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Carvedilol versus endoscopic band ligation for secondary prophylaxis of variceal bleeding – long term follow-up of a randomised control trial

Short Running Title: Carvedilol versus banding – outcomes

Philip Dunne [1] (MBChB), David Young [2] (PhD), Cher Shiong Chuah [3] (MBChB), Peter Hayes [3, 4] (PhD), Dhiraj Tripathi [3, 5, 6] (MD), Joanna Leithead [3, 7] (MD), Lyn Smith [1] (MBChB), Daniel Gaya [1, 8] (MD), Ewan Forrest [1, 8] (MD), Adrian Stanley [1, 8] (MD)

1. Department of Gastroenterology, Glasgow Royal Infirmary, Glasgow, UK
2. Department of Statistics, Strathclyde University, Glasgow, UK
3. Department of Hepatology, Royal Infirmary of Edinburgh, Edinburgh, UK
4. University of Edinburgh, Edinburgh, UK
5. Liver Unit, University Hospitals Birmingham NHS Foundation Trust, UK
6. Institute of Immunology and Immunotherapy, University of Birmingham, UK
7. Forth Valley Royal Hospital, Sterling, UK
8. University of Glasgow, Glasgow, UK

Correspondence to:

Dr Philip DJ Dunne

Registrar in Gastroenterology

Department of Gastroenterology

Walton Building, Glasgow Royal Infirmary

Glasgow, UK

G4 0SF

Email: philip.dunne@ggc.scot.nhs.uk

Tel: 0141 211 4000

DECLARTION OF INTERESTS

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AUTHOR CONTRIBUTIONS

Dr PDJ Dunne: Design of study, data collection, and draft of manuscript

Dr D Young: Statistical analysis of data, critical review of manuscript

Dr CH Chuah: data collection, critical review of manuscript

Prof D Tripathi: Critical review of manuscript

Dr J Leithead: Critical review of manuscript

Dr LA Smith: Critical review of manuscript

Dr D R Gaya: Critical review of manuscript

Prof EH Forrest: Critical review of manuscript

Prof PC Hayes: Critical review of manuscript, principal investigator of index study

Prof AJ Stanley: Design of index study, senior investigator of index study, design of follow-up study

All authors approved the final draft of this manuscript

GAURATOR OF ARTICLE

Prof AJ Stanley

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SUMMARY

Background & Aims: Carvedilol reduces rates of variceal bleeding and rebleeding by lowering portal pressure. However, an associated pleotropic survival benefit has been proposed. We aimed to assess long-term survival in a cohort of patients previously randomised to receive either carvedilol or endoscopic band ligation (EBL) following oesophageal variceal bleeding (OVB).

Methods: The index study randomised 64 cirrhotic patients with OVB between 2006-2011 to receive either carvedilol or EBL. Follow-up was undertaken to April 2020 by review of electronic patient records. The primary outcome was survival. Other outcomes including variceal rebleeding and liver decompensation events were compared.

Results: 26 out of 33 participants received carvedilol in the follow-up period and 28 out of 31 attended for regular EBL sessions. The median number of follow-up days for all patients recruited was 1459 (SE = 281.74). On intention to treat analysis, there was a trend towards improved survival in the carvedilol group (p=0.09). On per-protocol analysis, carvedilol use was associated with improved long-term survival (p=0.005, HR 3.083, 95%CI 1.397-6.809), fewer liver related deaths (0% vs 22.57%, p=0.013, OR ∞, 95%CI 1.565 - ∞), and fewer admissions with decompensated liver disease (12% vs 64.29% (p=0.0002, OR 13.2, 95%CI 3.026 – 47.23) compared to the EBL group. There was no statistically significant difference in variceal rebleeding rates

Conclusion: Following OVB in cirrhotic patients, carvedilol use is associated with survival benefit, fewer liver related deaths and fewer hospital admissions with decompensated liver disease. Further studies are needed to validate this finding.

