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REVISIÓN SISTEMÁTICA Y METAANÁLISIS: CARVEDILOL VS. PROPRANOLOL PARA HIPERTENSIÓN PORTAL EN PACIENTES CIRRÓTICOS

SYSTEMATIC REVIEW AND META-ANALYSIS: CARVEDILOL VS. PROPRANOLOL FOR PORTAL HYPERTENSION IN CIRRHOTIC PATIENTS

TESIS

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DRA. NANCY EDITH AGUILAR OLIVOS

Tutor:
DR. NORBERTO CARLOS CHÁVEZ TAPIA

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CONTENIDO

Systematic review and meta-analysis: Carvedilol vs. propranolol for portal hypertension in cirrhotic patients

Short title: Carvedilol for portal hypertension

N. Aguilar-Olivos*, N.C. Chávez-Tapia*

* Medica Sur Clinic & Foundation, Mexico City, Mexico.

Correspondence to:

N. C. Chavez-Tapia, Obesity and Digestive Diseases Unit, Medica Sur Clinic & Foundation, Puente de Piedra 150, Col. Toriello Guerra, Tlalpan 14050, Mexico City, Mexico.

E-mail: nchavezt@medicasur.org.mx

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SUMMARY

Background

Portal hypertension causes the most serious complications in cirrhotic patients. Carvedilol, a non-selective beta-blocker with weak anti-α1 adrenergic activity, appears to be more effective than propranolol in the treatment of portal hypertension in cirrhotic patients.

Aim

To compare the effects of carvedilol versus propranolol on systemic and splanchnic haemodynamics in cirrhotic patients and to evaluate the adverse events associated with these treatments.

Methods

We performed a systematic review following the Cochrane and PRISMA recommendations. Randomised controlled trials comparing carvedilol versus propranolol in the treatment of portal hypertension in cirrhotic patients with oesophageal varices with or without bleeding history were included. The primary outcome measure was the haemodynamic response to treatment. Fixed-effect and random-effect meta-analyses were performed.

Results

Four randomised trials and 145 patients were included; 76 patients received carvedilol (6.25–50 mg/d) and 69 patients received propranolol (10–320 mg/d). The hepatic vein pressure gradient (HVPG) decreased more with carvedilol than with propranolol (mean difference –2.22; 95% CI: –2.83 to –1.60, $P < 0.00001$). Carvedilol was superior to propranolol for reducing HVPG by ≥20% from the baseline value or to ≤12 mmHg (OR: 2.91; 95% CI: 1.46 to 5.77, $P = 0.002$). Sixty per cent of patients achieved this objective after

carvedilol treatment versus 35% after propranolol treatment. Overall adverse events did not differ between the carvedilol and propranolol groups.

Conclusions

Carvedilol is more effective than propranolol for improving the haemodynamic response in cirrhotic patients with portal hypertension; the occurrence of adverse effects does not differ between treatments.

INTRODUCTION

The exact worldwide prevalence of cirrhosis is undefined, but it is estimated at about 0.15% or 400,000 people in the USA[1]. Natural history of cirrhosis leads to portal hypertension and the development of varices and gastrointestinal bleeding[2-5]. At diagnosis, varices are present in 30–40% of compensated patients and in 60% of those with ascites[6]. In cirrhotic patients without varices, the annual incidence of new varices is 5–10%[7-9]. The first haemorrhagic event is a signal of decompensated disease; the 1-year rate of this event is about 5% for small varices and 15% for large varices[10]. Variceal bleeding is associated with a 6-week mortality rate of 10–20%[11], and the one-year mortality rate is 57%[2].

The risk of bleeding can be reduced significantly by decreasing the hepatic vein pressure gradient (HVPG) to <12 mmHg or by 20% from the baseline value[12,13]. The HVPG can be reduced by administration of a non-selective beta-blocker (NSBB), such as propranolol. NSBB alone is recommended for prevention of the first bleeding episode and in combination with band ligation for prevention of re-bleeding[11]. Propranolol is recommended widely in the treatment of portal hypertension; unfortunately, more than a half of patients fail to achieve the haemodynamic objective because of lack of drug efficacy, intolerance to the drug, or adverse effects.

