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REVIEW ARTICLE

Beta-blockers in portal hypertension: new developments and controversies

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Keywords
band ligation – carvedilol – cirrhosis – propranolol – variceal bleeding

Abbreviations
eNOS, endothelial nitric oxide synthase; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; ISMN, isosorbide-5-mononitrate; NO, nitric oxide; NSBB, non-cardioselective beta-blockers; RCT, randomized controlled trial; SBP, spontaneous bacterial peritonitis; sGC-PKG, soluble guanylyl cyclase/protein kinase G; TIPSS, transjugular intrahepatic portosystemic stent-shunt; VBL, variceal band ligation; VSMC, vascular smooth muscle cells; WHVP, wedge hepatic venous pressure.

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Abstract

There are many studies investigating the role of non-selective beta-blockers in portal hypertension. Satisfactory reduction in portal pressure is possible in a third to half of patients with propranolol and nadolol, although combining these drugs with nitrates may be more effective. Carvedilol is a more potent agent than propranolol in reducing portal pressure, particularly in non-responders, and is better tolerated. All these drugs have been studied in primary and secondary prophylaxis, sometimes in combination with band ligation and/or nitrates. There is some evidence to support combining these agents with band ligation, despite a lack of survival benefit and increased adverse events. Hemodynamic monitoring can help select non-responders who may benefit from additional therapies such as band ligation, as lack of response is associated with worse outcomes. Propranolol should be used with caution in patients with refractory ascites, although the current evidence is not of sufficient quality to justify not using these drugs in such situations. Beta-blockers have been shown to reduce bacterial translocation and spontaneous bacterial peritonitis in cirrhosis.

Since the introduction of propranolol (1), many studies have investigated non-cardioselective beta-blockers (NSBB) in portal hypertension. The aim of therapy is to reduce portal pressure to below 12 mmHg or by more than 20% (2, 3). This can only be achieved in approximately a third to half of patients with propranolol and nadolol (4, 5). The combination of these drugs with nitrates can result in an additional effect on portal pressure (6). These agents are effective in preventing variceal bleeding and rebleeding, although they have a significant side effect profile (7–9). Carvedilol can reduce portal pressure to a greater degree than propranolol, and is effective in primary and secondary prophylaxis (10–12).

Hepatic venous pressure gradient (HVPG) monitoring has a role predicting response to NSBB and long-term prognosis (13, 14). Hemodynamic monitoring of patients on NSBB therapy can assist in selecting non-responders for additional therapies, such as nitrates and endoscopic treatment.

Non-cardioselective beta-blockers can have beneficial effects on bacterial translocation in cirrhosis and may help reduce spontaneous bacterial peritonitis (SBP) (15). However, NSBB in patients with advanced cirrhosis and ascites may have detrimental effects on outcomes (16, 17). This is a particularly controversial issue because of the lack of controlled studies.

This review aims to summarize the clinical studies of beta-blocker use in portal hypertension, with emphasis on developments in the last decade. The following terms were used for searching for articles in Pubmed, Web of

Knowledge and Medline: propranolol, non-selective beta-blocker, nadolol, carvedilol, portal hypertension, variceal bleeding, randomized, meta-analysis. Papers were selected from a total of 294 retrieved.

Pathophysiology of portal hypertension and utility of hepatic venous pressure gradient

Portal hypertension results from three principal events. The first is a purely mechanical obstruction as a result of fibrosis or regenerative nodules increasing resistance to flow. The second event accounts for 20–30% of increased intrahepatic resistance to portal inflow. There is contraction of sinusoidal and perisinusoidal contractile cells [stellate cells and vascular smooth muscle cells (VSMCs)] with intrahepatic imbalance between vasoconstrictors (such as endothelin 1 and angiotensin) and vasodilators (such as nitric oxide and glucagon) (18). This imbalance leads to reduced intrahepatic eNOS activity. The third event is splanchnic vasodilatation in response to a relatively ischaemic liver or extrahepatic excess of NO, with sGC-PKG signalling and smooth muscle cell relaxation (19). The result is increased portal blood flow, which maintains portal hypertension. These hemodynamic changes lead to the hyperdynamic circulation, which manifests as high cardiac output with low systematic vascular resistance and arterial hypotension (18). The second and third events are amenable to drug therapy.

Portal pressure can be derived from the HVPG, which is normally 1–5 mmHg. The technique of measuring HVPG is described elsewhere (20). HVPG represents the gradient between portal and caval pressure, and is elevated in sinusoidal and post-sinusoidal portal hypertension:

$$\mathrm{HVPG} = \mathrm{WHVP} - \mathrm{FHVP}$$

Free hepatic venous pressure (FHVP) cancels out variations in abdominal pressure and acts as an internal zero. A reduction in HVPG to <12 mmHg or by more than 20% with drug therapy protects against variceal bleeding (2, 3). Varices are also more likely to develop if the HVPG is >10 mmHg (21).