INTRODUCTION

Several randomised control trials have demonstrated the efficacy of non-selective beta blockers (NSBBs) for both primary and secondary prevention of oesophageal variceal bleeding (OVB) [1-3] Current clinical guidelines recommend the combination of endoscopic band ligation (EBL) and NSBB following OVB, with combination therapy thought to be advantageous over monotherapy in the prevention of variceal rebleeding. [4, 5] However, there has been much interest of late in the potential additional benefits of NSBBs compared with other standards of care such as; improved survival following OVB compared to EBL, [6] improved survival for cirrhotic patients on a liver transplant waiting list, [7] reduction in decompensation due to ascites [8] and spontaneous bacterial peritonitis (SBP), [9] and reduction in rates of hepatocellular carcinoma (HCC). [10]

Carvedilol is a NSBB that has an additional intrinsic anti-α1 adrenergic effect. It has been shown to have a greater reduction in hepato-venous pressure gradient (HVPG) compared to other NSBB including propranolol or nadolol. [11-13] HVPG is used as a surrogate marker for portal pressure and higher levels are associated with variceal bleeding and other complications associated with portal hypertension. On comparison to other NSBBs, carvedilol has also been shown to have clinical effectiveness in propranolol "non-responders", [14] better clinical tolerance, [8] reduced long-term progression to ascites, [15] and improved renal perfusion and clinical outcomes in cirrhotics with ascites. [16] Additionally, carvedilol is associated with improved long-term survival when given as primary prophylaxis for OVB. [17]

Our index study [18] reported that carvedilol and EBL were equally effective for secondary prophylaxis of variceal bleeding. Additionally, there was a trend towards improved survival in carvedilol treated patients, after a median follow-up of 26.3 months, albeit short of statistical significance. To date, most studies assessing carvedilol in the prophylaxis of OVB had short-term follow-up. We aimed to

investigate the long-term outcomes for patients taking carvedilol following OVB, with survival (intention to treat and per-protocol) as our primary endpoints.

METHODS

Study design

This is a retrospective cohort analysis of 64 patients recruited to a multicentred randomised control study between June 2006 and December 2011. All patients had extended follow-up until April 2020. The index study was registered under trial number ISRCTN 69643049 and ethical approval was granted for each centre.

Index study protocol and participants

Patients with cirrhosis and endoscopically proven OVB who were stabilised following relevant initial endoscopic and pharmacological therapy (i.e., EBL, terlipressin and antibiotics) were recruited from 4 centres: Glasgow Royal Infirmary, Royal Infirmary Edinburgh, Gartnavel General Hospital Glasgow, and Southern General Hospital Glasgow. Following the index endoscopy and after informed consent, clinically stable participants were randomised, at day 5, on a 1:1 ratio to receive either carvedilol 6.25mg (titrated to 12.5mg if tolerated after one week), or to undergo further EBL at 2 weekly intervals until variceal eradication, with 6 monthly surveillance endoscopies thereafter.

Exclusion criteria were: age <18 or >75 years; advanced malignancy or comorbidity resulting in life expectancy <6 months; obstructive airways disease; baseline pulse rate <50 bpm or systolic blood pressure <90 mmHg; severe peripheral vascular disease; heart block or severe heart failure; pregnancy; type-I diabetes; portal vein thrombosis; previous transjugular intra-hepatic portosystemic shut (TIPSS) or porto-caval shunt surgery; a gastric variceal bleed; or treatment with NSBBs within 4 weeks of the index bleed.

Long term follow-up data collection

A standardised electronic data collection proforma was used across all centres and populated by a local, lead clinician following interrogation of electronic patient records. All data were cross-checked against the original data set. Long-term follow-up data regarding the progress of patients' chronic liver disease were collected. These included hospital admissions related to decompensated liver disease (variceal rebleeding, development or worsening of ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, acute alcoholic hepatitis, sepsis); orthotopic liver transplantation (OLT); and TIPSS insertion. Mortality data were also collected including date and cause of death. Death certification was cross-referenced with records held by the National Records of Scotland. Carvedilol compliance and side effect profile were assessed by patient history, review of liver clinic appointment letters and review of primary care repeat prescriptions. EBL compliance and outcome were assessed by review of electronic patient records including attendance at hospital for planned EBL sessions and procedure reports. Any cross-over between treatment groups during follow-up was documented.

