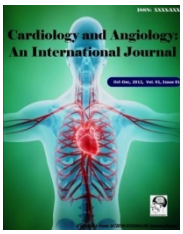


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# Heart Failure with Preserved Ejection Fraction and Therapeutic Approaches: A Systematic Review and Meta-analysis

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Author NM designed the article, performed the statistical analysis and wrote the first draft of the manuscript. Author ABM performed the literature search and revised the methods section of the manuscript. All authors read and approved the final manuscript.*

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## ABSTRACT

**Aims:** Evidence is still lacking regarding optimal treatment for patients with heart failure with preserved ejection fraction (HfPEF). Our objective is to present an individual evaluation for each of the current available heart failure medications using a meta-analytical model.

**Methods and Results:** Using meta-analytical techniques we assessed the impact of standard systolic heart failure medications on the combined endpoint of all-cause mortality and/or hospitalization for heart failure as a primary endpoint and on mortality and heart failure hospitalization as separate secondary endpoints for patients with HfPEF. Studies were heterogeneous (Q test, p=0.01) and a random effect model was adopted for analysis. A total of 22 randomized and prospective observational studies of 16,802 patients were included; mean follow up duration was 27 months. Only angiotensin converting enzyme inhibitors (ACEIs) significantly reduced the composite end point of all-cause mortality and /or hospitalization for heart failure (HR 0.74 & 95% CI [0.61-0.89], p=0.01). As for all-cause mortality, only ACEIs (HR 0.57 & 95% CI [0.45-0.71], p=0.005), beta blockers (HR 0.63 & 95% CI [0.41-0.98], p=0.03) and statins (HR 0.41 & 95% CI [0.23-0.72], p=0.001) offered a survival benefit. As for hospitalization for heart failure, only digoxin had a significant effect (HR 0.77 & 95% CI [0.61-0.98], p=0.02).

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**Conclusions:** Our analysis suggests that ACEI, beta blockers, statin and digoxin as potential medications that can improve outcomes in patients with HfPEF. However, prospective randomized studies are needed to better assess response to these medications.

*Keywords: Heart failure with preserved ejection fraction; all-cause mortality; heart failure related hospitalization.*

## 1. INTRODUCTION

Heart failure is a major challenge in developed countries and has become an economic and a health care burden [1]. In recent years there has been an increasing emphasis on "Heart failure with preserved ejection fraction (HfPEF)" in the absence of currently effective treatment modalities [2]. HfPEF has been shown to be an independent predictor of mortality (with rates as high as 21%) and readmission for heart failure (rates as high as 40%) [3]. Survival rate has been shown to be similar in patients with HfPEF compared to patients with systolic heart failure with 21% of the patients dying within one year and 65% dying within 5 years [3,4]. Recent reports estimate that 1–2% of all healthcare expenditure is devoted to heart failure in developed countries [4]. In the United States costs increased from $30.2 billion in 2007 to more than $37 billion in 2012 with the major part of expenditure related to hospital length of stay and readmission rate; almost half of this cost was attributed to HfPEF [2].

In this review, we present an individual evaluation for each of the current available heart failure medications on outcomes in patients with HfPEF using a meta-analysis model of published clinical trials and prospective observational studies.

### 1.1 Diagnostic Criteria for HfPEF

The European Society for Cardiology was the first to propose specific diagnostic criteria [5]. According to these initial guidelines, HfPEF is diagnosed in the presence of three criteria: 1) signs and symptoms of heart failure, 2) normal systolic function and 3) evidence of abnormal left ventricular relaxation, filling or stiffness [6]. The problem was the definition of "normal systolic function" and whether evidence of abnormal left ventricular (LV) diastolic function is needed to make the diagnosis [7,8]. The consensus nowadays is that HfPEF, is diagnosed in the presence of two criteria: 1) signs and symptoms of heart failure and 2) a normal ejection fraction (≥50%) [5,9]. Objective measures of LV diastolic function can further serve as confirmation but are not essential to make the diagnosis. Diastolic dysfunction refers to abnormality in the relaxation and ventricular filling of the heart during diastole [7]. This can occur in the presence or absence of signs and symptoms of heart failure.

## 2. METHODS

Here we present a separate meta-analysis for each class of medication that was studied in patients with HfPEF. Our analysis is based on the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group (MOOSE) [10].

