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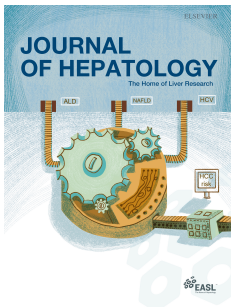

Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis

Càndid Villanueva, Ferran Torres, Shiv Kumar Sarin, Hasnain Ali Shah, Dhiraj Tripathi, Anna Brujats, Susana G. Rodrigues, Ankit Bhardwaj, Zahid Azam, Peter C. Hayes, Ankur Jindal, Shahab Abid, Edilmar Alvarado, Jaume Bosch, on behalf of the Carvedilol-IPD-MA-group, From the PREDESCI study (Ref. 7), From the study by Shah HA et al (Ref.16), From the study by Tripathi D et al (Ref.14), From the study by Bhardwaj A et al (Ref.15), the Baveno Cooperation: an EASL Consortium

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Carvedilol to improve risk of decompensation and survival in compensated cirrhosis

Competing-risk meta-analysis of individual patient data

Background / AIM

COMPENSATED CIRRHOSIS
Good Prognosis

Portal Hypertension

β-blockers
** Improve CSPH*
** Unclear if can prevent decompensation*

Carvedilol
NSBB with potential to ameliorate hepatic vascular resistance

DECOMPENSATED CIRRHOSIS
High mortality

AIM
assess whether carvedilol may prevent decompensation and improve survival in compensated cirrhosis with CSPH

Methods

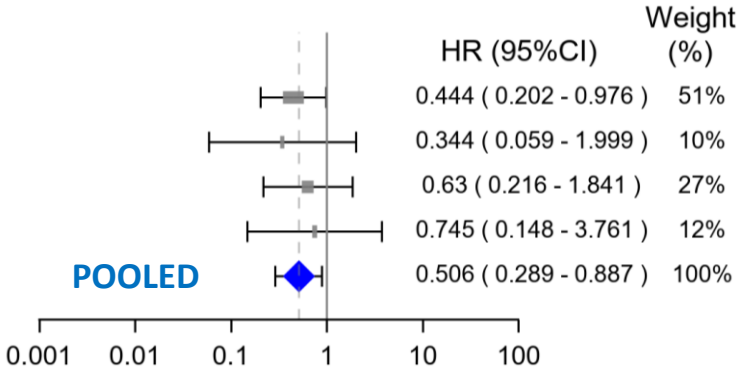
Systematic review to identify RCTs comparing
carvedilol *vs* **control therapy**
Only compensated patients included

To optimize statistical assessment we performed
individual patient data meta-analysis
using time-to-event with competing-risk regression models
adjusted by IPTW

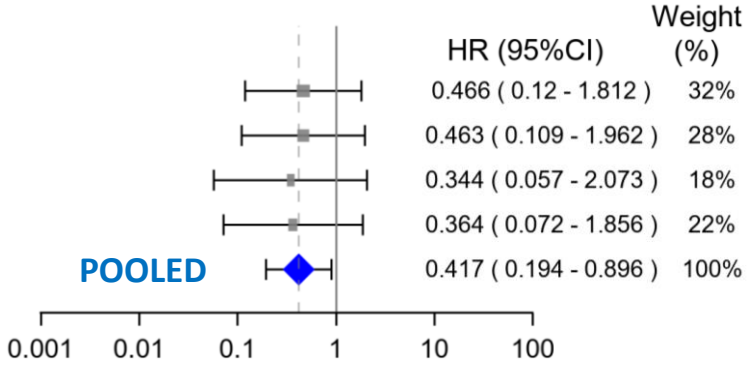
4 RCTs included
352 patients with compensated cirrhosis
* **181** *treated with carvedilol*
vs
* **171** *controls*
(79 received EVL and 92 placebo)

Results

Carvedilol significantly decrease the risk of developing decompensation
(competing events: death & liver transplant)



Carvedilol significantly improve survival
(liver transplant, competing event)



CONCLUSIONS

screening patients with compensated cirrhosis for CSPH to start carvedilol can prevent the progression of compensated cirrhosis to decompensation, improving survival and reducing health-care burden and cost

Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis

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Data availability statement: Due to the confidentiality agreements, the datasets generated and analyzed for this study are only available from the corresponding author upon reasonable request.

ABSTRACT

Whether non-selective β-blockers can prevent decompensation of cirrhosis needs clarification. Carvedilol might be particularly effective since its intrinsic vasodilatory activity may ameliorate hepatic vascular resistance, a major mechanism of portal-hypertension in early cirrhosis. We assessed whether carvedilol may prevent decompensation and improve survival in compensated cirrhosis with clinically significant portal hypertension (CSPH).

METHODS: By systematic review we identified RCTs comparing carvedilol vs control therapy (no-active treatment or EVL) in patients with cirrhosis and CSPH without previous bleeding. We performed a competing-risk time-to-event meta-analysis using individual patient data (IPD) obtained from principal investigators of RCTs. Only compensated patients were included. Primary outcomes were prevention of decompensation (OLT and death were competing-events) and death (OLT, competing-event). Models were adjusted using propensity score for baseline covariates with the IPTW approach.

RESULTS: Among 125 full-text studies evaluated, 4 RCTs were eligible. The four provided IPD and were included, comprising 352 patients with compensated cirrhosis, 181 treated with carvedilol and 171 controls (79 received EVL and 92 placebo). Baseline characteristics were similar between groups. Standardized differences were <10% by IPTW. The risk of developing decompensation of cirrhosis was lower with carvedilol than in controls (SHR=0.506, 95%CI=0.289-0.887, P=0.017; I^2=0.0%, Q-statistic-P=0.880), mainly due to a reduced risk of ascites (SHR=0.491, 95%CI=0.247-0.974, P=0.042; I^2=0.0%, Q-statistic-P=0.384). The risk of death was also lower with

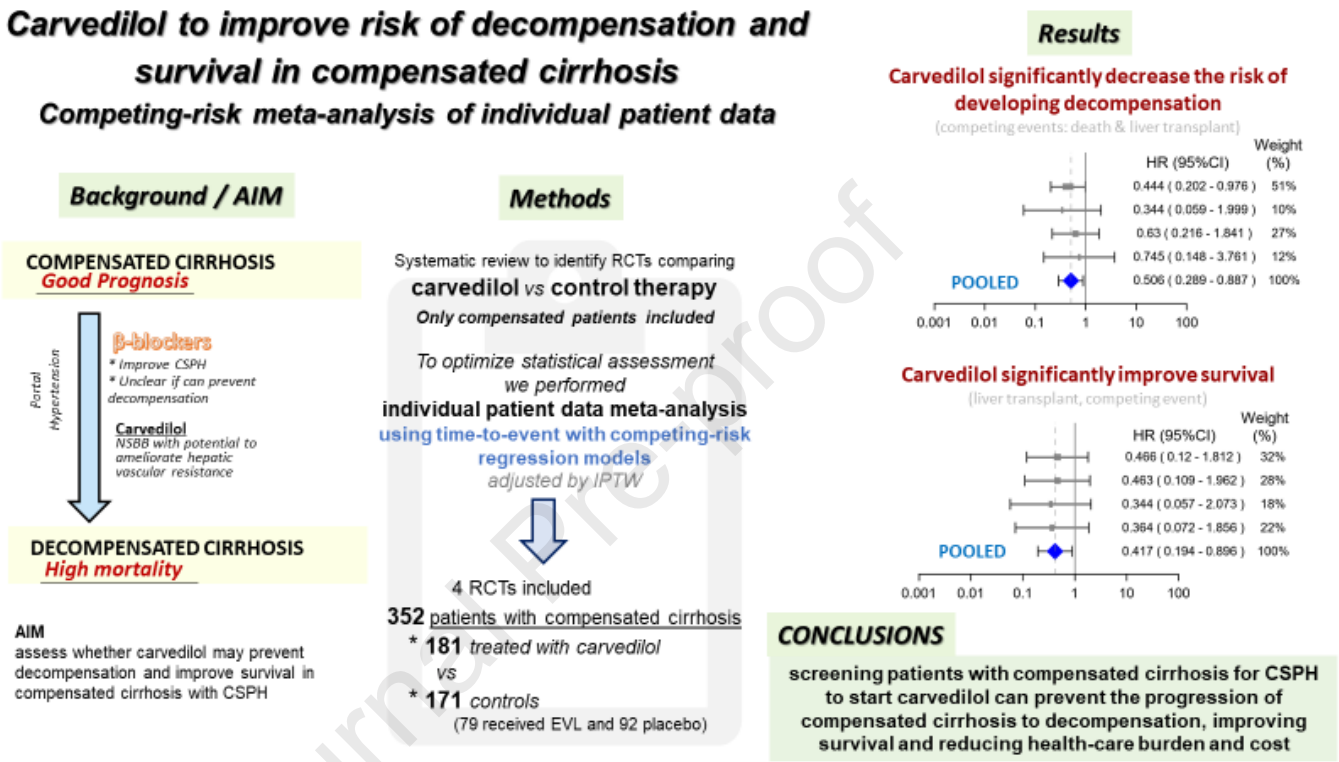
carvedilol (SHR=0.417, 95%CI=0.194-0.896, P=0.025; I^2=0.0%, Q-statistic-P=0.989).