Primary and secondary outcomes

Primary outcomes were transplant free survival on intention to treat and per-protocol analysis. Secondary outcomes were variceal rebleeding and liver decompensation events on both intention to treat and per-protocol analysis; compliance with treatment; and cross-over between groups.

Analysis

Initial data analyses were performed on an intention-to-treat basis, with per-protocol analysis undertaken thereafter. Per protocol analysis was performed on participants randomised to carvedilol who had taken the medication for any duration, and for those randomised to EBL who attended more than the first 2 planned EBL sessions. Participants were censored in the event of

failure of compliance, crossover of treatment arms, TIPSS placement, or at the end of the study period.

All statistical tests were two-sided using a 5% significance level. The probabilities of reaching the primary end point of survival were estimated by the Kaplan–Meier method and were compared using the log-rank test. Cox regression analysis was undertaken to determine if the following variables individually contributed towards survival: age, MELD, Child Pugh Score, ascites, variceal rebleeding, and liver related hospital admissions. The statistical software packages used for the analysis were SPSS (v17, IBM, Armonk, USA) and Prism (v8, GraphPad software, CA, USA).

RESULTS

All 64 patients included in the index study were followed up, 33 of whom were initially randomised to receive carvedilol, and 31 to receive EBL. Baseline patient characteristics are shown in Table 1. The median number of follow-up days for all patients recruited was 1459 (SE = 281.74).

Compliance and censoring

Of the 33 patients randomised to carvedilol, 5 did not commence the medication due to early rebleeding in 4 (2 of whom died) and 1 due to poor cognition. 3 patients discontinued the medication within 30 days due to side effects. 11 took the medication through to death or closure of the study period and further one patient until OLT. A second patient underwent OLT in the carvedilol group but had crossed over to EBL prior. One patient received TIPSS due to rebleeding. 6 patients crossed over to receive EBL, 5 due to rebleeding and one due to patient preference. 4 patients stopped carvedilol due to late side effects and a further one patient due to reasons unknown. Only one patient died within 100 days of discontinuing the medication. The overall median days of per protocol carvedilol administration was 1956 (SE = 548.01).

Of the 31 randomised to EBL, 3 did not attend their planned follow-up EBL sessions. Of these 3, one had a variceal rebleed and underwent urgent EBL (605 days). Of the 28 patients who complied with the planned EBL sessions, 2 experienced variceal rebleeding prior to their first planned follow-up EBL session and underwent further unscheduled EBL (8 and 14 days) and both attended planned EBL thereafter. 5 underwent TIPSS placement for variceal rebleeding, one had TIPSS for hydrothorax, and one had TIPSS for ascites. One crossed over to receive carvedilol for rebleeding, and one attended regular EBL until OLT.

Survival

On intention to treat analysis, there was no difference in median survival days between the Carvedilol and EBL groups, respectively (1956 vs 1125, p=0.16, HR 1.521, 95%CI 0.851-2.679) (Figure 1). However, on per-protocol analysis, those patients taking carvedilol were more likely to survive than those attending EBL sessions (p=0.005, HR 3.083, 95%CI 1.397-6.809) (Figure 2).

Cause of death

Overall causes of death are summarised in Table 2. On intention to treat analysis, there were no significant differences in causes of death between EBL and Carvedilol groups, in particular death due to liver failure = 25.81% vs 9.08% (p=0.102), respectively. However, on per protocol analysis, those taking carvedilol were significantly less likely to experience death due to liver failure compared to those in the banding group 0% vs 22.57% (p=0.013, OR ∞, 95%CI 1.565 - ∞), respectively.