Carvedilol, an NSBB with weak anti-α1 adrenergic activity, appears to be more effective than propranolol in the treatment of portal hypertension[14-17], but there is inconsistency between studies involving head-to-head comparisons of carvedilol versus propranolol treatment. The primary aim of this systematic review and meta-analysis was to compare carvedilol versus propranolol for haemodynamic control of portal hypertension in cirrhotic patients. The

secondary aim was to evaluate the adverse events associated with both interventions.

METHODS

Types of studies

The present systematic review and meta-analysis is based on Cochrane and PRISMA recommendations[18,19].

We included randomised clinical trials that compared the efficacy of carvedilol versus propranolol therapy for control of portal hypertension in cirrhotic patients. There was no restriction regarding time, language, or publication status.

Types of participants

All adult patients diagnosed with liver cirrhosis, portal hypertension and oesophageal varices with or without a history of variceal bleeding were included.

Types of interventions

Studies that compared the acute or chronic effect of carvedilol versus propranolol on haemodynamic control of portal hypertension were included. We excluded trials that evaluated interventions other than carvedilol vs. propranolol monotherapy.

Types of outcome measures

The primary outcome measure was the haemodynamic control of portal hypertension. Secondary outcome measures were other haemodynamic parameters, adverse events including hypotension, renal function deterioration, variceal bleeding, and bleeding-related mortality.

Search methods to identify studies

Electronic searches were performed in the Cochrane Library and MEDLINE. The literature search was performed using the medical subject headings terms “Propranolol” AND "Carvedilol" AND "Hypertension, Portal". No limits were applied. The search results were examined for abstracts and full versions, and suitable trials were identified. The search update was performed in March 2013.

Searching other resources

References of original and review articles were also reviewed to identify other relevant trials.

Selection of studies

Screening of abstracts and a selection of full-text articles were performed by two principal reviewers (NAO, NCT). They independently inspected each trial and applied the inclusion criteria. In case of disagreement, a third author reviewed the article. Justification for study exclusion was documented.

Data extraction and management

Data were extracted from reports by the same two authors in an independent manner. The extracted data included the year of trial, location, participants’ characteristics, number of subjects treated in each group, dose and duration of propranolol and carvedilol treatments, outcome measures, and risk of bias. Discrepancies were resolved through discussion with the other authors.

Assessment of risk of bias in included studies

The risk of bias was assessed following the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0[19]. The methodological quality of the trials focused on randomisation methods assessed by allocation sequence generation and allocation concealment. We

included evaluations of blinding, reporting bias, and handling of missing outcome data.

Measures of treatment effect and data analysis

Data analyses were performed using Review Manager (RevMan), version 5.2. (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). For summary measures, the results of continuous data are expressed as the mean difference (MD) with 95% confidence interval (CI), and dichotomous measures are presented as odds ratio (OR) with 95% CI. For synthesis of the results, we analysed the data using both fixed- and random-effects models; when both models produced similar estimates, the fixed-effect result is reported.

Assessment of heterogeneity

Heterogeneity of effects across trials was evaluated by visual inspection of the forest plots and χ^2 and I^2 tests for heterogeneity. Statistical heterogeneity was defined as a *P* value ≤0.10 for χ^2 or an I^2 value >25%.

Assessment of reporting biases

A funnel plot estimating the precision of trials (plot of logarithm of the OR against the sample size) was used to evaluate asymmetry and to detect potential publication bias. In addition, the standard normal deviate (SND), defined as the RR divided by its standard error, was regressed against the estimate's precision (regression equation: SND = a + b ´ precision) to quantify the bias captured by the funnel plot.

Sensitivity analysis

We analysed the data using both fixed- and random-effect models. When both models produced similar estimates, the fixed-effect result is reported. Outcomes are reported in an intention-to-treat manner.