CONCLUSIONS: Long-term carvedilol therapy reduced decompensation of cirrhosis and significantly improved survival in compensated patients with CSPH. This suggests that screening patients with compensated cirrhosis for CSPH to start therapy with carvedilol can improve outcomes.

LAY SUMMARY

Portal hypertension is a main determinant of the progression of cirrhosis from compensated to decompensation with the consequent increase in morbidity and worsening of life expectancy. It has been suggested that NSBBs can prevent decompensation, but this has not been clarified. Carvedilol might be particularly useful since its intrinsic vasodilatory activity may ameliorate hepatic vascular resistance, which is a major mechanism of portal hypertension in compensated cirrhosis. We aimed to investigate such possibility using an individual participant data with competing-risk meta-analysis, to optimize sample size and properly investigate cirrhosis as a multistate disease and outcomes as time-dependent events. The study shows that carvedilol significantly decreases the risk of decompensation in patients with compensated cirrhosis and CSPH, mainly by reducing the risk of developing ascites. Even more importantly, carvedilol improved survival in these patients. The findings suggest that screening patients with compensated cirrhosis for CSPH to start therapy with carvedilol, can prevent the progression of compensated cirrhosis to decompensation improving survival.

GRAPHICAL ABSTRACT



HIGHLIGHTS

* Portal hypertension is a main determinant of the progression of cirrhosis from compensated to decompensation. The potential effect of NSBBs to prevent decompensation should be clarified. Carvedilol might be particularly useful since its intrinsic vasodilatory activity may ameliorate hepatic vascular resistance, a major mechanism of portal hypertension in compensated cirrhosis.

* Carvedilol significantly decreases the risk of decompensation in patients with cirrhosis and CSPH, mainly by reducing the likelihood of developing ascites.

* Even more importantly, carvedilol significantly improve survival in compensated patients.

* Our findings suggest that screening patients with compensated cirrhosis for CSPH to start therapy with carvedilol, can prevent the progression of compensated cirrhosis to decompensation.

BACKGRUND & AIMS

Cirrhosis evolves over time from compensation to a decompensated stage, markedly declining life expectancy.(1) The progression of portal hypertension (PH) has a key role in this evolution. A hepatic venous pressure gradient (HVPG) ≥10mmHg defines clinically significant PH (CSPH) as decompensation may appear above this threshold.(2,3) Among compensated patients, those with CSPH have a more developed hyperdynamic circulation and better hemodynamic response to non-selective β-blockers (NSBBs) than those without CSPH.(4) NSBBs effectively prevent variceal bleeding in patients with large varices,(3,5,6) and the PREDESCI study suggests that NSBBs can prevent decompensation of cirrhosis with CSPH.(7) However, other studies have failed to show efficacy with NSBBs in early compensated cirrhosis,(8) and to date NSBBs have not shown a survival benefit in compensated cirrhosis.(7,8)

Carvedilol is a NSBB with intrinsic vasodilatory activity due to its anti-α-adrenergic activity and its capacity to enhance nitric oxide release.(11,12) Consequently, carvedilol might be particularly adequate in compensated cirrhosis, where an increased hepatic vascular resistance constitutes a predominant mechanism of PH.(4,13) Carvedilol has a greater HVPG-decreasing effect than propranolol.(9,10) Randomized controlled trials (RCTs) suggest efficacy with carvedilol to prevent enlargement of small varices, and to prevent bleeding in patients with high-risk varices and either compensated or decompensated cirrhosis.(14,15) However, other RCTs failed to show efficacy with carvedilol.(16,17) Furthermore, whether carvedilol may prevent decompensation and improve survival in patients with compensated cirrhosis has not been demonstrated. Individual participant data (IPD) meta-analyses can

be valuable to explore this by allowing reanalysis of the individual-level data of patients included in RCTs, using a time-to-event and competing-risk approach, thus properly investigating cirrhosis as a multistate disease and outcomes as time-dependent events.(18)

This study aimed to assess whether long-term treatment with carvedilol may prevent decompensation and improve survival in patients with compensated cirrhosis and CSPH, by performing an IPD-meta-analysis of available RCTs.

METHODS

This IPD-meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)–IPD guidelines for protocol registration, trial identification, data collection and integrity, assessment of bias, and sensitivity analyses.(19) This meta-analysis was registered in PROSPERO (registration number: CRD42019144786) and was performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. All included studies were approved by the local ethics committees of the respective participating hospital and were required to have ethical approval to share the data. The study protocol (available with supplementary material) was approved by the Research Ethics Committee of coordinating center (Hospital Sant Pau, Barcelona). All patient data was anonymized in order to preserve privacy.

STUDY DESIGN, SCOPE OF REVIEW AND ELIGIBILITY CRITERIA

This meta-analysis was designed to pool the data of individual patients participating in RCTs comparing carvedilol with a control group to prevent first bleeding from high-risk varices, to prevent enlargement of small to large varices, or to prevent decompensation of cirrhosis or appearance of varices in compensated cirrhosis with CSPH. We planned to include only individuals from RCTs allocating adult cirrhotic patients to receive carvedilol or to a control group receiving no specific therapy or placebo or monotherapy with endoscopic variceal ligation (EVL) in case of high-risk varices. From eligible RCTs, only patients with compensated cirrhosis at inclusion and without any previous decompensating event were included. RCTs were included if fully published, if

the original data sets were available with information regarding the presence of decompensation of cirrhosis at baseline and if information regarding the development of decompensation of cirrhosis after randomization and regarding death was available or could be obtained.

Studies with any of the following characteristics were excluded: nonrandomized or observational, those including patients with previous bleeding, restricted to decompensated patients, to patients with portal thrombosis or with hepatocarcinoma or with end-stage liver disease, those treating with agents different to carvedilol (such as classical NSBBs, nitrates or statins) or with TIPS or sclerotherapy, those limited to less than 12 months of follow-up and those including patients with noncirrhotic PH (details in Supplementary-Appendix).

SEARCH STRATEGY AND DATA-COLLECTION PROCESS

Comprehensive literature searches were performed in MEDLINE, PubMed, Embase, the Cochrane Collaboration Registry of Controlled Trials and the Cochrane Database of Systematic Reviews. We searched for published studies without language restrictions through February 2020. We used different terms and various combinations specified in the search details provided in Supplementary-Appendix, with a detailed description of search strategy.

Studies were initially selected by screening the titles and abstracts to identify those fulfilling the inclusion criteria, which were fully revised for eligibility. Principal investigators of trials meeting eligibility criteria were contacted to obtain individual patient data for all participants in their trials. Authors who did not respond to at least three contacts by different media (email, post-mail and

phone call) were deemed non-responders. At least two authors were contacted from each center. Original data from respondents were standardized (units, decimal places and data entry) and checked for completeness and consistency. Disparities in the data received were discussed with the original authors. Patient-level data were analyzed to extract baseline data on demographics, comorbidities, characteristics of liver disease, presence of present or previous decompensation at baseline and time-to-event outcomes during follow-up. Received data were converted into the same reporting format and aggregated into a single data set of IPD absolutely anonymized. The IPD set was compiled and centrally analyzed by the coordinating center. Full details of data collection process are provided in the Supplementary-Appendix.

OUTCOME MEASURES

The primary endpoints were the development of decompensation of cirrhosis during follow-up and mortality. Decompensation was defined by the development of ascites, gastrointestinal bleeding related to PH (i.e. due to esophageal or gastric varices or due to portal hypertensive gastropathy) or overt hepatic encephalopathy. Mortality was defined as death from any cause.

Secondary outcomes included the development of each complication included in the composite primary end-point (ascites, bleeding and overt encephalopathy), development of adverse events and liver-related death. Definitions are detailed in Supplementary-Appendix

STATISTICAL ANALYSIS

An IPD meta-analysis assessing time-to-event data was performed using the raw data from each study. All analyses were conducted according to the intention-to-treat principle by including all randomized patients from every single RCT, irrespective of whether they subsequently received the intended treatment. Categorical variables were expressed with frequencies and percentages. Continuous variables were expressed as means with standard deviation or as median and interquartile range (IQR: 25th-75th percentiles) in cases of a non-normal distribution.

