

## Anti-Hypertensive Medication in Geriatric Population with HFpEF

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### ABSTRACT

#### INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a condition where the left ventricular function is  $\geq 50\%$ . This population has a high morbidity and mortality compared to its counter-part heart failure with reduced ejection fraction (HFrEF). However treatment in this group remain spares. Hypertension medications are widely used in practice for patients with heart failure with reduced ejection fraction, however its efficacy in HFpEF is still an ongoing research.

#### METHOD

Evidence based research from various different search engines such as Medline<sup>®</sup>, Cochrane<sup>®</sup>, and Proquest<sup>®</sup> with inclusion of high quality evidence such as meta-analysis, systematic review, RCT, and cohort studies. The selected papers were screened for validity, importance and applicability to the case in question.

#### RESULT

The two different RCTs studies showed that ACE-I had no effects in HFpEF. Research by Kitzman et al. showed that ACE-I did not show any improvement of left ventricular mass, neuro-hormonal profile, and 6 minutes walking test. This was also confirmed by Zi et al., which in addition showed that ACE-I did not increase the quality of life in the geriatric subjects.

#### CONCLUSION

All in all, ACE-I as a type of anti-hypertensive medication does not benefit geriatric population of HFpEF.

#### KEYWORDS

ACE-I; HFpEF; Geriatric; 6 minutes' walk test; Echocardiography

#### 1. INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a condition where the left ventricle ejection fraction is still above  $\geq 50\%$ , besides the existence of impaired diastolic function and altered natriuretic peptide. The

typical sign and symptoms of heart failure could as well be found in HFpEF which lead to hospital admission [1]. A huge proportion of heart failure that develop in the elderly are HFpEF, this is particularly true in women. Patients with this condition have great tendency to be readmitted to a hospital due to the heart failure

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decompensation, which as well alter the patients' quality of life. A few researches have also shown that HFpEF patients have almost similar risk of mortality as compared to the counterpart HFrEF (heart failure with reduced ejection fraction, LVEF <40% [2]. Nonetheless, there is poor understanding of the disease progression and treatment, despite commonly being treated by the general heart failure guideline.

The currently accepted pathophysiology of HFpEF is an abnormality of the diastolic function at left ventricular. This event occurs due to an aberrant active relaxation of the left ventricle, which would be accompanied by the passive left ventricular stiffness. The condition would hamper the cardiac output, especially during exercise. The disease progression of HFpEF is thought to be caused by various factors such as hypertension that cause concentric remodeling, defective chronotropic, depletion of vasodilatory reserve, impaired oxygen perfusion, and excessive adipose density [3].

Based on the guideline of heart failure treatment, the common medication used to treat and control the disease are beta-blocker, ACE-I, CCB, aldosterone antagonist, ivabradine, and digoxin [1]. However these medication are proven to benefit patients with reduced ejection fraction. There is still not enough evidence in the treatment for HFpEF.

The epidemiological data from USA in 2010 showed that HFpEF counted for 44% - 72% of the total heart failure found at hospitals across the country. Meanwhile heart failure in general is known as a major cause of death as 1 in 9 American decreased caused by this HF [4].

## **2. CASE STUDY**

A 65-year-old women came to the clinic presented with dyspnea on exertion while doing a heavy daily activity such as walking to the market in the morning. Patient

denied any chest pain throughout her disease progression. She claimed that there is no difficulty in sleeping, she could sleep with just a single pillow. However, 10 years ago the patient had a history of collapse, although her consciousness regain after a minute, the problem kept on bothering her in an intermittent fashion. During the attack, usually the patient felt palpitation, headache, and light headedness. Despite not always leading to losing her consciousness, the problem kept on bothering her for years. She started seeking help 3 years ago since the problem became more frequent to 3 times in a week. That time she attained a referral letter to a heart specialist and was diagnosed with atrial fibrillation. Several test such as ECG, holter, and echocardiography were conducted. In one of those tests, it was found that the heart's left ventricular ejection fraction has decreased to 50%. She was then treated with digoxin, warfarin and ramipril from the doctor in charge. The patient denied any history of hypertension, although she was diagnosed with diabetes 15 years ago and ever since had been consuming metformin  $2 \times 500$  mg. She acclaimed that her blood glucose had always been controlled well together with appropriated lifestyle modification. In her family history, it was found that her father died out of stroke at the age of 82 years, while her mother died due to stroke at the age of 90 years, her siblings are all healthy and alive some with hypertension and diabetes.

## **3. QUESTION**

Does anti-hypertension medication has a potential benefit in the treatment of HFpEF?