Variceal rebleeding

Similar to the index study, there was no difference between EBL and carvedilol groups in days free of variceal rebleeding in both intention to treat (p=0.66, HR 1.191, HR 0.548-2.592), and per-protocol analysis (p=0.76, HR 1.156, 95%CI 0.451-2.962) (Figure 3).

Decompensated liver disease related hospital admissions

Total, cumulative admissions to hospital with decompensated liver disease (excluding admissions due to variceal rebleeding) are summarised in Table 3. On both intention to treat and per-protocol analysis, participants in the EBL group were more likely to experience a decompensated liver disease related hospital admission than the carvedilol group, respectively; intention to treat = 64.52% vs 30.3% (p=0.012, OR 4.182, 95%CI 1.442 – 12.42), per-protocol = 64.29% vs 12% (p=0.0002, OR 13.2, 95%CI 3.026 – 47.23). On per-protocol analysis, those in the carvedilol group had a higher probability than those in the EBL group of remaining free of decompensated liver disease throughout the follow-up period, median days 1467 vs 286 (p=0.016, HR 3.069, 95% CI 1.532-6.148), Figure 4.

Multivariate regression analysis for survival

Age, MELD, child-pugh score, ascites, carvedilol use and attendance at banding sessions were variables used to determine their individual impact on survival. Carvedilol was the only independent predictor, Table 4.

DISCUSSION

This multicentre study assessed the long-term outcomes of a randomised control trial, in which patients initially presenting with, and treated for, OVB received either carvedilol or EBL to prevent rebleeding. We found that long-term survival and variceal rebleeding were similar for carvedilol and EBL on intention to treat analysis. However, on per- protocol analysis, carvedilol use led to improved all-cause survival, in addition to a reduction in both liver related mortality and admissions to hospital with decompensated liver disease.

Despite ongoing success in the treatment and eradication of the hepatitis C virus, the global burden of chronic liver disease is still rising, predominantly due to alcohol and the metabolic syndrome. As a result, liver related mortality has increased in recent years. [19] The onset of portal hypertension is the

main driving force that precedes the deterioration of liver disease, with complications such as ascites, variceal bleeding or hepatic encephalopathy marking the transition from compensated to decompensated cirrhosis and are associated with a dramatic decrease in survival. [20]

In our study, carvedilol use was associated with improved long-term survival compared to those who attended for at least 2 consecutive follow-up EBL sessions or achieved variceal eradication. The survival benefit found appears to be due to a reduction in liver related mortality. In a previous study assessing the long terms outcomes of carvedilol versus EBL for primary prophylaxis of OVB, carvedilol was associated with survival benefit but not reduced liver related mortality or liver decompensation events.[17] This led to speculation as to the potential extra-hepatic benefits of carvedilol. It is, however, likely that the patients in our study were at a more advanced stage of liver disease, given the nature of recruitment being for secondary prophylaxis of OVB. We found that fewer patients in the carvedilol group were admitted to hospital with decompensated liver disease, to our knowledge we are the first to report this finding in the context of a randomised trial. Interestingly, more patients in the EBL group underwent TIPSS for various reasons however, despite this, the rates of admission with ascites were lower in the carvedilol group, perhaps emphasising the protective benefit of carvedilol even further.

Similar to other NSBBs, carvedilol reduces heart rate and cardiac output by antagonism of β1-adrenergic receptors. Through β2-adrenergic blockade, it causes splanchnic vasoconstriction due to unopposed adrenergic tone, leading to an additional decrease in portal-collateral blood flow. However, in contrast to other NSBBs, carvedilol also exhibits an intrinsic anti-α1 adrenergic effect, causing intrahepatic vasodilatation that decreases portal pressure further. Interestingly, we found that carvedilol reduced liver decompensation events but did not prevent variceal bleeding, compared to EBL. This supports the suggestion that carvedilol influences pleiotropic mechanisms that contribute towards liver decompensation out with HVPG reduction. Animal studies have

observed that carvedilol has antioxidant, anti-fibrotic and anti-inflammatory properties. [21, 22] Furthermore, carvedilol has been shown to increase insulin sensitivity, reduce glycosylated haemoglobin levels, slow the progression to microalbuminaemia, [23] and have a survival benefit compared to other NSBB in patients with heart disease. [24, 25]