To assess heterogeneity between groups for baseline covariates, standardized differences (STD) defined as differences between groups divided by pooled standard deviation, were investigated. The Inverse Probability of the Treatment Weights (IPTW) approach was used to balance the two groups across potentially confounding baseline covariates. Stabilized weights were calculated using propensity scores (PS) obtained from a logistic regression model aimed to minimize differences between arms. Covariate balance between groups was assessed before and after applying IPTW weights with the goal of achieving STD values <0.10 to define a non-relevant difference in potential confounders. The following covariates were included in the PS models: age, gender, cirrhosis etiology, MELD score, Child-Pugh class, presence of varices and baseline values of leukocytes, platelets, bilirubin, creatinine, albumin and BMI. Baseline categorical variables were compared using the chi-square test and continuous variables using ANOVA with rank-transformed data, for raw and IPTW adjusted analyses. Raw and IPTW weighted Cox regression models were used to

estimate risks. The treatment effect on the outcomes was estimated using a Cox proportional hazards regression model for competing-risk. In these analyses, the cumulative incidence function of the analyzed events was estimated in a competing-risk framework in which OLT was considered a competing event for death, and both OLT and death were considered competing events for decompensation and for decompensating events. Subdistribution hazard ratios (SHR) and 95% confidence intervals (95% CI) were estimated. The meta-analysis was conducted using a two-stage procedure, first estimating the risks by study with the IPTW competing-risk Cox models and then pooling them using random-effects model (detail in Suppl-Appendix). A prespecified assessment of the primary outcomes was also conducted, using competing-risk Cox regression models and performing uni and multivariable analyses, to adjust the effect of treatment for baseline potential confounders (detailed in the Suppl-Appendix). We had no missing data for primary and secondary outcomes and baseline covariates were described with no imputation. For the propensity score analysis with baseline covariates, we handled missingness by first converting continuous data into terciles and then assigning to missing observations of any variable an additional indicator category before inclusion in the multivariable logistic model.

Heterogeneity was evaluated using the I^2 and the Q heterogeneity test. Values of I^2 >50% were interpreted as meaningful heterogeneity. Q heterogeneity test were considered significant when p-values were <0.1.

Prespecified subgroup analyses were planned to assess the efficacy of carvedilol according to type of control therapy, liver function, cause of cirrhosis, presence of varices, and age. Subgroup analyses were calculated for the primary outcomes also using Cox regression models for competing-risk. To ascertain whether any variation in treatment effect across subgroups was consistent among the trials, we fitted three-way fixed interactions between trial, treatment and subgroup. We analyzed age, a continuous subgroup variable, by dividing the cohort into terciles.

All inferential analyses including tables and figures were IPTW weighted, except for the analysis of predictive factors or when otherwise specified. Statistical analysis was performed with SAS version 9.4 (SAS Institute Inc.,Cary,NC,USA) and the level of signification was established at two-sided 5%.

RESULTS

Figure1 shows a flowchart of the study selection process. Twelve RCTs comparing carvedilol with a control arm were eligible.(7,14-17,20-26) Of these, 8 studies with one or more exclusion criteria were excluded (Supplementary-tableS1).(17,20-26) IPD were requested and obtained from the remaining four RCTs, which were included in this aggregate data meta-analysis.(7,14-16) Only IPD of patients with compensated cirrhosis was requested from these studies. Patients with any previous decompensation were not included.

CHARACTERISTICS OF STUDIES INCLUDED

The characteristics of the studies included are reported in Supplementary-TableS2. All trials had two study arms comparing carvedilol with a control therapy, which was placebo in 2 studies (7,15) and EVL in 2 studies.(14,16) One single-blind RCT included patients with small esophageal varices without previous bleeding, aiming to assess whether carvedilol as compared to placebo prevented progression to large varices.(15) One double-blind RCT included compensated patients with CSPH confirmed by HVPG and without varices or with small varices, to assess whether β-blockers as compared to placebo prevented decompensation of cirrhosis.(7) In this study patients were stratified according to their hemodynamic response to intravenous propranolol, randomizing responders to be treated with propranolol or placebo and non-responders to be treated with carvedilol or placebo. Only patients of the stratum treated with carvedilol or placebo were included in this meta-analysis.(7) Two unblinded RCTs allocated patients with large esophageal varices, without

previous bleeding, to be treated with carvedilol or with EVL.(14,16) Carvedilol was administered up to 12.5 mg/day in 2 studies (14,16) and up to 25 mg/day in 2 studies (7,15). The mean follow-up in the RCTs included ranged from 13 to 36 months.

Methodological quality indices of included RCTs are reported in Supplementary-TableS3. All the trials included had an adequate generation of allocation sequence and adequate allocation concealment. Baseline characteristics of the carvedilol and the control groups were balanced in each RCT.

IPD DATA SET

The final IPD data set was built without exclusions, since information on decompensation of cirrhosis at baseline and development of primary and secondary end-points was obtained for all the patients included. The meta-analysis included individual data of 352 patients, 181 treated with carvedilol and 171 controls (92 of them treated with placebo and 79 treated with EVL). There were no major differences in baseline characteristics between patients treated with carvedilol and controls (Table1). With the IPTW approach, the STD was always ≤10% (Table1). The median dose of carvedilol was 12.5 mg/d (IQR, 12,5-18,75). Carvedilol was withdrawn in 14 patients (8%) due to side-effects or non-compliance.

HVPG measurements were performed in 2 studies,(7,15) in both at baseline and after 1-year of follow-up. In a post-hoc analysis, HVPG decreased in patients treated with carvedilol but not in controls and the proportion of patients

with a hemodynamic response was greater in carvedilol-group than in control-group (Supplementary-TableS4).

PRIMARY OUTCOMES

DECOMPENSATION OF CIRRHOSIS

Decompensation of cirrhosis occurred in 34 of 171 patients (20%) in the control-group and in 20 of 181 patients (11%) in the carvedilol-group, during 270 and 331 person-years of follow-up respectively (Figure2A). The risk of developing decompensation was significantly lower in the carvedilol-group than in controls (SHR= 0.506, 95%CI= 0.289 to 0.887; P= 0.017), without heterogeneity between trials (Q-statistic= 0.880; I^2= 0.0%, 95%CI= 0.0%-31.5%). The difference favoring carvedilol remained unchanged after adjusting for baseline risk factors (SHR= 0.466, 95%CI= 0.268-0.813; P= 0.007) (Supplementary-TableS5). The trial sequential analysis also indicated strong evidence favoring carvedilol (Suppl-Appendix). The cumulative incidence of decompensation was significantly lower in the carvedilol-group than in controls (Figure3A).

The benefit of therapy with carvedilol was consistent across exploratory subgroups reflecting liver function, etiology of cirrhosis, presence of varices, age and type of control therapy (Figure4A).

In a post-hoc analysis, in the overall series of patients (either treated with carvedilol or controls) the cumulative incidence of decompensation was lower in patients who at 1-year had an had an HVPG decrease greater than 10% from

baseline or to less than 10 mm Hg than in patients without such decreases (SHR=0.32, 95%CI=011-0.99) (Supplementary-TableS6).

SURVIVAL

Death occurred in 20 of 171 patients (12%) in the control-group and in 11 of 181 patients (6%) in the carvedilol-group, during 291 and 353 person-years of follow-up respectively (Figure2B). The risk of death was significantly lower in the carvedilol-group than in controls (SHR= 0.417, 95%CI= 0.194 to 0.896; P= 0.025), without heterogeneity between trials (Q-statistic= 0.989; I^2= 0.0%, 95%CI= 0.0%-0.0%). The difference favoring carvedilol remained unchanged after adjusting for baseline risk factors (SHR= 0.417, 95%CI= 0.202-0.858; P= 0.017) including Child-Pugh class and etiology of cirrhosis (Table3). The trial sequential analysis also indicated strong evidence favoring carvedilol (Suppl-Appendix). The cumulative incidence of death was lower in the carvedilol group than in the control group (Figure3B).

The risk of liver-related death was also significantly lower in the carvedilol-group than in the control-group (SHR= 0.320, 95%CI= 0.134-0.762; P= 0.010), without heterogeneity between trials (Table 2). It occurred in 18 of 171 patients (10%) in the control-group and in 8 of 181 patients (4%) in the carvedilol-group. In 16 of these 26 patients (61%) death occurred after decompensation. A breakdown of death causes is provided in the Supplementary-tableS7.

The survival benefit of therapy with carvedilol was consistent across exploratory subgroups reflecting liver function, etiology of cirrhosis, presence of varices, age and type of control therapy (Figure4B).

SECONDARY OUTCOMES

Ascites was the most frequent decompensating event occurring during follow-up (Figure5A,B). Ascites occurred in 28 patients (16%) in the control-group vs 13 (7%) in the carvedilol-group (Table 2). The risk of developing ascites was significantly lower in the carvedilol-group than in controls (SHR= 0.491, 95%CI= 0.247 to 0.974; P= 0.042), without heterogeneity between trials (Q-statistic= 0.384; I^2= 0.0%, 95%CI= 0.0%-45.8%).

Gastrointestinal bleeding related to portal-hypertension and overt hepatic encephalopathy were much less frequent than ascites (Figure5A,B). Bleeding occurred in 18 patients (11 of the control-group). The risk of bleeding was slightly lower in the carvedilol group than in the control group (SHR=0.496, 95%CI=0.186-1.324; P= 0.162), with significant Q heterogeneity test (Table2). Encephalopathy occurred in only 9 patients (3 of the control-group), with a similar risk in both groups (SHR=2.047, 95%CI=0.595-7.040; P= 0.256) and with significant Q heterogeneity test (Table2).