## **4. METHODS**

The literature search was conducted on the 5th October 2019, which gathered data from a few search engine such as Medline<sup>®</sup>, Cochrane<sup>®</sup>, and Proquest<sup>®</sup>. Each search engine corresponded by a different search keys as shown on Table 1. However the general search words included "anti-hypertension" "ACE-I" "CCB" "ARB" "geriatric"

and “HFpEF”. Other anti-hypertensive medication that are not widely available were not included. Meanwhile some MeSH terms were used to find the roots of each word and find synonyms of the word. The inclusion and exclusion criteria were written on Table 1, in general only

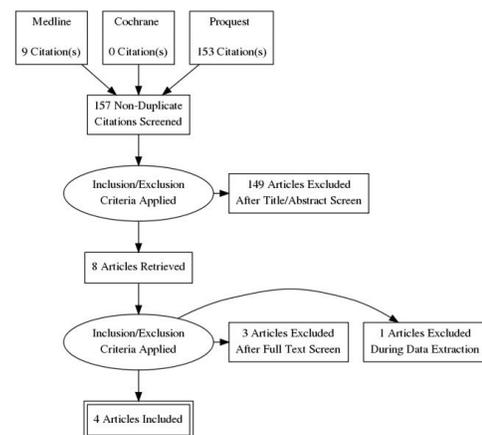
high level of evidence as meta-analysis, systematic review, and high evidence clinical trials were included. The appraisals of papers were based on the guideline used by Oxford University, center of evidence-based medicine (Figure 1).

Database	Search strategy	Limitation	Hit
Medline	((“calcium channel blockers”[Pharmacological Action] OR “calcium channel blockers”[MeSH Terms] OR (“calcium”[All Fields] AND “channel”[All Fields] AND “blockers”[All Fields]) OR “calcium channel blockers”[All Fields] OR (“calcium”[All Fields] AND “channel”[All Fields] AND “blocker”[All Fields]) OR “calcium channel blocker”[All Fields] OR CCB[All Fields] OR (“receptors, angiotensin”[MeSH Terms] OR (“receptors”[All Fields] AND “angiotensin”[All Fields]) OR “angiotensin receptors”[All Fields] OR (“angiotensin”[All Fields] AND “receptor”[All Fields]) OR “angiotensin receptor”[All Fields]) AND blocker[All Fields]) OR ARB[All Fields] OR (“angiotensin-converting enzyme inhibitors”[Pharmacological Action] OR “angiotensin-converting enzyme inhibitors”[MeSH Terms] OR (“angiotensin-converting”[All Fields] AND “enzyme”[All Fields] AND “inhibitors”[All Fields]) OR “angiotensin-converting enzyme inhibitors”[All Fields]) OR (“ace”[All Fields] AND “inhibitor”[All Fields]) OR “ace inhibitor”[All Fields] OR (“antihypertensive agents”[Pharmacological Action] OR “antihypertensive agents”[MeSH Terms] OR (“antihypertensive”[All Fields] AND “agents”[All Fields]) OR “antihypertensive agents”[All Fields] OR (“anti”[All Fields] AND “hypertensive”[All Fields]) OR “anti hypertensive”[All Fields])) AND Genatric[All Fields] AND (HFpEF[All Fields] OR (“heart failure”[MeSH Terms] OR (“heart”[All Fields] AND “failure”[All Fields]) OR “heart failure”[All Fields]) AND (“preservation, biological”[MeSH Terms] OR (“preservation”[All Fields] AND “biological”[All Fields]) OR “biological preservation”[All Fields] OR “preserved”[All Fields] AND ejection[All Fields] AND fraction[All Fields])) AND “humans”[MeSH Terms]	<ul style="list-style-type: none"> <li>Systematic review</li> <li>Randomized controlled trial</li> </ul>	9
Cochrane	(anti-hypertension OR anti-hypertensive OR ACE-i OR ARB OR CCB) AND Genatric AND (HFpEF OR Heart failure with preserved ejection fraction)	<ul style="list-style-type: none"> <li>Cochrane review</li> </ul>	0
Proquest	(anti-hypertension OR anti-hypertensive OR ARB OR ACE-i OR CCB OR calcium channel blocker) AND Genatric AND (HFpEF OR Heart failure with preserved ejection fraction)	<ul style="list-style-type: none"> <li>Systematic review</li> <li>RCT</li> <li>Meta-analysis</li> <li>NOT (Books AND Wire Feeds AND Reports AND Trade Journals)</li> <li>NOT (confidence intervals AND diabetes AND regression analysis AND chronic obstructive pulmonary disease AND hemodialysis AND kidney diseases AND kidney transplantation AND lung diseases AND rodents AND bias AND cancer therapies)</li> <li>NOT (General Information AND Conference Proceeding AND Literature Review AND Undefined)</li> <li>NOT (Agricultural &amp; Environmental Science Collection AND Environmental Science Index AND Environmental Science Collection AND Materials Science &amp; Engineering Collection AND Engineering Index AND Engineering Collection AND Psychology Database AND Engineering Database AND Agricultural Science Collection AND Agriculture Science Database AND Research Library: Business AND Advanced Technologies &amp; Aerospace Collection AND Sociology Database AND Advanced Technologies &amp; Aerospace Database AND Earth, Atmospheric &amp; Aquatic Science Collection AND Materials Science Collection AND PsycARTICLES AND Materials Science Database AND Research Library: Social Sciences AND Environmental Science Database AND Earth, Atmospheric &amp; Aquatic Science Database</li> </ul>	153

