Randomized Controlled Trial of Carvedilol Versus Variceal Band Ligation for the Prevention of the First Variceal Bleed

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Current therapy for preventing the first variceal bleed includes beta-blocker and variceal band ligation (VBL). VBL has lower bleeding rates, with no differences in survival, whereas beta-blocker therapy can be limited by side effects. Carvedilol, a non-cardioselective vasodilating beta-blocker, is more effective in reducing portal pressure than propranolol; however, there have been no clinical studies assessing the efficacy of carvedilol in primary prophylaxis. The goal of this study was to compare carvedilol and VBL for the prevention of the first variceal bleed in a randomized controlled multicenter trial. One hundred fifty-two cirrhotic patients from five different centers with grade II or larger esophageal varices were randomized to either carvedilol 12.5 mg once daily or VBL performed every 2 weeks until eradication using a multibander device. Seventy-seven patients were randomized to carvedilol and 75 to VBL. Baseline characteristics did not differ between the groups (alcoholic liver disease, 73%; median Child-Pugh score, 8; median age, 54 years; median follow-up, 20 months). On intention-to-treat analysis, carvedilol had lower rates of the first variceal bleed (10% versus 23%; relative hazard 0.41; 95% confidence interval 0.19-0.96 [$P = 0.04$]), with no significant differences in overall mortality (35% versus 37%, $P = 0.71$), and bleeding-related mortality (3% versus 1%, $P = 0.26$). Six patients in the VBL group bled as a result of banding ulcers. Per-protocol analysis revealed no significant differences in the outcomes. *Conclusion:* Carvedilol is effective in preventing the first variceal bleed. Carvedilol is an option for primary prophylaxis in patients with high-risk esophageal varices. (HEPATOLOGY **2009;50:825-833.**)

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The most serious complication of portal hypertension is variceal hemorrhage. The annual incidence of esophageal varices in patients with cirrhosis is approximately 5%,[1] and a third of these will bleed.[2,3] Current therapy with propranolol results in a reduction in the first variceal bleed and mortality compared with placebo.[4,5] There have been two recent meta-analyses with 16 trials studied in total.[6,7] The one showed variceal band ligation (VBL) to be more effective than beta-blockers in primary prevention of variceal hemorrhage, although there was no difference in survival.[7] The other showed similar overall results, although when trials with unclear bias control and follow-up less than 20 months were excluded, the difference in bleeding was not present.[6]

Carvedilol is a potent non-cardioselective beta-blocker, with weak vasodilating properties due to alpha-1 blockade.[8] A fall in both intrahepatic and portocollateral resistance contributes to the enhanced effects on portal pressure reduction through blockade of alpha-1 receptors as has been shown with prazosin.[9-11] A reduction in the hepatic venous pressure gradient (HVPG) of 8%-43% was observed with carvedilol in nine published hemodynamic studies involving 158 patients.[12-20] Carvedilol was also found to have a greater portal hypotensive effect than propranolol in randomized controlled hemodynamic studies.[15,17,19,20] To date, there are no published clinical

Abbreviations: HVPG, hepatic venous pressure gradient; ITT, intention-to-treat; TIPS, transjugular intrahepatic portosystemic shunt; VBL, variceal band ligation.

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trials using carvedilol for the primary or secondary prevention of variceal hemorrhage.

The aim of this randomized controlled study is to compare carvedilol versus VBL in the prevention of the first variceal bleed in patients with high-risk esophageal varices.

