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Safety and efficacy of rennin-angiotensin system inhibitors in heart failure with preserved ejection fraction

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ABSTRACT

Background: Approximately half of the patients with chronic heart failure have preserved left ventricular systolic function. The trials of rennin-angiotensin system inhibitors (RASIs) in this population have yielded mixed results. We performed a meta-analysis of these trials to evaluate the safety and efficacy of RASIs in heart failure with preserved ejection fraction patients.

Methods: A total of 8425 patients from six prospective randomized controlled trials were analyzed. The end points extracted were total mortality, cardiovascular mortality, hospitalization for heart failure, worsening of heart failure, worsening of renal failure, hyperkalemia, hypotension, six minute walk test, quality of life score. RASIs evaluated were perindopril, enalapril, ramipril, valsartan, candesartan and irbesartan. Combined odds ratios (OR) across all the studies and 95% confidence intervals (CI) were computed. A two-sided alpha error <0.05 was considered to be statistically significant. All studies were homogeneous for outcomes studied, so fixed effect model was used for this meta- analysis.

Results: Both groups share similar baseline characteristics. There was significant reduction in worsening of heart failure events [OR: 1.16, CI: 1.03-1.31; $p < 0.05$] with RASIs compared to placebo group. This was associated with a tendency toward reduced hospitalizations due to heart failure [OR: 1.11, CI: 0.99-1.24; $p = 0.052$] but it could not achieve statistical significance. RASIs also failed to show any benefit in total mortality [OR: 1.07, CI: 0.96-1.19; $p = 0.19$] or cardiovascular mortality [OR: 1.01, CI: 0.89-1.15; $p = 0.84$] [Figure 1]. However, treatment with RASI lead to significant improvement in six minute walking distance [$p < 0.05$] and quality of life score in RASIs group [$p = 0.002$] [Figure 1]. Safety analysis, as expected, revealed significantly more hyperkalemic events [OR: 0.53, CI: 0.29-0.95; $p < 0.05$] and worsening of renal failure [OR: 0.65, CI: 0.50-0.85; $p < 0.05$] in RASI group as compared to placebo group.

Conclusion: RASIs treatment in heart failure with preserve ejection fraction patients showed significant improvement in six minute walking distance, quality of life and significant reduction in worsening heart failure events but failed to reduce total and cardiovascular mortality.

Keywords: ACE inhibitor, Angiotensin receptor blocker, Heart failure with preserved ejection fraction

Background

Heart failure with preserved left ventricular ejection fraction [HF-PEF] is a clinically heterogeneous syndrome. It refers to a clinical syndrome in which patients have symptoms and signs of HF, normal or near normal left ventricular systolic function, and evidence of diastolic dysfunction (abnormal left ventricular filling and elevated filling pressures) [1,2]. Among patients with HF, as many as 40 to 60 percent have a normal or near normal left ventricular ejection fraction (LVEF) [1, 3-6]. It's prevalence tends to be higher in women and in older patients with hypertension, atrial fibrillation, or both [J1-3]. Diastolic dysfunction has initially been held as the single pathophysiological abnormality behind this syndrome [J4,20]. However, several different underlying mechanisms are operative among different patient subgroups [J21]. The prognosis of patients with HF-PEF is less well defined than in those with systolic HF. Data from the Framingham Heart Study, the V-HeFT trials, and several observational series revealed varying results [6-12]. In addition, the data are not clear on whether the long-term prognosis differs between diastolic and systolic HF [13].

Renin angiotensin system inhibitors (RASIs), including angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), play an important role in the treatment of the disease processes that underlie the development of diastolic heart failure, namely, hypertension, coronary artery disease and diabetes. RASIs are beneficial in hypertensive heart disease and by reducing systemic pressure, they cause regression of left ventricular hypertrophy (LVH) and a gradual improvement in diastolic function [14,15]. Also, RASIs have been shown to prevent progression of diastolic dysfunction in patients with mixed systolic and diastolic HF [16]. However, the trials of rennin-angiotensin system inhibitors (RASIs)

in patients with HF-PEF have yielded mixed results. We performed a meta-analysis of these trials to evaluate the efficacy and safety of RASIs in heart failure with preserved ejection fraction patients.

Methods

We performed this review in accordance with the Quality of Reporting of Meta-analysis (QUOROM) statement and the Consolidated Standards of Reporting Trials (CONSORT) Group recommendations [17]. A protocol was prospectively developed, detailing the objectives, criteria for study selection and approach to assessing the study quality, primary outcome and methodology.

Literature search: We performed a computerized search to identify all relevant studies published in English-language through July 2010 in EMBASE, CINAHL, Pub Med, and Cochrane database. The key words used for search were: *congestive heart failure, chronic heart failure, heart failure, left ventricular systolic dysfunction, Angiotensin converting enzyme inhibitors, angiotensin- II receptor blockers, angiotensin receptor blockers, combination angiotensin converting enzyme inhibitors and angiotensin- II receptor blockers (or angiotensin receptor blockers)* and the following generic names of individual agents in current practice: *candesartan, eprosartan, irbesartan, losartan, tasosartan, telmisartan, and valsartan.*

Study selection: The authors reviewed all titles and abstracts from the results of our computerized search. We also went into the related links of all relevant articles. In addition to our computerized search, we manually reviewed the reference list of all retrieved articles to complete our search. Study selection process is outlined in figure 1.

