**REVIEW ARTICLE** 



# Safety and Efficacy of Anti-Hypertensive Medications in Patients with Heart Failure with Preserved Ejection Fraction: A Systematic Review and Meta-analysis

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## Abstract

**Introduction** Hypertension (HTN) is a co-morbidity that is commonly associated with heart failure with preserved ejection fraction (HFpEF). However, it remains unclear whether treatment of hypertension in HFpEF patients is associated with improved cardiovascular outcomes.

**Aim** The purpose of this meta-analysis is to evaluate the association of anti-hypertensive medical therapy with cardiovascular outcomes in patients with HFpEF.

**Methods** We performed a database search for studies reporting on the association of anti-hypertensive medications with cardiovascular outcomes and safety endpoints in patients with HFpEF. The databases searched include OVID Medline, Web of Science, and Embase. The primary endpoint was all-cause mortality. Secondary endpoints include cardiovascular (CV) mortality, worsening heart failure (HF), CV hospitalization, composite major adverse cardiovascular events (MACE), hyperkalemia, worsening renal function, and hypotension.

**Results** A total of 12 studies with 14062 HFpEF participants (7010 treated with medical therapy versus 7052 treated with placebo) met inclusion criteria. Use of anti-hypertensive medications was not associated with lower all-cause mortality, CV mortality or CV hospitalization compared to treatment with placebo (OR 1.02, 95% CI 0.77–1.35; p = 0.9, OR 0.88, 95% CI 0.73–1.06; p = 0.19, OR 0.99, 95% CI 0.87–1.12; p = 0.83, OR 0.90, 95% CI 0.79–1.03; p = 0.11). Anti-hypertensive medications were not associated with lower risk of subsequent acute myocardial infarction (AMI) (OR 0.53, 95% CI 0.07–3.73; p = 0.5). Use of anti-hypertensive medications was associated with a statistically significant lower risk of MACE (OR 0.90, 95% CI 0.83–0.98; p = 0.02).

**Conclusions** While treatment with anti-hypertensive medications was not associated with lower risk of all-cause mortality, their use may be associated with reduce risk of adverse cardiovascular outcomes in patients with HFpEF regardless of whether they have HTN. Additional high quality studies are required to clarify this association and determine the effect based on specific classes of medications.

Keywords Antihypertensive  $\cdot$  HFpEF  $\cdot$  Mortality  $\cdot$  Outcomes

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## 1 Introduction

Approximately 1 in 4 individuals in developing nations suffer from hypertension (HTN), and nearly a third are asymptomatic upon diagnosis [1]. Chronic elevations in blood pressure results in increased afterload, which in turn can result in structural and functional changes to the heart [2]. Potentially substantial cardiovascular complications of HTN include coronary artery disease, heart failure (HF), atrial fibrillation, and aortic aneurysm. A specific classification of HF is heart failure with preserved ejection fraction (HFpEF), or diastolic heart failure with a left ventricular ejection

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fraction (LVEF) greater than 50% [3]. HFpEF, especially in patients with HTN, has posed a therapeutic challenge to physicians.

Given HTN is responsible for approximately 25% of HF cases, the presence of HF requires stricter goal-directed therapy [2]. However, HTN remains a difficult disease to treat especially with regards to pharmacological adherence given that patients are generally asymptomatic, the medications pose additional adverse side-effects and treatment is largely preventative [1]. Lifestyle changes, including targeting major modifiable risk factors (such as tobacco use, physical activity, diet), is the initial treatment of choice, but may not be enough. Thus, pharmacological therapy provides an adjunctive tool. Less than half of all HTN patients can be treated with monotherapy, and nearly a third require three or more agents [1]. Moreover, little is known regarding the cardiovascular (CV) benefits of these antihypertensive pharmacologic agents on patients with HFpEF.