Overall, side-effects were more common in the carvedilol-group than in the control-group (HR=3.08, 95%CI=1.53-6.21; P= 0.002) (Table2). However, the risk of developing major side-effects was similar in both groups (HR=1.96, 95%CI=0.78-4.91; P= 0.153), without heterogeneity between trials (Table2). Supplementary-TableS8 provides a detailed description of side effects.

Figures in the Supplementary-Appendix show risk and cumulative incidence of each secondary outcome.

DISCUSSION

The present study shows that, in compensated cirrhosis, long-term treatment with carvedilol can prevent decompensation, mainly by decreasing the incidence of ascites. Even more importantly carvedilol significantly improved survival. This has been shown by conducting an IPD meta-analysis, relaying on the collaborative use of individual patient data from multiple studies and centers, which has allowed an optimized statistical strategy. This may constitute a landmark study since up to now no therapy is recommended to prevent the decompensation of cirrhosis and no therapy has shown a survival benefit in patients with compensated cirrhosis.(3,27,28) Decompensated cirrhosis entails multiple hospitalizations and carries a marked decline in life expectancy.(1,3) Consequently, preventing decompensation can offer a great clinical benefit and may have a marked impact on healthcare burden and costs all over the world, particularly considering the low cost of carvedilol.

Indeed, we observed that long-term therapy with carvedilol significantly reduces the risk of developing hepatic decompensation in patients at risk as indicated by the presence of CSPH. Previously, some studies have shown benefit with carvedilol in patients with CSPH,(14,15,29) while other studies failed to show efficacy.(16,17) The present IPD meta-analysis has succeeded in gathering a large amount of data, which likely helped to demonstrate the overall efficacy of carvedilol in compensated cirrhosis. This is certainly a relevant strength of the present study. Furthermore, IPD analysis incorporating exclusively trials with random assignment also confers robustness and strength to the results by avoiding biases related to confounding by indication. In addition, performing a meta-analysis relying on IPD has also allowed assessing decompensating

events and survival using a time-to-event and competing-risk approach, properly approaching cirrhosis as a multistage disease and outcomes as time-depending events. Moreover, IPD analysis has allowed controlling for covariates thus further reducing bias risk.

This study shows that benefit favoring carvedilol is mainly due to a decreased likelihood of developing ascites, which is the most common complication occurring in compensated cirrhosis and is associated with a worsening of survival.(1,27) This beneficial effect is likely related to an improvement in PH we observed with carvedilol. Previous studies have shown that, in cirrhosis with PH an effective reduction of portal pressure such as that achieved with portal-systemic shunt procedures or in patients with HVPG-response to NSBBs, markedly improves the control of ascites.(27,30-32) Furthermore, the PREDESCI study has shown that long-term sustained decrease in PH translate into an almost 50% reduction in the risk of developing ascites in compensated cirrhosis with CSPH.(7) Our results are in concordance with these data. This reinforce the concept that carvedilol may change the paradigm in compensated cirrhosis by offering the possibility of preventing ascites, with no preventive therapy previously available.(1,27) In addition, our study shows a significant and pronounced improvement of survival in compensated patients favoring carvedilol. This constitutes a hallmark issue since no survival benefit has been previously demonstrated with NSBBs in compensated cirrhosis. In cirrhosis, death is frequently liver-related and occurs mainly after developing decompensation.(1,3,7) In keeping with this, our study also shows a significant improvement in liver-related mortality favoring carvedilol, with the majority of deaths occurring after decompensation. This strongly suggests that the

beneficial effect of carvedilol on survival may be largely related to the impact on preventing decompensation.

Data from our study support the concept that efficacy with carvedilol may be largely related to the effect on PH. We observed a significant decrease in HVPG with carvedilol, not observed in controls, and that patients with a substantial HVPG-decrease had a marked improvement in decompensation risk and in survival. This is in keeping with previous observational studies suggesting that patients with good hemodynamic response achieve maximal benefit.(32) All the patients included in this IPD-meta-analysis had compensated cirrhosis with CSPH and most had varices. The portal-pressure decreasing effect of NSBBs is particularly pronounced in such patients.(4) It is much less marked before developing CSPH, when hyperdynamic circulation is poorly developed,(4) and is also less pronounced once decompensation occurs.(33) Moreover, due to its anti-α-adrenergic activity and to an enhanced intrahepatic release of NO, carvedilol decrease intra-hepatic vascular resistance,(11,12) which is a key factor leading to PH in compensated cirrhosis.(7,13) Indeed, this confers to carvedilol a greater portal-pressure decreasing effect than classical NSBBs and allows achieving hemodynamic response in previous non-responders to propranolol.(9,10,34) Furthermore, the PREDESCI study showed a trend towards better outcomes and better adherence to therapy with carvedilol than with propranolol in compensated patients.(7) In addition to the effect on portal pressure, experimental studies suggest that carvedilol may also have pleiotropic actions such as anti-oxidant properties and may improve fibrosis and inflammation.(35,36) All these effects may account for the benefits we observed

favoring carvedilol in compensated cirrhosis. Whether traditional NSBBs may be as effective as carvedilol in these patients require further investigation.

Despite the beneficial effect of carvedilol on ascites, we did not observe benefit regarding other decompensating events, such as portal-hypertensive bleeding or encephalopathy. In the RCTs included in this IPD-meta-analysis, most patients with high-risk varices in control groups were treated with EVL to prevent bleeding.(14,16) The efficacy of EVL to achieve this goal is well documented and is similar to that of NSBBs.(5,6) Very likely, this influenced the results. Concerning encephalopathy, in addition to PH, other mechanisms on which carvedilol has little or no effect, such as portal-systemic shunting, may influence its development. On the other hand, and in keeping with previous studies,(7,10) we observed an acceptable safety profile with carvedilol in patients with compensated cirrhosis. Certainly, in our study the overall incidence of side-effects was higher with carvedilol than in controls. However, the incidence of severe side-effects was similar in the two groups and there were no deaths related to complications.

IPD-meta-analysis allowed to preplan a subgroup analysis, showing that the benefit of carvedilol was consistent across the prespecified subgroups reflecting etiology of cirrhosis, severity of liver dysfunction, age and type of control therapy used. Such benefit appears more pronounced in patients with varices than in those without, although the small sample size in the subgroup without varices precludes drawing conclusions. The subgroup analysis also showed that, even when EVL was used as a control therapy, carvedilol decreased the risk of overall decompensation, likely due to its effect on ascites since the effect on bleeding was similar with both therapies. This unique advantage afforded by

carvedilol in preventing ascites should be considered when advising therapy for compensated patients with high-risk varices. Hopefully, large ongoing RCTs may further clarify these issues (NCT03776955, ISRCTN73887615).

The present study has several limitations. Not all the RCTs included were double-blind,(14,16) which may have introduced bias. However, they all had correct randomization techniques thus minimizing such possibility and ensuring the overall quality of the data. In addition, we used an IPTW approach to balance for baseline covariates and we performed random mixed-effects regression analyses of IPD, thus further reducing the risk of bias. A potential limitation of IPD-analyses can derive from inconsistency defining end-points among trials, and decompensation was not an end-point in some of the studies included. However, the current primary end-points are objective and robust (i.e. cirrhosis decompensation and survival) and when initially lacking, information on decompensation could be reliably retrieved in every single case, thus clearly minimizing such a potential limitation. Moreover, IPD-analyses remain vulnerable to sources of bias such as those related to the likelihood of publication or data availability.(37) These possibilities were minimized by performing a rigorous systematic review searching multiple sources, using strict eligibility criteria and carefully seeking individual data from every identified RCT, finally succeeding to obtain all the IPD requested from eligible studies. Of course, our results cannot be applied to patients with decompensated cirrhosis. Given potential for causing systemic hypotension, carvedilol should be cautiously used in these patients and its value in this setting needs specific investigation.

In conclusion, this study shows that, in patients with compensated cirrhosis and CSPH, long-term therapy with carvedilol significantly decreases the risk of decompensation of cirrhosis mainly by reducing the risk of developing ascites, which is the most frequent decompensating event. Even more importantly, the study shows that carvedilol improves survival in compensated patients. Altogether our findings support screening patients with compensated cirrhosis for CSPH, which nowadays can be done noninvasively quite confidently, using techniques such as liver stiffness combined with platelet count,(28) in order to start therapy with carvedilol. This may prevent the progression of compensated cirrhosis to decompensation significantly improving survival and reducing the healthcare burden and cost of managing these patients.

