	.46	0.69	
			Secondary (n = 190) OR, 0.24 (0.12–0.48)	<.0001				Secondary OR, 0.36 (0.20–0.75)	.0007		

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

^aIn 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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