Stratifying risk in the prevention of recurrent variceal hemorrhage: Results of an individual patient meta-analysis

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Abstract

Endoscopic variceal ligation plus beta-blockers (EVL+BB) is currently recommended for variceal rebleeding prophylaxis, a recommendation that extends to all patients with cirrhosis with previous variceal bleeding irrespective of prognostic stage. Individualizing patient care is relevant and, in published studies on variceal rebleeding prophylaxis, there is a lack of information regarding response to therapy by prognostic stage. This study aimed at comparing EVL plus BB with monotherapy (EVL or BB) on all-source rebleeding and mortality in patients with cirrhosis and previous variceal bleeding stratified by cirrhosis severity (Child A vs. B/C) by means of individual time-to-event patient data meta-analysis (IPD) from randomized controlled trials. The study was IPD of 389 patients from 3 trials comparing EVL plus BB vs. BB and 416 patients from 4 trials comparing EVL plus BB vs. EVL. Compared with BB alone, EVL plus BB reduced overall rebleeding in Child A (incidence rate ratio 0.40; 95%CI 0.18–0.89; p=0.025), but not in Child B/C, without differences in mortality. The effect of EVL on rebleeding was different according to

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Child (p for interaction <0.001). Conversely, compared with EVL, EVL plus BB reduced rebleeding in both Child A and B/C, with a significant reduction in mortality in Child B/C (incidence rate ratio 0.46; 95%CI 0.25–0.85; p=0.013). Conclusion: Outcomes of therapies to prevent variceal rebleeding differ depending on cirrhosis severity. In patients with preserved liver function (Child A), combination therapy is recommended since it is more effective in preventing rebleeding, without modifying survival. In patients with advanced liver failure (Child B/C), EVL alone carries an increased risk of rebleeding and death as compared with combination therapy, underlining that BB is the key element of combination therapy.

Preventing recurrent variceal hemorrhage in patients with cirrhosis that have recovered from an episode of acute variceal hemorrhage is essential, because otherwise the 1-year rebleeding and mortality rates are unacceptably high, at 60% and 30% respectively (1). The current standard of care for the prevention of rebleeding is the combination of endoscopic variceal ligation (EVL) and non-selective beta-blockers (BB) (2, 3). This recommendation is supported by several meta-analyses that have pooled trials comparing combination therapy versus monotherapy (BB or EVL alone) (4–6). These meta-analyses uniformly concluded that combination therapy had greater efficacy in preventing recurrent variceal hemorrhage than either therapy alone, but this benefit did not translate into an improved survival.

However, because studies included in these meta-analyses did not report results by prognostic stage, this recommendation is extended to all patients with cirrhosis with a previous variceal bleeding, irrespective of cirrhosis stage. Cirrhosis is classified in two main prognostic stages: compensated and decompensated (7, 8) and the Child-Turcotte-Pugh (Child) classification is excellent at stratifying patients with cirrhosis (9), with Child A patients being mostly compensated and Child B/C patients being decompensated. Additionally, obtaining individual patient data (IPD) allows the performance of survival analysis as a time-dependent variable, which was not possible in published aggregate data meta-analyses on this topic.

Therefore, we performed a meta-analysis using IPD obtained from principal investigators of randomized controlled trials that compared combination therapy (EVL plus BB) versus monotherapy (EVL or BB) with the objective of comparing these strategies with regard to time-dependent rebleeding and mortality based on the stage of cirrhosis at the time of variceal hemorrhage using the Child-Turcotte-Pugh classification.

We hypothesized that the impact of each therapy, EVL or BB, on outcomes (rebleeding, mortality) would differ according to the severity of cirrhosis. This would be clinically relevant as risk stratification would allow tailoring therapy in accordance to patient characteristics. In the specific case of BB, it could provide information regarding their effect on outcomes in the two main stages of cirrhosis.

MATERIAL AND METHODS

The current meta-analysis was designed to pool the data of individual patients participating in randomized controlled trials that compared the efficacy of combination therapy (EVL plus BB) versus either therapy alone (EVL or BB) in preventing recurrent variceal hemorrhage vis-à-vis the two main prognostic stages of cirrhosis. We searched and identified the trials according to previously defined outcomes, revised the data and planned statistical analysis. To report the present review, we have adhered to the PRISMA-IPD guidelines for reporting meta-analysis of IPD (10).

Eligibility criteria

Studies that included patients with cirrhosis undergoing prevention of recurrent esophageal variceal hemorrhage were included in this analysis if they were published as full articles, if patients were randomly allocated to receive the combination of EVL plus BB versus either EVL or BB alone, if information regarding overall rebleeding and death was available, and if the original datasets of the trials were available.

Identifying studies, information sources and search

We performed a literature search up to December 30, 2015 in MEDLINE, EMBASE, the Cochrane Central Register of Controlled trials and the Cochrane Database of Systematic Reviews, using the terms rebleeding, recurrent hemorrhage, esophageal varices, variceal obliteration, beta-blockers, endoscopy, band ligation and cirrhosis. We also reviewed publications in personal reference lists and citation sections of the recovered articles; manually searched abstracts presented at meetings of the American Gastroenterological Association, the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, the American Society of Gastrointestinal Endoscopy, and the British Society of Gastroenterology and looked at authors of the abstracts to identify whether these abstracts had been published in full. Finally, we also searched clinical trials at www.controlled-trials.com and www.clinicaltrials.gov.

Study selection and data collection processes

Two reviewers independently selected the studies by screening the titles and abstracts to identify those that fulfilled the inclusion criteria (JM, AA). Principal investigators of the trials that met eligibility criteria were contacted to obtain individual patient data for all participants in their trials.

The original datasets were checked for completeness and internal consistency and amended through correspondence with the principal investigators. To build the final dataset of IPD, we excluded studies with insufficient information, and those that could not be obtained upon request.