Abbreviations: **BMI:** body mass index, **CI**: confidence interval, **CO**: cardiac output, **CSPH**: clinically significant portal hypertension, **EVL:** endoscopic variceal ligation, **FU**: follow-up, **HBV**: hepatitis B virus, **HCV**: hepatitis C virus, **HVPG**: hepatic venous pressure gradient, **INR**: international normalized ratio, **IPD:** individual participant data, **IPTW:** Inverse Probability of the Treatment Weights, **IQR:** interquartile range, **MELD**: model for end stage liver disease, **NASH:** nonalcoholic steatohepatitis, **NSBB**: non-selective β-blockers, **NO:** nitric oxide, **OLT**: ortothopic liver transplantation, **PH**: portal hypertension, **PS:** propensity score, **RCT:** randomized controlled trial, **SD:** standard deviation, **SHR**: subdistribution hazard ratio, **STD:** standardized differences.

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TABLE 1. Baseline characteristics of patients according to treatment groups

	RAW				IPTW			
	Carvedilol (N= 181)	**Control** (N= 171)	**P-value**	**STD**	**Carvedilol**	**Control**	**P-value**	**STD**
Male Sex (%)	139 (77)	131 (77)	0.967	0.4%	141 (78)	128 (75)	0.471	7.7%
Age, yr (IQR)	53 (45-60)	51 (44-59)	0.237	13.4%	52 (45-60)	51 (44-60)	0.822	3.2%
Cause of cirrhosis (%) Alcohol HCV HBV Others	 51 (28) 65 (36) 12 (7) 53 (29)	 39 (23) 75 (44) 19 (11) 38 (22)	0.107	25.3%	 45 (25) 73 (41) 16 (9) 46 (26)	 41 (24) 70 (41) 15 (9) 45 (26)	0.998	2.8%
Active alcohol intake (%)	43 (24)	37 (22)	0.635	5.1%	40 (22)	40 (23)	0.823	2.4%
Child-Pugh class (%) Class A Class B Class C [NMD]	 111 (61) 57 (32) 13 (7) [5]	 112 (65) 51 (30) 8 (5) [9]	0.429	15.1%	 112 (62) 53 (29) 15 (9)	 111 (65) 50 (29) 10 (6)	0.609	8.7%
Child-Pugh score (IQR) [NMD]	6.0 (5.0-7.0) [5]	6.0 (5.0-7.0) [9]	0.644	2%	6.0 (5.0-7.0)	6.0 (5.0-7.0)	0·719	5.8%
MELD score (IQR) [NMD]	8.2 (6.4-11.0) [24]	8.5 (6.9-11.0) [10]	0.972	3.5%	8.5 (6.4-11.7)	8.3 (6.9-11.0)	0.596	3%
Albumin, G/L (IQR) [NMD]	36 (30-40) [12]	34 (30-41) [28]	0.925	3.5%	36 (30-40)	36 (31-41)	0.728	6.9%
Bilirubin, mg/L (IQR) [NMD]	1.4 (1.0-2.3) [12]	1.5 (1.1-2.2) [32]	0.983	2.6%	1.4 (1.1-2.3)	1.4 (0.9-2.2)	0.407	3.3%
Prothrombin time, INR (IQR) [NMD]	1.2 (1.1-1.4) [7]	1.2 (1.1-1.4) [24]	0.949	1.6%	1.2 (1.1-1.4)	1.2 (1.1-1.4)	0.898	2.0%
Creatinine, mg/dL (IQR) [NMD]	0.8 (0.7-0.9) [20]	0.8 (0.6-1.0) [24]	0.576	2.3%	0.8 (0.7-0.9)	0.8 (0.6-1.0)	0.919	0.1%
Na, mEq/L (IQR) [NMD]	140 (138-142) [50]	141 (139-142) [39]	0.843		140 (137-141)	141 (139-142=	0.15	
Hemoglobin, G/L (IQR) [NMD]	126 (110-139) [38]	124 (108-137) [35]	0.773	1.4%	126 (112-138)	125 (110-139)	0.975	3.0%
Platelet, $x10^3$ (IQR) [NMD]	100 (75-150) [40]	99 (63-145) [40]	0.361	3.7%	99 (75-141)	100 (65-146)	0.834	5.1%
Leukocytes, $x10^3$ (IQR) [NMD]	5.1 (4.0-7.2) [40]	4.8 (3.5-6.5) [41]	0.128	16.2%	5.0 (3.9-6.8)	4.9 (3.6-6.5)	0.397	10.2%
Esophageal varices (%)	172 (95)	159 (93)	0.418	8.6%	166 (92)	160 (94)	0.430	8.5%
Large varices (%) *	104 (57)	102 (60)	0.653	16.4%	102 (57)	99 (58)	0.933	8.2%
Red Signs on varices (%) † [NMD]	5 (3) [17]	6 (3) [19]	0.799	8.1%	6 (3)	5 (3)	0.995	0%
Gastric varices (%) ‡ [NMD]	32 (18) [16]	31 (18) [13]	0.914	3.6%	34 (19)	30 (18)	0.876	8.7%
Weight, Kg (IQR) § [NMD]	74.2 (66.0-89.0) [49]	76.0 (69.0-84.7) [39]	0.915	9.7%	71.5 (66.0-82.5)	76.0 (68.0-85.0)	0.549	10.3%
Body mass index (IQR) [NMD]	27.5 (24.7-32.2) [49]	26.8 (24.5-30.1) [40]	0.501	20.9%	26.0 (24.7-30.8)	26.8 (24.3-31.6)	0.632	8.2%

LEGEND FOR TABLE 1:
HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NMD, number of missing data; STD, standardized differences.
STD, are absolute (i.e. ignoring arithmetic sign). No missing data (MD) unless otherwise specified in brackets [NMD].

* Large varices, defined as those not flattened by insufflation.
† Presence of red signs presence on the variceal wall.
‡ Patients with esophageal and fundal varices.

TABLE 2. Primary and secondary end-points by IPD with IPTW and competing risk meta-analysis (*)

	Carvedilol † (N=181)	**Control †** (N=171)	**SHR (95%CI) ‡**	**P-value**	**Q-statistic**	**I^2(95%CI) %**
Decompensation §						
Overall	20 (11) / 8 [8/0]	34 (20) / 13 [11/2]	0.506 (0.289-0.887)	0.017	0.670	0.0 (0.0-31.5)
Ascites	13 (7) / 11 [10/1]	28 (16) / 17 [12/5]	0.491 (0.247-0.974)	0.042	0.384	0.0 (0.0-45.8)
Bleeding	7 (4) / 10 [9/1]	11 (6) / 18 [16/2]	0.496 (0.186-1.324)	0.162	0.041	0.0 (0.0-0.0)
Encephalopathy	6 (3) / 9 [9/0]	3 (2) / 24 [18/6]	2.047 (0.595-7.040)	0.256	0.001	0.0 (0.0-0.0)
Death ¶						
Overall, *OLT as CE*	11 (6) / 1 [0/1]	20 (12) / 6 [0/6]	0.417 (0.194-0.896)	0.025	0.116	0.0 (0.0-0.0)
Death or OLT, *Unrelated death as CE* ‖	12 (7) / 3 [3/0]	26 (15) / 2 [2/0]	0.379 (0.175-821)	0.014	0.116	0.0 (0.0-0.0)
Liver-related *Unrelated death & OLT as CE*	8 (4) / 4 [3/1]	18 (11) / 8 [2/6]	0.320 (0.134-0.762)	0.010	0.239	0.0 (0.0-0.0)
Side effects **						
Overall	66	43	3.08 (1.53-6.21) ††	0.002	0.484	0.0 (0.0-85.6)
Severe	20	11	1.96 (0.78-4.91) ††	0.153	0.704	0.0 (0.0-70.4)

LEGEND FOR TABLE 2:
CE, competing events; OLT, orthotopic liver transplantation; SHR, subdistribution hazard ratio, CI, confidence interval.

* The table shows the pooled values.
† Descriptive statistics are events (%) / number of competing-events [death/OLT] when applicable
‡ Values indicate SHR in patients treated with carvedilol as compared to controls.
§ By competing-risk analysis (death & OLT as CE).
¶ By competing-risk analysis (competing events as specified).
‖ Death after OLT only occurred in one patient (of the control group).
** By IPTW non-competing risk. Carvedilol was withdrawn in 12 patients (7%) due to side-effects (N=9) or non-compliance (N=3). In the two studies comparing carvedilol vs placebo (1 double-blind and 1 single-blind), carvedilol was withdrawn in 6/96 patients (6%) and placebo in 4/92 (4%).
†† Values are HR (95%CI).