RESULTS

Study selection and study characteristics

The literature search identified 10 trials and no additional records after thorough examination of the references of review articles. A total of four head-to-head randomised trials[14-17] were included in the systematic review and meta-analysis (Figure 1). The trials were conducted in Spain[14,16], India[15], and Denmark[17], and included a total of 145 patients, 76 of whom were given carvedilol (dose 6.25–50 mg/d) and 69 were given propranolol (dose 10–320 mg/d). The characteristics of the included trials are shown in Table 1. Alcoholic cirrhosis was the principal aetiology reported. All patients had severe portal hypertension (HVGP >12 mmHg) and the presence of oesophageal varices with or without a history of variceal bleeding. The percentage of patients with primary prophylaxis was 36–100% in the studies. Three trials included patients with ascites[14-16].

All studies evaluated the intervention effect on HVGP. The first study evaluated only the acute effect (60 minutes)[14], the second trial reported the acute and chronic effect (90 minutes and 7 days)[15], the third investigated the longer-term response (77.7 days)[16], and the fourth evaluated both acute and chronic effects (90 minutes and 92.7 days)[17].

Assessment of risk of bias in trials

Random sequence generation was reported in three studies, and the allocation concealment was reported in only one trial (Table 2). The four trials used blinded assessment, but only one used blinding of participants and personnel[17]. Selective reporting of outcome measures was not registered in

any trial. Only one trial performed sample size calculations and met the required sample size[16].

Synthesis of results

Carvedilol was superior to propranolol in reducing HVPG by ≥20% from the baseline value or to ≤12 mmHg (OR: 2.91; 95% CI: 1.46 to 5.77, *P* = 0.002) (Figure 2). The percentage of patients achieving this objective was 60% with carvedilol versus 35% with propranolol, with a number needed to treat of 4. The magnitude of reduction in HVPG was also greater with carvedilol (MD: –2.22; 95% CI: –2.83 to –1.60, *P* < 0.00001) (Figure 3).

All haemodynamics parameters recorded are summarised in Table 3. The wedged hepatic venous pressure decreased significantly (MD: –2.79; 95% CI: –3.64 to –1.93, *P* < 0.00004), but the free hepatic venous pressure remained unchanged (MD: –0.58; 95% CI: –1.20 to 0.03, *P* = 0.6).

All studies reported mean arterial pressure (MAP), but only one[14] indicated statistically significant changes; however, the overall effect on MAP did not differ between groups (MD: –4.20; 95% CI: –10.71 to 2.31, *P* = 0.21) (Figure 4). Systemic vascular resistance (SVR) and cardiac output (CO) were reported only in the studies by Bañares *et al*.[14,16]. The first study by Bañares *et al*.[14] reported a significant decrease in SVR, but the second study did not[16]. Our meta-analysis showed a greater reduction in SVR in the carvedilol group (MD: –115.23; 95% CI: –182.76 to –47.70, *P* = 0.0008). For CO, results from individual studies and the overall meta-analysis did not differ between groups (MD: 0.09; 95% CI: –0.18 to 0.36, *P* = 0.52). Heart rate was reported in all studies and was higher with carvedilol (MD: 2.36; 95% CI: 0.69 to 4.03, *P* = 0.006).

Three studies[14-16] included mean pulmonary arterial pressure (MPAP), right arterial pressure (RAP), and wedge pulmonary arterial pressure (WPAP). Carvedilol decreased MPAP (MD: –4.32; 95% CI: –5.07 to –3.57, $P < 0.00001$), RAP (MD: –2.47; 95% CI: –3.13 to –1.81, $P < 0.00001$), and WPAP (MD: –4.17; 95% CI: –4.88 to –3.45, $P < 0.00001$).

Finally, the hepatic[14,16,17] and azygos[14,16] blood flow was evaluated. Hepatic blood flow was unchanged (MD: 0.04; 95% CI: –0.07 to 0.14, $P = 0.51$), but the azygos blood flow was increased in the carvedilol group (MD: 100.98; 95% CI: 57.28 to 144.68, $P < 0.00001$).