## 2.1 Search Strategies

We carefully searched MEDLINE (1966-2014), EMBASE (1966-2014) and COCHRANE (2000-2014) databases to identify relevant studies. We used the following keywords: “Heart Failure with preserved ejection fraction OR HfPEF”, “Heart failure with normal ejection fraction”, “Diastolic/drug therapy”, "Heart Failure, Diastolic therapy", “diastolic heart failure” , “Angiotensin Converting Enzyme Inhibitors”, “Angiotensin Receptor Antagonist OR Angiotensin Receptor Blocker”, “Beta Blocker”, “Calcium Channel Blocker”, “Diuretic”, “Digoxin”, “statin”, “aldosterone receptor antagonist or blocker”, “mortality” and “heart failure hospitalization”. Additionally, the “Related Articles” feature on PubMed was used and a manual search was done using bibliographies of review articles on this topic. Titles and abstracts were reviewed independently by two reviewers (NM & AB). Differences were resolved by consensus. The search strategy and results are shown in the flow diagram (Fig. 1).

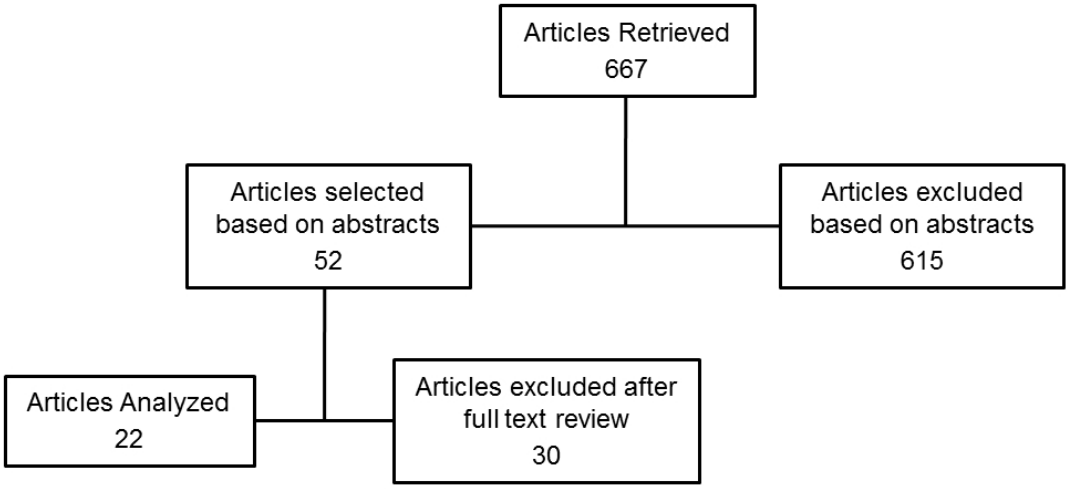


**Fig. 1. Flow diagram depicting selection process for our review**

*After a search of several databases, 667 articles were retrieved. Based on abstracts and titles, the full text for 52 articles was retrieved. After a review of the full text, 22 studies were used for final analysis*

## 3.2 Inclusion Criteria

The titles and abstracts were screened for studies that reported all-cause mortality and/or hospitalization for heart failure in patients with HfPEF. They were reviewed according to the following inclusion criteria: 1. randomized clinical trials and observational studies; 2. follow up duration of at least 6 months; 3. study patients had HPEF; 4. only human studies were included; and 5. studies had to be in English.

## 3.3 Study Characteristics and Extraction

Two blinded reviewers extracted the following data elements: 1. publication details like first author’s last name, year; 2. study design; 3. characteristics of the study population like gender, race, mean age, co-morbidities including hypertension, diabetes; 4. adjustment of

possible confounders in a multivariate analysis; and 5. adjusted hazard ratio (HR) or odds ratio (OR) with the 95% confidence interval.

## 3.4 Outcome Measure

The primary endpoint was the composite endpoint of all-cause mortality and/or hospitalization for heart failure. Secondary endpoints included: 1. all-cause mortality; and 2. hospitalization for heart failure as separate endpoints.