In this paper, we summarize the evidence evaluating the impact of antihypertensive medications on HFpEF patients with regard to CV outcomes: all-cause mortality, CV mortality, worsening HF, CV hospitalization, composite major adverse cardiovascular events (MACE), acute myocardial infarction (AMI). Moreover, we summarize the impact of antihypertensive medications on adverse pharmacologic side-effects in HFpEF patients, especially hyperkalemia, worsening renal function, and hypotension.

## 2 Methods

#### 2.1 Data Search

This systematic review was performed in adherence to the guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses). The review was performed using a protocol in May 2023. The primary endpoint was mortality. Secondary endpoints included CV mortality, worsening HF, CV hospitalization, composite MACE, AMI, hyperkalemia, worsening renal function, and hypotension.

#### 2.2 Search Strategy

A systematic search was conducted using Ovid MEDLINE, EMBASE, Scopus, Web of Science, and Google Scholar for relevant literature that reported an association between use of anti-hypertensive medications and all-cause mortality, CV mortality, worsening HF, CV hospitalization, composite MACE, AMI, hyperkalemia, worsening renal function, and hypotension. The search was not restricted to time or publication status. Two independent reviewers (MA and MT) performed an electronic search using the following keywords: "hypertension", "heart failure preserved ejection fraction", "hfpef", "antihypertensive medication", "antihypertensive", "antihypertension", "outcomes", "outcome", "mortality", and "Prediction". The references of the screened studies, systematic reviews, review articles, and meta-analyses were manually reviewed for potential studies. After identifying relevant studies, the full texts of the selected articles were examined by both reviewers based on preplanned inclusion criteria. Disagreements were resolved by consensus.

#### 2.3 Study Selection

Studies were selected using the PICO (patient/population, intervention, comparison and outcomes) format to include those that studied patients with HFpEF (Population), comparing use of antihypertensive medications (Intervention) to not using them (Comparison), and assessing for all-cause mortality, CV mortality, worsening HF, CV hospitalization, composite MACE, AMI, hyperkalemia, worsening renal function, and hypotension. (Outcomes). Studies that did not separate HFpEF and HFrEF populations were excluded. Patients with hypertrophic cardiomyopathy were excluded.

### 2.4 Data Extraction

Two reviewers (MA and MT) independently extracted the study data using a predefined data extraction sheet. Variables that were extracted from the studies included: lead author, year of publication, study design, total patients on antihypertension medications, total patients not on antihypertension medications, mean follow-up, mean age, mean LVEF, and gender.

#### 2.5 Statistical Analysis

Meta-analysis was performed using Cochrane Review Manager (RevMan) software, version 5. We used a randomeffects model to examine the association between strain imaging and outcomes, which were presented with an odds ratio (OR) with 95% confidence interval (CI). The extent of heterogeneity was determined by I2 (ranging from 0 to 100%). Statistical significance was considered with a P-value < 0.05 and all tests were 2-sided.

### **3 Results**

#### 3.1 Literature Search and Study Selection

We identified 2376 eligible studies from our literature search. After screening all studies, 123 eligible studies were selected for full text review. 15 studies were identified to be eligible for meta-analysis for the planned outcomes. Details of the selection process is presented in Fig. 1.

#### 3.2 Study and Patient Characteristics

A total of 12 studies with 14062 HFpEF participants (7010 treated with medical therapy versus 7052 treated with placebo) met inclusion criteria. Mean follow up was 31 months, mean age was 71 years, mean ejection fraction (EF) was 59%

and 50.3% were females. Details of baseline demographic data is presented in Table 1.

Use of anti-hypertensive medications was not associated with lower all-cause mortality, CV mortality or CV hospitalization compared to treatment with placebo (OR 1.02, 95% CI 0.77–1.35; p = 0.9, OR 0.88, 95% CI 0.73–1.06; p = 0.19, OR 0.99, 95% CI 0.87–1.12; p = 0.83, OR 0.90, 95% CI 0.79–1.03; p = 0.11) (Figs. 2, 3, 4, 5). Anti-hypertensive medications were not associated with lower risk of