Compliance with carvedilol was less than compliance with regular EBL, perhaps due to adverse effects associated with carvedilol. Three patients did not take the drug beyond 30 days (the likely time required to have adequate effect on HVPG [26-29]) due to side effects, and 4 more discontinued the medication beyond 30 days. However, the minimum time to discontinuation in those established on carvedilol for >30 days was longer than 12 months. At the doses taken in our study (6.25–12.5 mg/day) carvedilol does not appear to cause systemic hypotension but decreases portal pressure significantly more than propranolol, which may explain its better tolerability. [8]

The multicentre nature, pre-defined clinically relevant outcomes, and 100% patient follow-up should be considered strengths of this study. Additionally, we are the first to report long-term outcomes of carvedilol compared with EBL following OVB. One other study reported long-term of outcomes of carvedilol following OVB, however this was compared with propranolol. [15] Limitations of our study include the fact that long-term data collection was retrospective, therefore at risk of the biases associated with retrospective studies, however this can be effectively lessened given the patients we observed were initially recruited through a randomised trial. Although a thorough process was undertaken to assess treatment compliance, we cannot guarantee that all participants continued their allocated treatment for the duration of the study. We also acknowledge the limitations of per-protocol analyses. For instance, patients who discontinued carvedilol were censored at that point and if death occured thereafter, they were not counted as carvedilol related deaths. However only one patient died within 100 days of discontinuing carvedilol. Given that many more patients in the EBL group received TIPSS for indications associated with severe disease (rebleeding, hydrothorax

and ascites) and were also censored, we believe the survival benefit from carvedilol found in this study is of significant interest.

In conclusion, following OVB, carvedilol use is associated with improved survival, reduced liver related mortality and fewer hospital admissions with decompensated liver disease during long-term follow-up. Monotherapy with carvedilol or EBL has similar variceal rebleeding rates. These results suggest that carvedilol use provides additional benefits in cirrhotic patients, beyond the reduction of rebleeding. Further large randomised controlled trials are required to validate this finding and explore the potential benefits of carvedilol in other patients with chronic liver disease.

REFERENCES

1. Garcia-Tsao G., Bosch J. Management of varices and variceal hemorrhage in cirrhosis. *N Engl J Med.* 2010;362(9):823–832
2. Tsochatzis E.A., Bosch J., Burroughs A.K. Liver cirrhosis. *Lancet.* 2014;383(9930):1749–1761
3. Tripathi D, Ferguson JW, Kochar N, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. *Hepatology*. 2009;50(3):825-833
4. Tripathi D, Stanley AJ, Hayes PC, Patch D, et al. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut* 2015; 64: 1680–704
5. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018 Aug;69(2):406-460. doi: 10.1016/j.jhep.2018.03.024. Epub 2018 Apr 10. Erratum in: J Hepatol. 2018 Nov;69(5):1207.

6. Lo G.H., Chen W.C., Lin C.K., Tsai W.L., Chan H.H., Chen T.A. Improved survival in patients receiving medical therapy as compared with banding ligation for the prevention of esophageal variceal rebleeding. *Hepatology.* 2008;48(2):580–587
7. Leithead JA, Rajoriya N, Tehami N, et al. Non-selective β-blockers are associated with improved survival in patients with ascites listed for liver transplantation. *Gut*. 2015;64(7):1111-1119. doi:10.1136/gutjnl-2013-306502
8. Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, *Lancet*. 2019;393(10181):1597-1608.
9. Bang U.C., Benfield T., Hyldstrup L, et al. Effect of propranolol on survival in patients with decompensated cirrhosis: a nationwide study based Danish patient registers. *Liver Int.* 2016;36(9):1304–1312
10. Wijarnpreecha K, Li F, Xiang Y, et al. Nonselective beta-blockers are associated with a lower risk of hepatocellular carcinoma among cirrhotic patients in the United States. Aliment Pharmacol Ther. 2021 Jul 5.
11. Bañares R, Moitinho E, Piqueras B, et al. Carvedilol, a new nonselective beta-blocker with intrinsic anti- Alpha1-adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. *Hepatology*. 1999;30(1):79-83
12. Lin HC, Yang YY, Hou MC, Huang YT, Lee FY, Lee SD. Acute administration of carvedilol is more effective than propranolol plus isosorbide-5-mononitrate in the reduction of portal pressure in patients with viral cirrhosis. Am J Gastroenterol 2004;99:1953- 1958.
13. Bañares R, Moitinho E, Matilla A, et al. Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. Hepatology 2002;36:1367-1373

