β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial

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Summary

Background Clinical decompensation of cirrhosis is associated with poor prognosis. Clinically significant portal hypertension (CSPH), defined by a hepatic venous pressure gradient (HVPG) ≥10 mm Hg, is the strongest predictor of decompensation. This study aimed at assessing whether lowering HVPG with β blockers could decrease the risk of decompensation or death in compensated cirrhosis with CSPH.

Methods This study on β blockers to prevent decompensation of cirrhosis with portal hypertension (PREDESCI) was an investigator-initiated, double-blind, randomised controlled trial done in eight hospitals in Spain. We enrolled patients with compensated cirrhosis and CSPH without high-risk varices. All participants had HVPG measurements with assessment of acute HVPG-response to intravenous propranolol. Responders (HVPG-decrease ≥10%) were randomly assigned to propranolol (up to 160 mg twice a day) versus placebo and non-responders to carvedilol (≤25 mg/day) versus placebo. Doses were individually determined during an open-label titration period after which randomisation was done with 1:1 allocation by a centralised web-based system. The primary endpoint was incidence of cirrhosis decompensation (defined as development of ascites, bleeding, or overt encephalopathy) or death. Since death in compensated cirrhosis is usually unrelated to the liver, an intention-to-treat analysis considering deaths unrelated to the liver as competing events was done. This study is registered with ClinicalTrials.gov, number NCT01059396. The trial is now completed.

Findings Between Jan 18, 2010, and July 31, 2013, 631 patients were evaluated and 201 were randomly assigned. 101 patients received placebo and 100 received active treatment (67 propranolol and 33 carvedilol). The primary endpoint occurred in 16 (16%) of 100 patients in the β blockers group versus 27 (27%) of 101 in the placebo group (hazard ratio [HR] 0·51, 95% CI 0·26–0·97, p=0·041). The difference was due to a reduced incidence of ascites (HR 0·42, 95% CI 0·19–0·92, p=0·03). The overall incidence of adverse events was similar in both groups. Six patients (four in the β blockers group) had severe adverse events.

Interpretation Long-term treatment with β blockers could increase decompensation-free survival in patients with compensated cirrhosis and CSPH, mainly by reducing the incidence of ascites.

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Introduction

Liver cirrhosis evolves over time from a compensated to a decompensated stage, defined by the occurrence of ascites, variceal haemorrhage or hepatic encephalopathy.[1] The decompensation of cirrhosis determines a markedly declined life expectancy.[2] Portal hypertension is the main determinant of decompensation.[1,3] A portal pressure ≥10 mm Hg, usually estimated by the hepatic venous pressure gradient (HVPG), defines clinically significant portal hypertension (CSPH) as both varices and decompensation might appear after reaching this threshold.[3]

In patients with CSPH and large varices, non-selective β blockers effectively prevent variceal bleeding and reduce bleeding-related mortality.[4,5] However, in the timolol-trial[6] β blockers were ineffective in preventing the development of varices in compensated cirrhosis with or without CSPH. β blockers lower portal pressure by decreasing portal venous inflow, which in CSPH is increased because of hyperdynamic circulation.[7] Patients with compensated cirrhosis and CSPH have more advanced hyperdynamic circulation than do those without CSPH.[8] This finding is associated with much greater HVPG reduction by β blockers in patients with CSPH than in those without.[8] These observations suggest that β blockers might prevent decompensation in patients with CSPH, who were precisely those at risk of developing varices and decompensation in the timolol trial.[6]

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Research in context

Evidence before this study
Liver cirrhosis evolves over time from a compensated to a decompensated stage, which is associated with a marked decline in life expectancy. Portal hypertension (PH) is the main determinant of the progression to clinical decompensation, defined by the occurrence of ascites, bleeding, or encephalopathy. A portal pressure gradient ≥10 mm Hg defines clinically significant PH (CSPH), since decompensation might appear after reaching this threshold. Indeed, CSPH is the strongest predictor of clinical decompensation. Non-selective β blockers (NSBB) lower portal pressure by decreasing portal venous inflow, which is increased in patients with CSPH, but much less in those without CSPH, in whom the response to NSBB is almost negligible. We searched PubMed, Embase and the Cochrane Library (Feb 28, 2018), for clinical trials evaluating drug therapies to prevent decompensation of cirrhosis, without language or date restrictions. We used the terms "compensated cirrhosis", "prevent decompensation", "prevent ascites", "prevent bleeding", "prevent encephalopathy", and "β-blockers". We identified numerous randomised controlled trials and meta-analyses showing that NSBB effectively prevent first variceal bleeding. Only one randomised controlled trial evaluated whether NSBB could prevent the development of varices in compensated cirrhosis, but this study failed to demonstrate any beneficial effect. This negative result might have been due to the fact that part of the patients included had no CSPH, and therefore were very unlikely to respond to NSBB and to develop decompensation. On the other hand, current European (Baveno VI) and American Association for the Study of Liver Diseases (AASLD) recommendations indicate that the aim of treatment of portal hypertension in patients with compensated cirrhosis should be to prevent decompensation, rather than focusing only on variceal bleeding. However, no randomised controlled trial with this endpoint has been conducted so far. The present cooperative, double-blind randomised controlled trial aimed at investigating whether long-term treatment of patients with compensated cirrhosis and CSPH with NSBB might prevent progression to clinical decompensation or death.

Added value of this study
The present double-blind randomised controlled trial is the first study showing that long-term treatment with NSBB decreases approximately by half the risk of clinical decompensation or liver-related death. This is mainly due to a decreased likelihood of developing ascites, which is the most common and severe decompensating event, for which previously there was no effective preventive drug therapy. As a likely explanation of the beneficial effects of therapy, the study shows that NSBB, but not placebo, significantly reduced the portal pressure gradient at each yearly control.

Implications of all the available evidence
Our finding that in patients with compensated cirrhosis and CSPH continued therapy with NSBB significantly reduces the incidence of decompensation or death represents a landmark innovation in the management of patients with cirrhosis. It has important implications in clinical practice, suggesting that patients with compensated cirrhosis should be screened for development of CSPH, and that therapy with NSBB should be started from its detection, which nowadays can be done quite confidently using non-invasive tools, such as transient elastography (alone or associated with platelet count or spleen diameter measurements). This new indication of NSBB might have a major impact on patients' outcomes, health-care burden and costs, which would likely influence future clinical guidelines. Future research should confirm that it is indeed possible to accurately detect CSPH in patients with compensated cirrhosis using simple non-invasive methods, and further define specific biomarkers of response to therapy.

The present study aimed at assessing whether, in patients with compensated cirrhosis and CSPH, long-term treatment with β blockers might prevent disease progression to clinical decompensation or death.

Methods
Study design
The study on β blockers to prevent decompensation of cirrhosis with portal hypertension (PREDESCI) was an investigator initiated, randomised, double-blind, placebo-controlled, multicentre clinical trial. Eligible patients had a haemodynamic study to measure portal pressure, estimated by the HVPG. Only patients with baseline HVPG ≥10 mm Hg were included. Acute HVPG response to β blockers was evaluated 20 min after intravenous propranolol (0·15 mg/kg). Patients with decreasing HVPG >10% from baseline were considered

responders, and were randomly assigned to receive propranolol or placebo. Non-responders were randomly assigned to receive carvedilol or placebo.