Data items

Patient-level data were analyzed by two authors (JM and DA). The following data were extracted from the datasets: patient characteristics (age, sex, etiology of cirrhosis, serum bilirubin, serum albumin, prothrombin time, Child-Turcotte-Pugh (Child) class (11),

presence of ascites or encephalopathy, outcomes (all-source rebleeding, variceal rebleeding and mortality), and follow-up (time-to-event for each outcome). Careful initial evaluation was performed to ensure completeness of data, and to check consistency of the results of the primary analyses for each trial with published reports.

Outcomes

Primary end-points were all-source rebleeding and mortality, and secondary end-point was variceal rebleeding. As described by the principal investigators of the included trials, all-source and variceal rebleeding were defined as the presence of melena or hematemesis with an upper gastrointestinal or an esophageal variceal source, respectively, identified by emergency endoscopy after randomization. All-source rebleeding was chosen as a primary outcome because EVL may reduce the risk for variceal hemorrhage but can also cause bleeding from esophageal ulcers, leaving the number of bleeding events per patient unchanged. Mortality was defined as death from any cause. The rate of adverse events was also explored.

Statistical analysis

The main analysis was a one-stage IPD meta-analysis comparing time-to-event data. This utilizes the raw data from each study and allows for adjustments for confounders and tests for interactions. Since traditional meta-analysis models are not suited to analyze individual time-to-event patient data, multilevel Poisson mixed-effects model with random intercepts was used to model time-to-event data that are clustered within studies. In the Multilevel Poisson mixed-effects model, the effect of interventions is estimated as hazard ratio approximated by incidence rate-ratios (IRR). This approach models survival with a fixed treatment effect and a different baseline hazard function for each study. So, the assumption of proportional hazards for all studies is relaxed, while still assuming proportional hazards between treatment groups within each study (12). The effect of intervention was stratified by the severity of cirrhosis, as assessed by Child class (A versus B/C). We specifically checked for the modifier effect of Child on the interventions by including interaction terms in the models. A significant interaction would indicate that treatment effect was different between Child A and Child B/C patients.

Within each stratum, the model was further adjusted by including the following confounders: etiology (alcohol vs. viral vs. others), ascites (presence vs. absence), encephalopathy (presence vs. absence), and the continuous variables age, bilirubin and albumin. Prothrombin time was not included because of the variability in expressing the result of this variable among the trials (prothrombin time in some trials, prothrombin activity in others). Inclusion of confounders allows fine tuning of the model within each stratum as compared with the coarse adjustment using Child as the sole category. A covariate was considered a confounder factor if the difference between adjusted and unadjusted model coefficient for the intervention variables varied >10%. In such a case, the IRR was shown along with the list of confounders used for adjustment. Otherwise, we reported the model without adjustment for confounders. Heterogeneity among trials was measured with the random effect parameters of the model, transformed into Median Incidence Rate Ratios (MIRR). The MIRR shows the extent by which the probability of the event is determined by

the trial in which the patients were recruited. The closer the MIRR to 1 the lower the variability of the individual risk of an event among trials (13).

We performed two meta-analyses: The first explored trials that compared combination therapy versus BB alone (control group), while the second explored trials that compared combination therapy versus EVL alone (control group).

We carried out sensitivity analysis to verify the robustness of our results on all-source and variceal rebleeding. First, we considered death as a competing event for rebleeding, and we performed a competing risk analysis including study as a covariate. Secondly, we tested, using logistic multilevel regression the impact of including all the patients into the analysis of rebleeding, even those patients excluded from the main analysis because they lacked information on time-to-event. Finally, we performed a post-hoc exploratory analysis of the effect of the association of BB with ISMN in those four trials that compared pharmacological therapy and EVL versus EVL alone, two of which used BB alone as pharmacological therapy while the other two used BB with ISMN.

All analyses were done with Stata v13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) and "xtmepoisson" command.

RESULTS

Study selection

Our search strategy identified 798 potential references. We excluded 792 references: 771 because they were clearly ineligible by reading the title and the abstract and 17 because of duplicity (Figure 1). Four additional studies were also excluded: Two of them because they were in abstract form only and data could not be obtained from the authors (14, 15); another because its primary end-point was the incidence and natural history of portal hypertensive gastropathy in patients with previous variceal bleeding treated with EVL or BB (16; and the last one because it used the HVPG response to BB to allocate patients to combination therapy or BB alone, instead of randomly allocating consecutive patients (17). This left 6 studies for inclusion in the meta-analysis.

Study characteristics

Table 1 shows the general characteristics of the 6 studies that met inclusion criteria. All the trials, except the one by Ahmad et al., had two study groups that compared the combination of EVL and BB versus BB (3 trials) or versus EVL (4 trials). The trial by Ahmad et al. compared four groups, BB plus isosorbide-5-mononitrate (ISMN) combined with EVL, BB alone, BB plus ISMN, and EVL alone. The specific BB used was propranolol in 2 trials (18, 19) and nadolol in 4 trials (20–23), at a dose adjusted to reduce resting heart rate by 25% or to 55 bpm (18, 20–22), or to the maximum tolerated dose without reducing heart rate below 55 bpm (19, 23). In all studies, BB were started within 5 days of the index bleed. BB were associated with ISMN (20 mg bid) in the three trials that compared combination therapies with BB alone (18, 22, 23) and in two of the four studies that compared combination therapy with EVL alone (18, 19). In one of the other two trials, BB were administered together with sucralfate (22). EVL sessions were performed with multiband devices in all the trials, and

repeated at intervals that varied between 10 days and 4 weeks. The mean follow-up of the trials varied from 14 to 23 months.

The Child score was used to assess the severity of cirrhosis in all trials, and the publication by Pugh et al. (11) was only referenced in the trial by Lo et al. (21). In all trials, rebleeding was considered as such if significant (Table 1). Significant rebleeding was defined in all studies except the one by De la Peña et al. (20), by the need to transfuse >2 blood units or by a drop in hemoglobin >2 g/dl. De la Peña et al. required a drop in hemoglobin to consider rebleeding, but they did not describe the amount (20).

Supplementary Table 1 shows the methodological quality indices of the included trials (24). All trials had an adequate generation of allocation sequence, and adequate allocation concealment. The baseline characteristics of treatment and control groups were balanced in all trials. No trial had blinded investigators, only the trial by Kumar et al. had a blinded endoscopist (19). The reasons for withdrawal were clear in all trials.