Mechanism of action of beta-blockers in portal hypertension and principal hemodynamic effects

Non-cardioselective beta-blockers act in two principal ways to reduce portal pressure (Table 1). Firstly, there is beta 1 receptor blockade, which results in reduced cardiac output and splanchnic blood flow (22). Secondly, beta 2 receptor blockade results in splanchnic vasoconstriction caused by unopposed effect of alpha 1 receptors (23). Beta 2 effects occur principally after chronic use (24).

The effect of propranolol on HVPG is variable, with up to 31% reduction reported (Table 1). However, a third of patients do not have a hemodynamic response to propranolol, despite azygous blood flow studies, suggesting that all patients have a reduction in portocollateral flow (25). A rise in portocollateral resistance is a proposed mechanism (25). A recent study with nadolol supports this hypothesis (26). In this observational study of 24 patients, there was significant discrepancy between the acute and chronic effect on HVPG. Those patients who had poor chronic response demonstrated increased resistance to portal blood flow. Patients with hypertension exhibit a similar response to propranolol as those who are normotensive, with a reduction in mean arterial pressure only seen in hypertensive patients (27). Therefore, NSBB are a good choice in hypertensive patients with cirrhosis.

Nadolol has a longer half-life than propranolol as a result of low lipid solubility and hepatic metabolism (28). This permits once-daily dosage. Hemodynamic effects mirror those of propranolol, although effects on mean arterial pressure may not be so pronounced (Table 1) (4).

Table 1. Beta-blockers used in portal hypertension and the principal hemodynamic effects in clinical studies

		Effects on hemodynamic parameters (% decrease from baseline)					
Drug	Mechanism of action	Mean arterial pressure	Cardiac output/cardiac index	Hepatic venous pressure gradient	Estimated hepatic blood flow	Azygous blood flow	Clinical studies
Propranolol	Non-selective beta-blocker	0–14	10–31	10–31	0–39	29–47	Phase III
Nadolol	Non-selective beta-blocker	0–6	25–29	19–32	10–24	N/A	Phase III
Timolol	Non-selective beta-blocker	NS	N/A	20	N/A	N/A	Phase III
Atenolol	Selective beta 1 receptor blocker	NS	32	NS	N/A	N/A	Phase II
Metoprolol	Selective beta 1 receptor blocker	N/A	17	19–22	NS	N/A	Phase III
ICI 118551	Selective beta 2 receptor blocker	NS	14	11	N/A	N/A	Phase II
Mepindolol							
Carvedilol	Non-selective beta-blocker and alpha 1 receptor blocker	4–17	7–18	15–43	10–65	14–20	Phase III

N/A, data unavailable; NS, not significant compared to baseline.

Table 2. Hemodynamic studies of carvedilol vs propranolol in patients with portal hypertension

Study	Drug(s)/dose (number of patients)	Ascites (%)	Acute/chronic study	Mean arterial pressure	Cardiac output	Heart rate	Hepatic venous pressure gradient	Hemodynamic response (%)	Estimated hepatic blood flow	Azygous blood flow	Systemic vascular resistance	Sodium excretion
				(% difference from baseline unless otherwise stated)								
Banares 1999 (40)	Carvedilol 25 mg (14)	50	Acute	*−17*	*−10*	*−11*	*−21 (−23)**	*64*	−10	−20	*−10*	N/A
	Propranolol IV† (14)	50		*NS*	*−23*	*−16*	*−13*	*14*	−14	−24	*+20*	N/A
De 2002 (41)	Carvedilol 25 mg (18)	67	Acute	−11	N/A	−9	−28		N/A	N/A	N/A	N/A
	Propranolol 80 mg (18)	89		NS	N/A	−14	−23		N/A	N/A	N/A	N/A
	Carvedilol 12.5 mg (17)	65	Chronic	*−16*	N/A	−15	−28		N/A	N/A	N/A	N/A
	Propranolol 80 mg (18)	89	(7 days)	*−6.2*	N/A	−25	−22		N/A	N/A	N/A	N/A
Banares 2002 (10)	Carvedilol 31 mg (26)	39	Chronic	*−11*	*−15*	*−16*	*−19*		*NS*	−14	*NS*	NS
	Propranolol 73 mg (26)	24	(11 weeks)	*−5*	*−22*	*−24*	*−12*		*−19*	−24	*+19*	NS
Lin 2004 (68)	Carvedilol 25 mg (11)	N/A	Acute	NS	−18	−11	*−19*	N/A	+29	N/A	NS	N/A
	Propranolol 40 mg + ISMN 20 mg (11)	N/A		−10	−23	−15	*−10*	N/A	NS	N/A	NS	N/A
Hobolth 2012 (42)	Carvedilol (19)	N/A	Acute	N/A	N/A	−26	*−24*		N/A	N/A	N/A	N/A
	Propranolol 80 mg(16)	N/A		N/A	N/A	−19	*−13*		N/A	N/A	N/A	N/A
	Carvedilol 14 mg (21)	N/A	Chronic	NS	N/A	−18	−19		NS	N/A	N/A	N/A
	Propranolol 122 mg(17)	N/A	(90 days)	−8	N/A	−22	−13		−36	N/A	N/A	N/A
Reiberger 2013 (14)	Carvedilol 17 mg(67)	8	Chronic	−14	N/A	−17	*−19*		N/A	N/A	N/A	N/A
	Propranolol 98 mg(94)	11	(28 days)	−11	N/A	−23	*−12*		N/A	N/A	N/A	N/A

Values in *italics* indicate a significant difference between the two treatment arms.