Inclusion Criteria: All studies had to meet all the following criteria to be included in the analysis:

1. Randomized controlled trial design.
2. Include patients with HF-PEF.
3. Compare RASI therapy with placebo group.
4. Report at least one of the outcomes: all cause mortality, cardiovascular mortality, worsening of heart failure, hospitalizations for heart failure, worsening of renal function, incidence of hyperkalemia, exercise tolerance on six minute walk test, and quality of life index.

Exclusion Criteria: Studies that did not meet the above criteria were excluded.

Data abstraction: After identifying all relevant articles, we extracted characteristics of the study (author, year, design, duration, sample size, RASIs used, total mortality, cardiovascular mortality, bleeding complications and follow up percentage) and participants (age, gender). Two reviewers independently extracted data and assessed outcomes. The inter-rater agreement was 90%, and disagreements were resolved by consensus.

Quality Assessment

All the trials reported adequate concealment of the randomized treatment sequence. In all studies, follow-up was more than 90% complete.

Outcome Definitions

The definitions of endpoints were as used in individual trials. These are described below. Heart failure with preserved left ventricular ejection fraction was defined as LVEF \geq 45% (I-Preserve), LVEF \geq 40% (CHARM-Preserved), LVEF \geq 45% (Enalapril), LVEF $>$ 45% (Hongkong Study), LVEF $>$ 45% (PEP-CHF), LVEF \geq 40% (Valsartan Study).

Worsening of heart failure was defined based on clinical criteria and / or echocardiographic criteria [24-26]. Worsening of renal function was defined as doubling serum creatinine from the baseline [25,26]. A cut off value of potassium more than 6 mmol/L was taken to define presence of hyperkalemia [25,26]. Quality of life (QOL) was assessed using the Minnesota Heart Failure Symptom Questionnaire [27-29], which has been previously validated [18,19]. Exercise tolerance was measured using the Six minute walk distance test (6MWD) with two baseline tests according to previously defined protocol by Yusuf et al in heart failure trial using exercise endpoints [20].

Statistical analysis: The statistical analysis was performed by the Comprehensive Meta-Analysis software package (version CM 2.2, Biostat, Englewood, NJ). Heterogeneity of the studies was analyzed by the Cochran's Q statistics for each outcome. A systematic review of the literature revealed four eligible studies. As the studies were homogenous for all efficacy outcomes ($p < 0.05$), the combined relative risks (RR) across all the studies and the 95% confidence intervals were computed using the Mantel-Haenszel fixed effect model. For safety outcomes, studies were heterogeneous, so random effect model was used. For quality of life and exercise tolerance, standard difference in means was used to evaluate the treatment effect. A two-sided alpha error of less than 0.05 was considered to be statistically significant.

Results

Literature search

A total of 167 articles were identified of which 31 were potentially relevant studies and screened for retrieval. After title and abstract screening 10 studies were excluded and remaining 21 studies were retrieved for a more

detailed evaluation. Out of these 21 studies, 15 were excluded as they did not meet inclusion criteria [did not have control groups, three studies had different end points [21-23] or study population was different. Thus, six trials were included in the final analysis [24-29]. For the purpose of this meta-analysis, HongKong study was further classified in two substudies like HongKong ARB (Diuretics vs Irbesartan) and HongKong ACE (Diuretics vs Ramipril) [27] were considered separately for the purpose of this meta-analysis. Therefore, further description will refer to seven randomized controlled trials in this article.

Overview of study and patient characteristics

Study design was similar in five trials, comparison between a placebo arm and a treatment arm with either an ACE inhibitor (perindopril in PEP-CHF and enalapril in Enalapril study) or ARB (irbesartan in I-PRESERVE, candesartan in CHARM-Preserved and valsartan in Valsartan study). In HongKong substudies, comparison between a placebo arm (Diuretics) and a treatment arm with either an ACE inhibitor (Ramipril) or ARB (Irbesartan). The characteristics of included trials are mentioned in table 1.

End points

Out of seven, five trials [24-27] included in the study had total and cardiovascular mortality events as their end point. Three trials looked at worsening of heart failure and hospitalizations for heart failure [24-26]. Four trials had quality of life index and exercise tolerance as measured by distance walked in six minute walk test as one of their end points [27-29]. Only two trials had safety events as one of their end points which were worsening of renal functions and incidence of hyperkalemia [25,26].

Clinical Outcomes

The trials included in this meta-analysis consisted of a total of 8425 patients (Placebo group, n=4219; Treatment group, n=4206). The results of current meta-analysis are shown in figures 2-5 and summary of findings given in figure 6.

Total and cardiovascular mortality

Overall there were a total of 1478 [17.54%] deaths of which 746 [17.73%] were in RASI therapy group while 732 [17.35%] in the placebo group. There was no total or cardiovascular mortality noticed in one study [29]. The risk of both total mortality and cardiovascular mortality was similar in placebo and RASI therapy groups [Total Mortality OR: 1.07, CI: 0.96-1.19; p=0.19] or cardiovascular mortality [OR: 1.01, CI: 0.89-1.15; p= 0.84] [Fig 2].