Adverse events

Adverse events leading to withdrawal occurred with the same frequency (OR: 0.52; 95% CI: 0.18–1.54, $P = 0.24$) (Figure 5). The rate of orthostatic or symptomatic hypotension did not differ between groups (OR: 1.60; 95% CI: 0.64–4.02, $P = 0.32$) (Table 4). Other adverse effects such as dizziness, impotence, headache, chest pain, skin rash, cold extremities, diarrhoea, and encephalopathy were evaluated by one trial[17], which showed no differences between carvedilol and propranolol (Table 4).

Renal function, including glomerular filtration rate; serum concentrations of creatinine, urea, sodium, and potassium; urinary sodium excretion; plasma renin activity; and body weight did not differ between the treatments (Table 5). Bañares *et al.*[16] found a higher plasma volume in the carvedilol group (MD: 0.40; 95% CI: 0.12 to 0.68, $P = 0.005$), and two studies[16,17] reported a tendency toward increased diuretic consumption in the carvedilol group (OR: 2.65; 95% CI: 0.92 to 7.65, $P = 0.07$).

Finally, variceal bleeding and mortality were reported in two trials[15,17], and these did not differ significantly between treatments (Table 4).

DISCUSSION

This systematic review and meta-analysis analysed the current head-to-head randomised trials comparing carvedilol versus propranolol for portal hypertension in cirrhotic patients. Portal pressure decreased more with carvedilol compared with propranolol treatment. A higher percentage of patients showed a reduction in HVPG by ≥20% from the baseline value or to ≤12 mmHg after carvedilol than after propranolol administration. Analysis of adverse events showed no significant differences between carvedilol and propranolol. The results of this meta-analysis suggest that carvedilol is a better alternative for primary and secondary variceal bleeding prophylaxis in cirrhotic patients.

Differences in the specific doses of carvedilol and propranolol used to treat portal hypertension might have contributed to the differences between the studies. Studies with higher doses of carvedilol[14,16] were those that showed statistically significant differences in their favour. This agrees with the previous finding by Bañares *et al.* that the haemodynamic effect of carvedilol is dose dependent[14]. However, some studies have suggested that lower doses of carvedilol (12.5 mg/d) provide a good portal pressure-reducing effect with less systemic vasodilation[20,21].

Differences between baseline HVPG within individual studies also deserve mention. In particular, the study by De *et al.* noted that the superiority of carvedilol over propranolol could not be demonstrated probably because the mean baseline HVPG was lower in the propranolol group than in the carvedilol group (16.60 mmHg vs. 19.00 mmHg, respectively, $P = 0.0719$).

In clinical practice, the findings of our meta-analysis may benefit patients who are unresponsive to treatment with propranolol because a higher percentage of patients, about 25%, reached the target HVPG reduction after carvedilol administration. In this concern, the greater therapeutic potential of carvedilol over propranolol has recently been demonstrated in a pragmatic design[22].

In regard to adverse events, we did not find significant differences in the meta-analysis. Acute administration of carvedilol seems to cause significant systemic vasodilatation, but long-term effects of carvedilol on MAP and SVR are less pronounced that those observed after acute administration. This could be explained by tolerance (decrease of expression of α1-receptors) or pseudotolerance with haemodynamics adjustments, without adverse effects on renal function.

We found some limitations in this review. A low number of patients were considered in each trial and the results for some haemodynamics were obtained from a minimum number of patients. Another limitation is that there was no standardisation of the carvedilol and propranolol doses, so the ranges were broad. Finally, the studies were conducted with short follow-up periods, thus, there is no information from long-term comparisons and no data on clinical outcomes such as the long-term adverse effects, variceal bleeding, and mortality.

Future studies are needed with a larger number of patients and long-term monitoring, directed at clinical outcomes, mainly variceal bleeding and mortality.

In conclusion, this systematic review and meta-analysis showed that carvedilol is more effective than propranolol for improving the haemodynamic

response in cirrhotic patients with portal hypertension, and there are no important differences in adverse effects between these two drugs.

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Authorship Statement

Guarantor of the article: Dr. N. C. Chavez-Tapia.

