We would like to sincerely thank the reviewers for their relevant comments and criticisms, which we think have improved and strengthened the manuscript NO: 41072. We hope to have adequately addressed them.

ANSWERS TO REVIEWER 1

1. **I think Carvedilol prevent the frequency of variceal bleeding due to decrease in HVPG. Please tell me the etiology why Carvedilol prevent hepatic decompensation.**

Non-selective betablockers (NSBB) act upstream of the pathogenic cascade of decompensated cirrhosis by reducing portal hypertension and bacterial translocation. By acting upstream of the pathogenic cascade, NSBB offset downstream deleterious effects, not only regarding variceal bleeding, but also regarding other complications such as ascites or hepatic encephalopathy. In fact, reductions in HVPG >10-20% induced by use of NSBB in the prevention of first or recurrent variceal bleeding are also associated with a lower incidence of these other complications (Abraldes JC et al. Hepatology 2003;37:902-908; Turnes J et al. *Am J Gastroenterol* 2006; 101(3): 506-512; Villanueva C et al. *J Hepatol* 2004; 40(5): 757-765; Villanueva C et al. *Gastroenterology* 2009; 137(1): 119-128). This explanation was reflected in lines 9 to 13 in the first paragraph of Introduction.

While current evidence indicates that carvedilol is more effective in reducing HVPG than traditional NSBB through its intrinsic anti-α-1-adrenergic activity (it decreases both intrahepatic and portal-collateral resistance), no difference between them have been reported regarding their effects on bacterial translocation. Thus, we believe that the improved long-term prognosis (i.e. risk of decompensation and death) of acute non-responders treated with Carvedilol responds to its greater effects on reducing portal pressure.

2. **Carvedilol may cause arterial hypotension and worsen renal function potentially compromising its beneficial effect in the long term. Please comment renal function in Carvedilol.**

Data present in the manuscript shows no differences in creatinine levels between Carvedilol-treated vs. NSBB-treated patients (Table 1) or between chronic responders vs. non-responders in each group (Table 2), nor an association of creatinine levels with the risk of decompensation (Table 4) or death (Table 5). We have further analysed our data regarding this issue and no differences were found in renal function (i.e. change in creatinine levels -mg/dL-) in the long term between groups (Traditional NSBB: +0.0004 (0.0994) vs. Carvedilol: +0.0092 (0.0903); p=0.787). As our study did not include patients with very advanced liver disease, these results are in line with current evidence suggesting that these detrimental effects of Carvedilol on renal function might be restricted to the end stages of liver disease (García.Tsao et al. *Hepatology* 2017; 65(1): 310-335). We have included a mention to this issue in the Discussion (lines 17-19 of 3rd paragraph).

3. **I think higher doses of carvedilol (>12.5 mg/day) may not further decrease portal pressure, while increasing the risk of arterial hypotension and bradycardia. Therefore, comment about higher dose of carvedilol.**

As the reviewer indicates, the study by Reiberger et al (*Gut* 2013; **62**(11): 1634-1641) showed that increasing the dose of carvedilol beyond 12.5 mg (i.e. 25-50mg) significantly further decreased mean arterial pressure and heart rate without an additional effect on HVPG. In our study and according to current guidelines (García.Tsao et al. *Hepatology* 2017; 65(1): 310-335), in patients with concomitant arterial hypertension, carvedilol could be increased up to 12.5 mg b.i.d. Thus, three patients with arterial hypertension received higher doses with good tolerability: two patients were given 12.5 mg b.i.d, and the other 9.375 mg b.i.d. Furthermore, no significant changes from baseline (%) between groups were found regarding mean arterial pressure (high dose: -5.9 (9.5) vs. Conventional dose: +8.9 (11.2); p=0.090) or heart rate (high dose: +3.4 (28.5) vs. Conventional dose: -24.6 (10.3); p=0.228).