The oral dose of β blockers (or placebo) to be used during the study was individually determined during an open-label titration period. HVPG responders received propranolol starting with 40 mg twice a day increased up to 160 mg twice a day. Non-responders received carvedilol, starting with 6·25 mg/day and increased up to 25 mg/day. The dose was titrated against clinical tolerance, keeping heart rate above 55 beats per min and systolic blood pressure greater than 90 mm Hg, without repeating HVPG measurements. The titration periods lasted up to 3 weeks and patients were randomly assigned once the daily dose of β blocker had been determined. The study was approved by the Spanish Ministry of Health and by the institutional review board at each investigational site.

Participants

Patients were enrolled at eight hospitals in Spain from Jan 18, 2010 to July 31, 2013. Follow-up was planned until Oct 31, 2016. Patients with cirrhosis aged between 18 and 80 years inclusive, without any previous decompensation of cirrhosis and without high-risk oesophageal varices (ie, no varices or small varices without red signs), who gave written informed consent were considered for inclusion. Cirrhosis was diagnosed on the basis of previous biopsy or compatible clinical, biochemical, and ultrasonographic findings. Varices were investigated by gastroscopy and absence of ascites by ultrasound (both performed within 3 months pre-randomisation). Written informed consent was obtained from all patients.

Patients were excluded for any of the following criteria: previous decompensation of cirrhosis, absence of CSPH, portal thrombosis, hepatocellular carcinoma, baseline bilirubin greater than 3 mg/dL or platelets less than 30×10^3 or international normalised ratio of prothrombin time greater than 2·7 (Quick prothrombin time test <30%), renal failure (creatinine >2 mg/dL), comorbidity with life expectancy less than 12 months, contraindication or hypersensitivity to β blockers, previous treatment with β blockers or nitrates, anticoagulant treatment, active antiviral therapy for hepatitis C, pregnancy, or lactation.

Randomisation and masking

Once the dose of β blockers (or placebo) to be used during the study had been determined, patients were randomly assigned to active therapy or placebo. Randomisation was performed in a 1:1 ratio by a centralised web-based system with double-blinded assignment through an electronic code which was computer-generated in fixed random permuted blocks of ten and stratified according to the acute haemodynamic response to β blockers and to the participating centre. For each centre, blocks were created for the stratum propranolol–placebo and for the stratum carvedilol–placebo. The preparation of the study medication, containing the formulation of either active β blocker or matched placebo, was centralised in one of the participating study centres and was performed by investigational pharmacists who had access to the randomisation code through a password protected website. The pills prepared by the investigational pharmacists with active therapy or with placebo were identical in appearance and organoleptic properties and were administered in a double-blinded fashion.

Procedures

After random assignment, patients were seen at months 1 and 3, and then every 6 months, investigating occurrence of endpoints and adverse events. Extra visits were allowed in case of events. At each visit, heart rate, pill count, occurrence of adverse events as assessed by the investigators, and alcohol consumption were determined. Adjustment of the medication dose was allowed in the follow-up controls by increasing or decreasing the number of pills. To maintain study blinding, heart rate was measured by a study nurse and not by the investigators who remained unaware. Only in case of extreme values in repeated measurements was it planned to contact the investigator. Adherence to the study drug was assessed on the basis of pill counts in dispensed boxes and was considered adequate with counts greater than or equal to 70% and poor with counts less than 30%. Patients who failed a planned visit were contacted by telephone or email. Patients who discontinued the study drug were also contacted.

Treatment was considered to have failed and was discontinued when a patient reached the primary endpoint. In patients developing high-risk varices, endoscopic ligation was performed and treatment was continued. No preventive therapy for ascites (eg, diuretics) or for encephalopathy (eg, lactulose) was allowed before development of decompensation. Data collection was continued until the end of the study for all the patients included.

Every 6 months, blood samples were obtained for haematological and biochemical measurements and ultrasonography was performed. Upper endoscopy and haemodynamic studies were performed every year. Haemodynamic studies were performed following the recommended standards (appendix). Portal pressure was measured as the HVPG (the difference between wedged and free HVP). All intravascular pressure measurements were performed in triplicate. Permanent recordings of tracings were obtained. Cardiopulmonary pressures and cardiac output were measured.

See **Online** for appendix

Since the rate of events observed during the first years of study was lower than expected, an amendment of the initial protocol was introduced on Feb 15, 2013 to extend the follow-up. According to clinical guidelines no patient received antivirals for hepatitis-C during the study. However, guidelines changed during the trial owing to newly licensed direct-acting antivirals.[9] Accordingly, to allow antiviral therapy without interfering in the assessment of the study medication, the study was finished in June, 2015, once Spain's Ministry of Health approved treatment of patients with cirrhosis, instead of October, 2016 as planned.

Outcomes

The primary outcome measure was decompensation of cirrhosis or death. Decompensation was defined as appearance of ascites, gastrointestinal bleeding related to portal hypertension, or overt hepatic encephalopathy. Since in compensated cirrhosis, mortality before decompensation is mostly non-liver-related,[10] a competing-risk framework was predefined considering decompensation and liver related deaths as primary outcomes and non-liver related deaths as competing events.

Secondary outcomes included the development of each complication of portal hypertension individually (ascites, gastrointestinal bleeding, and overt hepatic
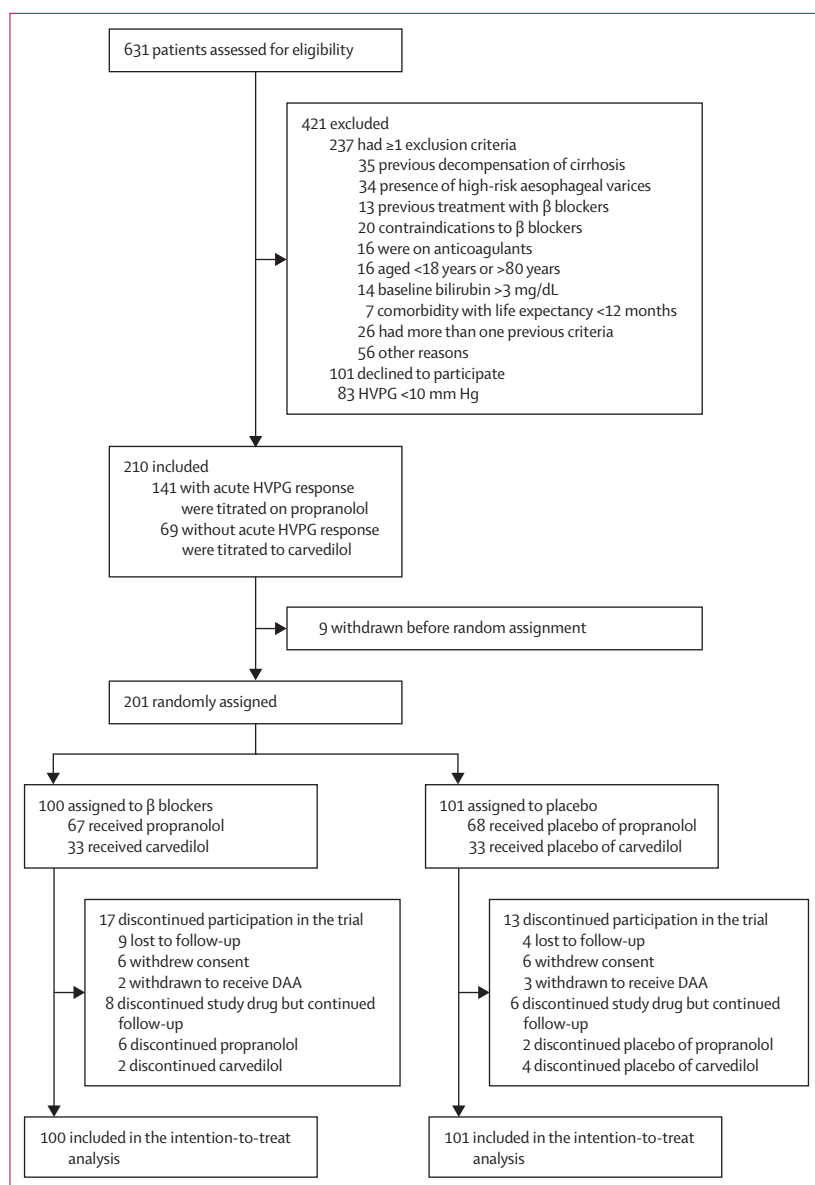
Figure 1: Study profile
HVPG=hepatic venous pressure gradient. DAA=direct acting antiviral.

