

Hemodynamic effects of renin-angiotensin-aldosterone inhibitor and β -blocker combination therapy vs. β -blocker monotherapy for portal hypertension in cirrhosis: A meta-analysis

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Received October 14, 2015; Accepted November 25, 2016

DOI: 10.3892/etm.2017.4210

Abstract. β -blockers are commonly used for the treatment of acute variceal bleeding in cirrhosis. Renin-angiotensin-aldosterone antagonists (angiotensin I-converting enzyme inhibitors, angiotensin receptor blockers and aldosterone antagonists) are potential therapies for portal hypertension. Several studies have compared the renin-angiotensin-aldosterone system (RAAS) inhibitor and β -blocker combination therapy vs. β -blocker monotherapy, with inconsistent results. The aim of the present study was to assess the efficacy of the RAAS inhibitor and β -blocker combination therapy vs. β -blocker monotherapy for hepatic vein pressure gradient (HVPG) reduction in cirrhosis. Studies were obtained using PubMed, Embase, Medline and Cochrane library databases up to July 2015, and the weighted mean difference (WMD) in HVPG reduction was used as a measure of treatment efficacy. In total, three studies (91 patients) were included. When compared to the β -blocker monotherapy, the RAAS inhibitor and β -blocker combination therapy resulted in a significant HVPG reduction [WMD 1.70; 95% confidence interval (CI): 0.52-2.88]. However, there was no significant difference in the heart rate reduction between

the monotherapy and combination therapy groups (WMD -0.11; 95% CI: -3.51-3.29). In addition, no significant difference in the hemodynamic response was observed between the two groups (WMD 1.46; 95% CI: 0.93-2.30). In conclusion, the RAAS inhibitor and β -blocker combination therapy reduces portal hypertension significantly and to a greater extent than β -blocker monotherapy. Both therapies reduced the heart rate to similar levels; however, the RAAS inhibitor and β -blocker combination therapy reduced the mean arterial pressure to a greater extent. Due to the limited number of studies included, the data available do not allow a satisfactory comparison of adverse events. Moreover, further larger-scale trials are required in order to strengthen the results of the present study.

Introduction

Portal hypertension is an important cause of morbidity and mortality in cirrhotic patients, which can lead to severe complications, including esophageal variceal bleeding (1,2), ascites, hepatic encephalopathy, hepatorenal syndrome, bacteremia and hypersplenism. To date, non-selective β -blockers (NSBBs) are the drugs of choice for the treatment of esophageal variceal bleeding in cirrhotic patients. However, it has been revealed that only 30-40% of the patients under long-term therapy with NSBBs demonstrate a good hemodynamic response (reduction in HVPG to ≤ 12 mmHg or at least a 20% reduction from the baseline), and another 15% do not tolerate NSBBs (3). In the past few years, studies have revealed that the renin-angiotensin-aldosterone system (RAAS) is important in chronic hepatic diseases and portal hypertension. Angiotensin II was found to stimulate hepatic stellate cells in order to increase intrahepatic resistance and promote fibrosis (4). Moreover, in addition to its established effect of increasing portal vein blood flow via water-sodium retention (5), aldosterone has been shown to increase inflammation, endothelial dysfunction, oxidative stress and insulin resistance (6). In addition, a previous systematic review and meta-analysis confirmed that

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Key words: angiotensin receptor blocker, aldosterone antagonist, angiotensin I-converting enzyme inhibitor, β -blockers, hepatic venous pressure gradient, portal hypertension

antagonists of the RAAS appear to be able to decrease HVPG in patients with compensated cirrhosis (7). Theoretically, as RAAS inhibitors and β -blockers function via different mechanisms to decrease the pressure of portal veins, it is possible that the RAAS inhibitor and β -blocker combination therapy may lead to a more significant reduction in portal venous pressure. Several studies (8-10) have previously compared the RAAS inhibitor and β -blocker combination therapy vs. β -blocker monotherapy. However, the results remain inconsistent.