Materials and Methods

Study Design. This was a multicenter randomized controlled trial involving five centers in Scotland. The trial was undertaken with the approval of the local research ethics committee, written informed consent of each subject, and in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Patients. Patients eligible for the trial were selected from those who underwent variceal surveillance. The entry criteria was presence of cirrhosis and esophageal varices grade II or larger in size without previous variceal bleeding.[21] Cirrhosis was diagnosed on the basis of clinical, radiological, or laboratory parameters and/or liver biopsy. Exclusion criteria were as follows: age <18 years or >75 years; pregnant or lactating patients; patients of childbearing age not on contraception; allergy to carvedilol; already on beta-blockers or nitrates; presence of malignancy that significantly affects survival; presence of severe systemic illness (cardiorespiratory, active sepsis); psychiatric disease or learning difficulty that will prevent the granting of informed consent; presence of obstructive airways disease; mean arterial pressure <55 mm Hg or pulse <50 beats per minute at baseline; and portal vein thrombosis. Between April 30, 2000, and May 24, 2006, a total of 171 patients were referred for entry into the trial, 19 of which were not eligible for the following reasons: already on beta-blockers or nitrates (n = 6); contraindication to beta-blockers (n = 3); hypotension (n = 2); refusal to consent (n = 4); no evidence of cirrhosis on liver biopsy (n = 1); outside of age limits (n = 1); previous variceal bleed (n = 1); and failure to attend index trial clinic (n = 1). Randomization was performed separately in each center using serially numbered sealed envelopes in batches of 20 that designated one of two treatments: carvedilol or VBL. Randomization occurred in the clinic after the patient underwent a screening endoscopy and was referred to the trial investigators. All the authors were involved in randomization and recruitment, with assistance from research nurses.

Treatments. In the banding arm, the first endoscopy following randomization was for VBL. This was performed using multibander devices (Speedbander, Boston Scientific, Herts, UK; 6-Shooter Saeed Multi-Band Ligator, Cook, Ireland; or Speedband Superview Super 7, Boston Scientific, Natick, MA) by senior fully trained endoscopists or under their direct supervision. Varices were banded starting at the gastroesophageal junction and approximately 5 cm proximally. Following randomization, patients underwent VBL every 2 weeks until eradication. VBL was performed as soon as possible following randomization, excluding the day of randomization. Eradication was defined as the absence of varices or presence of grade I esophageal varices. Following eradication, the interval for the next endoscopy was 3 months, and every 6 months thereafter if varices did not recur. Recurrent esophageal varices were banded, and repeat VBL was performed every 2 weeks until eradication and followed up after eradication as above. There was no routine use of acid suppression or muco-protectants. Secondary gastric varices were treated endoscopically only if they bled.

Carvedilol (Eucardic, Roche, Herts, UK) was administered orally at a start dose of 6.25 mg per day at 09:00. After 1 week, this was increased to a target dose of 12.5 mg per day if systolic blood pressure did not fall below 90 mm Hg. Higher doses have been reported to produce a greater effect on HVPG,[19] but other larger studies using the 12.5-mg dose have demonstrated reductions in the HVPG of 24%-43%,[12,17] particularly following chronic dosing.[12] Furthermore, doses higher than 12.5 mg have compromised tolerability due to symptomatic hypotension.[13,19,20]

Side effects or adverse reactions for both treatments arms were also recorded.

Follow-up. The initial clinic visit was 1 week after introduction of carvedilol and then at 6 weeks in both treatment arms. Follow-up intervals thereafter varied between 3-6 months. Full biochemical and hematological profile was obtained at each consultation. Clinical examination was performed and patients underwent 6 monthly ultrasound examinations as part of hepatoma surveillance. Compliance to carvedilol was assessed through direct questioning and collateral history from relatives and/or the patient's general practitioner. Where appropriate, continued alcohol consumption was assessed by direct questioning and random serum ethanol levels. Patients were censored if they were lost to follow-up, had a liver transplantation, or underwent a transjugular intrahepatic portosystemic shunt (TIPS). After recruitment of the last patient, follow-up was continued in both treatment arms for 6 months.

Definitions of End Points and Outcomes. The primary end point was the first variceal bleed, defined as hematemesis and/or melena with endoscopic evidence of variceal bleeding or stigmata of recent hemorrhage and at least a 2 g/dL reduction in hemoglobin within 24 hours of admission. The definition also included bleeding from

banding ulceration. Hemorrhage was managed in a standard manner using transfusion, terlipressin, antibiotics, endoscopic variceal banding, tissue adhesives or thrombin injection (for gastric varices), and in some cases salvage TIPS. Secondary end points included overall mortality, and bleeding-related mortality defined as death within 6 weeks of the index variceal bleed.[22]

Other outcomes assessed included side effects resulting in treatment discontinuation. Those intolerant of VBL were offered propranolol and not carvedilol, because the efficacy of carvedilol in primary prophylaxis was unknown at the time of study design. Those intolerant of carvedilol were entered into a banding arm because VBL was a proven alternative to beta-blockers for primary prophylaxis at the time of study design.