N/A, data unavailable; NS, not significant compared with baseline; ISMN, isosorbide-5-mononitrate.

*Value in brackets at 2 h in 6 patients.

†0.15 mg/kg initially followed by infusion of 0.2 mg/h.

Timolol, like nadolol, has low lipid solubility and is less likely to result in central side effects. Timolol also has a greater affinity for both beta 1 and, particularly, beta 2 receptors than propranolol or nadolol (28). Theoretically, this characteristic could result in a greater reduction in portal pressure. However, there are no comparative clinical studies of timolol and other drugs in portal hypertension (29).

There have been attempts to enhance the portal hypotensive effects of NSBB by combination with other agents, such as isosorbide-5-mononitrate (ISMN) (25). ISMN is an organic nitrate, which is believed to reduce portal pressure as a result of increased intrahepatic production of nitric oxide or cyclic-GMP (25). These effects reduce intrahepatic resistance. In combination with NSBB, the reduction in portal pressure can be enhanced by as much as 17% in non-responders to NSBB (25).

Studies of selective beta 1 blockade with atenolol have yielded results inferior to propranolol, despite theoretical advantages of fewer central side effects, long duration of action and better maintenance of hepatic blood flow (30). The results with metoprolol were more promising, with similar reductions in portal pressure compared with propranolol (31). However, one trial has demonstrated no advantage of metoprolol over placebo in preventing gastrointestinal bleeding (32). Selective beta 2 blockade offers no advantage over propranolol, and has the potential to reduce hepatic blood flow to a greater degree (33, 34).

Carvedilol is a NSBB with additional vasodilating actions as a result of alpha 1 receptor blockade. The latter reduces portocollateral resistance, and through effects on hepatic stellate cells intrahepatic resistance is reduced. Carvedilol has 2–4 times more potent action on beta receptors than propranolol. Carvedilol and propranolol are both extensively protein bound. Reduced albumin levels in advanced cirrhosis may also increase bioavailability of carvedilol, especially in those with ascites. There is no conclusive evidence to support worsening of ascites, despite a study suggesting this (10). As there is biliary excretion of the active metabolites, severe cholestasis can influence the efficacy of carvedilol (35). Carvedilol has also been reported to have antioxidant, antifibrotic and anti-inflammatory properties, and can improve mitochondrial function and enhance insulin sensitivity (36–38).

Hepatic venous pressure gradient is reduced by up to 43% after chronic use of carvedilol, and its efficacy is greater than propranolol (Table 2) (39). More patients exhibit a hemodynamic response to carvedilol compared with propranolol (40). A well-conducted study demonstrated that 56% of patients not responding to propranolol had a hemodynamic response to carvedilol (14). One study showed an acute HVPG response being predictive of long-term effects (41), although this was not confirmed by others (42). Doses higher than 6.25–12.5 mg per day increase the risk of hypotension without enhanced effect on HVPG, particularly in patients with advanced liver disease. It would be advisable to start at low doses such as 3.125–6.25 mg per day, and titrate up slowly.

Use of beta-blockers in patients with gastro-oesophageal varices

There are nearly 200 clinical trials investigating the role of beta-blockers in patients with varices. The common drugs used in clinical practice are detailed in Table 3.

Preprimary prophylaxis (patients without varices)

Plevris *et al.* showed no benefit of propranolol in an unselected group of patients with chronic liver disease (n = 319), which also included patients without

Table 3. Beta-blockers used in clinical practice for primary and secondary prophylaxis against variceal bleeding

Drug	Cost for 1 month's supply	Dosage	Major side effects/adverse events.	Cautions
Propranolol*	£1.70 (40 mg bd)	40 mg daily dose. Dose titrated to maximum tolerated or once HR 50–55 bpm reached to a maximum dose of 320 mg. Indefinite duration.	Fatigue, shortness of breath, symptomatic hypotension, bradycardia and conduction defects, sleep disturbance, peripheral circulation insufficiency including claudication and Raynaud's phenomenon, impotence	Asthma and obstructive airways disease. Uncontrolled heart failure. Severe peripheral vascular disease. Severe hepatic impairment, particularly with ascites where lower doses may be required. Severe renal impairment
Nadolol	£5.00 (80 mg od)	40 mg daily dose. Dose titrated to maximum tolerated or once HR 50–55 bpm reached a maximum dose of 240 mg. Indefinite duration		
Carvedilol	£1.30 (12.5 mg od)	6.25 mg once daily to increase to maintenance of 12.5 mg after a week if tolerated or once HR <50–55 bpm reached. Indefinite duration		

*Licensed for use in portal hypertension in the UK.