Author contributions: NAO developed the idea for this review, designed the protocol, performed literature search, analysed data and wrote the manuscript. NCT collaborated to design the protocol, performed literature search, analysed data, reviewed and edited the manuscript. MMK performed literature search and reviewed the manuscript. NMS and MU reviewed the manuscript. All authors have approved the final version of this article, including the authorship list.

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Table 1. Characteristics of head-to-head comparing included trials.

Study	Intervention	Dose mg/d P.O. (range)	Acute/chronic study (time)	Patients (n)	Mean age ±SD (y) at baseline	Aetiology Alcohol/Viral/Other n (%)	Primary prophylaxis at baseline n (%)	Secondary prophylaxis at baseline n (%)	Child C at baseline n (%)	Ascites at baseline n (%)	Outcome
Bañares *et al.*, 1999 (Spain)	Carvedilol	25*	Acute (60 min)	14	54.6 ± 8.8	8(57)/na/na	5 (36)	9 (64)	2 (14)	7 (50)	To compare the effects of carvedilol, propranolol and placebo on hepatic and systemic haemodynamics in patients with cirrhosis
	Propranolol	0.2**	Acute (60 min)	14	51.4 ± 8.5	8(57)/na/na	5 (36)	9 (64)	3 (21)	7 (50)	
	Placebo	0	Acute (60 min)	7	57 ± 10.8	4(57)/na/na	3 (43)	4 (57)	2(29)	6(86)	
De *et al.*, 2002 (India)	Carvedilol	25*	Acute (90 min)	18	42.3 ± 11.9	5(28)/9(50)/4(22)	11 (61)	7 (39)	4 (22)	12 (67)	To compare the effects of carvedilol and propranolol on HVPG, acutely and over 7 days, in cirrhotics with oesophageal varices. There was monitored blood pressure, pulse rate and renal function.
	Propranolol	80*	Acute (90 min)	18	47.3 ± 12.9	10(55)/5(28)/3(17)	11 (61)	7 (39)	5 (28)	16 (89)	
	Carvedilol	12.5*	Chronic (7 d)	15-17***	42.3 ± 11.9	-	11 (61)	7 (39)	4 (22)	12 (67)	
	Propranolol	80*	Chronic (7 d)	14-16***	47.3 ± 12.9	-	11 (61)	7 (39)	5 (28)	16 (89)	
Bañares *et al.*, 2002 (Spain)	Carvedilol	31 (12.5-50)	Chronic (77 ± 30 d)	26	57.9 ± 1.5	6(23)/19(69)/2(8)	26 (100)	0 (0)	3 (12)	10 (38)	To compare the effects of long-term carvedilol therapy versus propranolol on systemic and splanchnic haemodynamics and on renal function in a large series of patients with cirrhosis.
	Propranolol	73 (10-160)	Chronic (77 ± 30 d)	25	58.4 ± 2.2	9(36)/16(64)/0	25 (100)	0 (0)	4 (16)	6 (24)	
Hobolth *et al.*, 2012 (Denmark)	Carvedilol	6.25	Acute (90 min)	22	-	-	-	-	-	-	To compare the acute and long-term effects of carvedilol with those of propranolol on HVPG in patients with cirrhosis and portal hypertension.
	Propranolol	80	Acute (90 min)	22	-	-	-	-	-	-	
	Carvedilol	14 (6.25-25)**	Chronic (92.7 ± 13.6 d)	21	58.2 ± 6.8	18(86)/2(9)/1(5)	16(76)	5(24)	6(29)	na	
	Propranolol	122 (80-320)**	Chronic (92.7 ± 13.6 d)	17	56.2 ± 6.1	12(71)/1(6)/4(23)	12(71)	5(29)	4(24)	na	

*Fixed dose. **Intravenous infusion (mg/kg/h). ***It was reported different numbers of patients according to measurements. na, not available; HVPG, hepatic venous pressure gradient.

Table 2. Assessment of risk of bias summary for each included study.