The aim of the present study was to assess the efficacy of RAAS inhibitor and β -blocker combination therapy vs. β -blocker monotherapy on HVPG reduction in patients with cirrhosis.

Materials and methods

Inclusion and exclusion criteria. Studies were included using the following criteria: i) Full-text article; ii) randomized controlled trial; iii) cirrhosis; iv) clinically significant portal hypertension; v) if the study was a clinical trial comparing the effects of RAAS inhibitor and β -blocker combination therapy with β -blocker monotherapy on portal pressure; and vi) HVPG measurement before and after treatment. Moreover, studies were excluded if TIPS or a surgical shunt were present.

Search strategy. PubMed, Embase, Medline and the Cochrane Library were searched up to July 2015 to retrieve pertinent studies (11,12). We searched (losartan OR candesartan OR irbesartan OR valsartan OR telmisartan OR olmesartan OR enalapril OR quinapril OR ramipril OR lisinopril OR captopril OR fosinopril OR perindopril OR RAAS inhibitor OR ACEI OR ATII blocker OR angiotensin inhibitor OR renin angiotensin OR eplerenone OR spironolactone OR aldactone OR canrenone) AND (adrenergic β -antagonists OR β blockers OR propranolol OR nadolol OR timolol) AND (portal hypertension OR cirrhosis) AND controlled trials. A manual search of the reference lists of related articles and reviews was also performed. Moreover, related congresses were hand-searched.

Data extraction. Two authors (Dr Jianrong Wang and Dr Wenxia Lu) extracted data independently. Discrepancies were resolved through discussion before the analyses. The following data were extracted from each trial: i) Trial characteristics such as study population demographics, intervention and control and time of outcome measured; ii) patient characteristics such as the number of patients, age, gender ratio, Child-Pugh class, number of patients with previous variceal hemorrhage and ascites; iii) outcome such as the reduction in HVPG, number of patients achieving a hemodynamic response, change in heart rate and mean arterial pressure (MAP) as adverse events.

Methodological quality assessment. Methodological quality of the articles included was assessed using the Jadad scale and Schulz hidden grouping (13,14). A Jadad score of 1 to 2 was considered low quality, and a Jadad score of 3 to 5 was considered high quality. Moreover, the Schulz hidden grouping was described as 'adequate' 'inadequate' and 'unclear'.

Statistical analysis. Results of the studies included are reported as the number of observations, ratio or

mean \pm standard deviation. When the result was reported as the standard error, the standard deviation was calculated from the standard error.

Data analysis and graph synthesis were performed by RevMan (version 5.2; The Cochrane Collaboration, Oxford, UK). Continuous outcomes, including the reduction in HVPG between the control and experimental groups were reported as a weighted mean difference (WMD) with a 95% confidence interval (CI). Moreover, heterogeneity was assessed using the χ^2 test and I^2 -values (15). χ^2 statistics $P > 0.1$ were considered to have no heterogeneity. Moreover, I^2 -values $< 25\%$ were considered to have a low risk, 25-50% was considered a moderate risk and values $> 50\%$ were considered to have a high risk of heterogeneity. If there was significant heterogeneity, potential reasons for the heterogeneity were explored and combinability of trials was reassessed, respectively.

The WMD in the heart rate and MAP between the treatment and control groups was also assessed as a measure of an adverse effect.

Results

Study selection. The search was conducted in July 2015, and a total of 64 abstracts were identified. The full-text of 61 of these pertinent reports were reviewed, respectively. In total, 58 articles were excluded for the following reasons: i) They did not compare the RAAS inhibitor and β -blocker combination therapy with β -blocker monotherapy (24/61) (16-39); ii) there was no cirrhosis (17/61) (40-56); iii) there was a lack of HVPG measurements (4/61) (57-60); and iv) there were no RCTs (13/61) (61-73). The remaining three articles (8-10) met the inclusion criteria (Fig. 1).