NSBB, non-selective beta-blocker; HR, heart rate; HVPG, hepatic venous pressure gradient.

Table 4. Clinical trials of NSBB vs VBL in primary prophylaxis

Study	Patients (*n*)	ALD (%)	Childs's class (% A/B/C)	Mean age (y)	Follow-up (months)	Grade of oesophageal varices (%)	Red signs (%)	Bleeding (%)	Mortality (%)
Chen 1998 (69)†	26/30	N/A	N/A	N/A	12	N/A	N/A	4/7	12/11
Sarin 1999 (70)	45/44	27/41	(16/51/33)/(20/50/30)	44/39	13/14	III (71/77), IV (29/23)	N/A	9/27*	11/9
De 1999 (71)	15/15	14/20	(33/53/14)/(40/47/13)	42/39	18	III (13/27), IV (87/73)	N/A	33/7	7/0
Mora 2000 (72)†	12/12	N/A	N/A	N/A	N/A	N/A	N/A	8/16	0/8
Song 2000 (73)†	31/30	N/A	N/A	N/A	N/A	N/A	100/100	10/20	16/27
Gheorghe 2002 (74)†	25/28	N/A	N/A	N/A	15	N/A	N/A	12/46*	4/18
Lui 2002 (57)	44/66	73/62	(31/36/33)/(27/38/35)	54/55	18/21	II (91/82), III (9/18)	0/6	7/14	23/25
Abulfutuh 2003 (75)†	44/66		Child's score 8	55	30.1	N/A	N/A	9/15	36/29
Lo 2004 (56)‡	50/50	20/20	(44/42/14)/(48/34/18)	55/57	22/23	F2 (58/64), F3 (42/36)	34/34	10/18	24/22
Schepke 2004 (76)	75/77	53/49	(45/41/14)/(48/40/12)	54/57	32	II (43/46), III (57/54)	39/39	25/29	45/43
Jutabha 2005 (77)	31/31	13/10	(39/39/22)/(26/48/26)	54/55	18/12	3–5 mm varices + red signs (3/10), >5 mm varices (97/90)	For >5 mm varices (81/62)	0/13*	0/13*
Thuluvath 2005 (78)	16/15	31/7	(35/45/20)	50/54	27	F2/F3 varices in all – no further details	N/A	13/7	38/20
Psilopoulos 2005 (79)	30/30	27/23	(43/40/17)/(50/40/10)	62/59	27/28	II (77/77), III (23/23)	100/100	7/30*	40/33
Abdelfattah 2006 (80)†	51/52	N/A	N/A	N/A	18–24	N/A	N/A	8/26*	8/10
Lay 2006 (81)	50/50	20/22	(44/42/14)/(46/36/18)	56/55	35/35	F2/F3 varices in all	N/A	22/24	28/24
Norberto 2007 (82)	31/31	N/A	Child's score >7 in all	53/52	17/12	F2 (27/26), F3 (4/5)	100/100	7/10	10/10
Tripathi 2009 (11)**	75/77	72/74	(35/25/40)/(38/24/38)	55/54	26/26	II (89/92), III (11/8)	3/6	23/10*	37/35
Perez 2010 (83)	39/36	21/28	(59/36/5)/(47/42/11)	60/58	55	N/A	100/100	12/25	51/33
Drastich 2011 (84)	40/33	65/60	(45/50/5)/(61/30/9)	57/56	11/10	N/A	43/43	5/6	5/6

Results expressed as VBL/NSBB. ALD, Alcoholic liver disease; VBL, variceal band ligation; N/A, data unavailable; NSBB, Non-selective beta-blockers

†Abstract.

Propranolol used in all studies except where indicated: ‡Nadolol, **Carvedilol.

*$P < 0.05$.

cirrhosis and varices (43). The promising hemodynamic effects of timolol led to a well-designed randomized placebo controlled trial in patients with cirrhosis (n = 213) and baseline HVPG >6 mmHg, but without varices (21). This failed to demonstrate a difference in the primary end point of variceal bleeding, with more side effects in the timolol arm. However, patients with a HVPG >10 mmHg at baseline, or those with <10% annual reduction during follow-up were more likely to develop varices. Therefore, there is no conclusive evidence to support the use of NSBB in patients without varices.