Worsening and hospitalizations for heart failure

A total of 1317 [15.63%] worsening HF events occurred of which 618 [14.69%] were in RASI therapy group while 699 [16.56%] in the placebo group. There was significant reduction in worsening of heart failure events [OR: 1.16, CI: 1.03-1.31; p<0.05] with RASIs compared to placebo group.

There were total of 1685 [20.54%] hospitalizations for HF of which 807 [19.67%] were in RASI therapy group while 878 [21.40%] in the placebo group. There was a tendency toward reduced hospitalizations due to heart failure events in RASI therapy group [OR: 1.11, CI: 0.99-1.24; p=0.052] but it could not achieve statistical significance [Figure 3].

Quality of life and exercise tolerance

Treatment with RASI lead to significant improvement in six minute walking distance [Standard difference in means: 0.340, CI: 0.181-0.499; p<0.001] and quality of life score in RASIs group [Standard difference in

means: -0.308, CI: -0.503 to -0.113; $p=0.002$] [Figure 4].

Safety Analysis

Overall there were a total of 52 [0.72%] hyperkalemic events of which 34 [0.9%] were in RASI therapy group while 18 [0.5%] in the placebo group. Safety analysis, as expected, revealed significantly more hyperkalemic events [OR: 0.53, CI: 0.29-0.95; $p<0.05$] and worsening of renal failure [OR: 0.65, CI: 0.50-0.85; $p<0.05$] in RASI group as compared to placebo group [Figure 5].

Discussion

Our meta-analysis indicates that RASIs therapy in patients with HF-PEF does not alter the total or cardiovascular mortality but it does lead to significant reduction in the worsening of heart failures and hospitalization for heart failure events. Moreover, this analysis shows that RASI therapy in HF-PEF improves the quality of life and improves exercise tolerance. This is an important finding, as it indicates the potential benefit of RASI therapy in reducing the morbidity in this particular group of patients and may have implications for reducing the health care related costs due to recurrent hospitalizations and office visits.

With more than 5 million prevalent cases and nearly 1 million hospital discharges yearly, heart failure (HF) represents a rapidly growing therapeutic challenge for health care providers [30]. Risk factors for HFPEF include increasing age, female gender, hypertension, diabetes, obesity, coronary artery disease, and chronic kidney disease [31]. Like systolic heart failure, HFPEF is associated with considerable morbidity and mortality [32] and the risk of adverse outcome increases with the severity of diastolic dysfunction [33].

Inhibition of the Renin Angiotensin System (RAS) is an integral component of the modern management of HF with LV systolic

dysfunction. Current guidelines for the management of chronic heart failure considers initiation and maintenance of ACE inhibition or angiotensin-receptor blockade a class I indication in patients with HF and reduced LV function [34]. However, given the lack of randomized trials investigating modes of therapy for HF-PEF, only control of traditional cardiovascular risk factors is recommended.

Exact pathophysiological mechanism remains unclear, HF-PEF is most often associated with abnormal diastolic function [35,36] and manifestations of activated renin-angiotensin aldosterone system (RAAS), including hypertension, LV hypertrophy, myocardial fibrosis, and vascular dysfunction [37]. Patients with HFPEF have increased activation of RAAS, which contributes to the pathogenesis and progression of the condition [38]. Sustained RAS activation has been implicated in progressive ventricular hypertrophy and myocardial fibrosis, [39-41] both of which may be important contributors to the pathogenesis of diastolic dysfunction and RAS inhibition has been shown to be beneficial in a population of patients with vascular disease [42]. ACE inhibitors and ARBs have demonstrated beneficial effects in animal models of HFPEF [43,44]. Therapy targeted at RAS inhibition results in a significant reduction in neurohormone levels, attenuation of LV remodeling, and decreased HF morbidity and mortality [45-47].

Previous meta-analysis by Shah et al [48] showed reduction in hospitalization but inclusion of three newer trials in our analysis makes our results more robust and relevant to current clinical practice. We also analyzed the impact of RASIs therapy on quality of life and exercise tolerance, which are critically important issues from patient's perspective and from economic perspective. This has not been analysed in previous analysis.

As expected, there were more events of worsening of renal function and hyperkalemia

in RASIs therapy group. However, they did not lead to increased hospitalizations or mortality. Thus, overall implication of our results is that by close monitoring of these patients on RASIs therapy, a reduction in hospitalizations and improvement in quality of life can be achieved. Whether this leads to improvement in long-term mortality remains to be investigated. There are various possible explanations for lack of mortality benefit with RASIs therapy in patients with HF-PEF including differential effects according to stage of disease, and role of non-myocardial factors (central aortic stiffness, renal dysfunction) in pathogenesis of diastolic dysfunction. Moreover, recent data indicates equivalent efficacy of RAS-based and non-RAS based approaches for control of blood pressure for improvement of diastolic function [49] highlighting that control of blood pressure, rather than the choice of agent, may be the most important aspect of effective medical therapy.