**Table 1:** The search results and limitation from Medline®, Cochrane®, and Proquest® database.

### 5. RESULTS

Evidences from the search did not give rise to any significant benefit from the use of oral anti-hypertensive medication towards HFpEF in geriatric population. In one study by Kitzman et al., 35 and 36 randomly selected patients after prior screening were administered Enalapril (ACE-i) and placebo respectively. The study showed that after a 12 months follow-up there were no significant difference in any Doppler left ventricular diastolic function as depicted in the figure below [5] (table 2).



**Figure 1:** Prisma diagram of the search process.

	Enalapril			Placebo			P
	Baseline	4 mo	Final	Baseline	4 mo	Final	
<b>LV volumes and masses (MRI)</b>							
Mass, g	129 ± 20	125 ± 21	121 ± 18	118 ± 28	113 ± 26	113 ± 26	0.82
Mass/end-diastolic volume ratio	1.9 ± 0.5	1.8 ± 0.4	1.9 ± 0.4	1.8 ± 0.4	1.7 ± 0.4	1.7 ± 0.4	1
End-diastolic volume, mL	70 ± 16	72 ± 17	67 ± 14	68 ± 16	67 ± 18	70 ± 16	1
End-systolic volume, mL	24 ± 06	24 ± 07	23 ± 06	23 ± 07	23 ± 08	24 ± 08	0.88
Stroke volume, mL	46 ± 11	48 ± 12	44 ± 10	45 ± 13	44 ± 13	46 ± 11	1
EF, %	65 ± 06	66 ± 06	66 ± 06	66 ± 07	65 ± 07	66 ± 08	0.99
<b>Doppler LV diastolic function (ultrasound)</b>							
Early mitral annulus velocity, cm/s	9.4 ± 2.1	9.1 ± 2.0	8.4 ± 1.4	8.0 ± 1.7	7.5 ± 1.7	7.1 ± 1.5	0.1
Early deceleration time, ms	220 ± 45	220 ± 58	208 ± 58	237 ± 48	240 ± 60	242 ± 62	0.65
Isovolumetric relaxation time, ms	70 ± 19	70 ± 16	71 ± 13	77 ± 15	81 ± 18	76 ± 17	0.37
Early mitral flow velocity, cm/s	76 ± 17	78 ± 17	81 ± 16	71 ± 16	70 ± 15	73 ± 17	0.3
Early/atrial mitral flow velocity, cm/s	1.01 ± 0.5	1.02 ± 0.5	1.10 ± 0.7	0.84 ± 0.3	0.84 ± 0.2	0.84 ± 0.3	0.94
E/Ea	8.5 ± 2.2	8.9 ± 2.6	9.9 ± 2.4	9.4 ± 3.2	9.7 ± 2.7	10.8 ± 3.6	1

**Table 2:** Left ventricular function in the two different groups.

Another study by Zi et al. [6], which recruited 74 subjects, made an assessment based on exercise tolerance. It was found that the mean 6 minutes’ walk test increment was not statistically significant in quinapril (ACE-i) compared to placebo group. Similar results were found by Kitzman et al. [5] in assessing exercise performance by 6-minute walk test, and ventilator anaerobic, which showed only 0.1±0.4 mL/kg/min (0.7%; 95% CI, -0.6 mL/kg/min to 0.8 mL/kg/min) treatment effect compared to the control group [5,6].

A study by Berry et al. [4], which was a cohort that encompassed 528 subjects with heart failure of the mean age 72, had 29% proportion of HFpEF. In this study, the death rate between HFpEF and HFfrEF were compared, some proportion of HFpEF subjects in this study received ACE-I, the result showed that similar death rate were found in both groups [4]. Meanwhile, another cohort study by Tinetti et al., found that the elderly population in general with heart failure without previous assessment of the ejection fraction by echocardiography would benefit administration of RAS blocker which increase the survival ratio by 0.8 [2] (Table 3 & Table 4).