Per-Protocol Analysis. All data was primarily analyzed using an intention-to-treat (ITT) model, supplemented by per-protocol analysis. We included per-protocol analysis in order to control for patients who may not comply fully with the treatments. In this analysis, time zero was defined as the start of treatment following randomization. Thereafter, follow-up was valid only if the patients remained on the treatments to which they were randomized. Patients were followed up until they reached the end points, had a liver transplantation or TIPS, or were lost to follow-up.

Sample Size Calculation and Statistical Analysis. We postulated that carvedilol would be more effective than VBL with a bleeding rate of 5% versus 20% for VBL at 24 months. The latter figure was derived from published data available at the time of study design.[23] Assuming a power of 0.8 and alpha 0.05, 76 patients were recruited in each arm. There was no interim analysis planned or performed. Baseline parametric data were expressed as the mean ± standard deviation, and any differences in the groups were analyzed using an unpaired Student *t* test. Differences in parametric data over time were analyzed using the paired sample *t* test. Nonparametric data were analyzed using the chi-squared test. Cumulative bleeding and survival were expressed using the Kaplan-Meier method, and differences were assessed using the log-rank test. Cox proportional regression analysis was used to assess variables predicting the end points. Variables with $P < 0.1$ following univariate analysis were entered into multivariate analysis. SPSS (version 15, Chicago, IL), and Excel (Excel XP Version, 2002) statistical packages were used.

Results

A total of 152 patients were randomized for entry into the trial, 77 in the carvedilol arm and 75 in the VBL arm

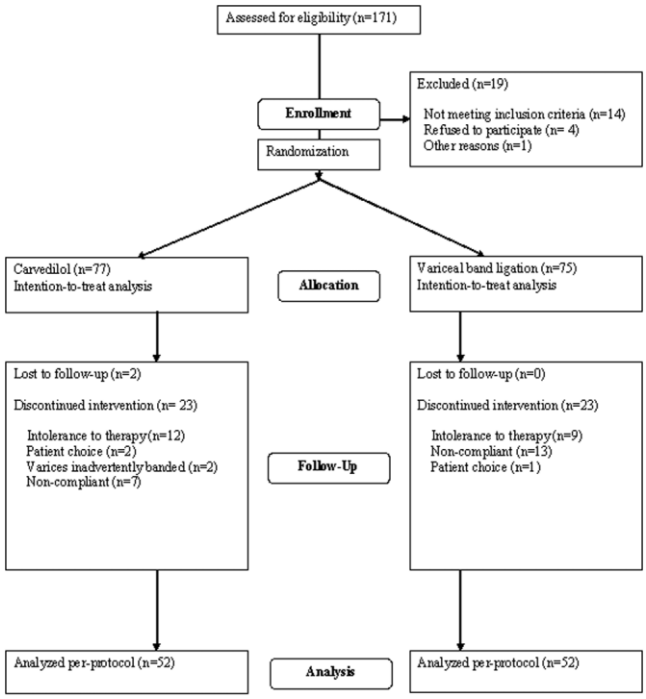


Fig. 1. Flow diagram of study recruitment and follow-up.

(Fig. 1). This clearly illustrates patients who were excluded from per-protocol analysis. The contribution from the five centers was as follows: Royal Infirmary, Edinburgh, n = 111; Gartnavel General Hospital, Glasgow, n = 17; Glasgow Royal Infirmary, n = 10; Victoria Infirmary, Glasgow, n = 8; and Royal Alexandria Hospital, Paisley, n = 6. The baseline characteristics were well-matched (Table 1) and events during follow-up recorded in Table 2.

Treatments

Carvedilol. In total, 39 patients experienced side effects. Most of these were minor and resolved with continued use. There were only 10 patients in whom side effects persisted and were intolerable, resulting in discontinuation of carvedilol. These side effects were shortness of breath (n = 3); impotence (n = 3); nausea and vomiting (n = 2); and symptomatic hypotension (n = 2). Three of these patients (two with ascites) experienced side effects only following dose escalation to the 12.5-mg dose. All those who withdrew were entered into a banding program. One of these patients bled during the follow-up period from esophageal varices. A total of seven patients, all with alcoholic liver disease, were noncompliant. Six patients were transplanted. Carvedilol was also discontinued due to development of chronic obstructive airways disease (n = 1); oral malignancy and inability to take oral medication (n = 1); patient choice (n = 2); and varices