As with any meta-analysis, one of the limitations of our study is the difference in the definitions of the end points in the component trials, such as the definition of definition of worsening of HF and Cut off value taken for LVEF to define heart failure with preserve ejection fraction was different in various studies. Similarly, baseline characteristics between the 2 groups cannot be compared completely in most meta-analyses because of differences in the study protocols across the component trials. In addition, there is a potential for publication bias but the trials in our analysis had different results and it should reduce this potential risk. In addition, many of these trials were small trials with limited ability to assess clinical outcomes.

Conclusion

RASIs treatment in heart failure with preserve ejection fraction patients showed significant

improvement in six minute walking distance, quality of life and significant reduction in worsening heart failure events but failed to reduce total and cardiovascular mortality [Figure 6].

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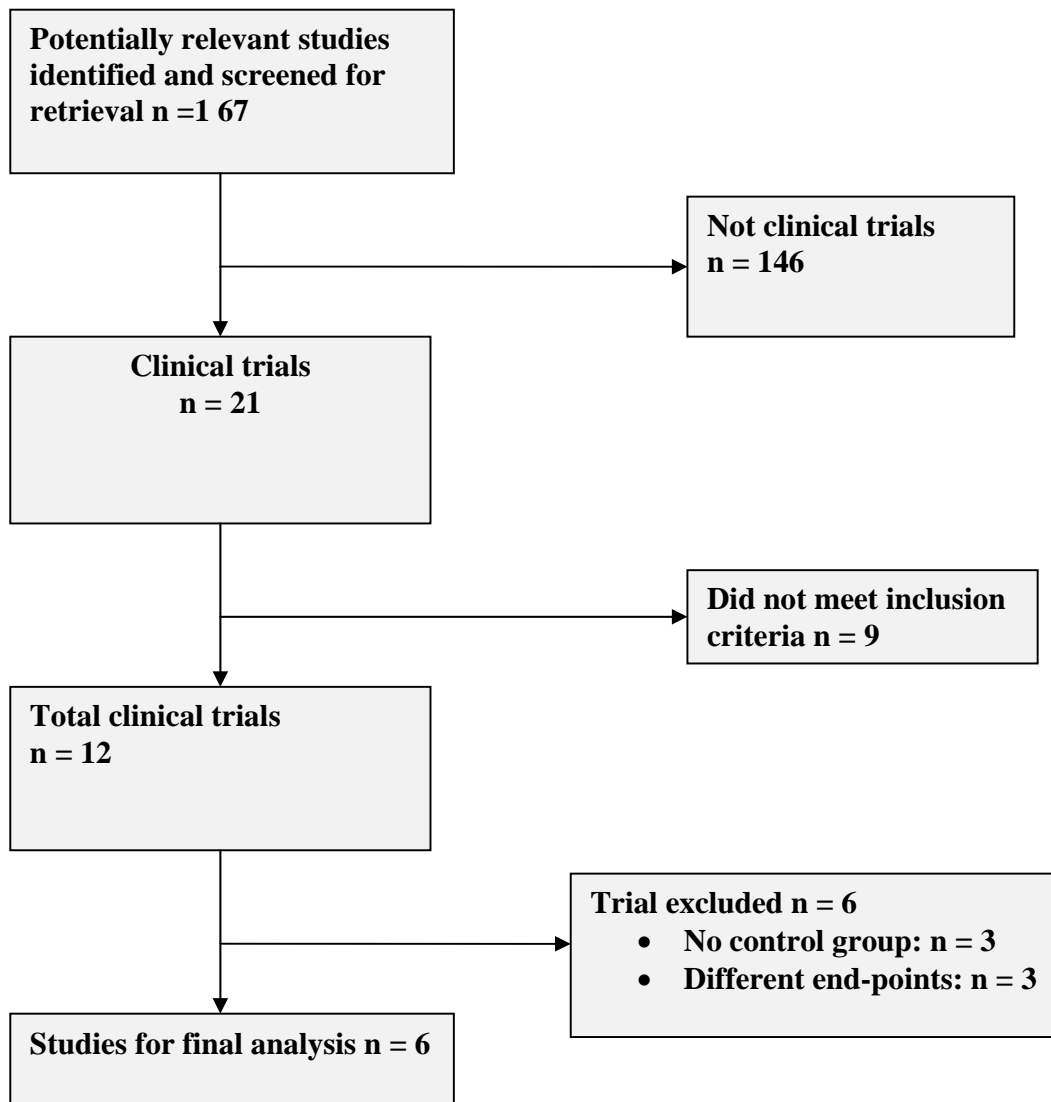