TABLE 3. Uni- and Multivariate competing-risk regression analysis to assess parameters related to death (liver-transplant as competing events)

	SURVIVAL (N= 321)	**DEATH** (N= 31)	**Univariate Analysis** SHR (95%CI)*	P value†	**Multivariate Analysis** SHR (95%CI)‡	P value§
Age (IQR)	52 (43-60)	51 (45-64)	0.92 (0.41-2.03)	0.148		
Gender male (%)	228 (76)	42 (78)	0.82 (0.35-0.89)	0.643		
MELD score (IQR) [NMD]	9.2 (6.4-10.9) [34]	10.8 (7.6-13.9) [0]	1.05 (1.01-1.09)	0.016		
Child-Pugh class, B-C (%) [NMD]	111 (35) [14]	18 (58) [0]	2.89 (1.43-5.87)	0.003	3.32 (1.63-6.76)	<0.001
Child-Pugh score (IQR) [NMD]	6 (5-7) [14]	7 (6-9) [0]	1.46 (1.22-1.75)	<0.001		
Etiology alcohol	75 (24)	15 (48)	2.21 (1.12-4.37)	0.022	2.58 (1.30-5.12)	0.007
Albumin, G/L (IQR) [NMD]	36 (31-41) [40]	31 (25-35) [0]	0.90 (0.86-0.95)	<0.001		
Bilirubin, mg/L [NMD]	1.4 (1.0-2.3) [44]	1.8 (1.2-2.6) [0]	1.09 (1.02-1.18)	0.010		
Prothrombin time, INR [NMD]	1.2 (1.1-1.4) [30]	1.2 (1.1-1.6) [1]	4.19 (1.2-10.78)	0.003		
Creatinine, mg/dL [NMD]	0.8 (0.6-1) [47]	0.8 (0.6-1) [1]	0.89 (0.56-1.42)	0.633		
Hemoglobin, G/L [NMD]	126 (109-138) [62]	116 (108-136) [11]	0.99 (0.97-1.01)	0.226		
Platelet count, $x10^3$ [NMD]	100 (68-150) [69]	95 (79-140) [11]	0.99 (0.98-1.01)	0.776		
Leukocytes count, $x10^3$ [NMD]	5.0 (3.8-6.6) [69]	5.2 (4.1-7) [12]	0.99 (0.86-1.16)	0.985		
Esophageal varices	302 (94)	29 (93)	1.28 (0.30-5.57)	0.738		
Treat with Carvedilol (%)	170 (53)	11 (35)	0.048 (0.23-0.99)	0.046	0.42 (0.21-0.86)	0.017
Control Tx with EVL	68 (21)	11 (35)	1.98 (0.96-4.07)	0.065		

LEGEND FOR TABLE 3:
CI, confidence interval; EVL, endoscopic variceal ligation; IQR, interquartile range; NMD, number of missing data; SHR, sub-distribution hazard ration. No missing data (MD) unless otherwise specified in brackets [NMD].

* Values indicate the hazard ratio of death for each characteristic shown in rows.
† Comparison by competing-risk regression (liver-transplant as competing events).
‡ Comparison of risk by competing-risk multivariate regression (liver-transplant as competing events).

FIGURE LEGENDS

<u>Figure 1.</u> FLOWCHART OF THE IPD-META-ANALYSIS

Flowchart of studies in the systematic review following PRISMA guideline and recommendation.

* 12 studies comparing carvedilol with a control arm in patients with cirrhosis and without previous variceal bleeding were eligible (Ref.7,14-17,20-26).

† 5 studies including arms treated with classical NSBBs were excluded (Ref.17,21-24). Three studies had 2 treatment arms (carvedilol vs propranolol: Ref.21,23,24), and two studies also include an arm treated with EVL (Ref.17,22). In addition: one study included patients with previous variceal bleeding (Ref.23), one study only included patients with cirrhosis and portal thrombosis (Ref.24), three studies had a follow-up of 12 months or less (Ref. 17,21,22) and three studies only were published as abstracts (21,23,24).

‡ One study comparing carvedilol plus EVL vs EVL alone, which also included patients with previous bleeding and only published as abstract, was excluded (Ref.25).

§ One study randomizing patients to carvedilol vs EVL for prevention of first variceal bleeding apparently included only decompensated patients, since presence of ascites was required to define cirrhosis and only patient with cirrhosis were included. Furthermore, the follow-up apparently was of only 6 months. The authors did not reply to the request to clarify. The study was excluded (Ref.20).

¶ One study which was not a RCT and gad a follow-up of 12 months, was excluded (Ref.26).

<u>Figure 2.</u> FOREST PLOTS OF THE PRIMARY END-POINTS

Summary of events and Forest-plots of the primary end-point by IPD with IPTW and competing-risk meta-analysis. Descriptive statistics are events (competing-events) / pooled nº of patients [person-years]. In the Forest-plots, squares represent the SHR and horizontal lines indicate the 95% CIs. Panel A, shows the risk of decompensation of cirrhosis with death and liver transplant as competing events. Panel B, shows mortality risk with liver transplant as a competing event.

<u>Figure 3.</u> CUMULATIVE INCIDENCE OF THE PRIMARY END-POINTS ACCORDING TO TREATMENT GROUP

Panel A shows the cumulative incidence of decompensation of cirrhosis in the two groups, considering death and OLT as competing events. Panel B shows the cumulative incidence of death in the two groups, considering OLT as a competing event.

<u>Figure 4.</u> SUBGROUPS ANALYSES OF PRIMARY END-POINTS

Exploratory subgroup analyses of the IPTW matched data are displayed as forest plots. Primary outcomes were used as dependent variable on categorized competing-risk regression models. Interactions of exploratory subgroup were tested using the subgroup-defining variable and treatment with or without

carvedilol as independent variables. Descriptive statistics are events (competing events) / pooled nº of patients [person-years]. In the Forest-plots, squares represent the SHR and horizontal lines indicate the 95% CIs, and the vertical dashed lines indicate the overall pooled estimate. Panel A shows the subgroup analysis for decompensation, considering death and OLT as competing events. Panel B shows the subgroup analysis for death, considering OLT as a competing event. For both outcomes, the benefit favoring carvedilol was consistent across exploratory subgroups. It was less evident in patients without varices, although the sample size in this subgroup was small.

Figure 5. CUMULATIVE INCIDENCE OF DECOMPENSATING EVENTS AND OF COMPETING EVENTS

Decompensating events were analyzed by competing risk regression models considering death and OLT as competing events. Figure shows the cumulative incidence of each decompensating event (ascites, bleeding and encephalopathy) and of competing events (death and OLT), for patients in the control-group (left panel) and for patients in the carvedilol-group (right panel). Ascites was the most frequent decompensating event in both groups.