Author	Random sequence generation	Allocation concealment	Blinding (detection bias)	Blinding of participants and personnel	Incomplete outcome data	Selecting reporting	Sample calculation
Bañares *et al.*, 1999	?	?	Yes	No	Yes	Yes	No
De *et al.*, 2002	Yes	?	Yes	?	Yes	Yes	No
Bañares *et al.*, 2002	Yes	?	Yes	No	No	Yes	Yes
Hobolth *et al.*, 2012	Yes	Yes	Yes	Yes	No	Yes	No

Table 3. Haemodynamics analyses from randomised clinical trials comparing efficiency of carvedilol vs. propranolol on portal hypertension in cirrhotic patients.

	Number of trials	Number of patients	MD (95% CI)	*P* value	I^2 Statistic (%)
HVPG (mmHg)	4	145	−2.21 (−2.83 to −1.60)	<0.00001	0
WHVP (mmHg)	3	112	−2.79 (−3.64 to −1.93)	<0.00001	0
FHVP (mmHg)	3	112	−0.58 (−1.20 to 0.03)	0.06	0
MAP (mmHg)	4	144	−4.20 (−10.71 to 2.31)	0.21	77
SVR (dyn·s/cm^5)	2	74	−115.23 (−182.76 to −47.70)	0.0008	0
CO (L/min)	2	74	0.09 (−0.18 to 0.36)	0.52	57
HR (beats/min)	4	144	2.36 (0.69 to 4.03)	0.006	59
MPAP (mmHg)	3	103	−4.32 (−5.07 to −3.57)	<0.00001	0
WPAP (mm/Hg)	3	103	−4.17 (−4.88 to −3.45)	<0.00001	42
RAP (mmHg)	3	104	−2.47 (−3.13 to −1.81)	<0.00001	52
ABF (mL/min)	2	74	100.98 (57.28 to 144.68)	<0.00001	60
HBF (L/min)	3	100	0.04 (−0.07 to 0.14)	0.51	43

HVPG, hepatic venous pressure gradient; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; ABF, azygos blood flow; HBF, hepatic blood flow; MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; MPAP, mean pulmonary artery pressure; WPAP, wedge pulmonary artery pressure (mmHg); RAP, right atrial pressure; SVR, systemic vascular resistance; MD, mean difference; CI, confidence interval.

Table 4. Summary of adverse events reported from randomised clinical trials comparing efficiency of carvedilol vs. propranolol on portal hypertension in cirrhotic patients.

	Number of trials	Carvedilol (n/N)	Propranolol (n/N)	OR (95% CI)	P value	I^2 Statistic (%)
Events leading to withdrawal	3[15-17]	6/68	10/65	0.52 (0.18–1.54)	0.24	0
Orthostatic or symptomatic hypotension	2[15-17]	14/68	9/65	1.60 (0.64–4.02)	0.32	0
Dizziness	1[17]	0/24	2/22	0.17 (0.01–3.69)	0.26	na
Impotence	1[17]	0/24	2/22	0.17 (0.01–3.69)	0.26	na
Headache	1[17]	1/24	1/22	0.91 (0.05–15.54)	0.95	na
Chest pain	1[17]	1/24	0/22	2.87 (0.11–74.26)	0.52	na
Skin rash	1[17]	1/24	0/22	2.87 (0.11–74.26)	0.52	na
Cold extremities	1[17]	5/24	3/22	1.67 (0.35–7.98)	0.52	na
Diarrhoea	1[17]	0/24	2/22	0.17 (0.01–3.69)	0.26	na
Encephalopathy	1[16]	3/26	4/25	0.68 (0.14–3.42)	0.64	na
Shortness of breath	2[16,17]	12/50	7/47	1.80 (0.64–5.07)	0.26	0
Increased diuretic use	2[16,17]	14/50	6/47	2.65 (0.92–7.65)	0.07	0
Variceal bleeding	2[15,17]	1/42	3/40	0.39 (0.06–2.78)	0.35	0
Mortality	2[15,17]	1/42	2/40	0.63 (0.10–3.93)	0.62	32

OR, odds ratio; CI, confidence interval; na, not applicable

Table 5. Renal function after carvedilol or propranolol treatment for portal hypertension in cirrhotic patients.