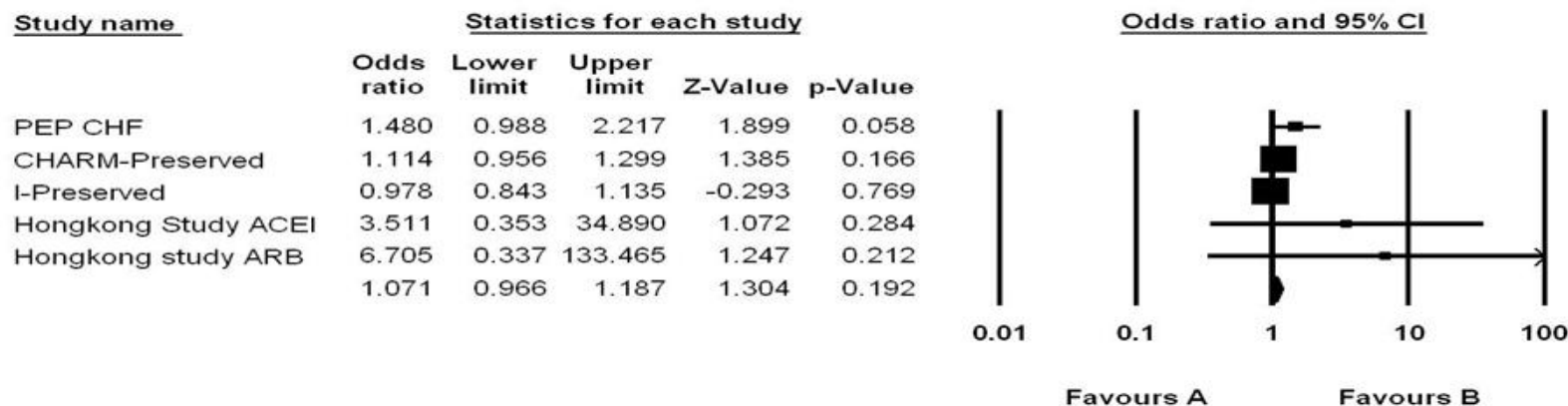
Figure 1: Study selection process

Table 1: Study characteristics

Trial	Design	Study Population (Placebo)	RASI	Number of subjects		Follow up (months)	End points studied
				Placebo	Control		
PEP-CHF	RCT	NYHA III/IV - 26%; LVEF – 64%, HTN – 79%; Ischemic – 26%	Perindopril	426	424	26.2	All causes death, CV mortality Hospitalization for HF, Worsening HF
CHARM PRESERVED	RCT	White – 92.3% NYHA III/IV – 40% LVEF - 54.1%, HTN – 23%, Ischemic – 56.5%	Candesartan	1514	1509	36.6	CV mortality, Worsening HF, Hospitalization for HF, Non fatal MI, Non fatal Stroke
ENALAPRIL	RCT	White – 94% NYHA III/IV – 25% LVEF – 60%, HTN – 75%; Ischemic - NR	Enalapril	36	35	49.5	Six MWDT, Quality of Life.
I-PRESERVED	RCT	White – 94% NYHA III/IV – 80% LVEF – 65%, HTN – 64%; Ischemic – 26%	Irbesartan	2061	2067	50	Death any causes, Death due to HF, Death – CV Causes, Hospitalization for CV causes, Worsening HF, QOL change
Hongkong ARB	RCT	NYHA III/IV – 28% LVEF – 69%, HTN – 76%; Ischemic – 18%	Diuretics vs Irbesartan	50	56	12	Six MWDT, Readmission HF, CV – Death, Other Causes Death, Change QOL
Hongkong ACEI			Diuretics vs Ramipril	50	45		
Valsartan	RCT	White – 93.9% NYHA III/IV - NR LVEF – 71.52% HTN – 89%, Ischemic NR	Valsartan	82	70	3.5	Exercise time

ARB = Angiotensin Receptor Blocker; ACEI = Angiotensin Converting Enzyme Inhibitor; RCT = Randomized control Trial; NR = Not Reported; NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction; HTN = Hypertension; CV = Cardiovascular; HF = Heart Failure; MI = Myocardial Infarction; MWDT = Minutes Walk Distance Test; QOL= Quality of Life