IPD obtained

The final IPD dataset was built after excluding patients with insufficient information in the original datasets, and in whom data could not be obtained upon request to the principal investigators. Supplementary table 2 shows the reasons for and the number of patients excluded from the original datasets: 2 lacked Child class (21), 1 lacked any clinical information (20), 26 with non-cirrhotic etiology of portal hypertension (19), and 10 lost to follow-up immediately after randomization and discharge (19). In addition, 150 patients from Ahmad's study (18) and 9 patients from Lo's study (21) were excluded from the main analysis, because they lacked information on time-to-event, but were included in the analysis of rebleeding using logistic multilevel regression models. The dataset from Lo's study lacked information regarding the source of rebleeding; thus 120 patients from this study were not included in the analysis of variceal rebleeding (22). All patients included in the final dataset had information regarding death. Because the studies lacked a uniform standard definitions of adverse events and the information reported in the databases was insufficient, we could not perform a safety analysis.

Patient characteristics

Characteristics of patients allocated to each treatment group in the 6 included trials are shown in Supplementary table 3. The final IPD base was built with 768 patients: 350 patients allocated to combination of EVL and BB, 206 to EVL alone, and 212 to BB alone. Patient characteristics were similar between the combination therapy arms of both sets of trials, and between the combination and the monotherapy arm of each set of trials (Table 2).

Primary outcomes in trials comparing combination therapy (EVL plus BB) versus BB alone

a) All-source rebleeding—As shown in Figure 2 and Supplementary table 2, 278 patients from two trials were used to assess overall rebleeding (22, 23). Fifty-four out of 140 (39%) patients rebled in the combination therapy group and 58 out of 138 (42%) patients did in the BB group. The IRR (adjusted for etiology, bilirubin and encephalopathy) for overall

rebleeding was 1.00 (95% CI: 0.68–1.47; p=0.996), that is, there were no differences in rebleeding between treatment groups in the overall group.

Sixty-eight out of the 278 patients were Child A, and 27 of them rebled (40%), 9 on combination therapy and 18 on BB. Eighty-five out of 210 Child B/C patients rebled (40%), 45 on combination therapy and 40 on BB. Combination of EVL plus BB was more effective than BB alone in preventing overall rebleeding in Child A patients (IRR 0.40; 95% CI: 0.18–0.89; p=0.025), but not in Child B/C patients (IRR, 1.36; 95% CI: 0.87–2.14; p=0.180) (adjusted for etiology, bilirubin and encephalopathy) (Figure 2). This interaction (i.e. difference in response to therapy by Child strata) was statistically significant (p=0.009). There was no statistical significant heterogeneity among trials (MIRR=1.25; 95%CI: 1.06–2.50; p=0.063).

b) Death—A total of 389 patients from 3 trials were used to assess mortality (Figure 2 and Supplementary table 2) (18, 22, 23). Overall, 39 out of 177 (22%) patients on combination therapy died compared to 43 out of the 212 (20%) patients on BB. Mortality was similar in both study groups [IRR (adjusted for bilirubin and encephalopathy) 1.19; 95% CI: 0.76–1.87; p=0.449].

Nine out of the 80 Child A patients (11%) died, 2 on combination therapy and 7 on BB, whereas 73 out of 309 Child B/C patients died (24%), 37 on combination therapy, and 36 on BB. Combination of EVL and BB was associated with a lower mortality compared to BB alone in Child A patients, although this effect was not statistically significant (IRR 0.29; 95% CI: 0.06–1.41; p=0.125). Mortality was greater in Child B/C patients on combination therapy than in those on BB, but again the difference was not statistically significant (IRR 1.40; 95% CI: 0.87–2.27; p=0.167) (Figure 2). Interaction (i.e. difference in response to therapy by Child strata) was not statistically significant (p=0.061). There was no statistical significant heterogeneity between trials (MIRR=1.25; 95%CI: 1.05–2.64; p=0.137).

Primary outcomes in trials comparing combination therapy (EVL plus BB) versus EVL alone

a) All-source rebleeding—As shown in Figure 2 and Supplementary Table 2, a total of 331 patients from 3 trials were used to assess overall rebleeding (that is, rebleeding from any source) (19–21). Twenty-one of 169 (12%) patients rebled in the combination therapy group compared to 50 of 162 (31%) patients in the EVL group. The IRR for overall rebleeding was significantly lower in patients in the combination therapy group (IRR 0.36; 95% CI: 0.21–0.59, p<0.001).

Ninety-one out of the 331 patients were Child A, and 9 of them rebled (10%), 2 on combination therapy and 7 on EVL. Sixty-two out of 240 Child B/C patients rebled (26%), 19 on combination therapy and 43 on EVL. Combination of EVL plus BB was more effective than EVL alone in preventing overall rebleeding both in Child A (IRR 0.20; 95% CI: 0.04–0.97; p=0.045) and in Child B/C patients (IRR 0.41; 95% CI: 0.24–0.70; p=0.001) (Figure 2). The effect of treatment was similar in both strata (p-value for the interaction of 0.405). There was no significant heterogeneity (MIRR 1.12; 95%CI: 1.00–16.56; p=0.357).

b) Death—A total of 416 patients from 4 trials contributed to the analysis of mortality (Figure 2 and Supplementary Table 2) (18–21). Seventeen out of the 210 (8%) patients on combination therapy died compared to 33 out of the 206 (16%) patients on EVL, being the IRR for mortality of 0.50 (95% CI: 0.28–0.89, p=0.019). Heterogeneity among trials was present for this analysis (MIRR=2.16, p<0.001).

Four out of the 104 Child A patients (4%) died, 2 on combination therapy and 2 on EVL, whereas 46 out of 312 Child B/C patients died (15%), 15 on combination therapy, and 31 on EVL. Therefore, combination of BB and EVL did not significantly influenced mortality in the low-risk Child A patients (IRR 1.11; 95% CI: 0.16–7.93; p=0.915). However, in Child B/C patients combination therapy did result in a significant lower mortality compared with treatment with EVL alone (IRR 0.46; 95% CI 0.25–0.85; p=0.013). Figure 3 shows that the cumulative probability of survival was significantly (p<0.01) lower in Child B/C on combination therapy, but not in Child A patients.