Table 1. Baseline Characteristics of Study Population

Characteristic	Carvedilol (n = 77)	VBL (n = 75)
Age, years	54.2 ± 9.4	54.5 ± 11.1
Pugh score, median (range)	8 (5–13)	8 (5–14)
Child grade, % (A/B/C)	38/24/38	35/25/40
Male:Female	54:23	55:20
Alcohol liver disease		
n (%)	57 (74)	54 (72)
Abstained, n (%)	17 (30)	12 (16)
Creatinine (μmol/L)	84.6 ± 18.3	83.1 ± 27.0
Ascites (%)	49	53
Bilirubin (μmol/L)	65.0 ± 68.4	95 ± 131.0
Albumin (g/L)	33.0 ± 6.8	32.6 ± 6.8
Prothrombin time (secs)	12.8 ± 3.1	13.1 ± 3.8
Varices		
Grade III esophageal varices, n (%)	6 (8)	7 (11)
Gastric varices, n (%)	10 (13)	8 (11)
PHG, n (%) 50 (65) 54 (72)		
Red signs, n (%)	5 (6)	2 (3)
Time from randomization to start of treatment, days, median (range)	0*	21 (1–173)
Follow-up from start of treatment, days	–	26.0 ± 23.0†
Overall follow-up (months)	26.2 ± 22.1	25.5 ± 21.9

All values are expressed as the mean ± standard deviation unless otherwise stated. There were no statistically significant differences between the treatment arms.

*Treatment started within 24 hours.

†Only includes patients who had variceal banding prior to the first variceal bleed.

being inadvertently banded (n = 2). All these patients were entered into a banding program, and none bled during follow-up. Two patients were lost to follow-up. There was no change in mean arterial pressure (92.8 ± 14.7 versus 91.1 ± 11.5 mm Hg [$P = 0.48$]) but a significant reduction in the pulse (83.2 ± 12.3 versus 70.1 ± 9.1 beats per minute, −16% [$P < 0.01$]) during follow-up. Serum creatinine was unaffected during follow-up (87.7 ± 23.2 versus 84.6 ± 13.0 μmol/L [$P = 0.38$]), and compared with the banding arm there was no difference in reports of increased ascites during follow-up (18% versus 21% [$P = 0.49$]).

Variceal Band Ligation. Varices were eradicated in 43 patients (58%) after a mean of 2.4 ± 1.9 sessions, and median of 6 bands in total (range, 1-26 bands). Median time to eradication was 60 days (range, 32-398 days). The median time from randomization to the first endoscopy for banding was 21 days (range, 1-173 days), with 73% of patients having band ligation within 30 days of randomization. A total of 13 patients were noncompliant with the banding protocol. VBL was discontinued due to patient not tolerating intubation with banding device (n = 1); difficulties in obtaining intravenous access (n =1); poor tolerability and/or discomfort during the procedure and patient refusing further VBL (n = 8). All these patients were treated with propranolol, and to date one patient has bled from gastric varices. Recurrent varices after eradication occurred in 23 patients. In those patients who did not have gastric varices at randomization (n = 64), secondary gastric varies were noted in 12 patients (19%). None of these gastric varices bled during follow-up. Ten patients were transplanted in total. There were no patients lost to follow-up.

Outcomes

Variceal Bleeding. Variceal bleeding occurred in eight patients (10%) in the carvedilol arm and 17 patients (23%) in the banding arm during the follow-up period. The 6-, 12-, and 24-month risks of variceal bleeding are detailed in Fig. 2A. Two patients were noted to be noncompliant with carvedilol, and five patients were noncompliant with the VBL protocol prior to the first variceal bleed. There were 10 patients in the VBL arm who bled prior to variceal eradication. Three of these patients bled prior to the first endoscopy after randomization, although two patients had defaulted scheduled banding appointments. Five patients in total bled as a result of banding ulcers, three prior to variceal eradication. None of these episodes was fatal. One patient with refractory bleeding required balloon tamponade and a salvage TIPS. In another patient with active bleeding, hemostasis was achieved with ethanolamine. In the remaining three patients there were stigmata of bleeding from banding ul-