ANSWERS TO REVIEWER 2

1. **The setting of required sample size is very important. Please mention the way to lead the size. If the sample size is too small, any comparison between two groups does not have significant difference. As a trial, I have calculated the required sample size by using the 2-years decompensation rate result (13.7 % and 20%, Figure 3A)(the setting as alfa-error of 0.05, power of 0.8), and the results was 938 patients. If the 2-years further decompensations (26.1% and 50.0%, Figure 3B) was set, the required size was 144 patients.**

The reviewer raises a very important point. By using the data in our manuscript as opposed to the risk at baseline (prior to any treatment), we think the reviewer has largely overestimated the sample size, which indirectly supports our conclusion regarding the benefit of carvedilol. Based on the risk of decompensation of acute and non-acute responders treated with traditional betablockers described in recent studies, our sample size has enough statistical power to make adequate comparisons if carvedilol does not improve the long-term prognosis of acute non-responders. In patients with compensated cirrhosis, the risk of decompensation at 2 years is three times higher in acute non-responders when they are treated with traditional NSBB (Hernandez-Gea V et al. *Am J Gastroenterol* 2012; **107**(3): 418-427). In acute responders this risk is around 20%. With a ratio of acute responders/non-responders of 2, an alfa-error of 0,05 and power of 0.8, the sample size required is 17 acute responders and 9 acute non-responders using the arcsin square root transformation. Similarly, in patients with decompensated cirrhosis the risk of decompensation at 2 years is between 2 to 10 times higher in acute non-responders when they are treated with traditional NSBB (Villanueva C et al. *Gastroenterology* 2009; **137**(1): 119-128; La Mura V et al. *J Hepatol* 2009; **51**(2): 279-287) and in acute responders this risk is around 25%. With similar settings and even a lower risk ratio of 2.5, the requiered sample size would be 29 acute responders and 15 non-responders. Nevertheless, we acknowledge that our sample size might

have limited the statistical power in some analyses. This issue has now been thoroughly commented in the 5th paragraph of the Discussion.

2. **Control group without taking any drug (neither NSBB nor carvedilol) is necessary for the comparison of NSBB or carvedilol group. Please add this control group.**

Our paper retrospectively reviewed the clinical outcome of a protocol for primary prophylaxis of variceal bleeding implemented in our institution since 2012, in which acute responders were treated with traditional NSBB and acute non-responders with carvedilol. Including a control group of patients without any type of treatment would not be ethically acceptable. A control group of patients treated with endoscopic band ligation was not included neither, as we indicate band ligation only in case of contraindication to NSBB or intolerance to these drugs. As shown in Figure 1, only 7 patients were treated with endoscopic band ligation, and therefore this small number of patients does not allow adequate comparisons.

3. **The authors mentioned (p14, lines 10), "The 2-year actuarial probability of variceal bleeding was 2.0% and 16.3%; this complication occurred in 2 patients in the traditional NSBB group and in 3 patients in the Carvedilol group (p=0.078)." This result is very important. Please add in the table 3. I think NSBB is more useful for preventing variceal bleeding from this result, even if the p value was 0.078. Please consider about this result in the discussion. If more patients were enrolled, there may be significant difference.**

Table 3 shows the absolute number and percentage of portal hypertension-related bleeding in each group over the whole follow-up period. The data that the reviewer is referring to corresponds with the 2-year actuarial probability of variceal bleeding. As the reviewer suggested, we have added a comment on the possible limited statistical power in this specific analysis in the 5th paragraph of the Discussion.

4. **In the last sentence of Introduction section, the authors mentioned the aim of this study, but it is different from the description of primary endpoint. Please revise this sentence.**

We have revised the sentence and changed accordingly. It now reads as follows:

"*The aim of the present study was to compare the risk of first or further decompensation of cirrhosis in each group since the implementation of the protocol in 2012*"

5. **In the abstract, there is the word as 'non-responders received carvedilol.' This word is very confusing for WJG readers, because we cannot find the target of non-responders. This word may cause misunderstanding as 'non-**

responder to carvedilol.' I think that some sentences describing non-responder in Core tip should be moved to abstract section.

We have clarified that the acute response or non-response refers to the administration of intravenous propranolol both in the Aim and Methods sections of the Abstract.

6. **In result part of the abstract, the result of primary endpoint should be described at first. The sentence (p4, lines 11), "No clinical, laboratory, endoscopic or hemodynamic parameter predicted the acute hemodynamic response." is not so important for your manuscript.**

As the reviewer suggests, we now first describe data related to the primary endpoint and the results of secondary endpoints are described in the last part of the Results section. We would like to point out, however, that we believe that the finding that no clinical, laboratory, endoscopic or hemodynamic parameter predicted the acute hemodynamic response is also important for two main reasons. First, because it is in line with the few studies that have tested the prognostic value of the acute hemodynamic response to i.v. propranolol. Second, and as highlighted in the Discussion, it also supports the inclusion of the acute hemodynamic test in the design of future randomized trials of primary prophylaxis of variceal bleeding for avoiding selection bias.