Secondary outcome

Rebleeding from a variceal source was assessed in 278 patients from the trials that compared combination therapy versus BB alone (22, 23). Forty-one out of 140 patients (29%) rebled from varices in the combination therapy group versus 51 out of 138 patients in the BB group (37%). The overall IRR (adjusted for bilirubin and encephalopathy) for variceal rebleeding was 0.81 (95% CI: 0.53–1.23; p=0.320). When stratified by Child, 68 out of the 278 patients were Child A, and 25 of them rebled (37%), 7 on combination therapy and 18 on BB therapy. Sixty-seven out of 210 Child B/C patients rebled (32%), 34 on combination therapy and 33 on BB. Combination therapy (BB plus EVL) was more effective than BB alone in preventing variceal rebleeding in Child A patients (IRR 0.26; 95% CI: 0.11–0.61; p=0.002), but not in Child B/C patients (IRR 1.24; 95% CI: 0.75–2.05); p=0.410), showing a significant interaction (p=0.002). No heterogeneity was detected among trials (MIRR 1.23; 1.05–2.70; p=0.109).

Variceal rebleeding was assessed in 220 patients from the trials that compared combination therapy versus EVL alone (19, 20). Twelve out of 115 (10%) patients rebled from varices in the combination therapy group versus 18 out of 105 (17%) patients in the EVL group. The overall IRR for variceal rebleeding was 0.52 (95% CI: 0.25–1.11; p=0.091). When stratified by Child, 71 out of the 220 patients were Child A, and 4 of them rebled (6%), 1 on combination therapy (25%) and 3 on EVL therapy (75%). Twenty-six out of 149 Child B/C patients rebled (17%), 11 on combination therapy and 15 on EVL. Therefore, combination of BB and EVL was not more effective than EVL in preventing variceal rebleeding either in Child A patients (IRR 0.22; 95% CI: 0.02–2.13; p=0.191 or in Child B/C patients (IRR 0.63; 95% CI: 0.28–1.41); p=0.264). There was no significant heterogeneity in this analysis (p=0.497).

Sensitivity analysis

We perform two sensitivity analyses for overall and variceal rebleeding, one considering death as a competing event and the other including all the patients in the analysis, even those without information on time-to-event.

As shown in Table 3, competing risk regression confirmed the estimates of the main analysis.

In the second sensitivity analysis, we tested whether exclusion of 159 patients from the studies by Ahmad et al. and Lo et al. who lacked time-to-event information could have biased the results (18, 21). Logistic multilevel regression analyses of all patients with information on Child class and treatment outcome independently of time-to-event also confirmed the estimates of the model using time-to-event data. The only different result was the P value for interaction in the response to EVL by Child strata, which in contrast to the main analysis was marginally significant in this analysis (p=0.067) (Table 3).

Additionally, the post-hoc exploratory analysis in the trials that compared combination therapy versus EVL alone showed that compared to EVL alone, trials that used BB without ISMN (20, 21) showed a statistically significant (p=0.007) larger impact on reducing all-source rebleeding than those trials associating ISMN to BB (18, 19), whereas the effect on mortality was not significant (Supplementary table 4)

DISCUSSION

Currently, combination therapy consisting of BB plus EVL is recommended in the prevention of recurrent variceal hemorrhage in all patients with cirrhosis who have recovered from variceal hemorrhage (2, 3). This recommendation is based on meta-analyses that have analyzed all patients with cirrhosis, independent of the severity of liver disease. Per recent Baveno VI consensus conference and the 2016 Practice Guidance by the AASLD on Portal Hypertensive Bleeding in Cirrhosis, risk stratification is essential in the treatment of portal hypertension (3, 25). Therefore, the objective of our IPD meta-analysis was to determine whether risk stratification would identify sub-groups of patients that would benefit the most from combination therapy.

The current IPD meta-analysis, in addition to increasing the statistical power of previous aggregate data meta-analyses, allowed us to examine the effect of combination therapy versus monotherapy depending on Child class (A versus B/C) and to analyze survival as a time-to-event variable. We elected to stratify patients by Child A versus B/C as this would stratify patients in the two main prognostic stages of cirrhosis, compensated and decompensated, as most Child A patients are compensated whereas the majority of Child B/C patients are decompensated (9). Because trials of combination therapy had either BB or EVL as control therapy, we could address the relative contribution of BB versus EVL to combination therapy by performing separate meta-analysis.

Our meta-analysis included IPD from 389 patients of 3 trials comparing combination therapy versus BB and 416 patients of 4 trials comparing combination therapy versus EVL.

The overall results of our meta-analysis confirm results from aggregate published meta-analysis (5, 6), that is, that combination therapy is associated with lower rebleeding rates when compared to EVL alone but not when compared to BB alone suggesting that BB therapy could be sufficient. It also supports results from aggregate meta-analysis demonstrating a lack of effect on mortality of combination therapy versus monotherapy.

Notably, there was a decrease in mortality with combination therapy in trials where it was compared to EVL alone but there was significant heterogeneity among trials and therefore this conclusion is not strong.

Importantly, our meta-analysis showed a different effect of combination therapy in the two main stages of cirrhosis.

In compensated (Child A) patients with cirrhosis, combination therapy (BB plus EVL) was clearly associated with lower *all-source* rebleeding whether it was compared to BB alone or to EVL alone but without an effect on mortality. Lower *variceal* rebleeding rates were observed when combination therapy was compared to EVL alone but not when compared to BB alone suggesting that BB therapy could be sufficient. However, as recently defined by consensus, the important outcome in a patient who has bled from varices is all-source rebleeding, rather than variceal rebleeding (2).