encephalopathy), development of spontaneous bacterial peritonitis and other bacterial infections, development of varices and of high-risk varices, changes in hepatic dysfunction assessed by Child-Pugh and model for end-stage liver disease scores, development of hepatocellular carcinoma, adverse events, and survival.

Gastrointestinal bleeding was defined as any episode of haematemesis or melaena, or both and was evaluated by endoscopy. Variceal bleeding was diagnosed according to Baveno criteria.[4] Ascites was defined by compatible signs on examination and was confirmed by ultrasonography or paracentesis. Intraperitoneal fluid only detectable by ultrasonography or the sole presence of ankle oedema was not considered an end point. Refractory ascites,

hepatorenal syndrome, spontaneous bacterial peritonitis, and overt hepatic encephalopathy were diagnosed according to guidelines.[11] Encephalopathy was defined according to West Haven criteria as signs and symptoms compatible to grade greater than II. Varices were diagnosed by endoscopy and were classified as large (not flattened by insufflation) or small (flattened by insufflation). Large varices and small varices with red wale marks or occurring in patients with Child-Pugh class C, were considered as high-risk varices according to Baveno criteria.[4]

Adverse events were defined as any event requiring diagnostic or therapeutic intervention. All adverse events, regardless of their possible association with study treatment, were recorded. An adverse event was judged severe if it was considered to endanger the health or safety of the patient.

Statistical analysis

Sample size was calculated assuming a 2-year decompensation risk of 25% in untreated compensated cirrhosis with CSPH on the basis of previous studies,[3] and estimating a 15% absolute risk-reduction (to 10%), as observed in compensated patients with HVPG-response to β blockers in prophylactic studies.[12] Using a two-tailed test with an α value of 0·05 and β value of 0·2, and accounting for a 5% loss to follow-up, 105 patients were required in each group.

Statistical analysis was done according to general regulatory recommendations,[13] and according to an intention-to-treat strategy (appendix). Categorical variables were compared with Fisher's exact test and continuous variables with the Student's t test (for paired data within each group). The Wilcoxon rank-sum test was used for skewed or ordinal data. Continuous variables measured repeatedly over time were analysed by the mixed-models repeated measure.

The primary and secondary outcomes were analysed as time-to-event variables, considering the stratum according to acute response to β blockers. Hazard ratios (HRs) and 95% CI were estimated. Since in compensated cirrhosis, death is frequently due to non-liver related causes,[10] a competing-risk analysis was predefined considering non-liver related deaths as competing events.[13,14] Probabilities were estimated with the use of cumulative incidence functions and comparisons relied on Gray's test. Data were censored at the time of death, liver transplantation, last visit, or end of follow-up period, whichever occurred earliest. Patients who received a liver transplant were censored as alive. Patients lost to follow-up, those who withdrew consent, and those who were withdrawn to receive antiviral therapy were censored as if they had not developed any outcome after the last visit documented. Cox models were used to compare the two study groups with respect to the primary endpoint, adjusting for baseline risk factors (Child-Pugh, cause of cirrhosis, and baseline HVPG). When required, survival function was estimated by means of the Kaplan-Meier method and

	Placebo group (n=101)	β-blockers group (n=100)
Baseline characteristics		
Sex		
Male	64 (63%)	59 (59%)
Female	37 (37%)	41 (41%)
Age (years)	59 (11)	60 (10)
Cause of cirrhosis		
Alcohol	14 (14%)	19 (19%)
Hepatitis C virus	59 (58%)	54 (54%)
Alcohol and hepatitis C virus	8 (8%)	9 (9%)
NASH	8 (8%)	5 (5%)
Others	12 (12%)	13 (13%)
Diabetes	21 (21%)	22 (22%)
Dyslipidaemia	15 (15%)	12 (12%)
Arterial hypertension	34 (34%)	45 (45%)
Child-Pugh class		
A	81 (80%)	80 (80%)
B	20 (20%)	20 (20%)
C	0	0
Child-Pugh score	5·8 (0·9)	5·7 (0·9)
Model for end-stage liver disease score	6·8 (0·3)	6·6 (0·3)
Oesophageal varices*		
None	43 (43%)	44 (44%)
Small	58 (57%)	56 (56%)
Gastric varices†	1 (1%)	2 (2%)
Portal-systemic collaterals by ultrasound‡	11 (11%)	18 (18%)
Splenomegaly§	67 (66%)	56 (56%)
Liver stiffness, kPa¶	30·4 (16)	28·7 (13)
Weight, kg	76 (16)	76 (15)
BMI, kg/m²	27 (5)	27 (4)
(Table 1 continues in next column)		

	Placebo group (n=101)	β-blockers group (n=100)
(Continued from previous column)		
Procedural characteristics		
Duration of follow-up (months)		
Mean	37 (16)	36 (16)
Median (IQR)	37 (27–47)	37 (26–47)
Lost to follow-up‖	4 (4%)	9 (9%)
Abstinence from alcohol**	88 (87%)	82 (82%)
Development of portal thrombosis	5 (5%)	3 (3%)
Liver transplantation††	1 (1%)	3 (3%)
Randomised to propranolol (or identical tablets of placebo)		
Number of patients	68 (67%)	67 (76%)
Dose (mg/day)		
Mean	95 (81)	95 (76)
Median (IQR)	80 (40–90)	80 (40–120)
Withdrawal‡‡	2	6
Randomised to carvedilol (or identical tablets of placebo)		
Number of patients	33 (33%)	33 (33%)
Dose (mg/day)		
Mean	20 (6)	19 (7)
Median (IQR)	18·8 (18·8–25)	18·8 (12·5–25)
Withdrawal§§	4	2