Article	Year	Randomized	Comparable groups	Additional treatment	Loss to follow up	Double blinded	CI
Kitzman et al.	2010	+	+	-	<20%	+	95%
Zi et al.	2003	+	+	+	N/A	+	95%
Berry et al.	2005	-	+	-	16%	-	95%
Tinetti et al.	2015	-	-	-	1.3%	-	95%

**Table 3:** Critical appraisal of three papers based on the center of evidence-based Medicine University of Oxford.

Author	Title	Population	Study design	Results	Summary
Kitzman et al. 2010 [5]	A Randomized Double-Blind Trial of Enalapril in Older Patients With Heart Failure and Preserved Ejection Fraction	71 stable elderly patients (70±1 years, 80% women) with compensated HFpEF, blood pressure controlled.	Randomized double-blind controlled trial of enalapril 20mg/d with placebo for 12 months.  Assessments: exercise oxygen consumption, 6 minutes walking test, Minnesota living with HF questionnaire, MRI, Doppler, Echocardiography, vascular ultrasound.  25 subjects given Enalapril (ACE-inhibitor) and 34 control placebo.	There is a slight reduction in peak exercise oxygen consumption (0.7%), tendency of improved Minnesota Living with HF Questionnaire (p=0.07), reduction of systolic blood pressure during peak exercise (p=0.02), and carotid arterial distensibility (p=0.04)  No difference in 6 minutes walking test, aortic distensibility, left ventricular mass, and neurohormonal profile.	ACE-I anti-hypertension treatment in HFpEF did not show a beneficial effect of exercise tolerance and quality of life in elderly.
Zi et al. 2003 [6]	The effect of quinapril on functional status of elderly patients with diastolic heart failure.	74 geriatric subjects (mean SD 78 (7) years) NYHA ii-iii and normal to mildly impaired EF (>=40%)	Randomized controlled trial (RCT)	Mean 6 minute walk test increased in quinapril group compared to placebo group, although not statistically significant p=0.04. There is no significant change in quality of life score.	ACE-I anti-hypertension treatment in HFpEF did not show a beneficial effect of exercise tolerance and quality of life in elderly.
Berry et al. 2005	Heart failure with preserved left ventricular systolic function: a hospital cohort study	528 emergency patients (average age 72(13)) admitted with heart failure, with ejection fraction data available for 84% of the subjects	Prospective Cohort	130 subjects (29%) had HFpEF. Less HFpEF subjects received ACE-I than HFfrEF. However warfarin was found to be used in a lot of HFpEF patients for AF. Result of using those medications shows similar death rate and/or readmission for unspecified reasons.	HFpEF subjects had more comorbid, however similar prognosis despite being given different medication
Tinetti et al. 2015	Association between guideline recommended drugs and death in older adults with multiple chronic conditions: population based cohort study	8578 older adults followed through 2011	Prospective Cohort	Patients with heart failure shows survival benefit from Renin-angiotensin system blocker by 0.8 hazard ratio.	Although it shows increase in survival the research does not assess the patient's ejection fraction by echocardiography, it is possible to be interlaced with HFpEF.

**Table 4:** Results and study characteristics.

## 6. DISCUSSION

Based on various literature assessing the applicability of anti-hypertensive medication such as ACE-I for geriatric population with heart failure, especially the one with

preserved ejection fraction, there were no positive outcome interims of the exercise test, as well as Doppler of the left heart function. Although medication serving as hypertension lowering agent for instance ACE-I found to have a strong evidence to benefit heart failure patients

with reduced ejection fraction [1], RCTs by Kitzman et al. [5] and Zi et al. [6] declined any beneficial outcome for the geriatric HFpEF patients [5,6]. Other cohort study by Berry et al also found that HFpEF and HFrEF patients had similar death rate, although some proportion of HFpEF subjects which was not specified in the study group had been treated by ACE-I [4]. However, a cohort by Tinetti et al which encompassed a huge number of patients (8578 elderly) found that RAS blocker would benefit this the elderly population with heart failure despite knowing the ejection fraction. The limitation of this study by Tinetti et al. was that the proportion of HFpEF and HFrEF patients were not adequately performed due to the limitation in echocardiography resources [2].

Strong evidence based on the two RCT by Kitzman et al. [5] and Zi et al. [6] concluded that ACE-I applicability for patients with HFpEF was not going to be beneficial as assessed by exercise performance and cardiac Doppler functioning. In addition it was found that women were

more predominantly subjected to HFpEF among the elderly population as depicted by the data from Kitzman et al. [5].

Further understanding of the disease and various trials could benefit this population in the future. Although ACE-I alone did not show any positive correlation in these studies. Another study which is due in 2019 aimed at inducing the production of cGMP in the myocardial cells and modifying the fibrosis process using a combination of Sacubitril-Valsartan (ARNi/angiotensin receptor-neprilysin inhibitor) could be the future advance for the population [7].

## **7. CONCLUSION**

Therefore it is possible to conclude that ACE-I as a subtype of anti-hypertensive lowering agent is not beneficial interims of improving exercise tolerance, left ventricular function, and lowering mortality rate.

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