FIGURE 1

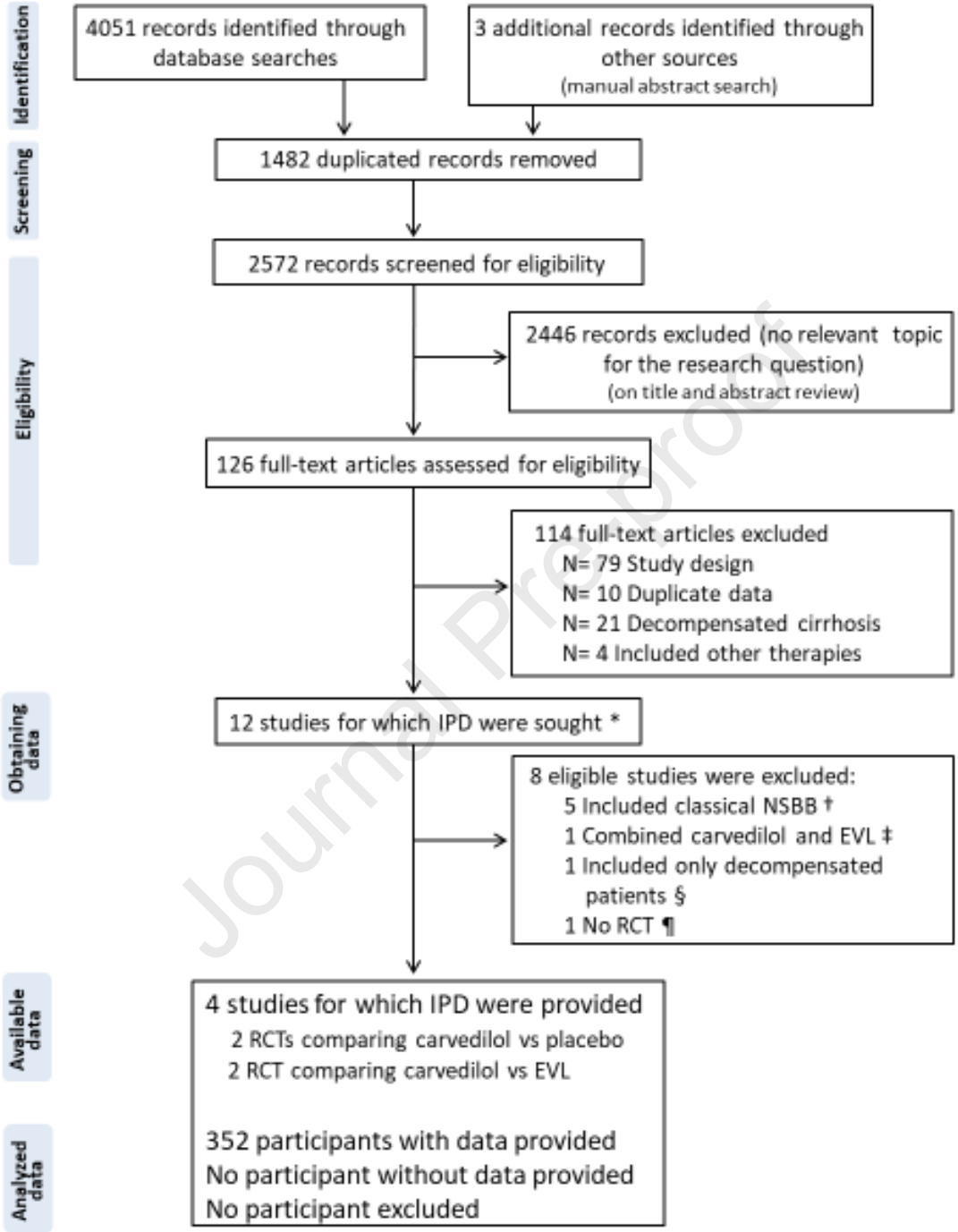


FIGURE 2

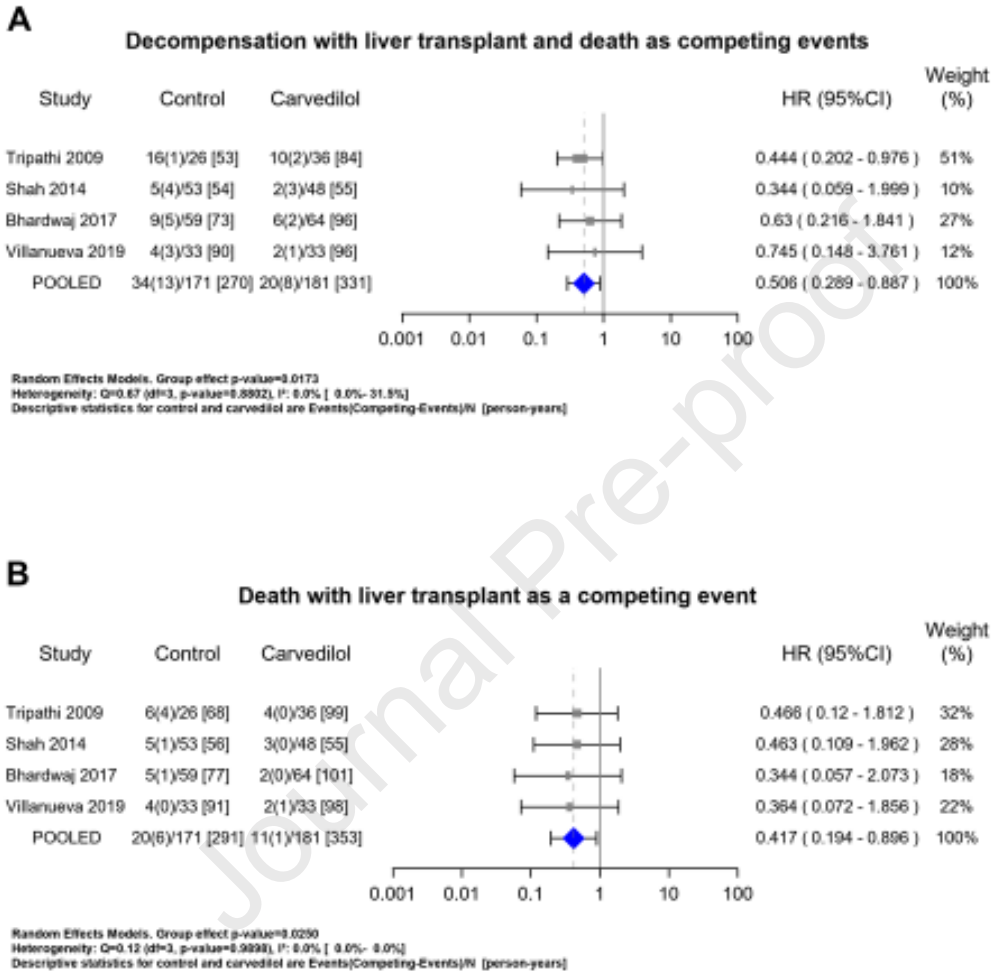


FIGURE 3

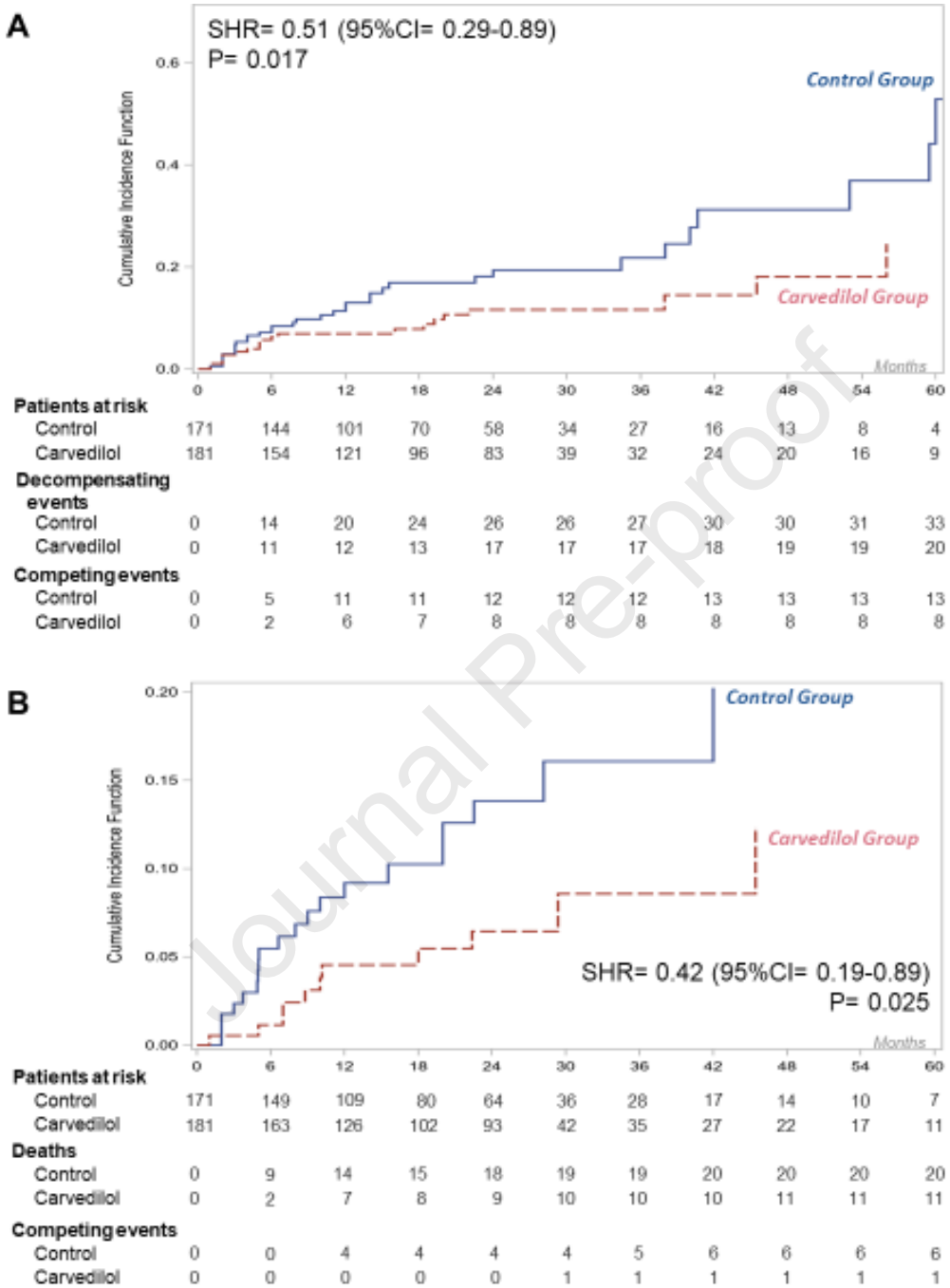
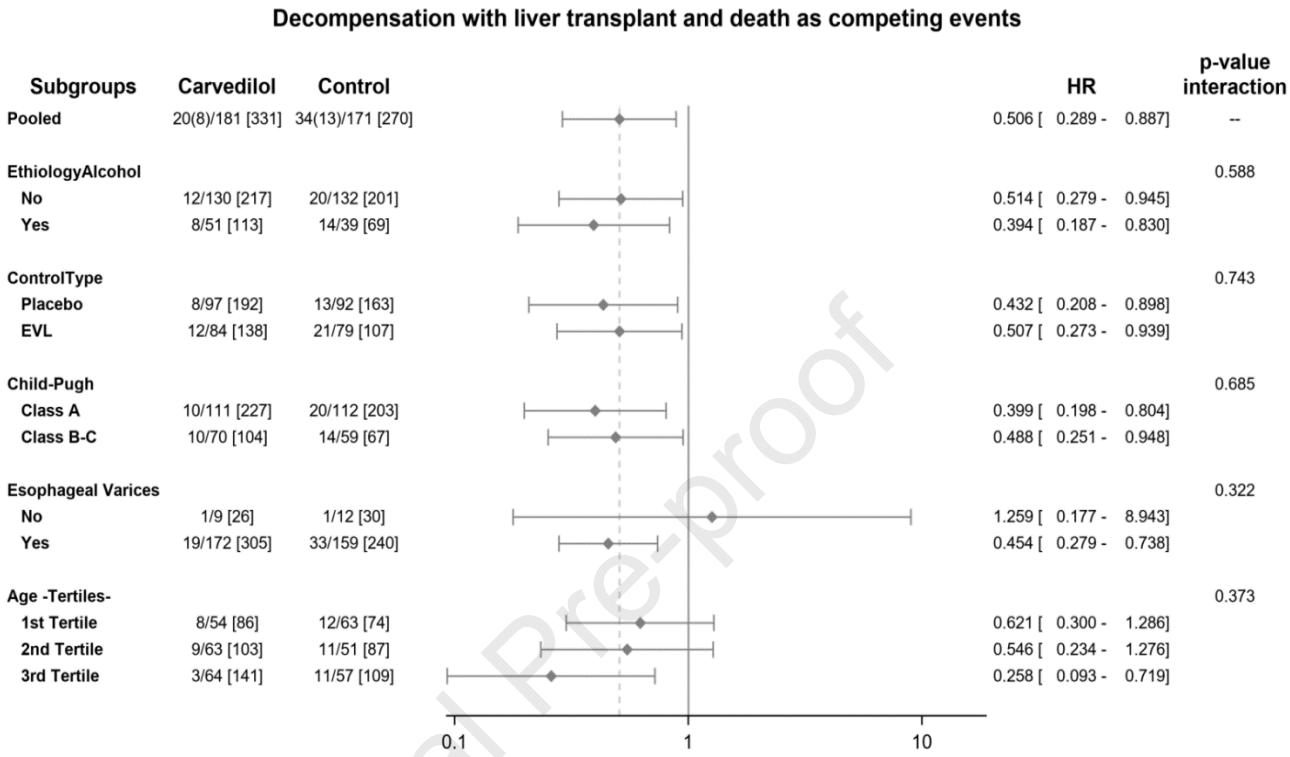