Description of studies included. The characteristics of the studies included are summarized in Table I. A total of three studies comparing the RAAS inhibitor and β -blocker combination therapy with β -blocker monotherapy were included. In one study (8), the treated group was administered propranolol 40 mg bid and spironolactone 100 mg qd, while the control group was administered propranolol at a dose of 40 mg bid and a placebo tablet. Moreover, the dose of propranolol was gradually increased until there was a decrease in pulse rate of $> 20\%$ from the baseline, or a pulse rate of 60 beats per minute was achieved. Hemodynamic measurements were repeated after eight days of treatment. In another study (9), the treated group was administered irbesartan at a starting dose of 75 mg/day followed by a step-up dose to 300 mg/day (mean dose, 271.9 ± 13.1 mg/day) with propranolol 20 mg bid, while the control group was administered propranolol 20 mg bid. Hemodynamic measurements were repeated after eight weeks of treatment. In the remaining study (10), the treated group was administered spironolactone 100 mg/day with a mean dose of nadolol of 76 ± 62 mg/day, while the control group was administered a mean dose of nadolol 80 ± 60 mg/day. Moreover, a hemodynamic study was conducted after 2-3 months of treatment.

The characteristics of the 91 patients included are summarized in Table II. The mean patient age was 52.2 years. In total, only two studies (8,9) mentioned the gender ratio and Child-Pugh class. Moreover, $\sim 70\%$ of patients were male, and

Table I. Characteristics of the trials included.

Author, year	Monotherapy group	Combination group	Time of HVPG assessment	Ref
De, 2008	Propranolol 40 mg twice daily (mean dose, 92.94±23.39 mg/day)	Spirololactone 100 mg/day + propranolol 40 mg twice daily (mean dose, 88.89±20.83 mg/day)	8 days	(8)
Schepke, 2008	Propranolol 20 mg b.i.d	Irbesartan (step-up dosage titration up to 300 mg/day) (mean dose 271.9±13.1 mg/day)+propranolol 20 mg b.i.d	8 weeks	(9)
Abecasis, 2003	Nadolol (mean dose, 80±60 mg/day)	Spirololactone (100 mg/day)+nadolol (mean dose, 76±62 mg/day)	8-12 weeks	(10)

HVPG, hepatic venous pressure gradient.

Table II. Characteristics of participants in the studies included.

Author, year	Treatment group	Patients, n	Age, years (mean ± SD)	Gender ratio, male/female	Child-Pugh class, A/B/C	Previous portal hypertension-related bleeding, %	Ascites, %	Ref
De, 2008	Monotherapy	17	44.3±7.98	12/5	3/8/6	100	58.82	(8)
	Combination	18	46.61±8.71	15/3	4/9/5	100	44.44	
Schepke, 2008	Monotherapy	15	55.8±3.6	10/5	7/7/1	40	26.67	(9)
	Combination	17	51.7±2.5	10/7	6/11/0	41.18	41.18	
Abecasis, 2003	Monotherapy	12	56±10	NR	NR	0	0	(10)
	Combination	12	59±11	NR	NR	0	0	

SD, standard deviation; Monotherapy, β-blockers monotherapy; Combined, RAAS inhibitor and β-blocker combination therapy; NR, not reported.

the Child-Pugh class A/B/C was 20/35/12, respectively. In addition, the proportion of patients with previous esophageal variceal hemorrhage was 29 of 91 (31.87%), and 48 of 91 (52.75%) patients previously had ascites.

Methodological quality. The methodological quality of the included articles is listed in Table III. All three articles obtained a Jadad score of 5, two studies had adequate allocation concealment and one study had unclear allocation concealment, which revealed that all three studies were of high quality.