Values are mean (SD) or n (%), unless otherwise stated. NASH=non-alcoholic steatohepatitis. BMI=body-mass index. *None denotes absence of oesophageal varices on endoscopy and small varices denotes varices that were flattened by insufflation. †Patients with oesophageal and fundal varices (gastro-oesophageal varices type 2 according to Sarin's classification). ‡Among patients with portal-systemic collaterals, small oesophageal varices were present in 13 (72%) of 18 patients in the placebo group and in five (45%) of 11 in the β blockers group. §Spleen diameter >12 cm on ultrasound. ¶Liver stiffness by transient elastography. ‖For patients lost to follow-up, mean follow-up time in the placebo group was 18 months (IQR 14–24) and in the β-blockers group was 18 months (IQR 9–20). Ten (77%) of the 13 patients lost to follow-up had history of active or previous alcohol intake versus 78 (41%) of 188 who were not lost to follow-up; there were no other significant differences between patients lost and not lost to follow-up. **In the placebo group 17 (77%) of the 22 patients with alcoholic cause of cirrhosis (14 alcohol only and eight alcohol plus hepatitis C virus) were abstinent, as compared with 15 (54%) of the 28 patients with alcoholic cause of cirrhosis in the β-blockers group (19 alcohol, nine alcohol plus hepatitis C virus). ††In the placebo group one patient received an orthoptic liver transplant at month 39 from inclusion and in the β-blockers group three patients received an orthoptic liver transplant between month 27 and 48 from inclusion. Previous decompensation of cirrhosis occurred in the four patients who received a liver transplantation (all had ascites and three of them also had encephalopathy). Two of them (one in the placebo group) also developed a hepatocellular carcinoma. ‡‡Withdrawal of placebo or propranolol (due to side-effects or non-compliance) occurred in two patients of the placebo group after a median period of 22 months (IQR 18–34) and in six patients of the β blockers group after a median period of 26 months (15–30). §§Withdrawal of placebo or carvedilol (due to side-effects or non-compliance) occurred in four patients of the placebo group after a median period of 24 months (IQR 19–37) and in two patients of the β blockers group after a median period of 28 months (21–33).

Table 1: Baseline and procedural characteristics

event rates of endpoints were compared by use of the stratified log-rank test for the time to the first event after randomisation.

Prespecified subgroup analyses were planned to assess the efficacy of therapy according to liver function, cause of cirrhosis, presence of varices, and baseline HVPG. Calculations were performed with the SAS-9.4 statistical package. An independent Data Safety Monitoring Board committee over saw the study. This study is registered with ClinicalTrials.gov, number NCT01059396 and EUDRACT 2009-010396-25.

Role of the funding source

Results
Between Jan 18, 2010, and July 31, 2013, 631 patients with compensated cirrhosis were screened, 320 were excluded, and 101 declined to participate (figure 1, table 1). The median length of follow-up was 37 months (IQR 27–47). 13 patients were lost to follow-up: most of them had a history of alcohol intake (table 1). Adherence
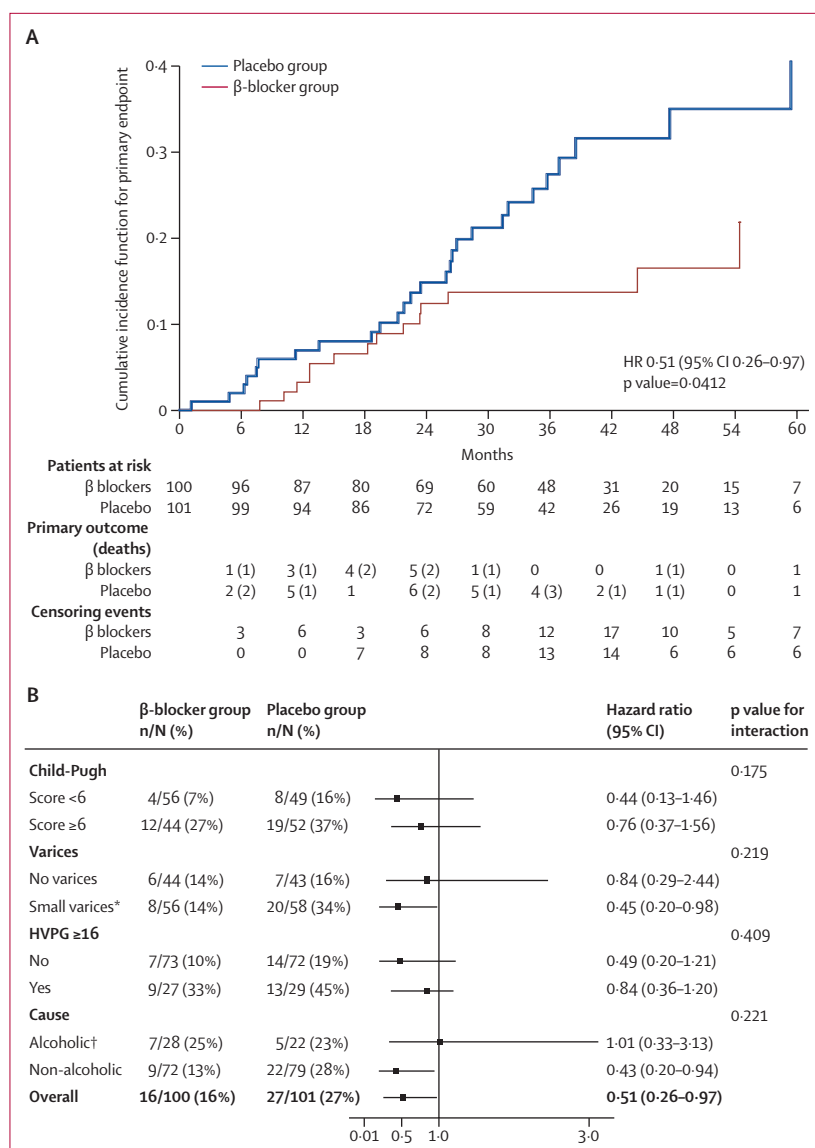
Figure 2: Primary endpoint (decompensation or death) according to treatment group
(A) Cumulative incidence. (B) Forest plots. Benefit of β-blockers therapy was consistent across prespecified subgroups and seemed particularly pronounced in patients with small varices and in patients with non-alcoholic cirrhosis. *Risk of primary endpoint was greater in patients with small varices than in those without varices (HR 1·67, 95% CI 1·00–3·34). †In the subgroup of patients with alcoholic cirrhosis, in a post-hoc analysis adjusting for abstinence the HR was 1·02 with 95% CI 0·31–3·34.