Total Mortality



Cardiovascular mortality

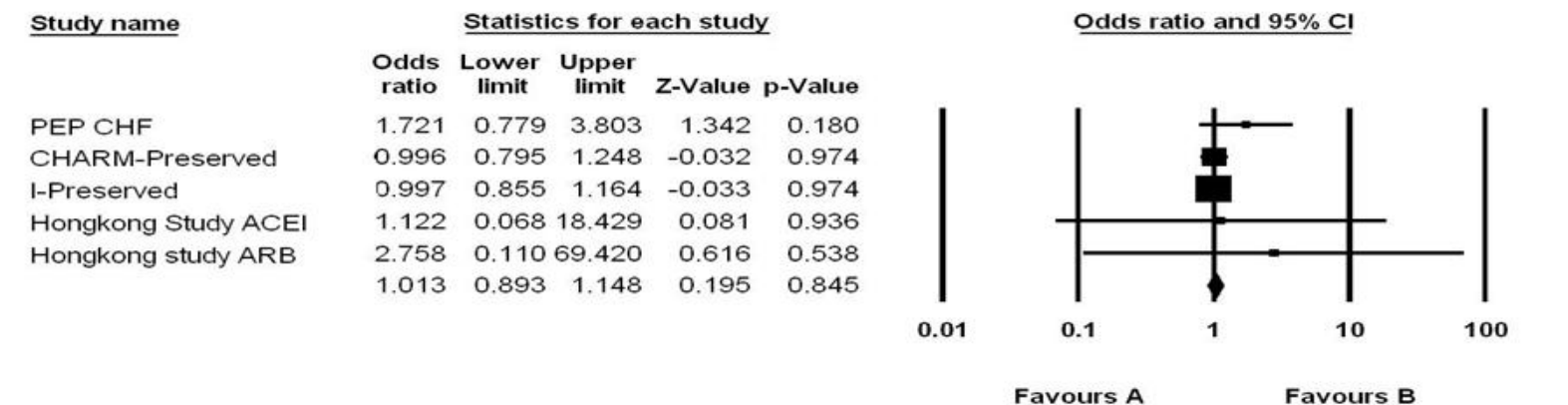
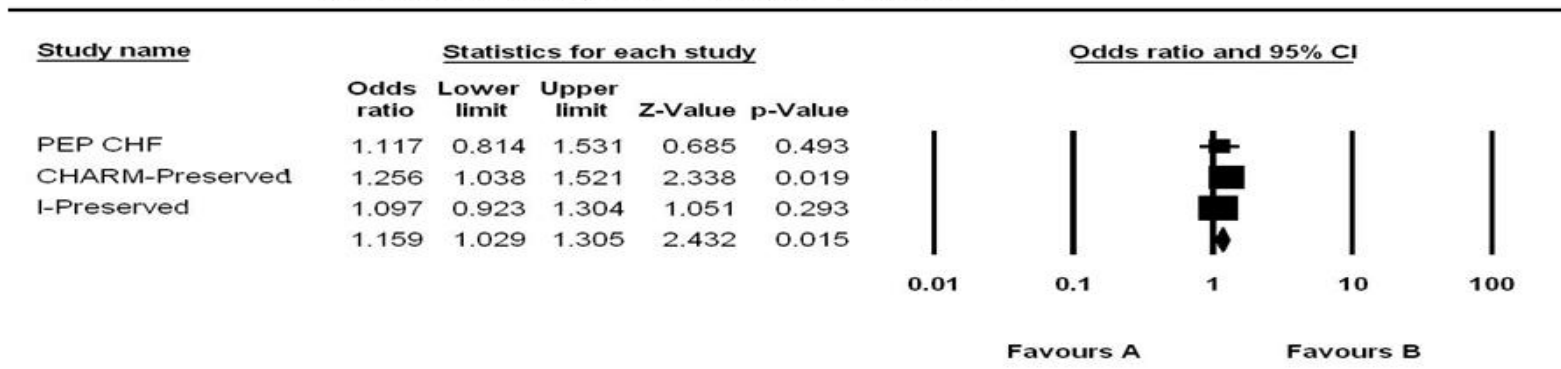


Figure 2: Total mortality (Upper panel) and cardiovascular mortality (Lower panel)

Worsening of Heart Failure



Hospitalizations for Heart Failure

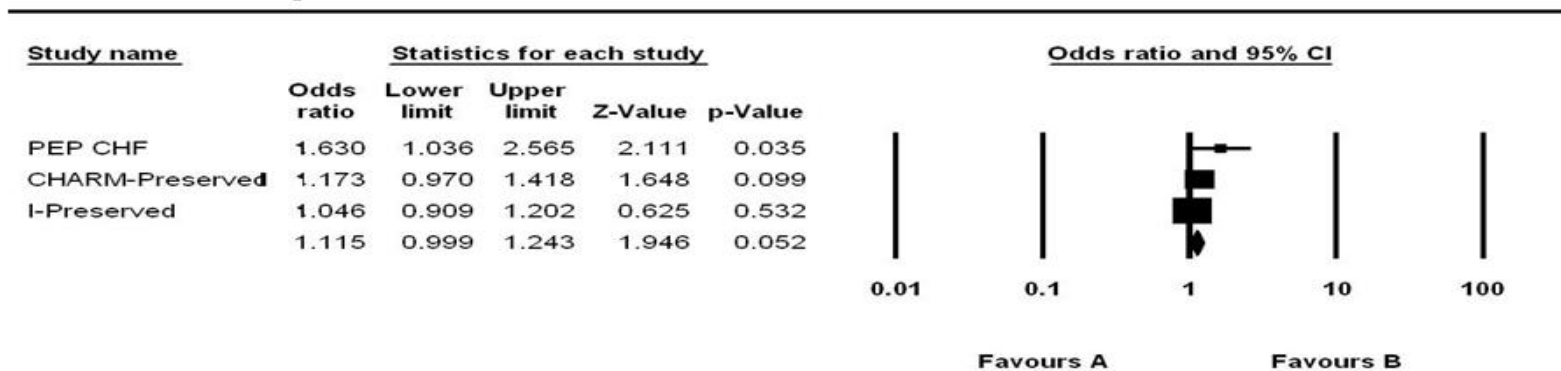
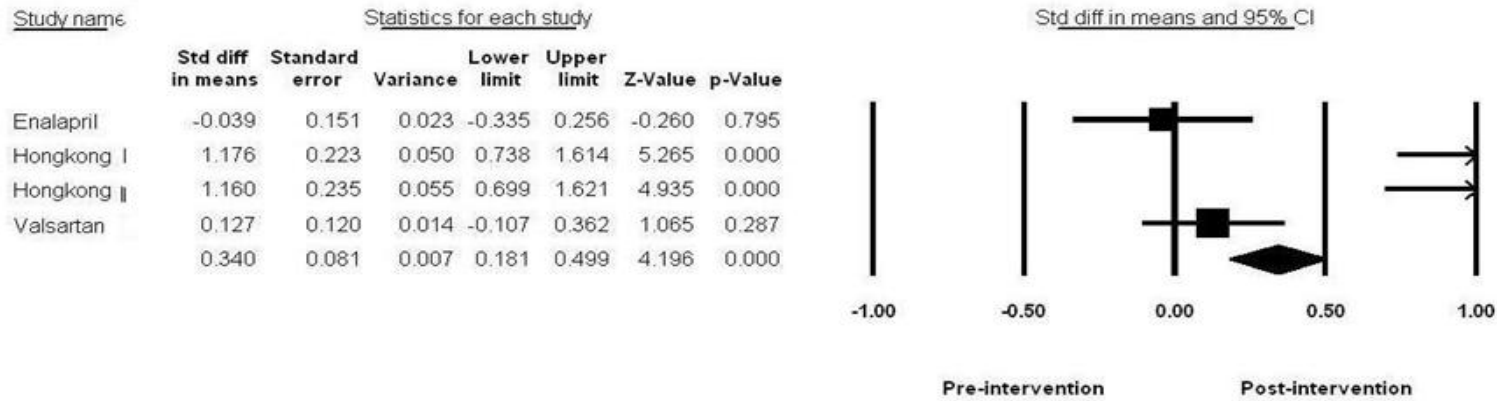