Outcome evaluation

Mean change in the HVPG. The pooled WMD of HVPG reductions in the two groups was 1.70 (0.52, 2.88; fixed-effect model), test for overall effect: Z=2.83 (P=0.005), indicating a significantly higher HVPG reduction with the RAAS inhibitor and β-blocker combination therapy compared to β-blocker monotherapy. Moreover, no heterogeneity was observed in the analysis of combination therapy vs. monotherapy (P=0.30; I²=17%) (Fig. 2). As there were only three articles included, influence analysis was performed in order to study the effect of individual research on the total combined effect quantity. The

result revealed that the second article (8) has a large influence on the total consolidation effect quantity (Fig. 3).

A total of 26 of 46 patients (56.52%) in the RAAS inhibitor and β-blocker combination therapy group and 17 of 44 patients (38.64%) in the β-blocker monotherapy group revealed a hemodynamic response. The pooled relative risk of achieving a hemodynamic response in the two groups was 1.46 (0.93, 2.30; fixed-effect model), indicating that there was no significant difference between the hemodynamic response with RAAS inhibitor plus β-blocker combination therapy and β-blocker monotherapy. Moreover, no heterogeneity was identified in the pooled analysis of the trials (P=0.26; I²=26%) (Fig. 4).

Adverse events. The pooled WMD in the heart rate change in the two groups was -0.11 (-3.51, 3.29; fixed-effect model), test for overall effect: Z=0.06 (P=0.95), indicating that there was no significant heart rate change with the RAAS inhibitor plus β-blocker combination therapy and β-blocker monotherapy. Moreover, no heterogeneity was identified (P=0.31; I²=14%) (Fig. 5).

In the studies by Abecasis *et al* (10) and Schepke *et al* (9), there was a significant change in the MAP between the two treatment groups. However, the RAAS inhibitor and

Table III. Methodological quality assessment of the trials included.

Author, year	Generation of the allocation sequence	Blinding	Dropouts and withdrawals	Jadad score	Allocation concealment	Ref
De, 2008	2	2	1	5	Adequate	(8)
Schepke, 2008	2	2	1	5	Adequate	(9)
Abecasis, 2003	2	2	1	5	Unclear	(10)

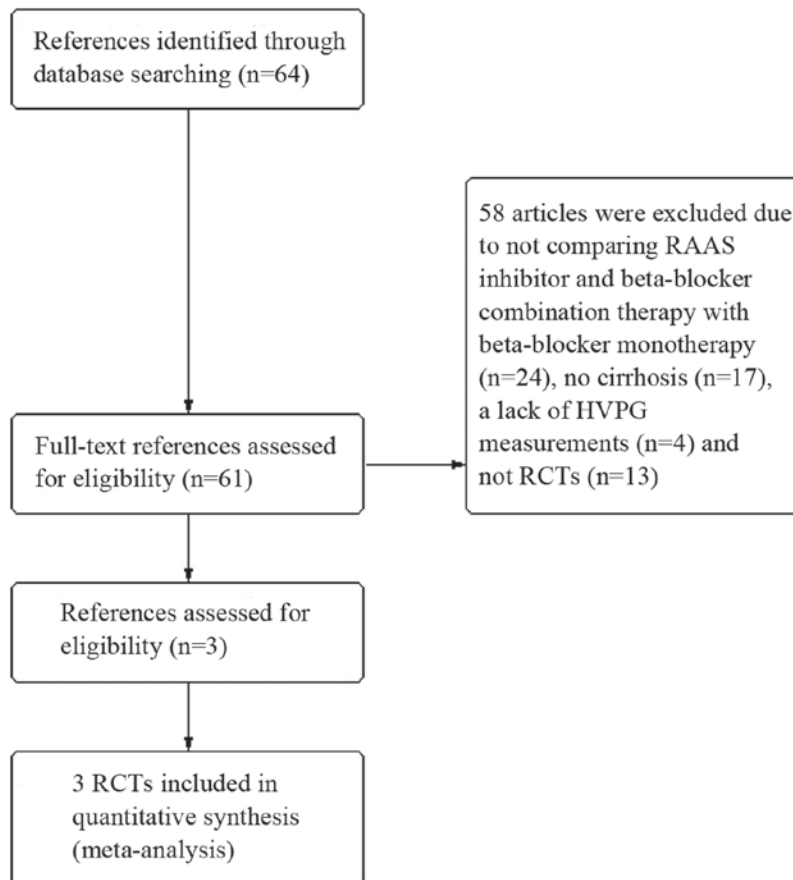


Figure 1. Flow diagram of the studies included in the meta-analysis. RAAS, renin-angiotensin-aldosterone system; HVPG, hepatic venous pressure gradient; RCT, randomized controlled trials.