## 3.5 Statistical Analysis

All studies employed Cox Proportional Hazard Models. For our current analysis, we assumed OR and RR to be valid approximations of HR. This allowed us to use one measure throughout the whole analysis. HRs were transformed logarithmically since they do not follow a normal distribution. The standard error was calculated from Log HR and the corresponding 95% confidence interval. We used the inverse variance method to achieve a weighted estimate of the combined overall effect. We considered the presence of significant heterogeneity at the 5% level of significance (for the Q test) and values of $I^2$ exceeding 56% as an indicator of significant heterogeneity. Studies were noted to be heterogeneous (Q test, $p<0.01$ and $I^2=74\%\pm18\%$) which prompted us to adopt the random effect model (Mantel–Haenszel method) [10]. This model entails that rather than assuming one true effect size, we allow a distribution of the true effect size [11]. Hence, the combined effect (expressed as combined HR in this case) represents the mean of the population of the true effects. It takes into account within-study and between study variance. Publication bias was assessed by visual examination of the funnel plots and by using Egger's asymmetry test. Data was then analyzed using Microsoft Excel version 2010 and was represented as forest plots.

# 3. RESULTS

A total of 22 studies were identified for final analysis after applying our inclusion and exclusion criteria (Fig. 1). Baseline population characteristics of the studies included are shown in (Table 1).

## 3.1 Primary Endpoint

Combined all cause-mortality and/or hospitalization for heart failure.

### 3.1.1 Angiotensin converting enzyme inhibitors (ACEI)

Eight studies satisfying our inclusion criteria were included. Five out of eight studies were included for analysis of the primary endpoint. ACEI was found to be associated with a statistically significant reduction in the composite endpoint of all-cause mortality and or hospitalization for heart failure (HR 0.74 & 95% CI [0.61-0.89], p=0.01) (Fig. 2).

### 3.1.2 Angiotensin receptor blocker (ARB)

Only two randomized clinical trials satisfying inclusion criteria were included. Analysis revealed that ARB was not associated with a statistically significant reduction in the combined endpoint of all-cause mortality and/or hospitalization for heart failure (HR 0.97 & 95% CI [0.87-1.08], p=0.45).

**Table 1. Baseline characteristics of studies included in our analysis. There was a total of 22 studies, 11 of which (50%) were RCTs with the rest being prospective observational studies encompassing a population of 16,802 patients. Mean and median follow up were 27 and 24 months respectively. Average age was 75 years and approximately 55% of the total population was female**

| Study and/or author | Year | Study design | Total no. of patients | Female (%) | Mean age (years) | EF (%) | Follow up (months) | Risk estimate |
|---|---|---|---|---|---|---|---|---|
| Anc-Dig [23] | 2006 | RCT | 988 | 41 | 67 | 55 | 37 | HR |
| Anronow [26] | 1997 | RCT | 158 | 70 | 81 | 56 | 32 | RR |
| CHARM [19] | 2003 | RCT | 3,023 | 41 | 67 | ≥41% | 37 | HR |
| Cohere [27] | 2007 | Prospective | 700 | 48 | 68 | 52 | 12 | HR |
| Dobre [28] | 2006 | Prospective | 443 | 53 | 78 | 54 | 25 | HR |
| Farasat [29] | 2010 | Prospective | 56 | 80 | 71 | ≥50 | 6 | OR |
| Fukuta [30] | 2005 | RCT | 137 | 57 | 65 | 62 | 21 | HR |
| Gomez [31] | 2008 | Prospective | 1,120 | 52 | 71 | ≥50 | 60 | HR |
| Grigorian [32] | 2006 | Prospective | 416 | 51 | 73 | ≥50% | 26 | OR |
| Heart and Soul [33] | 2010 | Prospective | 909 | 18 | 67 | 62 | 60 | HR |
| I-PRESERVE [20] | 2008 | RCT | 4,128 | 60 | 72 | 60 | 50 | HR |
| Min Zi [34] | 2003 | RCT | 64 | 65 | 78 | 59% had an EF≥40% | 6 | OR |
| PEP-CHF | | RCT | 850 | 56 | 75 | 65 | 24 | HR |
| Philibin [35] | 1997 | Prospective | 350 | 65 | 75 | 51% had an EF≥40% | 6 | OR |
| Philibin [36] | 2000 | Prospective | 529 | 66 | 75 | 50% had an EF≥40% | 6 | OR |
| PREAMI [37] | 2006 | RCT | 1,252 | 35 | 72 | 59 | 12 | RR |
| Prop-Dig [38] | 2008 | RCT | 916 | 38 | 67 | 55 | 24 | HR |
| SENIORS [39] | 2005 | RCT | 61 | 30 | 75 | 54 | 12 | RR |
| Swedic [40] | 2004 | RCT | 97 | 43 | 66 | >40 | 6 | RR |
| Tehrani [41] | 2008 | Prospective | 270 | 66 | 79 | 62 | 60 | RR |
| Tribouilloy [42] | 2008 | Prospective | 240 | 53 | 76 | 62% had an EF≥50% | 60 | OR |
| Yip [43] | 2008 | RCT | 95 | 59 | 74 | 65% had an EF≥45% | 12 | OR |