Primary prophylaxis (patients with varices that have not previously bled)

The role of NSBB in patients with small or grade I oesophageal varices has been studied in two randomized controlled trials (RCTs). The first trial of propranolol in patients with small, or no, varices showed that more patients developed varices in the treatment arm (44). This trial was criticized for including patients without varices, loss of follow-up of a third of patients, and the dosing regime of propranolol being fixed and not titrated to heart rate. The second trial included only patients with small varices, and showed that nadolol therapy reduced the incidence of variceal bleeding, but without survival benefit and increased adverse events (45). Therefore, using NSBB in all patients with small varices is controversial, but could be considered in patients with more advanced liver failure and/or red signs on endoscopy at higher risk of bleeding (46, 47).

Non-cardioselective beta-blocker therapy has been studied extensively in patients with at least medium-sized or grade II oesophageal varices. Randomized placebo controlled trials have demonstrated benefits of NSBB in preventing bleeding, with improved survival in a meta-analysis (48). ISMN has been compared with propranolol or nadolol, with no effect on survival and a tendency towards worse survival in those over 50 (49, 50). ISMN in combination with NSBB has yielded mixed results, and has a worse side effect profile (51, 52).

Non-cardioselective beta-blockers have been compared with endoscopic therapy in a large number of trials. Sclerotherapy is inferior to variceal band ligation (VBL) with increased adverse events, and offers no benefit when combined with NSBB over monotherapy with NSBB (53–55). Therefore, recent trials have focused on comparing NSBB with VBL in patients with at least medium-sized varices. Nineteen RCTs (1504 patients) were reviewed in a recent Cochrane meta-analysis (8). The drugs used were propranolol (mean dose 70 mg per day) in 17 trials (Table 4), nadolol (mean dose 60 mg per day)(56) and carvedilol (12.5 mg target dose) (11). The results are detailed in Fig. 1 and demonstrate less bleeding with VBL. However, in trials with low selection and attrition bias or just published papers, the difference was no longer present. There was no difference in bleeding-related or overall mortality. Adverse events included bleeding after VBL, and hypotension, dizziness and impotence with NSBB. Carvedilol has a good side effect profile compared with propranolol, with only 10% experiencing significant problems (11, 57). Another meta-analysis demonstrated that NSBB resulted in fewer fatal adverse events (OR 0.14; 95% 0.02–0.99) (58). A further trial with carvedilol has been published in abstract form, showing similar efficacy to VBL (59).

Although the above trials did not utilize hemodynamic monitoring, this has been used in other studies to

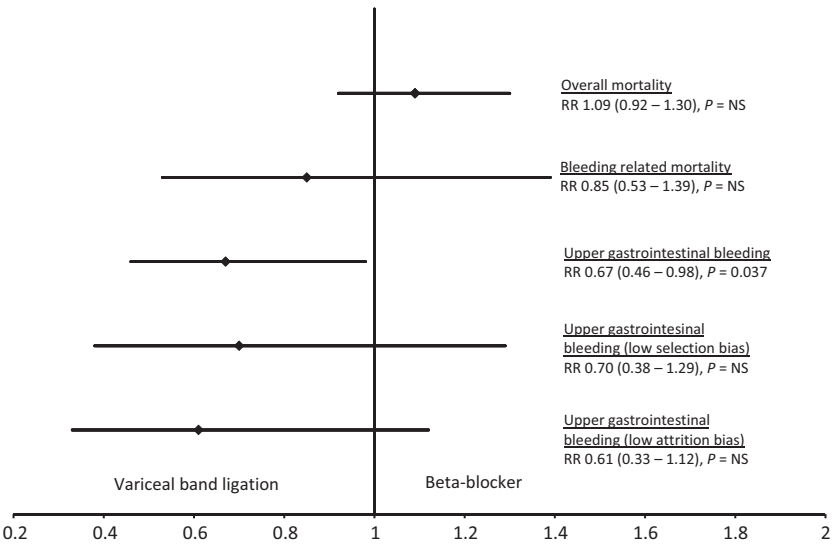

Fig. 1. Forest plot of outcomes in trials of primary prophylaxis [variceal band ligation (VBL) vs beta-blocker] (8).