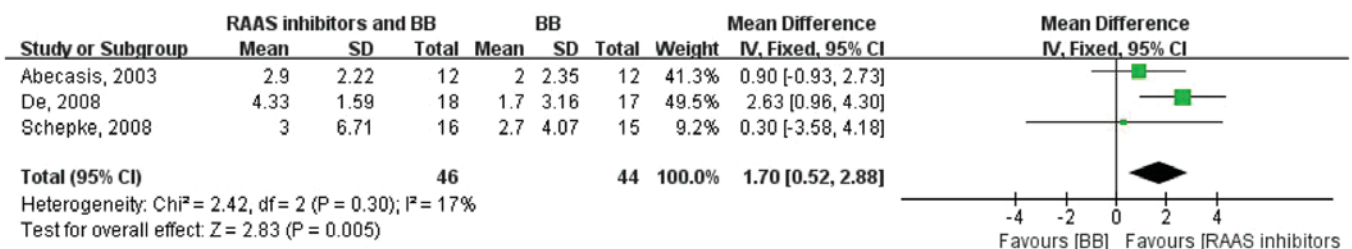


Figure 2. Change in portal pressure: RAAS inhibitor and BB combination therapy vs. BB monotherapy treatment. RAAs, renin-angiotensin-aldosterone system; BB, β -blocker; SD, standard deviation; CI, confidence interval.

β -blocker combination therapy reduced MAP to a greater extent compared to β -blocker monotherapy. Moreover, the pooled WMD was 9.50 (4.12, 14.89; fixed-effect model), and

no heterogeneity was identified (P=0.80; I²=0%) (Fig. 6). In the study by Schepke *et al* (9), one patient in the combination therapy group suffered severe esophageal variceal bleeding