Table 2. Summary of Outcomes

	Carvedilol, n (%)	VBL, n (%)	Relative Hazard (95% Confidence Interval)
Intention-to-treat			
First variceal bleed			
6 months	2 (3.0%)	8 (11%)	
12 months	6 (10.5%)	13 (22%)	0.41 (0.19–0.96), $P = 0.04$
24 months	7 (13.4%)	14 (24%)	
Mortality			
6 months	13 (17%)	9 (14%)	
12 months	16 (22%)	13 (21%)	0.91 (0.53–1.55), $P = 0.71$
24 months	20 (30%)	16 (27%)	
Bleeding mortality			
6 months	2 (3%)	1 (2%)	
12 months	2 (3%)	1 (2%)	1.98 (0.59–6.59), $P = 0.26$
24 months	2 (3%)	2 (2%)	
Per-protocol			
First variceal bleed			
6 months	2 (4.1%)	3 (5.8%)	
12 months	3 (6.5%)	4 (7.8%)	0.68 (0.4–1.91), $P = 0.47$
24 months	5 (11.8%)	7 (16.1%)	
Mortality			
6 months	6 (11.5%)	4 (8.5%)	
12 months	10 (19.2%)	8 (17.3%)	0.84 (0.44–1.59), $P = 0.60$
24 months	14 (28.5%)	12 (27.9%)	
Bleeding mortality			
6 months	2 (3%)	1 (2%)	
12 months	2 (3%)	1 (2%)	3.63 (0.75–17.51), $P = 0.11$
24 months	2 (3%)	2 (2%)	

Table 3. Cox Regression Analysis

	First Variceal Bleed			
	Univariate Analysis		Multivariate Analysis	
Variable	Relative Hazard (95% Confidence Interval)	*P* Value	Relative Hazard (95% Confidence Interval)	*P* Value
First variceal bleed				
Treatment arm (carvedilol)	0.407 (0.167–0.990)	0.047	0.417 (0.180–0.968)	0.042
Age (<55 years)	0.965 (0.917–0.999)	0.044	0.954 (0.914–0.995)	0.029
Sex (M)	0.723 (0.319–1.637)	0.436	–	–
Pugh score	1.084 (0.924–1.271)	0.324	–	–
Alcohol etiology	0.689 (0.304–1.561)	0.372	–	–
Continued alcohol consumption	0.832 (0.310–2.233)	0.715	–	–
Gastric varices	0.547 (0.504–3.642)	0.547	–	–
Grade III esophageal varices	2.698 (1.007–7.227)	0.048	2.718 (1.014–7.288)	0.047
Creatinine	0.999 (0.982–1.016)	0.915	–	–
Recruitment center (Royal Infirmary)	0.732 (0.292–1.834)	0.506	–	–
Time from randomization to start of treatment	1.007 (0.992–1.021)	0.362	–	–
Mortality				
Treatment arm (carvedilol)	0.905 (0.530–1.545)	0.713	–	–
Age (<55 years)	1.012 (0.983–1.041)	0.418	–	–
Sex (M)	1.008 (0.555–1.831)	0.979	–	–
Pugh score	1.239 (1.109–1.384)	<0.001	1.174 (1.040–1.326)	0.010
Alcohol etiology	3.540 (1.410–8.889)	0.007	–	–
Continued alcohol consumption	0.652 (0.341–1.247)	0.196	–	–
Gastric varices	0.394 (0.141–1.098)	0.075	–	–
Grade III esophageal varices	0.753 (0.270–2.102)	0.589	–	–
Creatinine	0.993 (0.982–1.004)	0.225	–	–
Recruitment center (Royal Infirmary)	0.871 (0.471–1.608)	0.658	–	–
Time from randomization to start of treatment	1.004 (0.994–1.014	0.456	–	

cers, with residual grade II varices that were banded. All patients who bled from banding ulcers received proton pump inhibitors, and terlipressin was administered in the first patient who underwent a salvage TIPS. Three patients bled from gastric varices, with two patients in the VBL arm. There were significantly more patients who required a salvage TIPS for variceal bleeding in the banding arm (9 versus 2 [$P = 0.02$]). One of these patients in the VBL arm had been on propranolol due to intolerance of VBL. Univariate and multivariate analyses of prognostic variables are detailed in Table 3. Randomization to the banding arm, age >55 years, and grade III esophageal varices at baseline were variables that predicted variceal bleeding following multivariate analysis (Table 3).