**Cohere and SENIORS: these were sub studies of the original randomized clinical trials. (RCT=randomized clinical trial, EF=ejection fraction; HR=hazard ratio; OR=odds ratio; RR= risk ratio; N=total number*

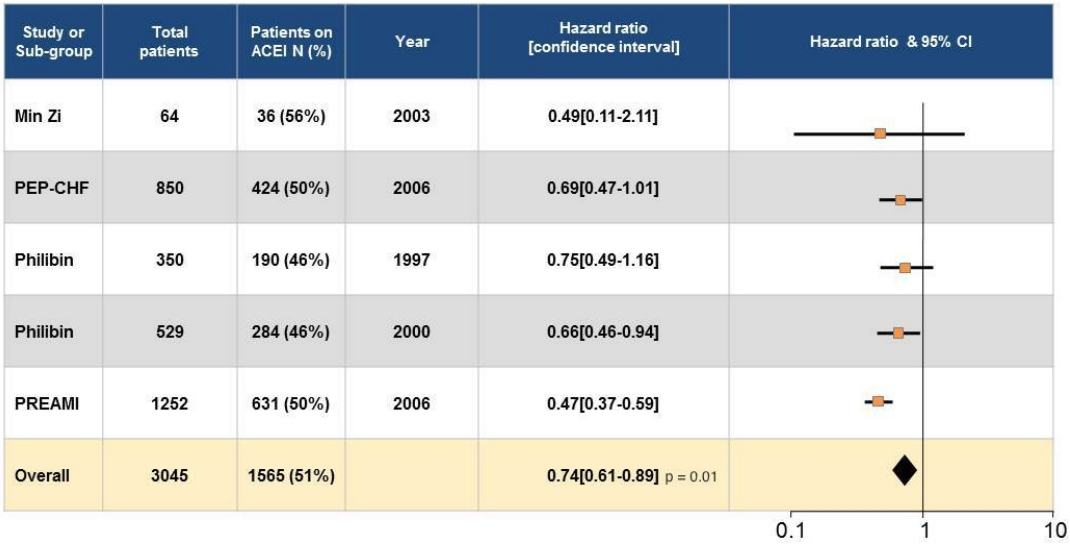


**Fig. 2. Forest plot for effect of ACEI on our primary endpoint**

*Effect of ACEI on all-cause mortality and/or hospitalization for heart failure (our primary endpoint) in patients with HfPEF. ACEI use was associated with a statistically significant reduction in the primary endpoint (HR=0.74 & 95% CI [0.61-0.89], p=0.01) in patients who satisfied the criteria for HfPEF*

### 3.1.3 Beta blockers (BB)

Data was not sufficient for pooled analysis for effect on composite endpoint of all-cause mortality and/or hospitalization.

### 3.1.4 Digoxin

Data was not sufficient to analyze effect of digoxin on the composite endpoint of all-cause mortality and/or hospitalization for heart failure.

### 3.1.5 Statin

Data was not sufficient to analyze effect of statins on the composite endpoint of all-cause mortality and/or hospitalization for heart failure.

## 3.2 Secondary Endpoints

### 3.2.1 All-cause mortality

*3.2.1.1 ACEI*

Eight studies satisfying our inclusion criteria were included. All of them were included for analysis of all-cause mortality. Analysis showed that ACEI was associated with significant reduction in all-cause mortality (HR 0.57 & 95% CI [0.45-0.71], p=0.005) (Fig. 3a).

*3.2.1.2 ARB*

Only two randomized clinical trials satisfying inclusion criteria were included. There was no significant reduction in all-cause mortality with use of ARB (HR 1.02 and 95% CI [1.01-1.03], p=0.65).