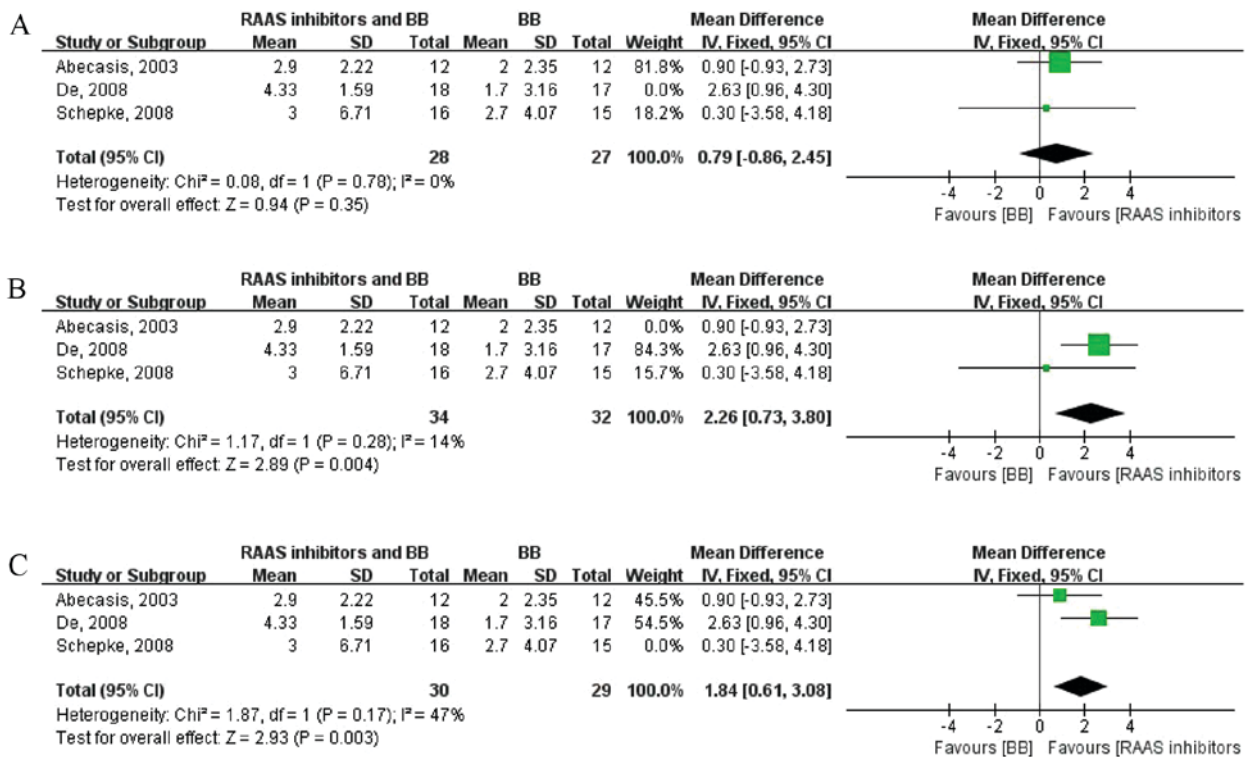


Figure 3. Sensitivity analysis. (A) Study the effect of individual research (Abecasis, 2003) on total combined effect quantity. (B) Study the effect of individual research (De, 2008) on total combined effect quantity. (C) Study the effect of individual research (Schepke, 2008) on total combined effect quantity. RAAS, renin-angiotensin-aldosterone system; BB, β -blocker; SD, standard deviation; CI, confidence interval.

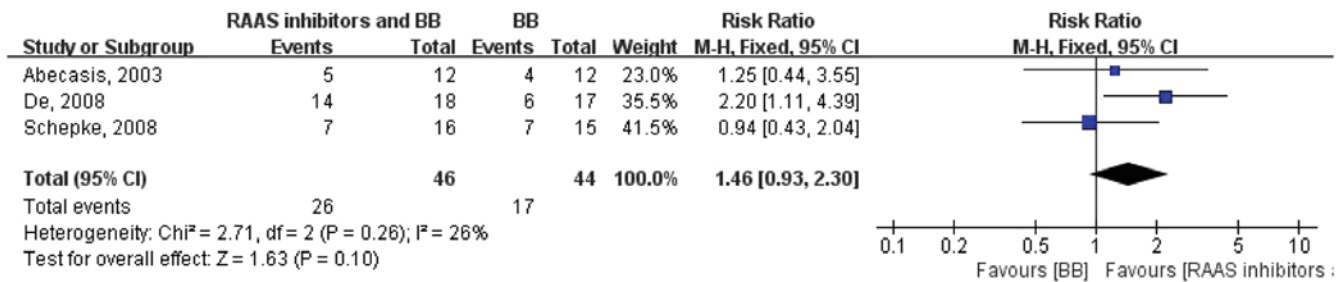


Figure 4. Relative risk of treatment response (reduction in hepatic venous pressure gradient of $\geq 20\%$ of baseline or to < 12 mmHg achieved) with RAAS inhibitor and BB combination therapy compared with BB monotherapy. RAAS, renin-angiotensin-aldosterone system; BB, β -blocker; CI, confidence interval.

following five weeks of treatment. Thus, the hemodynamic measurements were not repeated. In total, four patients reported minor dizziness in the RAAS inhibitor and β -blocker combination therapy group, which was thought to be associated with the hypotensive effects of the RAAS inhibitor.