7. **The limitation should be described more in detailed.**

We have further described the limitations of the study in the Discussion, especially concerning the points 1 and 3 raised by the reviewer.

ANSWERS TO REVIEWER 3

1. **The authors concluded "carvedilol improved the long-term outcome of acute non-responders, presumably by its greater effects on reducing portal pressure, and should be the preferred choice over NSBB for primary prophylaxis of variceal bleeding when hemodynamic testing is not available". However, it seems carvedilol's greater effects on reducing portal pressure haven't been fully validated in the results. Furthermore, could this study claim that carvedilol should be the preferred choice?**

The reviewer raises an important point. Recent studies showed that the acute test to i.v. propranolol predicted the chronic hemodynamic response to traditional NSBB. Thus, acute non-responders did not achieve the chronic hemodynamic response when they were treated with traditional NSBB. In our study, a high proportion of acute non-responders (69.2%) achieved a chronic hemodynamic response with carvedilol. This finding is in line with the study of Reiberger et al (*Gut* 2013; **62**(11): 1634-1641) in which 56% of patients who had no chronic hemodynamic response to propranolol were able to achieve a hemodynamic response after switching to carvedilol. Although a second hemodynamic study was not available in all patients, we believe that our

results support current evidence of carvedilol´s greater effects on reducing portal pressure.

The design of our study cannot definitively conclude that carvedilol should become the beta-blocker of choice in patients starting primary prophylaxis of variceal bleeding. In order to confirm this possibility, a randomized controlled trial with a control group of acute non-responders treated with traditional NSBB would be needed. However, we believe that our results together with those of prior studies **suggest** (please notice that we have used this verb in order to highlight that no definitive conclusion can be drawn from our study) that carvedilol improved the long-term outcome of acute non-responders and therefore it should become the beta-blocker of choice in centers with no available hepatic hemodynamic testing until adequate clinical trials are performed. All these issues have been highlighted in the Discussion.

2. **Paragraph 2 in "Introduction" "the role of the acute hemodynamic response to guide therapy has never been assessed in the setting of primary prophylaxis of variceal bleeding". In fact, ref.6 was just about this.**

The study of Ref.6 (Villanueva et al, Gastroenterology 2009; 137(1): 119-128) showed that the acute hemodynamic response to beta-blockers can be used to predict the long-term risk of first bleeding and established a HVPG reduction >10% from baseline as the best target to define response in primary prophylaxis of variceal bleeding. However, the authors did not use this test to guide the type of NSBB to be used, as both acute responders and non-responders were treated with traditional NSBB. This was also the case in the studies of La Mura et al (*J Hepatol* 2009; **51**(2): 279-287) and Hernandez-Gea et al (*Am J Gastroenterol* 2012; 107(3): 418-427). Therefore, we humbly think that the statement that "the role of the acute hemodynamic response to **guide therapy** has never been assessed in the setting of primary prophylaxis of variceal bleeding" is still correct. We have included a sentence in the 1st paragraph of Discussion (lines 5-7) to clarify this issue.

3. **Hemodynamic measurements:"a Swan-Ganz catheter into the pulmonary artery under fluoroscopic guidance". Is this needed in HVPG measurement?**

It is not needed for the purpose only of HVPG measurement. However, it provides valuable information of the cardiopulmonary status (e.g. it may uncover patients with clinically silent portopulmonary hypertension or heart disease). In Europe and certainly in Spain, all experienced centers that routinely perform hemodynamic studies in patients starting primary or secondary prophylaxis of variceal bleeding perform these measurements. Accordingly, most of the studies referenced in our paper have included these measurements in their results whenever a hemodynamic study was performed (e.g.

Hernandez-Gea et al. *Am J Gastroenterol* 2012; 107(3): 418-427; Villanueva et al. Gastroenterology 2009; 137(1): 119-128).

4. **In the result chronic hemodynamic response: "...had a second hemodynamic study performed after 26.3 (12.8) and 28.0 (18.8)[] weeks, respectively" What does 26.3(12.8) mean?**

It refers to the mean duration with the corresponding standard deviation. We have clarified this issue in the text.