*3.2.1.3 BB*

A total of eight studies, including randomized and prospective observational, were included. BB use was associated with a statistical significant reduction in all-cause mortality (HR 0.63 & 95% CI [0.41-0.98], p=0.03) (Fig. 4a).

*3.2.1.4 Digoxin*

Data was not sufficient to analyze effect of digoxin on all-cause mortality.

*3.2.1.5 Statin*

There were only three studies that addressed the effect of statin on all-cause mortality in HfPEF. Analysis showed that statin was associated with a statistical significant reduction in all-cause mortality (HR 0.41 & 95% CI [0.23-0.72], p=0.001) (Fig. 5).

**3.2.2 Hospitalization for heart failure**

*3.2.2.1 ACEI*

Eight studies satisfying our inclusion criteria were included. Six out of eight studies were included for this endpoint. There was no significant reduction in hospitalization for heart failure (HR 0.81 & 95% CI [0.65-1.01], p=0.67) (see Fig. 3b).

*3.2.2.2 ARB*

Only two randomized clinical trials satisfying inclusion criteria were included .There was no significant reduction in hospitalization for heart failure (HR 0.96 and 95% CI [0.84-1.09], p=0.71).

*3.2.2.3 BB*

A total of eight studies, including randomized and prospective observational, were included. BB use had no effect on hospitalization for heart failure (HR 0.96 & 95% CI [0.48-1.92], p=0.68) (Fig. 4b).

*3.2.2.4 Digoxin*

A total of two randomized clinical trials satisfying our inclusion criteria were included. Analysis revealed that digoxin was associated with a statistical significant reduction in heart failure hospitalization (HR 0.77 & 95% CI [0.61-0.98], p=0.02).

*3.2.2.5 Statin*

Data was not sufficient to analyze effect of statins on hospitalization for heart failure.

*3.2.2.6 Publication bias*

There was no evidence of publication bias for the included studies by visual inspection of the funnel plot and by using the Egger test (p=0.10).

**Fig. 3-a effect of ACEI on all-cause mortality**

| Study or Sub-group | Total patients | Patients on ACEI N (%) | Year | Hazard ratio [confidence interval] | Hazard ratio & 95% CI |
|---|---|---|---|---|---|
| Grigorian | 416 | 210 (50%) | 2006 | 0.36 [0.24-0.54] | |
| Min Zi | 64 | 36 (56%) | 2003 | 1.06 [0.06-17.48] | |
| PEP-CHF | 850 | 424 (50%) | 2006 | 0.90 [0.47-1.73] | |
| Philbin | 350 | 190 (46%) | 1997 | 0.60 [0.33-1.07] | |
| Philbin | 529 | 284 (46%) | 2000 | 0.53 [0.33-0.88] | |
| PREAMI | 1252 | 631 (50%) | 2006 | 0.70 [0.44-1.12] | |
| Tribouilloy | 240 | 120 (50%) | 2008 | 0.61 [0.43-0.87] | |
| Yip | 95 | 45 (47%) | 2008 | 0.15 [0.01-2.97] | |
| Overall | 3796 | 1940 (51%) | | 0.57 [0.45-0.71] p = 0.005 | |

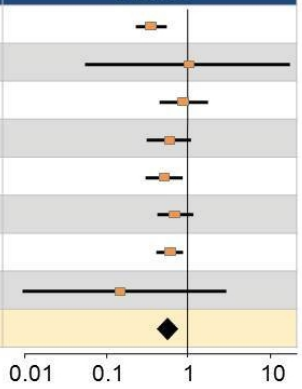


**Fig. 3-b effect of ACEI on heart failure hospitalization**

| Study or subgroup | Total patients | Patients on ACEI N (%) | Year | Hazard ratio [confidence interval] | Hazard ratio & 95% CI |
|---|---|---|---|---|---|
| Hong Kong | 151 | 45 (30%) | 2008 | 0.91 [0.36-2.31] | |
| Min Zi | 64 | 36 (56%) | 2003 | 0.39 [0.07-2.15] | |
| PEP-CHF | 850 | 424 (50%) | 2006 | 0.63 [0.41-0.97] | |
| Philibin | 350 | 190 (46%) | 1997 | 0.60 [0.33-1.07] | |
| Philibin | 529 | 284 (46%) | 2000 | 0.53 [0.33-0.88] | |
| PREAMI | 1252 | 631 (50%) | 2006 | 0.71 [0.41-1.25] | |
| Overall | 3196 | 1610 (50%) | | 0.81 [0.64-1.01] p = 0.06 | |