	Number of trials	Number of patients	MD (95% CI)	*P* value	I^2 Statistic (%)
GFR (mL/min)	1[16]	46	–13.00 (–29.85 to 3.85)	0.13	na
Serum creatinine (mg/dL)	2[15,16]	79	0.03 (–0.08 to 0.13)	0.65	0
Urea (mg/dL)	1[15]	33	–13.00 (–37.46 to 11.46)	0.30	na
Serum sodium (mEq/L)	1[16]	46	–0.10 (–2.18 to 1.98)	0.93	na
Serum potassium (mEq/L)	1[16]	46	–0.10 (–0.38 to 0.18)	0.48	na
Urinary sodium excretion (mEq/d)	1[16]	46	36.00 (–13.00 to 85.00)	0.15	na
Plasma renin activity (μg/mL/h)	1[16]	46	–0.43 (–2.56 to 1.70)	0.69	na
Body weight (kg)	1[16]	46	4.30 (–2.53 to 11.13)	0.22	na
Plasma volume (L)	1[16]	46	0.40 (0.12 to 0.68)	0.005	na

GFR, glomerular filtration rate; MD, mean difference; CI, confidence interval; na, not applicable.

Figures

Figure 1. Study screening flow chart.

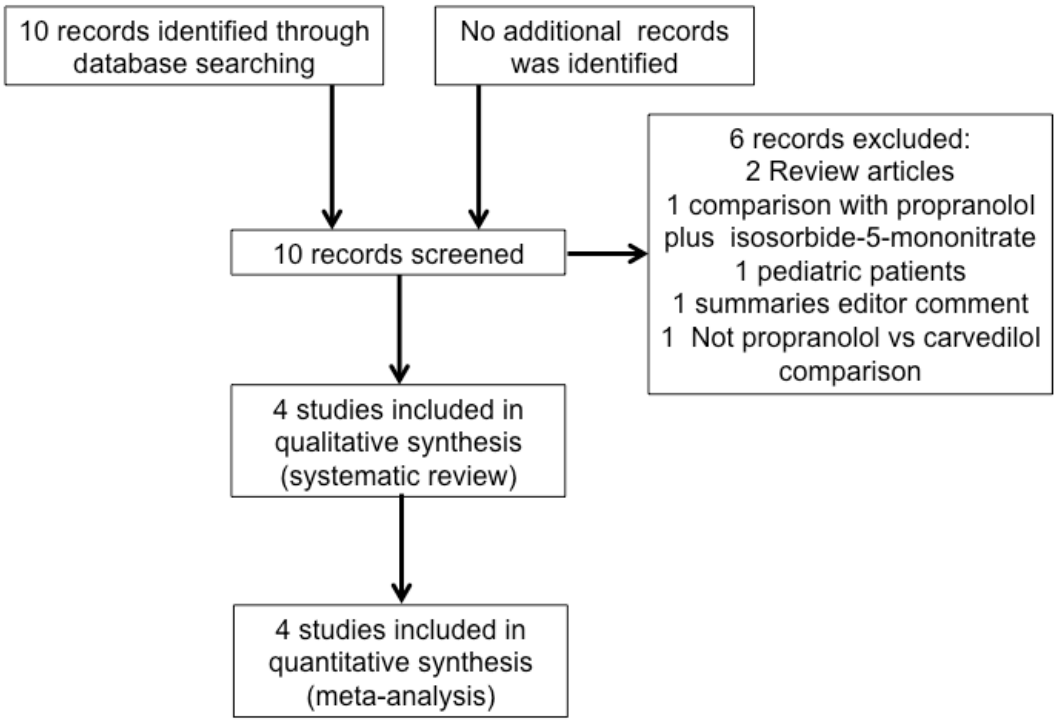

Figure 2. Forest plot of the comparison carvedilol vs. propranolol. Outcome: HVPG decrease ≥20% from baseline value or to <12 mmHg.