Figure 3: Worsening of heart failure (Upper panel) and hospitalizations for heart failure (Lower panel)

Distance walked in six minute walk test



Quality of life change with RASI

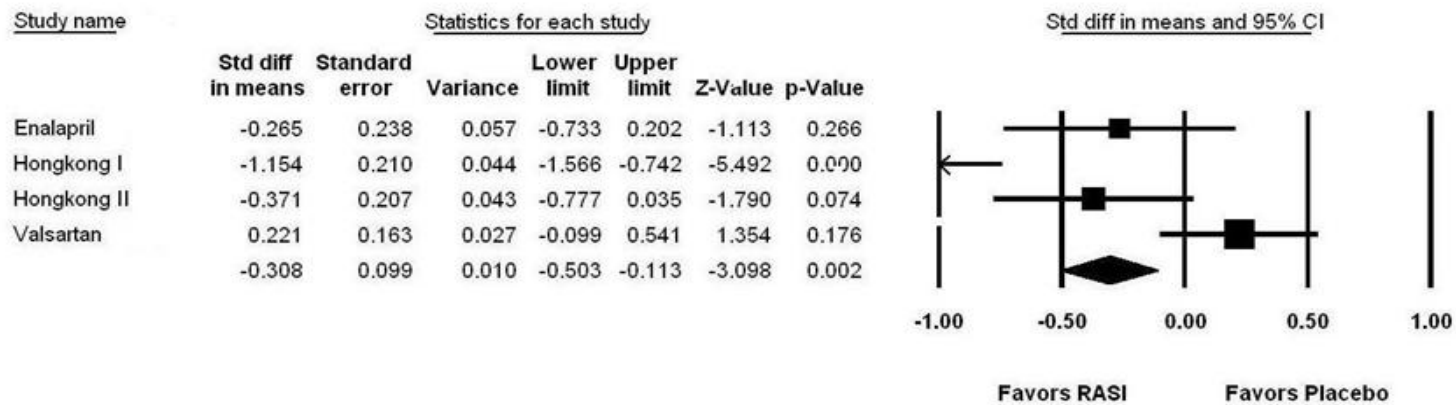
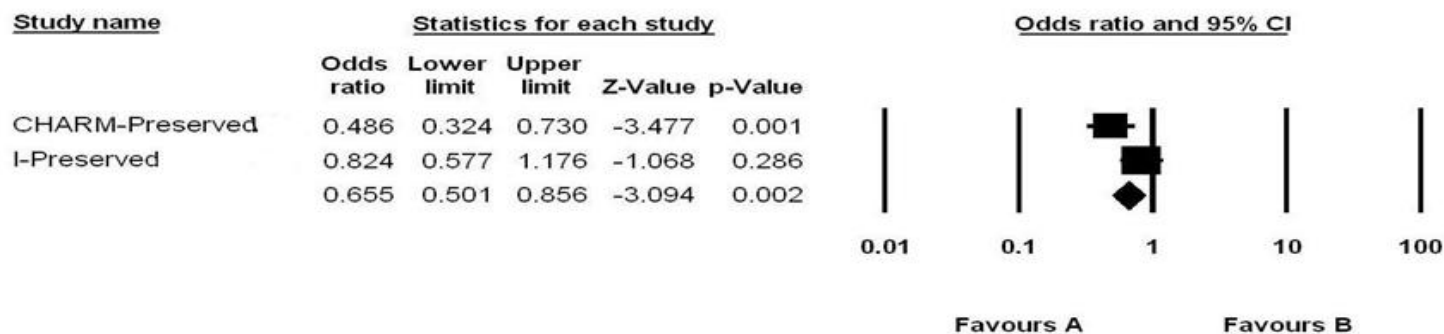


Figure 4: Quality of life (Upper panel) and distance walked in six minute walk test (Upper panel)