**Fig. 3a. Forest plot for effect of ACEI on all-cause mortality. Fig. 3b. Forest plot for effect of ACEI on heart failure hospitalization**

*Effect of ACEI on all-cause mortality. ACEI was associated with a statistically significant reduction in all-cause mortality (HR=0.57 & 95% CI [0.45-0.71], p=0.005) in patients who satisfied the criteria for HfPEF. Effect of ACEI on hospitalization for heart failure in patients with HfPEF. ACEI had no significant effect on the rate of hospitalization for heart failure (HR=0.81 & 95% CI [0.64-1.01], p=0.06). *Hong Kong study is the same study as the one conducted by Yip et al.*

*3.3 Other Adjunctive Medications*

## 3.3.1 Aldosterone antagonists

To the best of our knowledge there are no randomized trials addressing effect of aldosterone antagonist on all-cause mortality or hospitalization for heart failure in patients with HfPEF. However, spironolactone has been shown to improve diastolic parameters (left atrial size and left ventricular end diastolic pressure) in ambulatory hypertensive patients with isolated LV diastolic dysfunction over a period of six months when a small dose was used (25 mg/day) [12]. In addition, eplerenone (an aldosterone antagonist) has been shown to be

associated with significant reduction in serum collagen markers (procollagen type I) and improvement in echo parameters (significant reduction in the E/E' ratio) over a period of 26 weeks in patients with HfPEF [13].

### 3.3.2 Calcium channel blockers (CCB)

We were not able to find any studies that addressed the effect of CCBs on death or hospitalization for heart failure in patients with HfPEF. However, CCB use has been associated with 33% improvement in exercise capacity with mild decrease in diastolic blood pressure compared to control, but effect on morbidity and mortality was not addressed [14].

**Fig 4-a Effect of beta blockers on all-cause mortality**

| Study or subgroup | Total Patients | Patients on BB N (%) | Year | Hazard ratio [confidence interval] | Hazard ratio & 95% CI |
|---|---|---|---|---|---|
| Anronow | 158 | 79 (50%) | 1997 | 0.40 [0.2-0.79] | |
| Dobre | 443 | 227 (51%) | 2006 | 0.42 [0.27-0.65] | |
| Fukata | 137 | 68 (50%) | 2005 | 0.76 [0.32-1.83] | |
| Heart & Soul | 909 | 534 (59%) | 2010 | 1.26 [0.41-3.84] | |
| SENIORS | 61 | 27 (44%) | 2005 | 0.92 [0.59-1.45] | |
| Overall | 1708 | 935 (55%) | | 0.63 [0.41-0.98] p = 0.03 | |

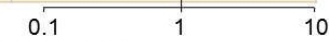


**Fig 4-b Effect of beta blockers on heart failure hospitilzation**

| Study or subgroup | Total patients | Patients on BB N (%) | Year | Hazard ratio [confidence interval] | Hazard ratio & 95% CI |
|---|---|---|---|---|---|
| Cohere | 700 | 700 (100%) | 2007 | 0.62 [0.46-0.83] | |
| Farasat [1] | 21 | 15 (71%) | 2010 | 0.25 [0.03-1.92] | |
| Farasat [2] | 45 | 28 (62%) | 2010 | 14.00 [3.1-63.32] | |
| Heart & Soul | 909 | 534 (59%) | 2010 | 0.47 [0.207-1.071] | |
| SENIORS | 61 | 27 (44%) | 2005 | 0.84 [0.47-1.51] | |
| Swedic | 97 | 47 (49%) | 2004 | 2.06 [0.365-11.631] | |
| Overall | 1833 | 1351 (74%) | | 0.96 [0.48-1.92] p = 0.68 | |


**Fig. 4a. Forest plot for effect of beta blockers on all-cause mortality. Fig. 4b. Forest plot for effect of beta blockers on heart failure hospitalization**

*Beta blockers were associated with a statistical significant reduction of all-cause mortality (HR=0.63 & 95% CI [0.0.41-0.98], p=0.03) in patients who satisfied the criteria for HfEPF. BB had no significant effect on hospitalization for heart failure (HR=0.96 & 95% CI [0.48-1.92], p=0.68) in patients who satisfied the criteria for HfPEF*

### 3.3.3 Diuretics

To the best of our knowledge there are no randomized trials addressing effect of diuretics on all-cause mortality or hospitalization for heart failure in patients with HfPEF. Current studies

have demonstrated greater improvement in diastolic parameters and reduction in left ventricular mass with diuretics when compared to CCB [14].