100 in the β-blockers group. The cumulative incidence of decompensation or death during follow-up was significantly lower in the β-blockers group than in the placebo group (HR 0·51, 95% CI 0·26–0·97; p=0·041 by Gray's test, figure 2), and remained unchanged after adjusting for baseline risk factors (0·47, 95% CI 0·25–0·91; p=0·025). The difference was largely due to a significantly reduced incidence of ascites which occurred in 20 patients (20%) in the placebo group and in nine (9%) in the β-blockers group (HR 0·42, 95% CI 0·19–0·92, p=0·03 by Gray-test). The benefit of therapy with β blockers was consistent across prespecified subgroups and was particularly pronounced in patients with small varices and in patients with non-alcoholic cirrhosis (figure 2). The primary endpoint occurred in 9 of the 33 patients (27%) treated with placebo of carvedilol and in 3 of the 33 (9%) treated with active carvedilol (HR 0·39, 95% CI 0·10–1·49; p=0·16), and occurred in 18 of the 68 patients (26%) treated with placebo of propranolol and in 13 of the 67 (19%) treated with active-propranolol (HR 0·69, 0·34–1·38; p=0·29).

Baseline haemodynamic parameters were similar in both groups (table 2). Patients in the β-blockers group had a significant degree of β blockade, not observed in patients in the placebo group. This was shown by significant decreases in heart rate and cardiac index at all assessments throughout follow-up in the β-blockers group (table 2). Mean arterial pressure decreased mildly and similarly in both groups and cardio-pulmonary pressures increased slightly with β blockers.

HVPG was significantly decreased at each yearly assessment during follow-up in patients in the β-blockers group whereas it did not change with placebo (table 2). Except at baseline, HVPG values were lower in the β-blockers group than in the placebo group in each yearly control. The average reduction of HVPG from baseline in the β-blockers group was 11% (2·1). In post-hoc analyses, the proportion of patients with an HVPG decrease greater than or equal to 10% from baseline at 1 year was higher in the β-blockers group than in the placebo group (40 [51%] of 78 vs 23 [29%] of 78, p=0·0088), as well as the proportion of patients with an HVPG decrease greater than or equal to 20% (28 [36%] of 78 vs 13 [17%] of 78, p=0·010). At 1 year, the HVPG was less than 10 mm Hg in 19 (24%) of 78 patients in the β-blockers group versus 13 (17%) of 78 in the placebo group (p=0·32), and was less than 12 mm Hg in 41 (53%) of 78 cases in the β-blockers group versus 28 (36%) of 78 in the placebo group (p=0·053). Carvedilol decreased the HVPG more than propranolol, despite being given to non-responders to intravenous propranolol, with significantly higher percentage decreases at 12 months (16% [3·7%] vs 10% [2·8%], p=0·036) and 24 months (15% [4·2%] vs 9% [3·4%], p=0·048).

More than two-thirds of patients developing high-risk varices received oesophageal variceal ligation (table 3). Since this ligation could influence the incidence of

to treatment was considered adequate in 83 (82%) of 100 patients in the β blockers group (30 [91%] of 33 treated with carvedilol and 53 [79%] of 67 treated with propranolol) and 83 (83%) in the placebo group. Adherence was poor in two (2%) patients in the β-blockers group versus four (4%) in the placebo group. The study medication was withdrawn in eight patients in the β-blockers group after a median period of 27 months (IQR 15–33) and in six patients in the placebo group after a median period of 23 months (18–37).

Decompensation or death occurred in 27 patients (27%) of 101 in the placebo group and in 16 (16%) of

	Baseline	12 months follow-up	24 months follow-up	36 months follow-up	p values*
Patients†					
β blockers	100/100	78/88	44/69	22/40	..
Placebo	101/101	78/87	42/69	25/46	..
Hepatic venous pressure gradient					
Absolute values, mm Hg	..	..	..	..	p_{treat}<0·001; $p_{treat*time}$=0·075; p_{time}=0·98; $p_{stratum}$=0·94
β blockers	14·5 (14 to 15)	12·8 (12 to 14)	13·0 (12 to 14)	12·9 (12 to 14)	..
Placebo	14·8 (14 to 16)	15·0 (14 to 16)	14·9 (14 to 16)	14·6 (13 to 16)	..
Change from baseline, %					
β blockers	..	−12 (−15 to −8)	−10 (−12 to −5)	−10 (−15 to −4)	..
Placebo	..	1·5 (−2 to 5)	1·2 (−3 to 6)	−0·9 (−6 to 5)	..
Cardiac output					
Absolute values, L/min	..	..	..	..	p_{treat}=0·049; $p_{treat*time}$=0·056; p_{time}=0·86; $p_{stratum}$=0·50
β blockers	6·0 (5·6 to 6·5)	5·3 (4·8 to 5·7)	5·4 (4·9 to 5·9)	5·5 (4·9 to 6·1)	..
Placebo	5·9 (5·5 to 6·4)	5·9 (5·5 to 6·4)	5·7 (5·1 to 6·1)	5·9 (5·3 to 6·5)	..
Change from baseline, %					
β blockers	..	−12 (−15 to −7)	−8 (−13 to −2)	−7 (−13 to −1)	..
Placebo	..	0·6 (−3 to 4)	−5 (−11 to −1)	−0·3 (−6 to 6)	..
Cardiac index					
Absolute values, L/min per m²	..	..	..	..	p_{treat}=0·010; $p_{treat*time}$=0·074; p_{time}=0·29; $p_{stratum}$=0·58
β blockers	3·4 (3·1 to 3·6)	2·9 (2·7 to 3·2)	2·9 (2·7 to 3·3)	3·0 (2·7 to 3·4)	..
Placebo	3·2 (3·0 to 3·4)	3·5 (3·2 to 3·8)	3·2 (2·8 to 3·5)	3·2 (2·9 to 3·6)	..
Change from baseline, %					
β blockers	..	−15 (−21 to −7)	−11 (−19 to −3)	−10 (−20 to 0)	..
Placebo	..	11 (4 to 18)	−3 (−14 to 4)	−2 (−12 to 8)	..
Mean arterial pressure					
Absolute values, mm Hg	..	..	..	..	p_{treat}=0·007; $p_{treat*time}$=0·227; p_{time}=0·28; $p_{stratum}$=0·70
β blockers	98 (95 to 100)	92 (89 to 95)	92 (89 to 96)	95 (91 to 99)	..
Placebo	96 (93 to 98)	91 (88 to 94)	92 (88 to 95)	93 (88 to 97)	..
Change from baseline, %					
β blockers	..	−5 (−7 to 2)	−5 (−8 to −2)	−2 (−6 to 2)	..
Placebo	..	−3 (−5 to −1)	−2 (−5 to 1)	−2 (−5 to 2)	..
Heart rate					
Absolute values, beats per min	..	..	..	..	p_{treat}=<0·001; $p_{treat*time}$=0·80; p_{time}=0·004; $p_{stratum}$<0·001
β blockers	74 (72 to 76)	61 (59 to 64)	62 (59 to 65)	60 (57 to 64)	..
Placebo	73 (71 to 75)	72 (69 to 74)	69 (65 to 72)	71 (67 to 74)	..
Change from baseline, %					
β blockers	..	−16 (−19 to 14)	−16 (−18 to −12)	−17 (−21 to −13)	..
Placebo	..	−1 (−3 to 1)	−5 (−7 to −2)	−3 (−6 to 1)	..
Pulmonary artery pressure					
Absolute values, mm Hg	..	..	..	..	p_{treat}=0·81; $p_{treat*time}$=0·97; p_{time}=0·08; $p_{stratum}$=0·67
β blockers	16·5 (15 to 18)	17·3 (16 to 19)	18·6 (17 to 20)	21·6 (19 to 24)	..
Placebo	16·5 (15 to 18)	17·0 (15 to 18)	18·7 (17 to 21)	17·0 (15 to 19)	..
Change from baseline, %					
β blockers	..	7·5 (−1 to 16)	18 (5 to 29)	19 (17 to 21)	..
Placebo	..	5 (−3 to 13)	18 (5 to 31)	4 (−11 to 19)	..
Pulmonary wedge pressure					
Absolute values, mm Hg	..	..	..	..	p_{treat}=0·37; $p_{treat*time}$=0·89; p_{time}=0·35; $p_{stratum}$=0·10
β blockers	8·8 (8 to 10)	10·3 (9 to 11)	10·9 (9 to 12)	13·4 (11 to 15)	..
Placebo	9·7 (9 to 11)	10·0 (9 to 11)	10·6 (9 to 12)	10·1 (8 to 12)	..
Change from baseline, %					
β blockers	..	35 (21 to 53)	66 (39 to 93)	81 (46 to 117)	..
Placebo	..	13 (−7 to 32)	29 (1 to 57)	22 (−11 to 56)	..