In decompensated (Child B/C) patients with cirrhosis, combination therapy was associated with lower all-source rebleeding rates only in trials where it was compared to EVL alone but no significant differences in all-source rebleeding were shown when combination therapy was compared to BB alone, suggesting that BB alone could be sufficient to prevent all-source rebleeding in this setting. More importantly, mortality was significantly lower only in trials in which combination therapy was compared to EVL alone with a tendency for a higher mortality with combination therapy in trials where it was compared to BB alone, suggesting a deleterious effect of EVL on mortality. This deleterious effect was confirmed in time-to-event analysis that, in Child B/C patients, showed a significantly higher probability of survival with combination therapy when compared to EVL alone. This confirms that, in the setting of decompensated cirrhosis, combination therapy actually improves survival and that BB use is the key element of combination therapy. The different behavior of EVL according to Child class is further supported by the statistically significant interaction between both variables on rebleeding. Such a finding is in line with the studies observing an inverse relationship between the severity of liver disease and the efficacy of endoscopic therapy on rebleeding prevention (26).

It is likely that BB improve survival in cirrhosis by lowering the rates of rebleeding and of other complications of cirrhosis through hemodynamic (reduction in splanchnic blood flow, gastroesophageal collateral blood flow and portal pressure) and non-hemodynamic (reduction in gut bacterial translocation) mechanisms. Since portal hypertension and bacterial translocation worsen as cirrhosis progresses to the decompensated stage, the benefit of BB on rebleeding and mortality extends through the whole spectrum of the disease.

The absence of impact of BB on mortality in Child A in our study is probably related to the very low number of events (deaths) in this population. Alternatively, it can be suggested that effective prevention of rebleeding has a limited contribution in prolonging survival in initial stages of cirrhosis, and that BB are only able to reduce mortality when cirrhosis progresses and the patient is at risk of complications other than bleeding. In fact, much of the observed differences in the survival curves between patients on combination therapy and those on EVL occurred beyond 18 months, which suggests an improvement in the natural history of

cirrhosis by BB in the long-term. These results are in agreement with those of Lo et al. who also observed a survival benefit of BB independently of rebleeding prevention (27).

The availability and analysis of a large number of IPD is the main strength of the present study. Indeed, obtaining IPD data is a worthy effort. The final database was built after a through revision of the original datasets to detect inconsistencies and errors, which provided a robust database for analysis on a topic in which new trials with current therapies are unlikely. As it is the case in our study, it is commonly acknowledged that IPD meta-analysis provides further insights to the estimation of treatment effects as compared to more frequently performed aggregate data meta-analysis (28). Besides, using aggregate data limits the possibility of assessing the impact of covariates to trial-level ones. Using IPD overcomes this limitation allowing evaluating the impact of patient-level covariates on the estimation of efficacy of interventions (29). Specifically, our IPD meta-analysis has been able to analyze the modifier effect of individual patient's clinical characteristics as the severity of the disease (i.e. Child) on the efficacy of combined therapy. This is of importance as the severity of liver failure is the main prognostic determinant in patients with cirrhosis surviving an episode of variceal bleeding. We have obtained deeper insights on the differential effect of the combined therapy depending on individual patient's Child score (A vs. B/C). IPD allowed us to perform a multivariate adjustment of the effect of combined therapy by other confounders, when needed. So, we can reassure that the significant decrease of mortality and rebleeding are not affected by none of the covariates included neither by their distribution among the studies. Furthermore, the results of our main analysis on all-source and variceal rebleeding were reinforced by two sensitivity analyses, a competing risk analysis, considering death as a competing event, and a logistic multilevel regression analysis, including all the patients regardless of time-to-event information.

The association of ISMN to BB in some, but not all trials deserves a comment. ISMN was associated to BB in all 3 trials comparing combination therapy (BB and EVL) versus BB alone, fact that should be taken into account when considering therapy in this context. The effect of pharmacological therapy using BB and ISMN (versus BB) could be explored in trials comparing combination therapy versus EVL alone. Interestingly, combination pharmacological therapy (BB and ISMN) had a lower effect in reducing all-source rebleeding compared to BB alone. These results indicate that BB exert their beneficial effect combined with EVL, effect that may be hampered by the concomitant use of ISMN.

Our study however has several limitations. i) As in every meta-analysis, the overall quality depends on that of the individual data. We built the final dataset of IPD after checking for completeness and internal consistency, and excluding those IPD with insufficient information, in whom it could not be obtained upon request. For these reasons and in order to build a robust database, we excluded from the variceal rebleeding analysis those patients from trials lacking individual source of bleeding information (18, 21). ii) The absence of uniform standard definitions and the insufficient information of adverse events precluded performing safety analysis. iii) The accuracy of conclusions in Child A is limited by the rather, but otherwise expected, low number of events in this population.

Altogether, our results, while confirming results from aggregate meta-analysis, point out differences in response to secondary prophylaxis therapies in patients with compensated versus decompensated cirrhosis. In those with compensated cirrhosis, combination therapy is indicated to prevent all-source rebleeding (although without an effect on mortality) while in those with decompensated cirrhosis in whom the key outcome is mortality, combination therapy, but mostly the BB component of combination therapy, is associated with a reduction in mortality. The study demonstrates that EVL should not be used as monotherapy, as this is associated with lower overall efficacy in preventing rebleeding, and with increased mortality in Child B/C patients. Current evidence does not support a harmful effect of BB in patients with decompensated cirrhosis but rather a beneficial effect. Therefore, careful thought should be given before discontinuing BB (or before considering not initiating them when indicated) in patients with cirrhosis, particularly in those at a decompensated stage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

List of Abbreviations

BB	beta-blockers
EVL	endoscopic variceal ligation
IPD	individual patient data
MIRR	median incidence rate ratios
IRR	incidence rate ratios

References

1. Bosch J, García-Pagán JC. Prevention of variceal rebleeding. Lancet. 2003; 361:952–954. [PubMed: 12648985]

2. de Franchis R. Baveno V Faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol. 2010; 53:762–768. [PubMed: 20638742]

3. Garcia-Tsao G, Abraldes J, Berzigotti A, Bosch J. Portal Hypertensive Bleedingin Cirrhosis: Risk Stratification, Diagnosis and Management - 2016 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2017; 65:310–85. [PubMed: 27786365]