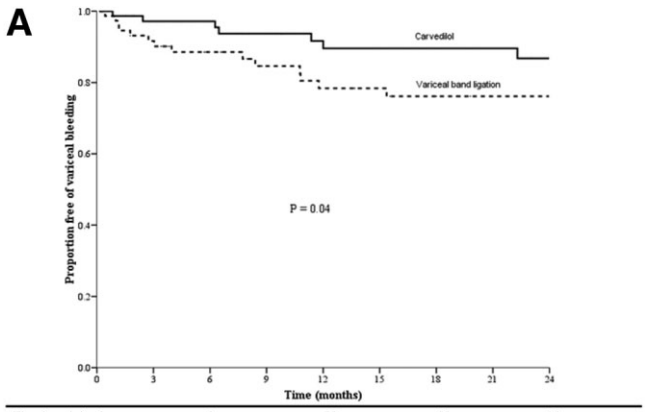
Mortality. There was no evidence of a difference in overall mortality (35% versus 37% [$P = 0.71$]) (Fig. 3A, Table 2), and bleeding related mortality (3% versus 2% [$P = 0.26$]) (Table 2) in the carvedilol and VBL arms, respectively. The development of hepatocellular carcinoma was responsible for one death in each treatment arm. Table 3 shows variables predicting mortality following univariate and multivariate analyses. Child-Pugh score was the only variable predicting mortality following multivariate analysis. Table 4 illustrates the causes of death.

Per-Protocol Analysis. In total, 29 patients in the carvedilol arm experienced side effects compared with five patients in the banding arm. Varices were eradicated in 38 patients (73%) after a mean of 3.5 ± 2.0 sessions, and a median of seven bands in total (range, 1-26 bands). Median time to eradication was 100 days (range, 32-398 days). Recurrent varices after eradication occurred in 20 patients. There was no significant difference in the number of patients requiring a salvage TIPS (2 versus 3 [$P = 0.24$]).

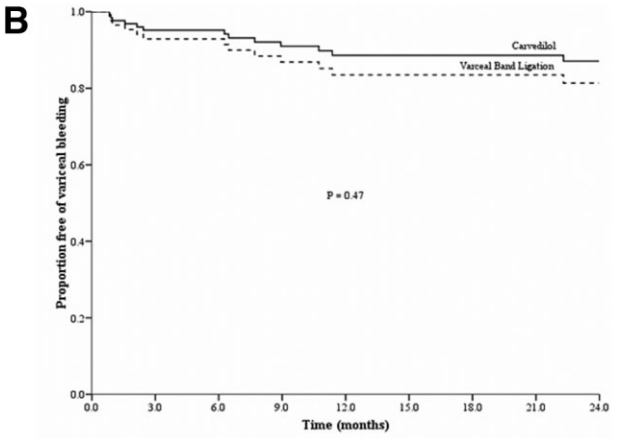
The results of per-protocol analysis are illustrated in Table 2 and in Figs. 2B and 3B. There were no significant differences between the treatment arms for overall mortality bleed (relative hazard 0.84; 95% confidence interval 0.44 – 1.59; $P=0.60$) or variceal bleed (relative hazard 0.68; 95% confidence interval 0.24 – 1.92; $P=0.47$). In the patients who bled in the banding arm, 56% bled prior to variceal eradication.

Table 4. Causes of Death

Cause of Death	Carvedilol (n = 77)	VBL (n = 75)
Variceal bleed	3	2
Infection	3	3
End-stage liver failure	12	15
Hepatocellular carcinoma	1	1
Respiratory failure	–	2
Nonvariceal bleeding	3	1
Cerebrovascular accident	2	2
Cardiovascular event	2	–
Other	–	1



Time (months)	0	6	12	18	24
Carvedilol (n)	77	57	43	35	29
VBL (n)	75	51	37	32	27



Time (months)	0	6	12	18	24
Carvedilol (n)	52	41	30	26	21
VBL (n)	52	46	29	26	23

Fig. 2. Kaplan-Meier analysis of (A) ITT variceal bleeding and (B) per-protocol variceal bleeding.