Table 5. Summary of trials of VBL and drug therapy for secondary prophylaxis

Study	Treatment arms	Total no. patients	Childs's class (% A/B/C)	Follow-up	Bleeding (%)	Mortality (%)
VBL vs drugs						
Agarwal 2002 (85)†	VBL vs Propranolol + ISMN	104	N/A	18/16 months	19/36	13/14
Villanueva 2001 (86)	VBL vs Nadolol + ISMN	144	(15/60/25)/(26/55/19)	22/20 months	50/36	42/32
Patch 2002 (87)	VBL vs Propranolol + ISMN	102	(9/35/56)/(16/38/46)	356/248 days	53/37	33/33
Sarin 2005 (88)	VBL vs Propranolol + ISMN	137	(49/38/13)/(41/42/17)	12/11 months	14/27	8/6
Shiha 2005 (89)†	VBL vs Propranolol vs Propranolol + ISMN	181	N/A	12 months	28/42/52	13/15/18
Lo 2008 (64)	VBL vs Nadolol + ISMN	121	(22/58/20)/(21/57/21)	82/81 months	47/80*	70/49*
Smith 2013 (66)†	VBL vs Carvedilol	63	N/A (mean CPS = 9)	23 months	29/35	52/25
VBL + drugs vs VBL or drugs alone						
Abdel-Rahim 2000 (90)†	VBL + Propranolol vs VBL	50	N/A	3/3 months	N/A	8/12
Lo 2000 (91)	VBL + Nadolol + sucralfate vs VBL	122	(18/50/32)/(19/45/36)	22/21 months	23/47*	17/32
Lo 2001 (92)	VBL + Propranolol vs VBL	77	(8/49/43)/(10/53/37)	17/17 months	24/33	N/A
Sollano 2001 (93)†	VBL + Propranolol vs VBL	31	N/A	10/9 months	0/13	6/0
de la Peña 2005 (94)	VBL + Nadolol vs VBL	80	(14/58/28)/(16/54/30)	18/15 months	14/40*	12/11
Lo 2009 (95)	VBL + Nadolol + ISMN vs Nadolol + ISMN	120	(33/49/18)/(35/52/13)	23/23 months	38/52	27/22
Garcia-Pagan 2009 (96)	VBL + Nadolol + ISMN vs Nadolol + ISMN	158	(20/58/22)/(23/54/23)	15/14 months	28/35	20/22
Ahmad 2009 (97)	VBL + Propranolol + ISMN vs Propranolol or Propranolol + ISMN or VBL	150	(11/73/16) (15/59/26) (6/54/40) (18/59/23)	10/8 months	VBL + drugs vs VBL: 22/31 VBL + drugs vs drugs: 22/32	VBL + drugs vs VBL: 18/21 VBL + drugs vs drugs: 19/20
Kumar 2009 (98)	VBL + Propranolol + ISMN vs VBL	177	(46/41/13)/(35/45/20)	15/15 months	17/19	2/4

VBL, variceal band ligation; ISMN, Isosorbide-5-mononitrate; CPS, Child-Pugh Score; N/A, not available.

†Abstract.

*$P < 0.05$.

predict response to drug therapy and prognosis. A meta-analysis of three trials (60), two of which included combination NSBB and ISMN therapy, demonstrated that patients with HVPG reduction by 20% or to <12 mmHg were less likely to bleed (RR 0.24; 95% CI 0.10–0.56). An observational study showed that >10% HVPG reduction acutely with intravenous propranolol significantly reduced risk of variceal bleeding (4% vs 43%, $P < 0.001$), and development of ascites (67% vs 25%, $P = 0.001$) (61). There was a trend towards improved survival. Another study has confirmed these findings using a cut-off HVPG response of >12% (62).

In the study mentioned earlier, hemodynamic non-responders to propranolol were treated with carvedilol (14). Patients responding to carvedilol continued this drug, while non-responders were treated with VBL alone. Bleeding, hepatic decompensation and mortality over 2 years were particularly worse in patients on VBL compared with hemodynamic responders to propranolol or carvedilol. This would suggest that patients not responding to NSBB should be considered for combination therapy with VBL + NSBB, rather than VBL alone. However, the study was not randomized and selected higher risk patients for VBL.

The current AASLD guidelines and Baveno V consensus statements recommend NSBB or VBL as primary prophylaxis in patients with medium/large varices (46, 47). VBL could be considered in patients with advanced liver disease and red signs on endoscopy (47).

Secondary prophylaxis (prevention of variceal rebleeding

The mortality following a variceal bleed is 40% at 1 year (Table 5). Variceal rebleeding occurs in 60% at 1 year, with 6-week mortality of 20% for every variceal rebleed (47). Therefore, secondary prophylaxis must be commenced from day 5 onwards (46). In a meta-analysis of 12 RCTs (769 patients) comparing NSBB with no treatment or placebo, there was more variceal rebleeding (OR 2.38; 95% CI 1.6–3.5) and higher mortality (OR 1.4; 95% CI 1–1.9) with control (63). Combining NSBB and ISMN does not offer any benefit over NSBB alone, and results in more adverse events and discontinuation of therapy (7) (Fig. 2). NSBB + ISMN compared with VBL or sclerotherapy does not offer any benefit in bleeding, and reduced mortality was not confirmed on trial sequential analysis in a meta-analysis (7) (Fig. 3). There was no difference in bleeding-related mortality; thus, improved mortality may be the result of enhanced portal pressure reduction with NSBB + ISMN (64). In a recent study, NSBB reduced bacterial translocation and variceal bleeding, which correlated with the degree of portal hypertension (65).