Discussion

There are three main aspects in the pathophysiology of portal hypertension (74). The first is structural changes caused by fibrosis, vascular occlusion and regenerative nodule formation or remodeling. The second aspect is sinusoidal endothelial dysfunction and contraction of stellate cells, which further increases 20-30% of the intrahepatic resistance. Finally, the third aspect is splanchnic vasodilatation and hyperkinetic circulation, which maintains and worsens portal hypertension.

Currently, β -blockers have become the recommended medicine for the therapy of portal hypertension, which decrease portal pressure in two main ways. Firstly, they block β -1 cardiac receptors, which results in decreased cardiac output and MAP (75). Secondly, β -blockers function by blocking β -2 vascular receptors, leading to splanchnic vasoconstriction results from the unopposed effect of alpha-1 receptors (76). In recent years, studies (4,6,24,77) have increasingly revealed that the RAAS system is important in the pathophysiology of portal hypertension.

Angiotensin II is a vasoconstrictor, which has an elevated serum concentration in patients with cirrhosis. A prior study (4), which investigated the effect of angiotensin II on activated human hepatic stellate cells, demonstrated that angiotensin II can increase cell contraction and proliferation, which were rarely detected in resting cells. These results indicate that angiotensin II induces hepatic stellate cell activation

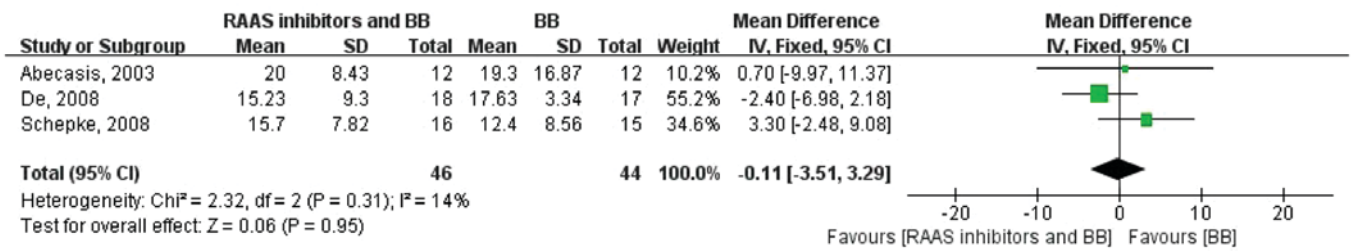


Figure 5. Change in heart rate: RAAS inhibitor and BB combination therapy vs. BB monotherapy treatment. RAAS, renin-angiotensin-aldosterone system; BB, β -blocker; SD, standard deviation; CI, confidence interval.

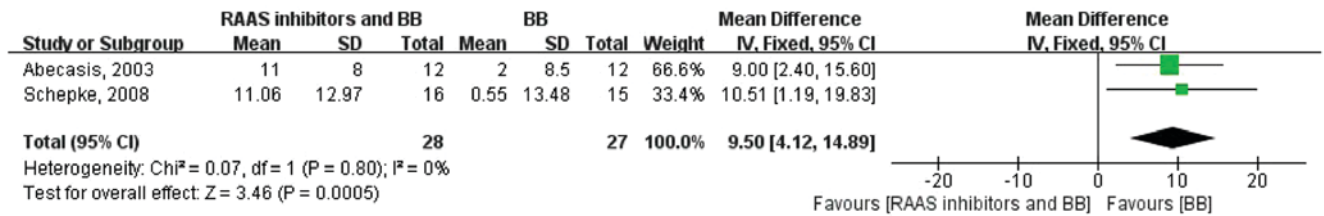


Figure 6. Change in mean arterial pressure: RAAS inhibitor and BB combination therapy vs. BB monotherapy treatment. RAAS, renin-angiotensin-aldosterone system; BB, β -blocker; SD, standard deviation; CI, confidence interval.

in order to increase intrahepatic resistance. In addition, angiotensin type1 (AT1) receptor antagonists were reported to reduce the progression of hepatic fibrosis and decrease portal pressure in rats (77). A previous study investigated the long-term effects of the AT1 receptor on portal hypertension and demonstrated that 25% of patients achieved a reduction >20%. Moreover, HVPG significantly decreased in the treated group (-8.4%±2.4) vs. (+5.6%±2.9) in the controlled group (21). In addition to the effect of decreasing portal vein pressure by reducing the plasma volume and the vascular relaxing activity (24), aldosterone antagonist has also been reported to suppress inflammation, improve endothelial dysfunction, reduce oxidative stress, decrease insulin resistance and slow down the progress of liver fibrosis (6).