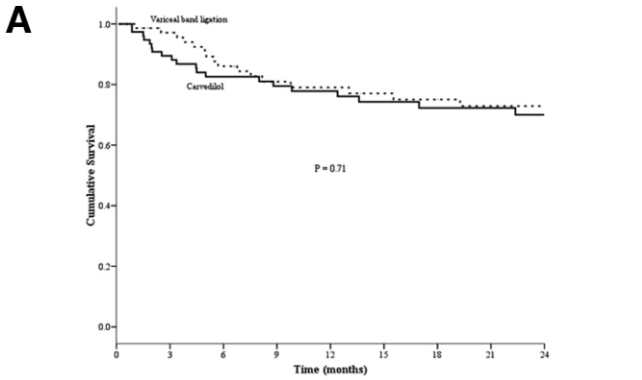
Discussion

This study is the first randomized controlled trial to assess the role of carvedilol in the prevention of the first variceal bleed in patients with high-risk varices. We have found carvedilol to have lower bleeding rates than VBL, with no difference in survival.

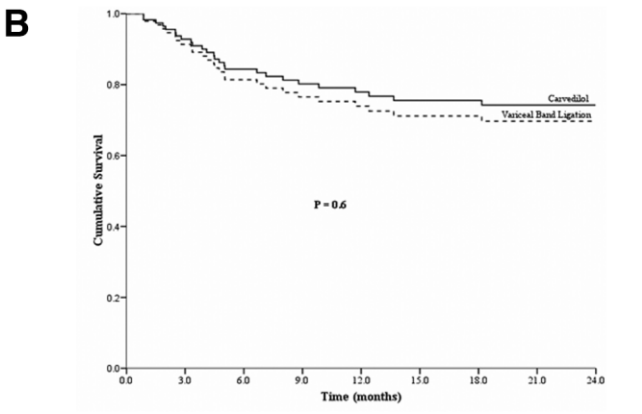
The greater efficacy of carvedilol in the prevention of the first variceal bleed (relative hazard 0.41; 95% confidence interval 0.19-0.96 [$P = 0.04$]) (Table 2 and Fig. 2A) is an important finding of this study. No other randomized trial has demonstrated drug therapy to have an advantage over VBL. The individual results of three trials demonstrated superiority of VBL,[23-25] with high bleeding rates in the beta-blocker arm in two trials (27%[23] and 30%[25]). The 12.5-mg target dose of carvedilol is based on previous studies.[12,17] Caution is required in patients with more advanced liver disease due to increased bioavailability of carvedilol.[26,27]

The 23% rate of variceal bleeding in the banding arm is higher than in the last study published from our unit,[28] but other studies with larger numbers of patients and longer follow-up in the banding arms reported rates between 14% and 25%.[29-31] The variceal eradication rate at 58% is lower than in other trials, although a trial with an eradication rate of 70% had no bleeding in the VBL arm.[24] The eradication rate is greater at 73% in the per-protocol analysis, and may explain the better results with VBL, where the 2-year bleeding rate was 16% compared with 24% in the ITT analysis (Table 2). Clearly eradication is important, because over 55% of patients bled prior to variceal eradication in both ITT and per-protocol analyses.

A noteworthy finding in this study is the high rate of banding-induced bleeding. None of these episodes was fatal, and the banding protocol was similar to other patients in the banding arm. Banding-induced ulceration was responsible for bleeding in 10 patients in the previous trials, with three fatalities.[31-33] The need for short inter-



Time (months)	0	6	12	18	24
Carvedilol (n)	77	62	49	41	33
VBL (n)	75	58	44	39	35



Time (months)	0	6	12	18	24
Carvedilol (n)	52	41	30	26	21
VBL (n)	52	38	30	27	25

Fig. 3. Kaplan-Meier analysis of (A) ITT mortality and (B) per-protocol mortality.