(Table 1 coninues on next page)

	Baseline	12 months follow-up	24 months follow-up	36 months follow-up	p values*
(Continued from previous page)					
Right atrial pressure					
Absolute values, mm Hg	..	..	..	..	p_{treat}=0·94; $p_{treat*time}$=0·44; p_{time}=0·066; $p_{stratum}$=0·64
β blockers	5·6 (5 to 6)	6·1 (5 to 7)	7·0 (6 to 8)	8·2 (7 to 10)	
Placebo	6·4 (6 to 7)	6·5 (5 to 7)	6·8 (6 to 8)	6·6 (5 to 8)	
Change from baseline, %					
β blockers	..	45 (12 to 78)	87 (45 to 129)	103 (49 to 158)	
Placebo	..	24 (–8 to 55)	65 (20 to 110)	64 (21 to 117)	
Serum creatinine					
Absolute values, mg/100 mL	..	..	..	..	p_{treat}=0·35; $p_{treat*time}$= 0·47; p_{time}=0·61; $p_{stratum}$=0·44
β blockers	0·8 (0·5 to 1·1)	0·8 (0·5 to 1·1)	0·8 (0·5 to 1·1)	0·9 (0·6 to 1·4)	..
Placebo	1·1 (1·0 to 1·5)	0·9 (0·5 to 1·1)	0·8 (0·5 to 1·1)	0·8 (0·4 to 1·2)	..
Change from baseline, %					
β blockers	..	0·2 (–7 to 8)	0·5 (–4 to 10)	4 (–7 to 12)	..
Placebo	..	–4 (–16 to 7)	–4 (–17 to 8)	–3 (–14 to 8)	..
Weight					
Absolute values, kg	..	..	..	..	p_{treat}=0·072; $p_{treat*time}$=0·083; p_{time}=0·26; $p_{stratum}$=0·91
β blockers	76 (73 to 79)	77 (75 to 79)	77 (74 to 81)	78 (75 to 81)	..
Placebo	76 (73 to 80)	77 (75 to 79)	77 (74 to 80)	77 (74 to 80)	..
Change from baseline, %					
β blockers	..	2·3 (1 to 4)	1·7 (0·2 to 3)	2·9 (1 to 4)	..
Placebo	..	1 (–0·4 to 2)	1 (–0·6 to 2)	0·5 (–1·3 to 2)	..
Child-Pugh score					
Absolute values	..	..	..	..	p_{treat}=0·21; $p_{treat*time}$=0·63; p_{time}=0·020; $p_{stratum}$=0·023
β blockers	5·7 (5·5 to 5·9)	5·9 (5·7 to 6·1)	5·7 (5·5 to 5·9)	5·8 (5·4 to 5·9)	..
Placebo	5·8 (5·5 to 5·9)	5·8 (5·5 to 5·9)	5·7 (5·5 to 5·9)	5·9 (5·6 to 6·2)	..
Change from baseline, %					
β blockers	..	6 (3 to 10)	2 (–2 to 5)	3 (–2 to 6)	..
Placebo	..	2 (–1 to 5)	–1 (–3 to 2)	3 (–1 to 7)	..
Model for end-stage liver disease score‡					
Absolute values	..	..	..	..	p_{treat}=0·085; $p_{treat*time}$=0·56; p_{time}=0·35; $p_{stratum}$=0·11
β blockers	6·6 (5·9 to 7·3)	7·2 (6·5 to 7·9)	7·2 (6·4 to 8·1)	7·5 (6·6 to 8·5)	..
Placebo	6·8 (6·1 to 7·5)	6·1 (5·3 to 6·8)	6·5 (5·6 to 7·3)	7·8 (6·7 to 9·8)	..
Change from baseline, %					
β blockers	..	26 (–8 to 51)	19 (–18 to 55)	30 (–13 to 66)	..
Placebo	..	–11 (–27 to 42)	24 (–15 to 64)	68 (20 to 116)	..

Values are mean (95% CI). A second haemodynamic study at 1 year of follow-up was performed in 156 patients (86%) of the 181 remaining in the study. A third haemodynamic study at 2 years was performed in 86 patients (61%) of the 141 remaining in the study. A fourth study at 3 years was performed in 47 patients (52%) of the 90 remaining in the study. *p values from the mixed model for repeated measurements analysis for the terms treatment effect, treatment-by-time interaction, time effect, and randomisation stratum. p values for the baseline measurement term were always <0·001. †At each time period, haemodynamic studies and laboratory controls were performed in patients who remained in the study and accepted to repeat the procedure. In the β-blockers-group, 94 patients remained in the study at 1 year of follow-up, 72 at 2 years, and 42 at 3 years of follow-up. In the placebo group, 87 patients remained in the study at 1 year of follow-up, 69 at 2 years, and 48 at 3 years of follow-up. ‡Liver function was assessed at each time period by Child-Pugh score and model for end-stage liver disease score. During follow-up, these scores were available in patients remaining in the study, not in those with previous decompensation or death.

Table 2: Baseline and follow-up haemodynamic variables and liver and renal function

bleeding, we performed a post-hoc exploratory analysis excluding bleeding which showed a greater benefit favouring the β-blockers group. The primary outcome occurred in 14 patients (14%) of the β-blockers group and in 27 (27%) of the placebo group (HR 0·42, 95% CI 0·21–0·84; p=0·012 by Gray's test).

Thirty-six patients (24 treated with placebo) developed decompensation of cirrhosis and 13 of them died (nine treated with placebo). Six patients died without decompensation and in four of them (two treated with placebo) death was liver related. Two patients, both in the β-blockers group, died of non-liver related causes: one myocardial infarction and one haemorrhagic stroke. At death, both patients had compensated cirrhosis and preserved liver function (both were Child-Pugh class A and had a Model for End-stage Liver Disesase score <8). Such cardiovascular deaths are unlikely to be related to β blockers. Specific causes of death are provided (appendix). The four patients who received liver transplantation had decompensated previously (table 1).