14. Reiberger T, Ulbrich G, Ferlitsch A*, et al* Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol *Gut* 2013;62:1634-1641
15. Sharma S, Agarwal S, Gunjan D, et al. Long-term outcomes with carvedilol versus propranolol in patients with index variceal bleed: 6-year follow-up study. *J Clin Exp Hepatol*. 2020. doi:10.1016/j.jceh.2020.08.009
16. Kalambokis GN, Christaki M, Tsiakas I, Despotis G, Fillipas-Ntekouan S, Fotopoulos A, Tsiouris S, Xourgia X, Lakkas L, Pappas K, Michalis LK, Sergianiti F, Baltayiannis G, Christodoulou D, Koustousi C, Aggelis N, Milionis H. Conversion of Propranolol to Carvedilol Improves Renal Perfusion and Outcome in Patients With Cirrhosis and Ascites. J Clin Gastroenterol. 2020 Oct 13.
17. McDowell HR, Chuah CS, Tripathi D, Stanley AJ, Forrest EH, Hayes PC. Carvedilol is associated with improved survival in patients with cirrhosis: a long-term follow-up study. Aliment Pharmacol Ther. 2021 Feb;53(4):531-539
18. Stanley A.J., Dickson S., Hayes P.C., Forrest E.H., Mills P.R., Tripathi D. Multicentre randomised controlled study comparing carvedilol with variceal band ligation in the prevention of variceal rebleeding. *J Hepatol.* 2014;61(5):1014–1019
19. Moon AM, Singal AG, Tapper EB. Contemporary epidemiology of chronic liver disease and cirrhosis. *Clin Gastroenterol Hepatol*. 2020; 18: 2650- 2666
20. Ripoll C, Groszmann R, Garcia–Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology*. 2007; 133: 481- 488.
21. Akbas H, Ozden M, Kanko M, et al. Protective antioxidant effects of carvedilol in a rat model of ischaemia-reperfusion injury. J Int Med Res 2005; 33: 528–36.

22. Hamdy N, El Demerdash E. New therapeutic aspect for carvedilol: antifibrotic effects of carvedilol in chronic carbon tetrachloride-induced liver damage. Toxicol Appl Pharmacol 2012; 261: 292–9
23. Bakris GL, Fonseca V, Katholi RE, et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. JAMA 2004; 292: 2227–36.
24. DiNicolantonio JJ, Lavie CJ, Fares H, Menezes AR, O'Keefe JH. Meta-analysis of carvedilol versus beta 1 selective beta-blockers (atenolol, bisoprolol, metoprolol, and nebivolol). *Am J Cardiol*. 2013;111(5):765-769
25. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation*. 2002;106(17):2194-2199
26. Schwarzer R, Kivaranovic D, Paternostro R, et al. Carvedilol for reducing portal pressure in primary prophylaxis of variceal bleeding: a dose-response study. *Aliment Pharmacol Ther*. 2018; 47: 1162- 1169
27. Sauerbruch T, Mengel M, Dollinger M, Zipprich A, Rössle M, Panther E, Wiest R, Caca K, Hoffmeister A, Lutz H, Schoo R, Lorenzen H, Trebicka J, Appenrodt B, Schepke M, Fimmers R; German Study Group for Prophylaxis of Variceal Rebleeding. Prevention of Rebleeding From Esophageal Varices in Patients With Cirrhosis Receiving Small-Diameter Stents Versus Hemodynamically Controlled Medical Therapy. Gastroenterology. 2015 Sep;149(3):660-8.e1
28. Stanley A.J., Therapondos G., Helmy A., Hayes P.C. Acute and chronic haemodynamic and renal effects of carvedilol in patients with cirrhosis. *J Hepatol.* 1999;30(March (3)):479–484
29. Tripathi D., Therapondos G., Lui H.F., Stanley A.J., Hayes P.C. Haemodynamic effects of acute and chronic administration of low-dose carvedilol, a vasodilating beta-blocker, in patients with cirrhosis and portal hypertension. *Aliment Pharmacol Ther.* 2002;16(March (3)):373–380