FIGURE 4

A



B

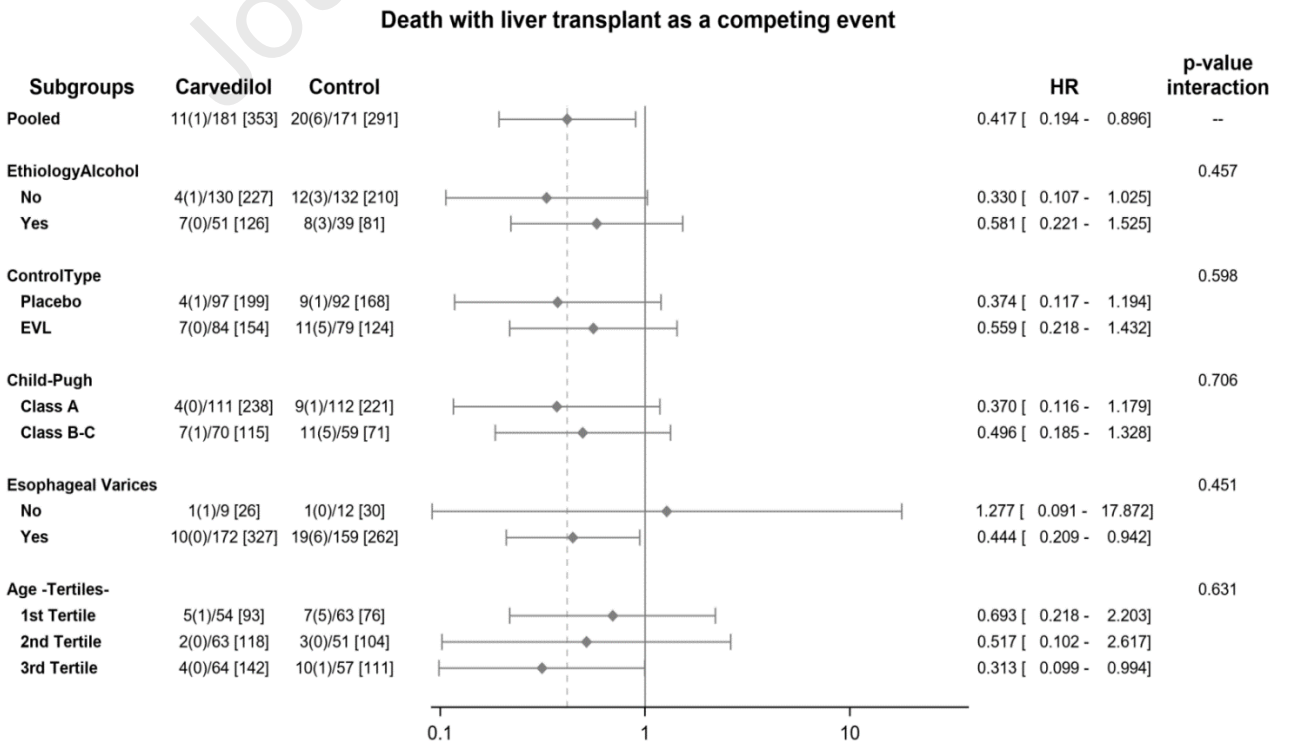
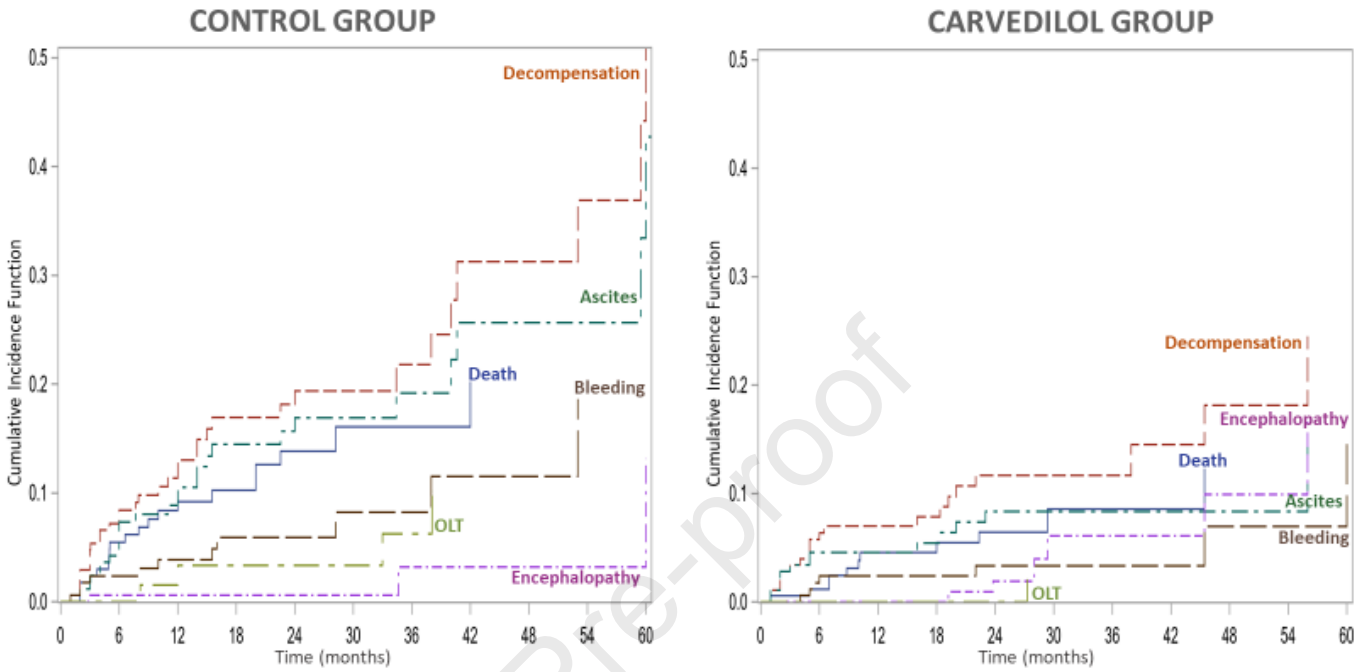


FIGURE 5



HIGHLIGHTS

* Portal hypertension is a main determinant of the progression of cirrhosis from compensated to decompensation. The potential effect of NSBB to prevent decompensation should be clarified. Carvedilol might be particularly useful since its intrinsic vasodilatory activity may ameliorate hepatic vascular resistance, a major mechanism of portal hypertension in compensated cirrhosis.

* Carvedilol significantly decreases the risk of decompensation in patients with cirrhosis and CSPH, mainly by reducing the likelihood of developing ascites.

* Even more importantly, carvedilol significantly improve survival in compensated patients.

* Our findings suggest that screening patients with compensated cirrhosis for CSPH to start therapy with carvedilol, can prevent the progression of compensated cirrhosis to decompensation.