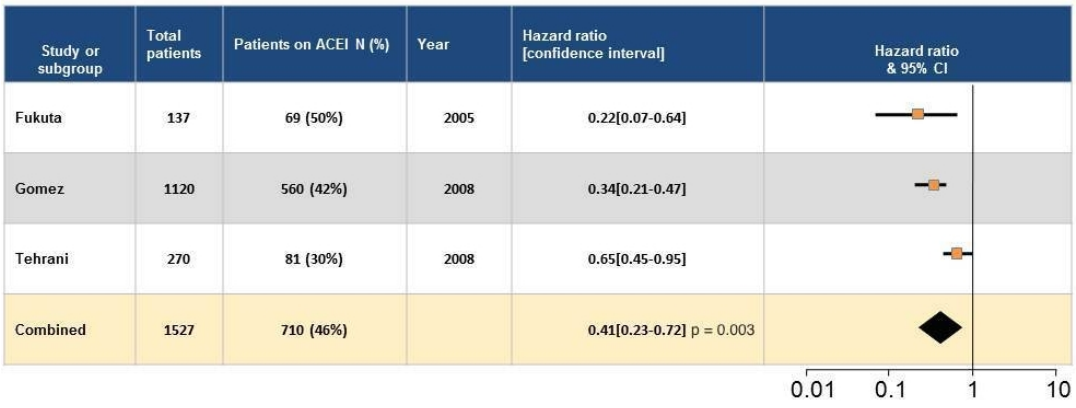


**Fig. 5. Forest plot for effect of statins on all-cause mortality**

*Statins were associated with a statistical significant reduction in all-cause mortality (HR=0.41 & 95% CI [0.23-0.72], p=0.003) in patients who satisfied the criteria for HfPEF*

## 4. DISCUSSION

Based on our analysis, only ACEIs were found to cause a statistical significant reduction of the composite endpoint of all-cause mortality and/or hospitalization for heart failure in patients with HfPEF. However, ACEI, beta blockers and statins were the only medications that significantly lowered all-cause mortality. As for hospitalization for heart failure, only digoxin showed a statistical significant reduction.

There has been considerable controversy regarding the optimal therapeutic approach to patients with HfPEF. Current guidelines recommend treatment of underlying etiologies but the benefits of available therapies on mortality and/or heart failure related hospitalization have not been proven [15]. Our analysis adds to the existing literature by providing the first report of individual analysis for each class of available standard heart failure medications.

Two meta-analyses have evaluated effect of heart failure medication on all-cause mortality in patients with HfPEF [16,17]. Holland et al. [16] conducted a comprehensive meta-analysis of prospective randomized and observational studies published till 2009 with 53,878 patients demonstrating that pharmacotherapy improved exercise tolerance but not all-cause mortality. In this study, additional analysis was done to assess effect of three different subgroups (ACEI/ARBS, chronotropic agents and vasodilators) on all-cause mortality. However, there was inconsistency in the medications included within each subgroup (e.g. chronotropic agents consisted of BB in some studies while in other studies they consistent of a combination of CCB and BB) which limited generalizability of the data. Furthermore, the study conducted by Holland et al. [16] did not provide individual analysis for digoxin and statin in relation to mortality and/or hospitalization for heart failure. Our report updates that study by including newer studies till 2013. In addition, our study provides a detailed individual analysis for each class of medication separately; this helps limit potential inconsistencies when trying to combine medications into subgroups. Moreover, we also analyzed role of statins and digoxin and examined the effect of therapy on hospitalization for

heart failure as an additional endpoint, all of which was not addressed in the study conducted by Holland et al.

Fu et al. [17] published a comprehensive met-analysis of seven randomized prospective trials with 2,554 patients addressing effect of ACEIs on mortality and hospitalization for heart failure in patients with HFPEF. He demonstrated that ACEI use was associated with reduction in all-cause mortality but not heart failure related hospitalization [17]. Our reports adds to this analysis by including individual evaluations of ARB, BB, digoxin and statin on all-cause mortality and hospitalization for heart failure.