TABLES AND FIGURES

Table 1. Patient characteristics at recruitment

Characteristic	Carvedilol (n=33)	VBL (n=31)
Age, years; mean ± SD	51.4±10.8	49.6±12.87
Male : Female	22:11	21:10
Child-Pugh Score	9 (7.0 – 10.5)	9 (8.0 – 11.0)
MELD	13 (8.25 – 18.5)	14 (11.0 – 16.0)
Bilirubin, µmol/L	39 (19.5 – 63.0)	35 (23.0 – 82.0)
Albumin, g/L	27 (22.5 – 31.5)	27 (24.0 – 33.0)
Prothrombin, time (s)	15 (13.0 – 19.0)	16 (14.0 – 17.0)
Ascites, n (%)	12 (36.3%)	12 (38.7%)

All values expressed as Median (IQR) unless otherwise stated

Fig. 1. Survival: Endoscopic band ligation versus carvedilol, intention to treat

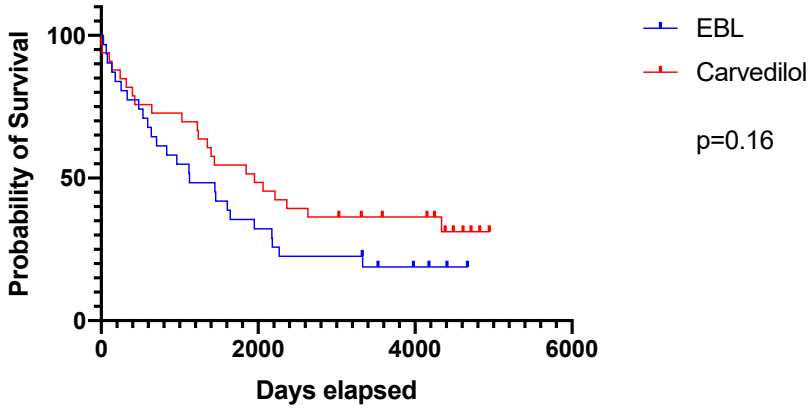

Fig. 2. Survival: Endoscopic band ligation versus carvedilol, per protocol

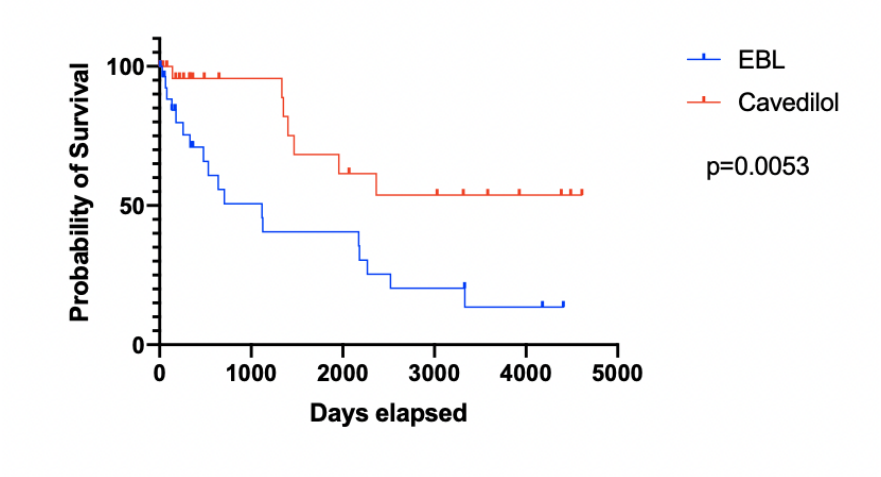

Table 2. Causes of death

Cause of Death	Carvedilol (n=33)	EBL (n=31)	P-value
Liver failure:			
- Intention to treat (%)	3 (9.08)	8 (25.81)	0.102
- Per-protocol (%)	0 (0.0)	7 (22.57)	**0.004**
GI Bleeding	3	6	0.296
Cardiovascular	4	1	0.356
Sepsis	2	4	0.419
HCC	0	1	0.484

Fig. 3. Variceal rebleeding: Endoscopic band ligation versus carvedilol, per-protocol

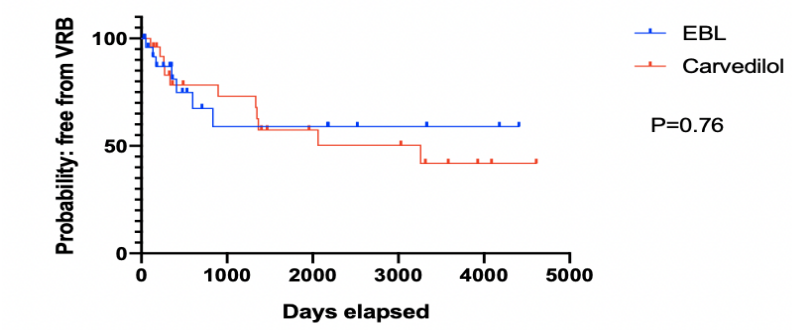

Table 3. Overall hospital admission with decompensated liver disease

Decompensation	Carvedilol (n=33)	VBL (n=31)
Ascites	5	14