A recent meta-analysis showed that medical therapy combined with VBL resulted in less rebleeding than monotherapy (VBL or drug therapy), although this was only seen when VBL + drug therapy was compared with VBL alone (Fig. 4). There was no effect on overall mortality, although bleeding-related mortality was reduced (9). The reasons why reduced bleeding-related mortality did not translate to reduced overall mortality are not clear, but may be because of small numbers in the trials, quality of trials (only one had adequate overall bias control) or loss of patients to follow-up. Combination medical therapy + VBL also resulted in more serious adverse events, such as banding-induced bleeding (Fig. 4). Therefore, combination banding and drug therapy offers little benefit over drug or VBL therapy alone.

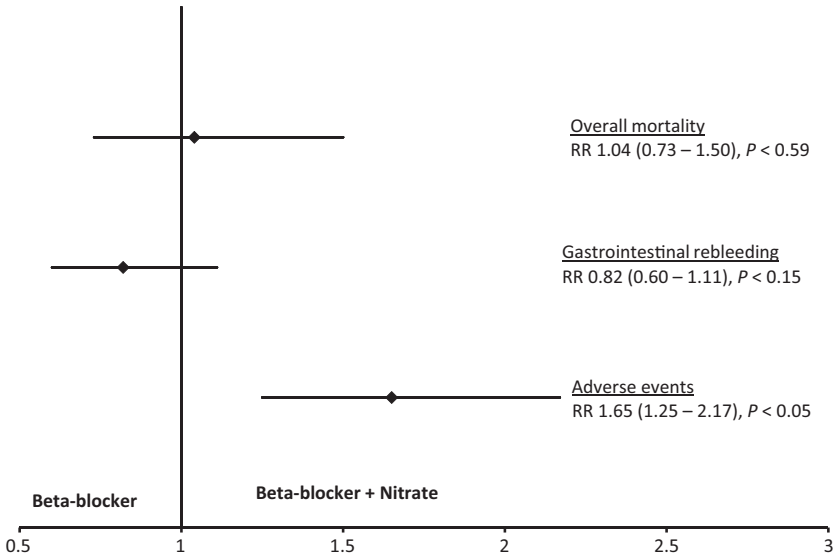

Fig. 2. Forest plot of outcomes in trials of secondary prophylaxis (beta-blocker vs beta-blocker + nitrate) (7).

There is one published RCT reporting on the use of carvedilol in secondary prophylaxis (12). Carvedilol at a mean dose 10.4 mg/24 h was compared with nadolol + ISMN. There was no difference in variceal rebleeding or mortality, but increased adverse events with nadolol + ISMN. The high rebleeding rate of 51% may reflect inadequate dosing of carvedilol, and there was no HVPG monitoring. Another RCT published in abstract form compared carvedilol with variceal band ligation (66). This showed similar results with a trend towards reduced mortality in the carvedilol arm. However, the current recommendations for VBL + drug therapy were not followed (46, 47). Another abstract comparing VBL + carvedilol vs VBL in primary and secondary prophylaxis showed similar outcomes with reduced recurrence of varices in the primary prophylaxis group (67). Therefore, carvedilol is an attractive therapy owing to similar efficacy to current therapies with the potential for improved tolerability.

There are several studies investigating the role of hemodynamic monitoring. A meta-analysis of six trials (60) showed that patients with a hemodynamic response to NSBB (+ISMN in 5 trials) were less likely to rebleed (RR 0.35; 95% CI 0.16–0.80). For all trials of primary and secondary prophylaxis, there was a significant reduction in liver-related mortality in responders to

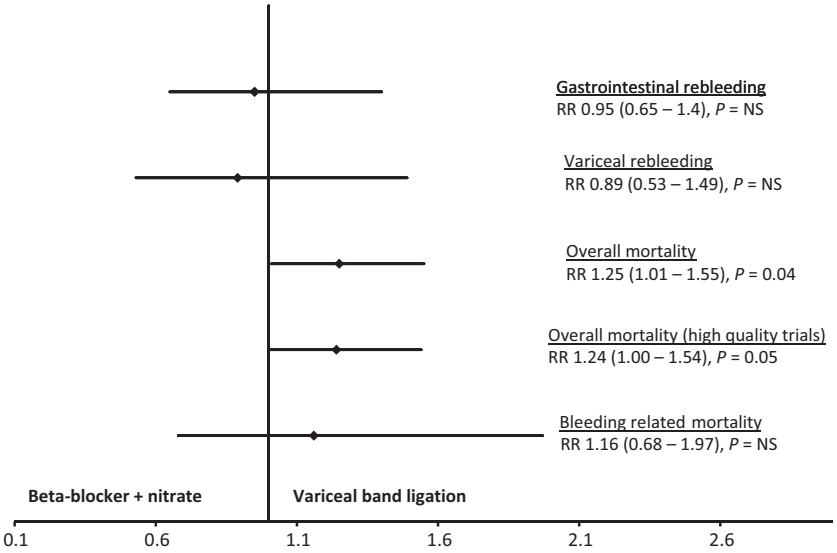

Fig. 3. Forest plot of outcomes in trials of secondary prophylaxis [beta-blocker+ nitrate vs variceal band ligation (VBL)] (7).