4. Cheung J, Zeman M, van Zanten SV, et al. Systematic review: secondary prevention with band ligation, pharmacotherapy or combination therapy after bleeding from oesophageal varices. Aliment Pharmacol Ther. 2009; 30:577–588. [PubMed: 19558563]

5. Gonzalez R, Zamora J, Gomez-Camarero J, et al. Meta-analysis: Combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. Ann Intern Med. 2008; 149:109–122. [PubMed: 18626050]

6. Puente A, Hernández-Gea V, Graupera I, et al. Drugs plus ligation to prevent rebleeding in cirrhosis: an updated systematic review. Liver Int. 2014; 34:823–833. [PubMed: 24373180]

7. Ripoll C, Bari K, Garcia-Tsao G. Serum albumin can identify patients With compensated cirrhosis with a good prognosis. J Clin Gastroenterol. 2015; 49:613–9. [PubMed: 25203362]

8. D'Amico G, García-Tsao G, Pagliaro L. Natural history and prgnostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol. 2006; 44:217–231. [PubMed: 16298014]

9. Garcia-Tsao G. The Child-Turcotte classification: From Gestalt to sophisticated statistics and back. Dig Dis Sci. 2016; 61:3102–3104. [PubMed: 27696097]

10. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD Statement. JAMA. 2015; 313:1657–1665. [PubMed: 25919529]

11. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973; 60:646–9. [PubMed: 4541913]

12. Rabe-Hesketh S, Skrondal A. Classical latent variable models for medical research. Stat Methods Med Res. 2008; 17:5–32. [PubMed: 17855748]

13. Merlo J, Chaix B, Ohlsson H, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. J Epidemiol Community Health. 2006; 60:290–297. [PubMed: 16537344]

14. Abdel-Rhaim AY, Abdel-Ghany MS, El-Kholy B. Band ligation alone versus band ligation and propranolol in the management of bleeding esophageal varices (Abstract). Am J Gastroenterol. 2000; 95:2442.

15. Sollano JD, Melchor RJ, Chan M, et al. Propranolol prevents rebleeding after variceal ligation. Gastrointest Endosc. 2002; 53:AB143.

16. Lo GH, Lai KH, Cheng JS, et al. The effects of endoscopic variceal ligation and propranolol on portal hypertensive gastropathy: a prospective, controlled trial. Gastrointest Endosc. 2001; 53:579–584. [PubMed: 11323582]

17. Villanueva C, Aracil C, Colomo A, et al. Clinical trial: a randomized controlled study on prevention of variceal rebleeding comparing nadolol plus ligation vs. hepatic venous pressure gradient-guided pharmacological therapy. Aliment Pharmacol Ther. 2009; 29:397–408. [PubMed: 19006538]

18. Ahmad I, Khan A, Alam A, et al. Propranolol, isosorbide mononitrate and endoscopic band ligation – alone or in varying combinations for the prevention of esophageal variceal rebleeding. J Coll Physicians Surg Pak. 2009; 19:283–286. [PubMed: 19409159]

19. Kumar A, Jha SK, Sharma P, et al. Addition of propranolol and isosorbide mononitrate to endoscopic variceal ligation does not reduce variceal rebleeding incidence. Gastroenterology. 2009; 137:892–901. [PubMed: 19481079]

20. De la Peña J, Brullet E, Sanchez-Hernández E, et al. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. Hepatology. 2005; 41:572–8. [PubMed: 15726659]

21. Lo GH, Lai KH, Cheng JS, et al. Endoscopic variceal ligation plus nadolol and sucralfate compared with ligation alone for the prevention of variceal rebleeding: a prospective, randomized trial. Hepatology. 2000; 32:461–565. [PubMed: 10960435]

22. Lo GH, Chen WC, Chan HH, et al. A randomized, controlled trial of banding ligation plus drug therapy versus drug therapy alone in the prevention of esophageal variceal rebleeding. J Gastroenterol Hepatol. 2009; 24:982–987. [PubMed: 19638080]

23. Garcia-Pagan JC, Villanueva C, Albillos A, et al. Nadolol plus isosorbide mononitrate alone or associated with band ligation in the prevention of recurrent bleeding: a multicenter randomized controlled trial. Gut. 2009; 58:1144–1150. [PubMed: 19218249]

24. Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. BMJ. 2001; 323:42–46. [PubMed: 11440947]

25. de Franchis R. Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015; 63:743–752. [PubMed: 26047908]

26. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of oesophageal variceal bleeding. A meta-analysis. Ann Intern Med. 1995; 123:280–287. [PubMed: 7611595]

27. Lo GH, Chen WC, Lin CK, et al. Improved survival in patients receiving medical therapy as compared with banding ligation for the prevention of esophageal variceal rebleeding. Hepatology. 2008; 48:580–587. [PubMed: 18666235]

28. Riley RD, Steyerberg EW. Meta-analysis of a binary outcome using individual participant data and aggregate data. Res Synth Methods. 2010; 1:2–19. [PubMed: 26056090]

29. Gore SM, Pocock SJ, Kerr GR. Regression Models and Non-Proportional Hazards in the Analysis of Breast Cancer Survival. J R Stat Soc C Appl Stat. 1984; 33:176–195.
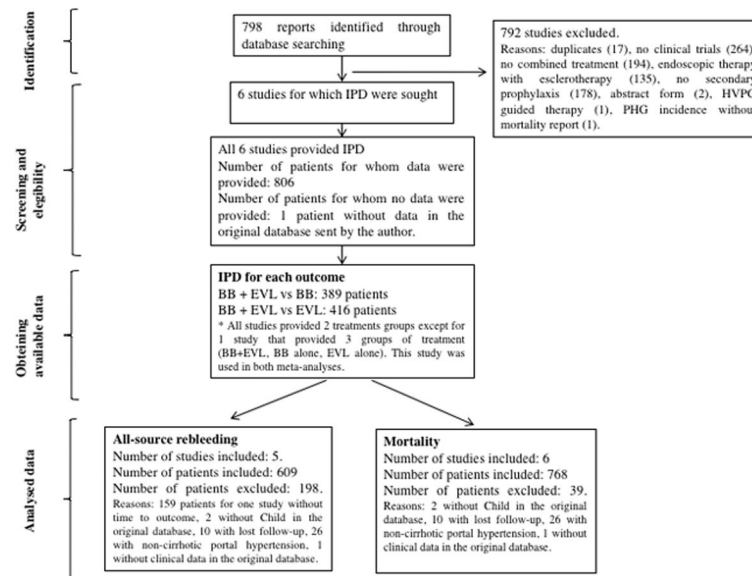
Identification

798 reports identified through database searching

792 studies excluded.
Reasons: duplicates (17), no clinical trials (264), no combined treatment (194), endoscopic therapy with esclerotherapy (135), no secondary prophylaxis (178), abstract form (2), HVPG guided therapy (1), PHG incidence without mortality report (1).