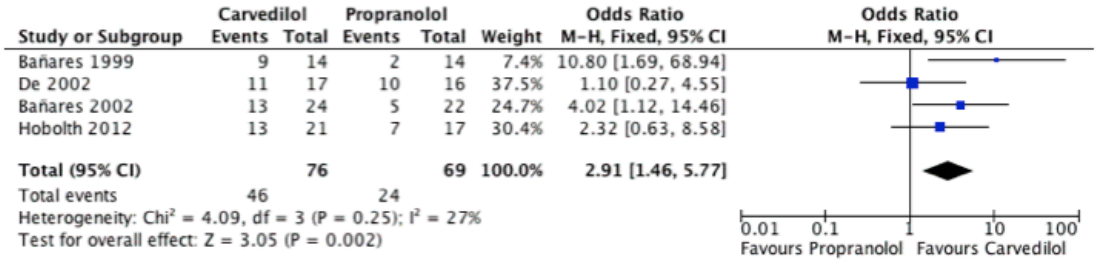

Figure 3. Forest plot of the comparison: carvedilol vs. propranolol. Outcome: reduction in HVPG.

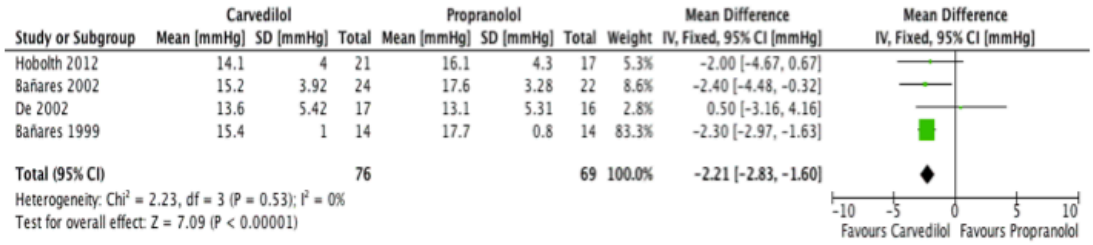

Figure 4. Forest plot of the comparison carvedilol vs. propranolol. Outcome: events leading to withdrawal of medication.

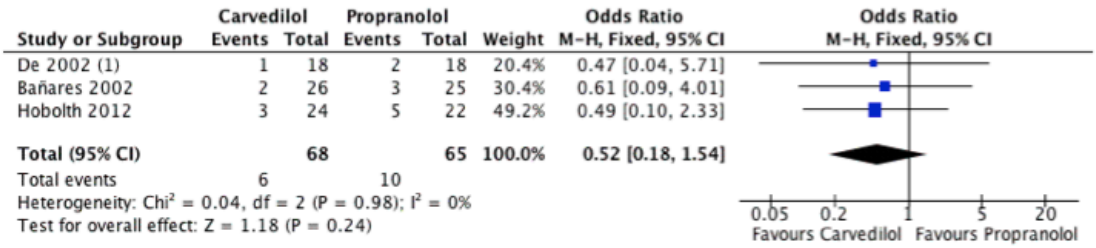

Figure 5. Forest plot of the comparison carvedilol vs. propranolol. Outcome: orthostatic or symptomatic hypotension.

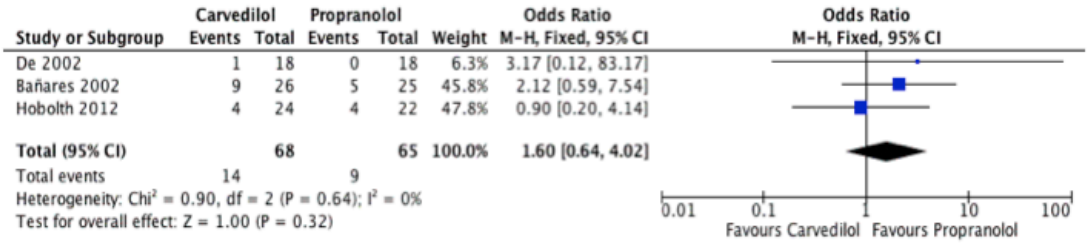

Figure 6. Forest plot of the comparison carvedilol vs. propranolol. Outcome: mean artery pressure.