It seems that ACEIs may have a more important role in reducing mortality or hospitalization for heart failure than what is currently being recognized in the literature. This shouldn't be surprising as angiotensin II promotes interstitial fibrosis, causes myocardial thickening and decreases ventricular compliance impairing relaxation in the process [18]. Notably none of the RCTs demonstrated an improvement in primary outcomes with the use of renin-angiotensin antagonists (RAAS-ACEI and/or ARB) [9,19,20]. However, benefit could have been concealed by selection bias or high cross over rate [21]. In a recent prospective observational study of a matched cohort of 16,216 patients with HFPEF, Lund et al. demonstrated reduction in all-cause mortality with the use of RAAS (ACEI and/or ARB) (hazard ratio (HR) of 0.91 (95% CI, 0.85-0.98; *P*=.008)).[22] Furthermore, a dose-response analysis was conducted in this study revealing reduction in all-cause mortality with 50% or greater of target RAAS dose (HR was 0.85 (95% CI, 0.78-0.83; *P*<0.001)) [22]. This coincides with our analysis where observational studies demonstrated survival benefit with ACEI and/or ARB versus RCTs that did not show any difference in primary outcomes. Even though RCTs limit confounding and bias when compared to observational studies, the randomized trials conducted on ACEI and or ARBs are limited by selection bias and potential under powering due to close monitoring and inclusion of a healthier population of patients [21].

Another interesting finding was that only digoxin reduced the rate of hospitalization for heart failure. The role of digoxin in reducing heart failure related hospitalization for patients with systolic heart failure is well established. However, current guidelines still do not address the role of digoxin in management of HfPEF [15]. Potential explanations for the beneficial role of digoxin in patients with HFPEF include: 1. favorable effect of digoxin on neurohormonal profile; 2. potential role in suppressing the RAAS axis and in improving the active energy-dependent early myocardial diastolic function [7,23]. It is noteworthy mentioning recent concerns about use of digoxin. Digoxin use has been associated with an increasing (though not statistically significant) trend toward hospitalization for unstable angina in patients with HFPEF [23]. In a recent analysis of the AFFIRM study, digoxin use has been associated with increased all-cause mortality among patients with atrial fibrillation even after adjusting for clinical characteristics and co-morbidities [24]. This could stem from the reported (but not yet proven) role of digoxin in increasing endothelial and platelet activation [25]. Further studies are needed to assess effect of digoxin on mortality in patients with HFPEF.

Our meta-analysis indicates that ACEIs reduce the composite endpoint of all-cause mortality and heart failure related hospitalization. In addition, our analysis suggests that beta blockers and statins reduce all-cause mortality while digoxin reduces heart failure related hospitalization.

## 5. LIMITATION

First, definition of HfPEF was not consistent among the included studies. Some included diastolic dysfunction as a necessary criterion (e.g. PEP-CHF[9]) whiles others did not. Secondly, most of the included studies were observational and confounded by indications for therapy, contraindications and prevalent user bias. Thirdly, most studies identified patients by virtue of clinical heart failure as serum BNP/NT-BNP and echocardiographic parameters were not available in recruited patients; these markers could have improved diagnostic yield even though they are not essential to make the diagnosis of HfPEF. Another limitation is that we were not able to conduct separate meta-analyses for randomized trials and observational studies due to lack of data for pooled analysis. Another important issue is that the etiology of HfPEF is diverse as previously mentioned above; this fact may bias the statistical analysis made in this manuscript. Moreover, as there is no available specific therapy for HfPEF, any reported benefit in our analysis may be related to the underlying disease. Another potential limitation is that included studies differed in the methods, endpoints and number of patients recruited. Last, an important issue pertains to differences in patient demographics between RCTs and observational trials. Patients in observational studies were older, more often women, and had a greater number of comorbidities.

## 6. CONCLUSION

Despite mortality approaching that of systolic heart failure, evidence is still lacking in regards to the most appropriate treatment in patients with HfPEF. Our analysis suggests that ACEI, BB, statin and digoxin to be potential medications that can improve outcomes in patients with HfPEF. However, prospective randomized studies are needed to better assess response to these treatment approaches.

## CONSENT

Not applicable.

## ETHICAL APPROVAL

Ethical approval is not applicable as we did not have access to patient data directly. Our analysis is considered to be exempt from IRB approval.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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