6 studies for which IPD were sought

Screening and eligibility

All 6 studies provided IPD
Number of patients for whom data were provided: 806
Number of patients for whom no data were provided: 1 patient without data in the original database sent by the author.

Obteining available data

IPD for each outcome
BB + EVL vs BB: 389 patients
BB + EVL vs EVL: 416 patients
* All studies provided 2 treatments groups except for 1 study that provided 3 groups of treatment (BB+EVL, BB alone, EVL alone). This study was used in both meta-analyses.

Analysed data

All-source rebleeding
Number of studies included: 5.
Number of patients included: 609
Number of patients excluded: 198.
Reasons: 159 patients for one study without time to outcome, 2 without Child in the original database, 10 with lost follow-up, 26 with non-cirrhotic portal hypertension, 1 without clinical data in the original database.

Mortality
Number of studies included: 6
Number of patients included: 768
Number of patients excluded: 39.
Reasons: 2 without Child in the original database, 10 with lost follow-up, 26 with non-cirrhotic portal hypertension, 1 without clinical data in the original database.

Figure 1. Flow diagram of the individual patient data (IPD) meta-analyses following PRISMA guideline and recommendation

IPD, individual patient data; EVL, endoscopic variceal ligation; BB, non-selective beta-blockers, PHG, portal hypertensive gastropathy.
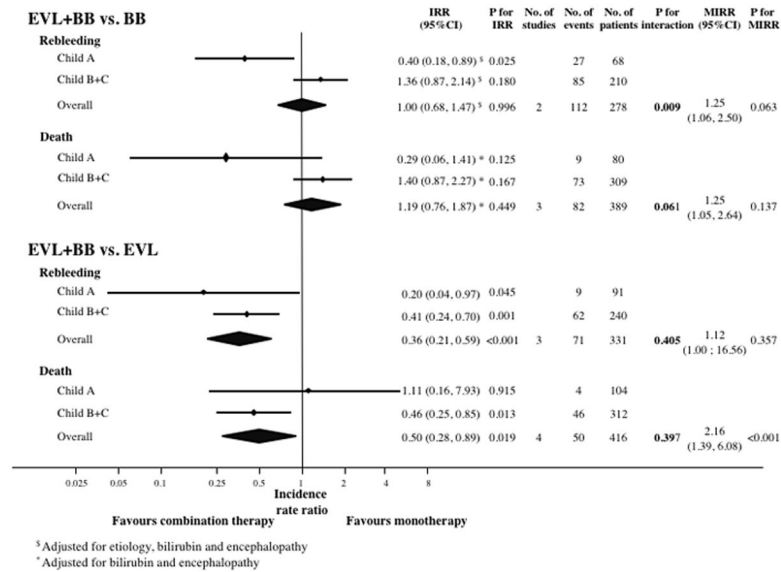
Figure 2. Forrest plots of overall rebleeding (*top*) and mortality (*bottom*) in trials comparing combination of endoscopic variceal ligation (EVL) and beta-blockers (BB) with either therapy alone

Diamonds represent the incidence rate ratios (IRR). Horizontal lines indicate the 95% CIs.

Heterogeneity measured as Median Incidence Rate Ratios (MIRR). Comparison between Child subgroups for each outcome is shown by p for interaction.
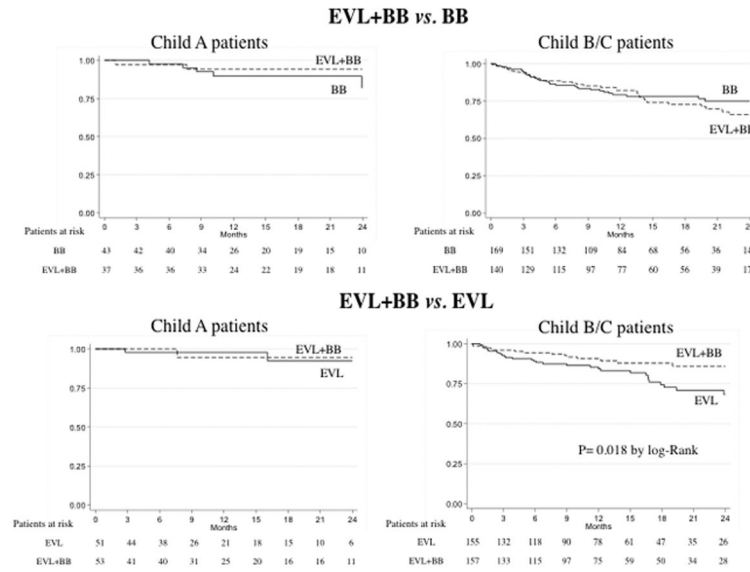
Figure 3.
Survival probability according to treatment and Child class with combination of endoscopic variceal ligation (EVL) and beta-blockers (BB) versus BB alone (*top*) or versus EVL alone (*bottom*), as estimated by Kaplan-Meier.

Table 1

Characteristics of the 6 studies included in the meta-analyses.