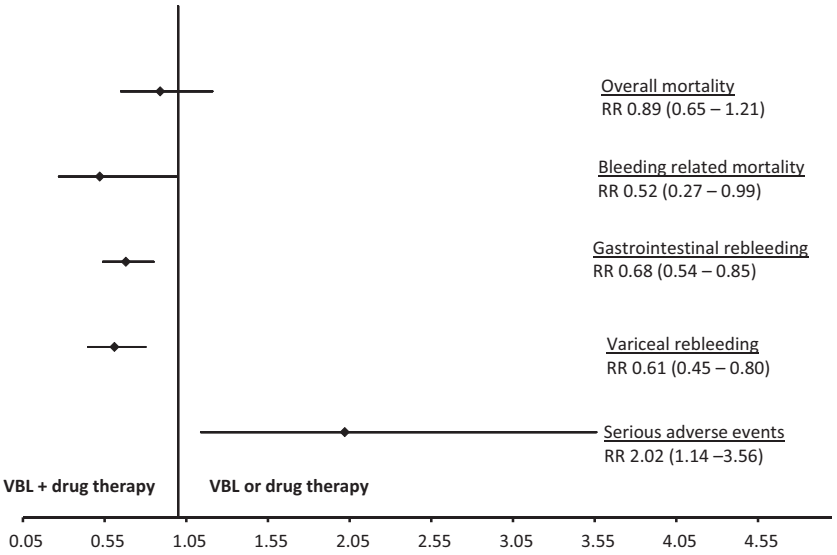

Fig. 4. Forest plot of outcomes in trials of secondary prophylaxis [variceal band ligation (VBL)+ drug therapy vs drug therapy or VBL] (9).

drug therapy (RR 0.58; 95% CI 0.37–0.91). A longer interval between HVPG measurements reduced the accuracy of hemodynamic response in predicting bleeding. A limitation was the inclusion of observational studies as opposed to only RCTs, and heterogeneity as a result of the different time intervals between repeat HVPG measurements. Patients without a hemodynamic response to drug therapy treated with additional VBL have good outcomes. One of the larger series with a follow-up of 48 months studied 103 patients with annual HVPG measurements if they were hemodynamic responders (47%) (13). Patients who lost hemodynamic response (35%) had worse outcomes, and all abstinent patients with alcoholic liver disease maintained long-term response compared to 36% for those not abstinent.

The current published guidelines recommend a combination of NSBB and VBL as optimal therapy for secondary prophylaxis, and that hemodynamic monitoring with addition of ISMN in non-responders may improve efficacy (46,47).

Controversies in the use of beta-blockers in patients with advanced cirrhosis and ascites

The studies of primary and secondary prophylaxis mostly excluded patients with advanced liver disease and ascites. There has been much controversy about the role of beta-blockers in advanced cirrhosis, in particular, the potential for detrimental effects in patients with ascites as reported by recent studies. Serste el al showed that, in an observational single study of 151 patients with refractory ascites, patients treated with propranolol had worse 1-year survival (19% vs 64%, $P < 0.0001$) (16). Child's class C, hyponatraemia, renal dysfunction and NSBB therapy were independent predictors of mortality. HVPG was similar in both groups, although it was available in only 37% of patients. However, there were more patients with varices, and slightly sicker patients in the propranolol group. Many deaths were as a result of hepatocellular carcinoma, which cannot be attributed to propranolol. Finally, the trial was not controlled. The same group also showed that, in patients with refractory ascites, propranolol increased the risk of paracentesis-induced circulatory dysfunction in a pilot study of 10 patients (17). These studies have fuelled much debate about the role of NSBB in refractory ascites. It is very important to bear in mind that the studies are uncontrolled and had design flaws greatly limiting the validity of their conclusions. Furthermore, randomized studies and a meta-analysis have reported on the benefits of NSBB in preventing spontaneous bacterial peritonitis (SBP) (15). It is premature to conclude that NSBB can cause harm in patients with advanced cirrhosis without well-conducted RCTs. Nevertheless, it would be sensible to closely monitor patients with refractory ascites on NSBB and have a low threshold to discontinue therapy and offer alternatives, such as VBL.

Conclusions

Non-cardioselective beta-blockers have transformed the management of patients with portal hypertension. A limitation of propranolol and nadolol is that a third of patients do not show a hemodynamic response. Carvedilol is more effective than propranolol, with up to 80% hemodynamic response. Therefore, hemodynamic monitoring is probably not necessary for carvedilol. Clinical trials of primary and secondary prophylaxis strongly support the use of NSBB. Combining NSBB + ISMN is of little benefit, although combination drug and VBL can reduce bleeding in secondary prophylaxis without a mortality benefit. Carvedilol is highly effective in patients not responding to propranolol, with the potential for better tolerability. The reported detrimental effects of propranolol on patients with refractory ascites are not universally accepted based on current low-level evidence.

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