Overall, in a post-hoc analysis HVPG decreased in patients surviving without decompensation (treated with either β blockers or placebo) but not in those developing the primary endpoint, with greater percentage changes at 12 months (–10% [1%] *vs* 3% [2%], p=0·001) and 24 months (–9% [2%] *vs* 1% [4%], p=0·020). In a post-hoc analysis, the cumulative incidence of the primary endpoint was lower in patients who at 1 year had an HVPG decrease greater than 10% from baseline or to less than 10 mm Hg than in patients without such decreases: 6 (9%) of 67 patients versus 26 (29%) of 89 patients (HR 0·32, 95% CI 0·13–0·75; p=0·0077).

The incidence of decompensation was lower in the β-blockers group than in the placebo group. Decompensation occurred in 12 patients (12%) of the β-blockers group and in 24 (24%) of the placebo group (HR 0·49, 95% CI 0·24–0·98, p=0·047). Ascites was the most frequent decompensation, occurring in 29 patients (14%) whereas variceal bleeding occurred in seven (3%) and encephalopathy in nine (4%).

During follow-up, fewer patients in the β-blockers group than in the placebo group developed ascites (table 3). In a post-hoc analysis, the risk of ascites was lower in patients with an HVPG decrease greater than 10% or to less than 10 mm Hg at 1 year (treated with either β blockers or placebo) than in patients without such decreases: four (6%) of 67 versus 21 (24%) of 89 (HR 0·27, 95% CI 0·09–0·75, p=0·012).

Incidence of high risk varices, death from any cause, and other secondary outcomes, did not differ between groups (table 3). Liver function, assessed by Child-Pugh score and model for end-stage liver disease score, was unchanged in both groups (table 2).

Regarding ascites, the benefit of β blockers versus placebo was slightly more apparent in the carvedilol stratum (HR 0·22, 95% CI 0·02–1·94) than in the propranolol stratum (0·50, 95% CI 0·22–1·18). Regarding death from any cause, the benefit of β blockers was also slightly greater in the carvedilol stratum (0·44, 95% CI 0·08–2·43) than in the propranolol stratum (0·94, 95% CI 0·31–2·78).

172 patients (86%) reported adverse events. The overall incidence was similar in each group, as were the incidences of adverse events considered by the investigator to be probably or very probably related to treatment (table 4). Severe adverse events occurred in six patients (four in the β-blockers group); none was fatal.

Discussion

In patients with compensated cirrhosis and CSPH, long-term treatment with non-selective β blockers improves decompensation-free survival, mainly by decreasing the incidence of ascites. This finding might represent a new indication for β blockers in patients with compensated cirrhosis.[4,5]

Survival without developing any decompensation of cirrhosis was the primary endpoint of the study. However,

	Placebo group (n=101)	β-blockers group (n=100)	Risk (95% CI)*	p value†
Decompensation or death				
Overall‡	27 (27%)	16 (16%)	0·51 (0·26–0·97)	0·0412
Secondary outcomes				
Ascites	20 (20%)	9 (9%)	0·42 (0·19–0·92)	0·030
Gastrointestinal bleeding	3 (3%)	4 (4%)	1·52 (0·34–6·82)	0·61
Overt hepatic encephalopathy	5 (5%)	4 (4%)	0·92 (0·40–2·21)	0·98
Death from any cause	11 (11%)	8 (8%)	0·54 (0·20–1·48)	0·23
Varices	56 (56%)	58 (58%)	1·15 (0·65–2·02)	0·72
High-risk varices§	25 (25%)	16 (16%)	0·60 (0·30–1·21)	0·15
Spontaneous bacterial peritonitis	4 (4%)	2 (2%)	0·49 (0·10–2·70)	0·40
Other bacterial infections¶	19 (19%)	15 (15%)	0·81 (0·41–1·59)	0·54
Hepatorenal syndrome	1 (1%)	1 (1%)	0·99 (0·06–15·96)	0·96
Hepatocellular carcinoma	17 (17%)	13 (13%)	0·76 (0·37–1·54)	0·43

Percentages are crude incidences of events occurring at any time during the follow-up. *Values indicate the hazard ratio of an outcome in the β-blockers group as compared with the placebo group. †Comparison of cumulative incidences by competing-risk analysis (differences assessed by Gray's test). ‡The absolute reduction in the incidence of the primary outcome was of 11% (95% CI 0–22). §Among patients with high-risk varices, oesophageal variceal ligation to prevent bleeding was performed in 18 (72%) of 25 patients in the placebo group versus 11 (69%) of 16 in the non-selective β-blockers group. ¶Including spontaneous bacterial peritonitis, and other documented bacterial infections during follow-up.

Table 3: **Long-term outcomes**

in cirrhosis, most deaths occur after decompensation, whereas in compensated cirrhosis, liver function is preserved and deaths are few and usually non-liver-related.[10,14] Therapies targeting prevention of decompensation of cirrhosis cannot avoid non-liver related deaths. Accordingly, we used competing-risk analysis to assess the primary outcome, considering non-liver related death as a competing event.

Beyond this observation, the most relevant finding of the study was the improvement in decompensation risk observed with β blockers. To our knowledge, this outcome has not been shown in any randomised controlled trial. Our findings do not appear to be due to any selection bias, as the risk of decompensation that we observed in the placebo group was similar to that reported in previous studies assessing the natural history of cirrhosis of different causes.[15–20] Furthermore, the decompensation risk that we observed with β blockers is in keeping with previous observational studies suggesting a lower risk of decompensation in patients with good haemodynamic response to β blockers.[21–23]

Our results indicate that pharmacological therapy to decrease portal pressure can effectively prevent the progression of cirrhosis to decompensation, and is associated with marked prognostic improvement. The study shows that this benefit is mainly due to a decreased likelihood of developing ascites, the most common and severe decompensating event, for which no preventive drug therapy has previously shown efficacy.[5,11] In addition, the study indicates that a long-term sustained decrease of portal hypertension is associated with reduced incidence of ascites, which underlines the pathogenic relevance of

	Placebo group (n=101)	β blockers group (n=100)
Overall	88 (87%)	84 (84%)
Probably related to treatment*	30 (30%)	39 (39%)
Very probably related to treatment†	15 (15%)	16 (16%)
Total number of adverse events‡	45	57
Major adverse events§	2 (2%)	4 (4%)
Syncope	1	2
Bradyarrhythmia	0	1
Heart failure	0	1
Acute coronary syndrome	1	0
Minor adverse events¶	28 (28%)	36 (36%)
Weakness	17	23
Shortness of breath	2	4
Dizziness or hypotension	9	9
Bradycardia	2	3
Headache	1	2
Impotence	3	2
Gastrointestinal symptoms	3	2
Other	6	7

*Adverse events that were subjectively considered by the investigator to be probably related to drug treatment. †Adverse events that were subjectively considered by the investigator to be very probably related to drug treatment. ‡Some patients had more than one type of adverse event probably or very probably related to treatment: in the placebo group, 101 patients had 45 adverse events and in the β-blockers group 100 patients had 57 adverse events. §Adverse effects were considered severe if the health or safety of the patient was endangered. ¶In the placebo group, 28 patients had 43 minor adverse events. In the β-blockers group, 36 patients had 52 minor adverse events and, in this group, two patients had both minor and major complications.