vals of 1 to 2 weeks between banding sessions was questioned by recent evidence showing better eradication of esophageal varices with two monthly (rather than weekly) band ligations,[35] and one study actually showed a reduced risk of rebleeding from esophageal varices.[35] However, our protocol is in keeping with most trials and recent guidelines published by the AASLD.[36] A recent study comparing banding with placebo in patients intolerant of beta-blocker for primary prophylaxis was terminated early due to VBL-related bleeding in three patients, although there were no statistical differences in bleeding or mortality.[37] A notable observation was that 60% of the patients had small (<5 mm) varices. This study emphasizes the need for careful patient selection, and VBL should be restricted to those with moderate to large varices. The role of acid suppression during a banding program is uncertain, but the two trials where proton pump inhibitors were used did not have any significant banding-related complications.[24,25] Another placebo-controlled randomized controlled trial using pantoprazole as an adjunct to VBL resulted in smaller ulcers with pantoprazole, with no difference in ulcer number.[38] There were three bleeds from postbanding ulcers in the control arm, although this was not significantly different from the treatment group. Further study is necessary to define the optimum banding protocol, and clinicians may feel less anxious about longer intervals between VBL for primary prophylaxis as opposed to secondary prophylaxis. Likewise, the benefit of vasoconstrictors such as terlipressin for postbanding bleeding is not clear, and we only used terlipressin in one patient with refractory bleeding requiring a salvage TIPS.

There were no significant differences in overall and bleeding-related mortality. This study was not powered to show a difference in mortality. It is clear that the chance of death from a bleeding episode is low at 2% to 3%, and mortality reflects the underlying severity of liver disease rather than variceal bleeding. There is only one trial, by Jutabha et al.,[24] that is remarkable for having no episodes of bleeding and improved survival in the VBL arm. The results of this study were available after the last patient in our trial was recruited. We therefore did not see any reason to perform an interim analysis.

The side effect profile for carvedilol may be more favorable than propranolol, where up to a third of patients had to discontinue therapy due to side effects in the previous study from our unit with a similar population.[28] Clearly direct comparison with propranolol is necessary to confirm this, because other large studies have reported better tolerability with propranolol.[29-31] The dose titration from 6.25 mg to 12.5 mg may help to improve tolerability of carvedilol. This is particularly important for patients with advanced liver disease and ascites, and one could argue that such patients should be started on even lower doses. Carvedilol clearly had a biological effect in our study due to a reduction in the pulse, although blood pressure was unaffected. An observation noted in a previous hemodynamic study was that of increased plasma volume and weight gain with carvedilol.[20] We did not find any differences in the reporting of increased ascites in patients on carvedilol compared with VBL. We recognize that there may be significant variation in the reporting of ascites, and where possible we attempted to back up clinical findings with radiology, because all patients were scanned regularly.

A potential limitation of this study is the exclusion of propranolol. At the time of study design, VBL was found to have a lower bleeding rate than propranolol.[23] We wanted to compare carvedilol with the best available current therapy, hence the use of VBL. Delays in banding following randomization may have contributed to three bleeding episodes prior to the first endoscopy for VBL, although two of these patients did not attend scheduled banding appointments. Carvedilol can be prescribed in the clinic following randomization, whereas this is not possible with VBL. However, despite delays in randomization to VBL, this was not a variable predicting variceal bleeding following univariate analysis, and with a *P* value of 0.362, the variable could not be entered into multivariate analysis (Table 3).

We did not perform HVPG measurements, although we recognize that HVPG is useful in assessing efficacy and identifying nonresponders to propranolol or nadolol.[39] However, high-quality studies demonstrate carvedilol to have a greater effect on HVPG than propranolol, with over 60% of patients having a hemodynamic response, defined as a reduction in HPVG ≤12 mm Hg or by ≥20% of baseline.[19,20] In a study performed in our unit using 12.5 mg once daily carvedilol, almost 90% of patients had a hemodynamic response.[12] One could therefore argue whether HVPG monitoring is necessary with carvedilol therapy, particularly when it is used for primary prophylaxis and given the low rate of bleeding with carvedilol in this study of 10%. Furthermore, given this low event rate, a large number of patients will be required to provide any meaningful statistics when correlating HVPG with clinical outcome. It is also important to appreciate that most centers outside of large university teaching hospitals are unlikely to have the expertise or facility to perform HVPG monitoring.

In conclusion, we have shown that carvedilol is effective in preventing the first variceal bleed, and is well tolerated. The difference in favor of carvedilol in the ITT analysis has to be interpreted with caution in view of the difficulties in adherence to the banding protocol in our

patient population. Further studies should aim to increase compliance with VBL protocols, with particular emphasis on variceal eradication. However, we believe that carvedilol can be considered a treatment option for primary prophylaxis of variceal bleeding. VBL is currently the only alternative in patients intolerant of carvedilol or those unlikely to comply with drug therapy. Patient choice and local availability should also be taken in to account.

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