Since only 30-40% of the patients under long-term therapy with β -blockers achieve a good hemodynamic response (3), it is hypothesized that the RAAS inhibitor and β -blocker combination therapy may achieve a better effect.

The present meta-analysis aimed to assess the efficacy of the RAAS inhibitor and β -blocker combination therapy compared with β -blocker monotherapy on HVPG reduction in patients with cirrhosis. The results demonstrated that the RAAS inhibitor and β -blocker combination therapy reduced HVPG to a more significant extent compared to β -blocker monotherapy. In addition, the pooled WMD between HVPG reduction with RAAS inhibitor plus β -blocker combination therapy and β -blocker monotherapy was 1.70 (95% CI: 0.52-2.88), and no heterogeneity was identified.

The number of patients achieving a hemodynamic response was reported in all studies included and was higher with the RAAS inhibitor and β -blocker combination therapy (26/46 vs. 17/44). However, there were no significant differences in the pooled relative risk of achieving a hemodynamic response with RAAS inhibitor and β -blocker combination therapy compared with β -blocker monotherapy (1.46; 95% CI: 0.93-2.30).

Only one study (9) completely described the adverse events. In total, four patients reported minor dizziness in the RAAS inhibitor and β -blocker combination therapy group, which may have been associated with the hypotensive effects of the RAAS inhibitor. A previous article comparing irbesartan with placebo in patients with cirrhosis (78) confirmed that the activation of RAAS is associated to circulatory complications. Thus, a low starting dose followed by a slow step-up dose of the RAAS inhibitor may be recommended to prevent hypotension. Moreover, the pooled mean weighed change in the heart rate in the two groups was -0.11 (95% CI: -3.51-3.29), indicating that the difference in heart rate change between the two groups was not statistically significant. These observations demonstrate that the RAAS inhibitor and β -blocker combination therapy does not increase the change in heart rate compared with β -blocker monotherapy. In two of the studies included (9,10), MAP was measured before and after treatment. The pooled WMD of MAP change in the two groups was 9.50 (95% CI: 4.12-14.89), indicating that the RAAS inhibitor and β -blocker combination therapy reduced MAP more than β -blocker monotherapy.

Nevertheless, there are many limitations in the present study. Firstly, the number of available studies and patients included was too small, which mitigated the achievement of satisfactory results. Secondly, the course of the selected trials was not the same, and the span was large. In addition, angiotensin I-converting enzyme inhibitors, angiotensin receptor blockers and aldosterone antagonists were regarded as the same drugs to be analyzed, while they function through different targets, which may result in a different hemodynamic response. However, despite these limitations, to the best of our knowledge the present study is the first meta-analysis comparing the RAAS inhibitor and β -blocker combination therapy with the β -blocker monotherapy effect on portal pressure, and included all high quality randomized controlled trials.

In conclusion, the RAAS inhibitor and β -blocker combination therapy reduces portal hypertension to a more significant extent than β -blocker monotherapy. Although both therapies reduced the heart rate to similar levels, the RAAS inhibitor and β -blocker combination therapy reduced the MAP to a greater extent compared to β -blocker monotherapy. Further larger-scale trials are required in order to determine the efficacy and safety of the RAAS inhibitor and β -blocker combination therapy for the reduction of HVPG in patients with cirrhosis.

Acknowledgements

The present study was supported by the Shanghai Health System Important Disease Joint Research Project (grant no. 2014ZYJB0201).

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