Author, year, reference	Number of patients	Additional inclusion criteria	Exclusion criteria (*)	Trial design	Included patients	Treatment groups	Definition of rebleeding	Mean sessions to variceal obliteration	Time to start BB (days)	Drug therapy. Mean dose (range or SD)	Follow-up. Median or mean
Endoscopic variceal ligation (EVL) and beta-blockers (BB) vs. BB											
Ahmad, 2009, (18)	160	First episode of bleeding	Acute-on-chronic liver failure	Single center No blinding	111	EVL+BB: 37 BB: 74	Hematemesis/melena with >2 blood units transfusion or drop in hemoglobin >2 g/dl	3.0	5	EVL+BB: Propranolol 50±21 mg/d ISMN 33±10mg/d BB: Propranolol 53±21mg/d ISMN 35±9mg/d	24 months EVL+BB: 24 BB: 24
Lo, 2009(22)	120	No	Bilirubin >10mg/dl Hepatic encephalopathy >grade II	Single center Endoscopy blinded	120	EVL+BB: 60 BB: 60	Hematemesis/melena with >2 blood units transfusion or drop in hemoglobin >2 g/dl	3.8	2	Both groups: Nadolol 40mg/d (20–120) ISMN 20mg/d (0–40)	23 months EVL+BB: 23 BB: 22.7
García-Pagán, 2009,(23)	158	No		Multicenter No blinding	158	EVL+BB: 80 BB: 78	Hematemesis/melena with >2 blood units transfusion	2	5	EVL+BB: Nadolol 102±52 mg/d ISMN 36±9mg/d BB: Nadolol 90±48mg/d ISMN 36±10mg/d	15 months EVL+BB: 14 BB: 15.3
Endoscopic variceal ligation (EVL), and beta-blockers (BB) vs. EVL											
Ahmad, 2009, (18)	160	Firstepisode of bleeding	Acute-on-chronic liver failure	Single center No blinding	76	EVL+BB: 37 EVL: 39	Hematemesis/melena with >2 blood units transfusion or drop in hemoglobin >2 g/dl	EVL+BB: 3.0 EVL: 3.5	5	Propranolol 53±21mg/d ISMN 35±9mg/d	23 months EVL+BB: 24 EVL: 21
Kumar 2009, (19)	177	NCPH^ Wide interval from bleed to inclusion		Single center No blinding	177	EVL+BB: 88 EVL: 89	Hematemesis/melena with >2 blood units transfusion	EVL+BB: 4.6 EVL: 4.6	5	Propranolol 120mg/d ISMN 40mg/d	15 months EVL+BB: 15 EVL: 15
De la Peña, 2005, (20)	80	No	Refractory ascites	Multicenter No blinding	80	EVL+BB: 43 EVL: 37	Hematemesis/melena with fall in hemoglobin	EVL+BB:3 EVL.:3	5	Nadolol 58mg/d	16,4 months EVL+BB: 17 EVL: 15
Lo, 2000, (22)	122	No	Hepatic encephalopathy >grade II	Single center No blinding	122	EVL+BB: 60 EVL: 62	Hematemesis/melena with >2 blood units transfusion or drop in hemoglobin >2 g/dl	EVL+BB: 3.3 EVL: 3.6	2	Nadolol(60mg/d) + sucralfate	21,5 months EVL+BB: 22 EVL: 21

*
Exclusion criteria common to all studies were: previous therapy with endoscopy or beta-blockers, bleeding from gastric varices, presence of hepatocellular carcinoma, portal hypertensive gastropathy bleeding, debilitating disease, TIPS, pregnancy.

^
NCPH: Non cirrhotic portal hypertension

Table 2

Baseline demographic, clinical and laboratory characteristics of patients with cirrhosis allocated to each IPD meta-analyses.

	Endoscopic variceal ligation (EVL) and beta-blockers (BB) vs. BB		Endoscopic variceal ligation (EVL) and beta-blockers (BB) vs. EVL	
	EVL+BB (n=177)	**BB (n=212)**	**EVL+BB (n=210)**	**EVL (n=206)**
Age (years)	53.6 ± 0.9	54.1 ± 0.7	51.1 ± 0.8	50.7 ± 0.9
Sex (male/female) (%)	66/34	68/32	72/28	79/21
Etiology (%)				
Alcohol	45	41	49	44
Virus	47	53	39	40
Others	8	6	12	16
Bilirubin (md/dl)	2.3 ± 0.2	2.2 ± 0.1	2.4 ± 0.1	2.5 ± 0.2
Albumin (g/dl)	3.0 ± 0.2	3.1 ± 0.1	3.0 ± 0.2	3.0 ± 0.4
Prothrombin ratio (%)	69 ± 14	68 ± 14	69 ± 15	67 ± 19
Child-Pugh (%)				
A	21	20	25	24
B/C	79	80	74	76

Data are shown as mean±SD or as %

Table 3

Sensitivity analyses

		Competing risk regression analysis		Multilevel logistic regression analysis	
		SHR[a]	P-Value[b]	OR[c]	P-Value[b]
EVL and BB vs. BB					
All-source rebleeding	Child A	0.46 (0.21; 1.04)		0.38 (0.14; 1.00)	
	Child B/C	1.35 (0.86; 2.12)	0.024	1.05 (0.64; 1.72)	0.067
Variceal rebleeding	Child A	0.32 (0.14; 0.76)		0.27 (0.09; 0.76)	
	Child B/C	1.23 (0.73; 2.06)	0.009	0.88 (0.53; 1.47)	0.043
EVL and BB vs. EVL					
All-source rebleeding	Child A	0.21 (0.04; 0.97)		0.21 (0.04; 1.03)	
	Child B/C	0.39 (0.23; 0.68)	0.444	0.62 (0.36; 1.07)	0.206
Variceal rebleeding	Child A	0.23 (0.02; 2.17)		0.43 (0.04; 4.98)	
	Child B/C	0.59 (0.26; 1.33)	0.429	0.89 (0.41; 1.89)	0.579

[a] Sub-hazard Ratio (SHR) for the effect of combination of endoscopic variceal ligation (EVL) and beta-blockers (BB) versus monotherapy (BB or EVL) (as reference)

[b] P-Value for the interaction between treatment effect and Child-Pugh groups

[c] Odds ratio (OR) for the effect of combination EVL and BB versus monotherapy (BB or EVL)(as reference)