Table 4: Adverse outcomes

portal hypertension in the development of ascites. In keeping with this finding, portal-systemic shunts (either surgical or transcutaneous intrahepatic portosystemic shunt), which markedly decrease portal pressure, improve the management of ascites.[24] Our study shows that ascites can be effectively prevented by decreasing portal pressure with β blockers, without administering diuretics, resulting in an improved decompensation-free survival. In addition, our results show that patients remaining compensated have lower portal pressure during follow-up than those developing decompensation.

We observed a significant reduction in heart rate and cardiac index, indicating an adequate β blockade, in patients receiving active therapy but not in those receiving placebo. Furthermore, patients treated with β blockers had an improvement in HVPG during follow-up not observed with placebo. Baseline portal pressure was similar in both groups, but the HVPG was significantly lower at each yearly assessment in patients receiving β blockers whereas it did not change in the placebo group. The proportion of patients with sustained HVPG decreases with clinical prognostic significance, such as a reduction of greater than 10% from baseline or to less than 10 mm Hg, was greater in those treated with

β blockers. It is probable that such an effect on portal pressure might have accounted for the beneficial effects that we observed with β blockers on prevention of cirrhosis decompensation.[12,22]

Our results contrast with a previous randomised controlled trial showing inefficacy of timolol to prevent the development of varices in compensated cirrhosis with HVPG either greater than or equal to 10 mm Hg or less than 10 mm Hg.[6] A major finding in that study was a lower risk of developing varices when the HVPG was below 10 mm Hg. A subsequent nested study confirmed a much greater risk of decompensation when HVPG was greater than or equal to 10 mm Hg.[3] Furthermore, the current study shows that in compensated cirrhosis with HVPG greater than or equal to 10 mm Hg the presence of varices confers a higher risk of decompensation, and only patients without varices were included in the timolol trial. Thus, the timolol trial included a considerable proportion of low-risk patients. Precisely because of the findings of that trial, in the current study, inclusion was restricted to patients with HVPG greater than or equal to 10 mm Hg. Moreover, the effect of β blockers decreasing HVPG is due to the attenuation of the increased portal inflow which follows hyperdynamic circulation.[7,8] In cirrhosis with HVPG less than 10 mm Hg, the hyperdynamic syndrome is still underdeveloped and β blockers induce a much lower effect on portal pressure than when CSPH develops.[8] Concordantly, the present study showed a reduction in portal pressure at each yearly control with β blockers but not with placebo. This was not achieved at any timepoint in the timolol trial. Altogether, the available data suggest that patient selection might have contributed to the different results observed in both randomised controlled trials. In the timolol trial, as in the current study, patients decreasing the HVPG by more than 10% of baseline had a decreased risk of decompensation.[3,6]

Observational studies suggest that HVPG monitoring might be useful to stratify risk and guide therapy.[21,22] Accordingly, we incorporated monitoring of the acute HVPG response to β blockers in order to treat responders with propranolol and non-responders with carvedilol, because carvedilol has a greater HVPG decreasing effect than propranolol and might achieve response in non-responders.[25,26] Certainly, the long-term HVPG-reduction that we observed with carvedilol in non-responders was better than that obtained with propranolol in responders. Moreover, studies suggest that carvedilol might be particularly adequate in early compensated cirrhosis,[27,28] since its intrinsic vasodilator activity (due to anti-α-adrenergic activity and enhanced release of nitric oxide) might decrease hepatic vascular resistance, the predominant mechanism of portal hypertension in the early stages of cirrhosis.[7,8] Indeed, we observed a slight improvement in outcomes and better adherence to therapy with carvedilol than with propranolol, altogether suggesting that carvedilol might be the preferable β blocker in this setting. All these data gained after this

study was planned, suggest that instead of selecting the drug on the basis of its effects on portal pressure, all patients could have been treated upfront with carvedilol, thus omitting the need to assess HVPG response.

In compensated cirrhosis, the presence of CSPH either with or without varices, is associated with an increased risk of decompensation.[3,10] The preplanned subgroup analysis of this study showed that patients with CSPH could be subdivided according to the presence or absence of small varices, as varices carry a higher risk of de-compensation. Among patients with CSPH, those with varices have a more developed hyperdynamic circulation and higher portal pressure than those without varices.[8] These haemodynamic disturbances might account for the increased risk of decompensation. It is important to note that in our study, treatment with β blockers was particularly successful in patients with small varices, who up to now received no treatment until developing high-risk varices according to existing guidelines. These guidelines recommend prophylactic treatment with β blockers or oesophageal variceal ligation to prevent bleeding once high-risk varices develop.[4,5] Our study shows that β blockers can also prevent ascites, which occurs more frequently than bleeding. This additional benefit should be considered when advising therapy for high-risk varices since it is not afforded by endoscopic band ligation. Furthermore, our findings support use of β blockers in patients with small varices, in concordance with studies suggesting that β blockers might prevent the progression of small to large varices.[5,28]

In this study the benefit of β blockers was mainly apparent after the first 24 months of follow-up, progressively increasing thereafter. This suggests that a longer follow-up might have detected a greater benefit. However, a substantial proportion of our patients had hepatitis C virus-related cirrhosis with active infection and the new direct-acting antivirals were introduced during the last year of the study.[9] These agents are safe and highly effective to achieve sustained virological response, which can improve liver fibrosis and portal hypertension and can prevent decompensation.[29] This prompted study termination before planned, to allow the treatment of patients with hepatitis C virus-cirrhosis without jeopardising the results of the study by the potential benefit of direct-acting antivirals on disease progression and on preventing decompensation. Never-theless, studies have shown that despite achieving sustained virological response a large proportion of patients with cirrhosis and CSPH still maintain CSPH and are at risk of decompensation, even if HVPG improves.[29] This finding suggests that β blockers might still be needed after virological response, which should be investigated in future studies that are adequately powered and with appropriate follow-up length.

Our trial has several limitations. The results cannot be generalised to all patients with cirrhosis, because we excluded those with high-risk varices who are known to

benefit from prophylactic therapy. Using HVPG to select patients also constitutes a limitation. At present, this is the gold-standard to identify CSPH.[5,22] However, several non-invasive tools, such as elastography, are now available to accurately identify this specific population (liver stiffness ≥20–25 kPa by transient elastography is highly suggestive of CSPH in virus related cirrhosis).[4,30] Furthermore, imaging techniques by detecting varices or portal-systemic collaterals can also identify CSPH.[4] These observations suggest that patient selection might soon be easier and non-invasive. Factors such as the open-label titration period or heart-rate changes might affect inadvertently study blindness. To limit this, a study nurse measured vital signs to keep investigators unaware. Even if assessment of blinding effectiveness was not planned, observer bias is unlikely owing to the objectivity of the primary outcome. Some eligible patients refused participation which might introduce inadvertent selection bias. Nevertheless, the study was double blind and placebo controlled which should have minimised this and other frequent sources of bias in clinical trials. Finally, although the study is relatively small, the sample size assumption was reached, and the HR and 95% CI observed regarding the primary outcome and the main secondary outcome (ie, ascites) clearly favours β blockers and confers robustness and consistency to our results.

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