Hepatic Encephalopathy	7	8
Hepatorenal Syndrome	2	2
Acute Alcoholic Hepatitis	4	7
Spontaneous Bacterial Peritonitis	1	4
TOTAL	19	35

Fig. 4. Days to first decompensated liver disease hospital admission: Endoscopic band ligation versus carvedilol, per-protocol

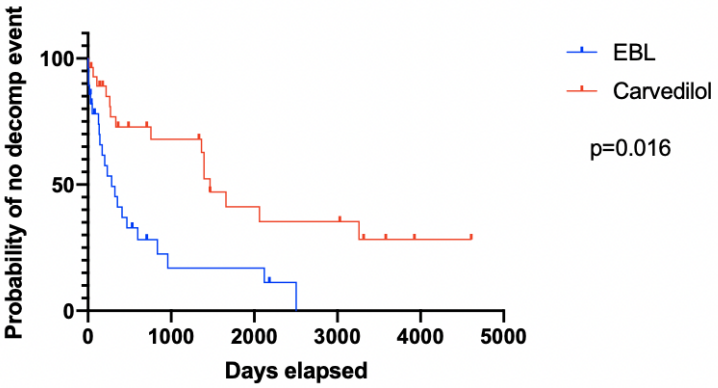

Table 4. Multivariate Cox regression analysis for survival

Variable	Standard error	95% CI	P value
Age	16.51	-44.14 to 22.02	0.5057
MELD	38.82	-135.0 to 20.56	0.1462
Child Pugh Score	83.27	-150.2 to 183.4	0.8426
Ascites [yes]	422.4	-719.2 to 973.2	0.7648
Carvedilol use	0.1578	0.3008 to 0.9329	**0.0003**
Attended banding [yes]	405.0	-867.0 to 755.7	0.8912

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	na
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	na
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	7
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	na
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	16
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	na
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8-10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8-10
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-12
Other information			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	12
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.