Worsening of Renal Function



Hyperkalemia

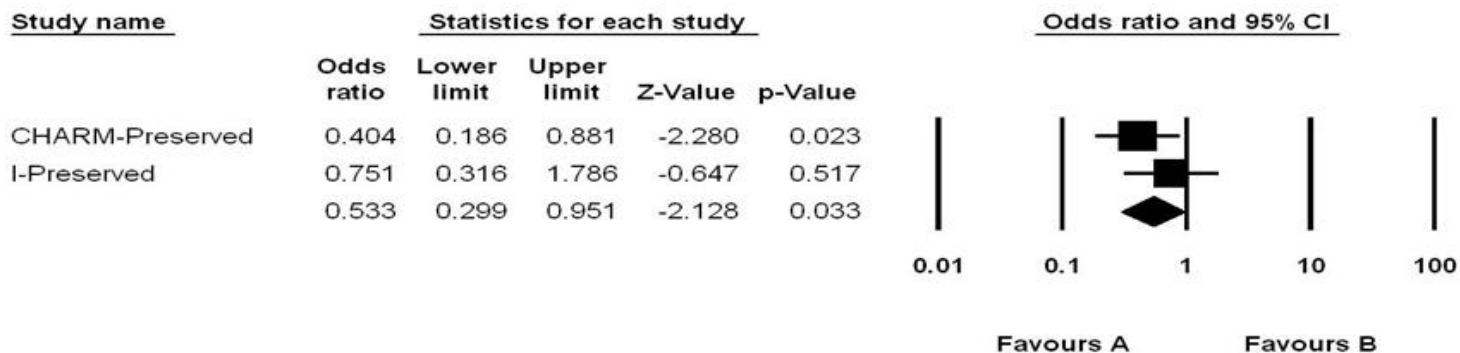


Figure 5: Worsening of renal functions (Upper panel) and hyperkalemia (Lower panel)

Efficacy and safety of RASI in patients with heart failure and preserved left ventricular ejection fraction

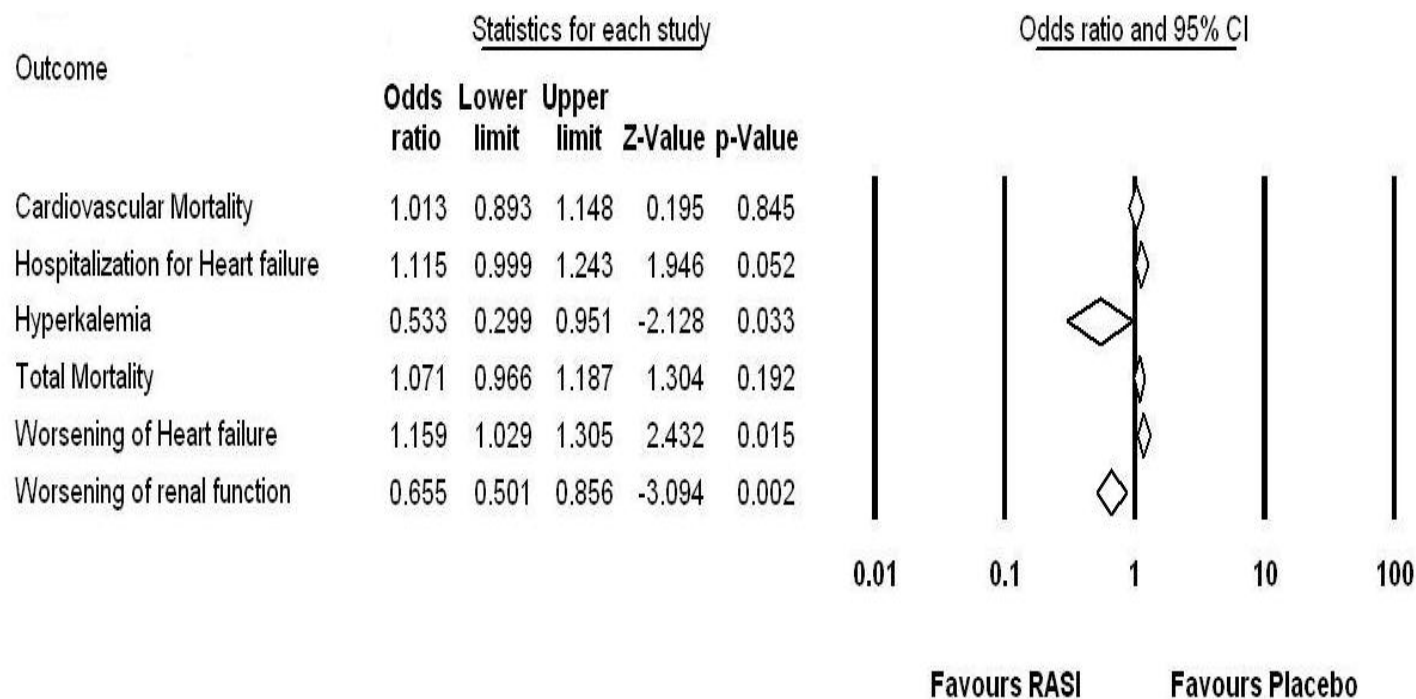


Figure 6: Summary Figure