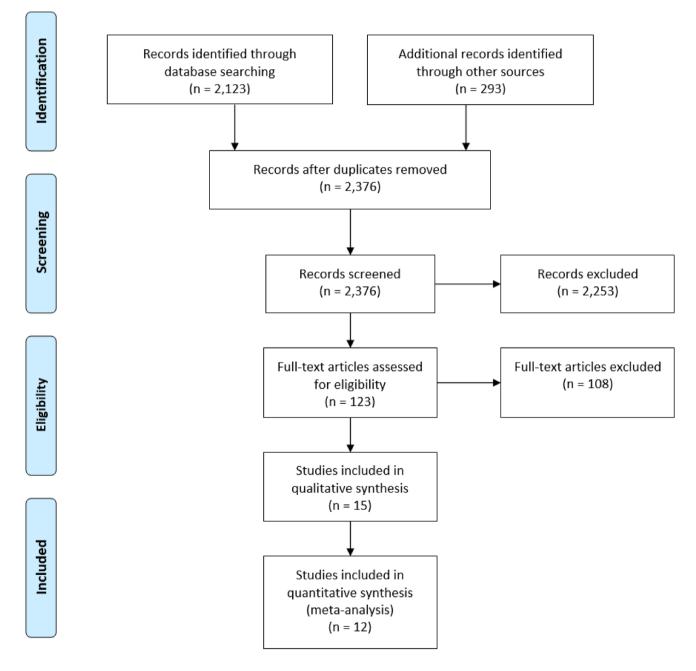


Fig. 1 PRISMA flow chart. Flow diagram depicts study selection for inclusion in the meta-analysis according to the PRISMA statement for reporting systematic reviews and meta-analyses

Table 1 Demographic data of the included studies

Name	Туре	Follow up (month)	Age (years)	Female (%)	EF (%)	Hypertension (Yes/No)	Medication	Total (n) on Medication	Total (n) not on Medication
Zi 2003	RCT	6	78	65	50	No	ACE	36	38
Yusuf 2003	RCT	37	67	39	54	No	ARB	1514	1509
Cleland 2006	RCT	27	75	54	65	No	ACE	424	426
Yip 2007	RCT	12	74	67	50	No	ACE	45	50
Yip 2007	RCT	12	74	62	50	No	ARB	56	50
Massie 2008	RCT	49	72	59	59	No	ARB	2067	2061
Deswal 2011	RCT	6	70	8	62	Yes	MRA	21	23
Edelmann 2013	RCT	12	67	52	68	No	MRA	213	209
Yamamoto 2014	RCT	38	72	42	62	No	BB	120	125
Miura 2016	RTC	52	66	30	63	Yes	ARB	363	346
Gu 2016	Retro	86	66	58	65	Yes	MRA	65	130
Tsujimoto 2020	RCT	<u>39</u>	<u>69</u>	51	51	Yes	MRA	505	499
Tsujimoto 2020	RCT	<u>39</u>	<u>68</u>	50	51	No	MRA	1216	1221
Lam 2022	Retro	30	78	67	58	Yes	HCTZ/CCB	365	365

RCT randomized controlled trial, *Retro* retrospective, *EF* ejection fraction, *ACE* angiotensin converting enzyme inhibitors, *ARB* angiotensin receptors blockers, *MRA* mineralocorticoids receptors antagonists, *HCTZ* thiazides, *CCB* calcium channel blockers

	Ме	k	No M	ed		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.2.1 HTN Only							
Lam 2022	243	365	242	499	15.5%	2.12 [1.60, 2.80]	-
Miura 2016	43	363	46	346	12.5%	0.88 [0.56, 1.37]	_ <b>_</b>
Tsujimoto 2020	49	505	74	499	13.6%	0.62 [0.42, 0.91]	
Subtotal (95% CI)		1233		1344	41.6%	1.06 [0.47, 2.36]	<b>•</b>
Total events	335		362				
Heterogeneity: Tau <sup>2</sup> =	= 0.47; Cl	hi <sup>2</sup> = 29	9.00, df =	= 2 (P <	< 0.00001	l); I <sup>2</sup> = 93%	
Test for overall effect	: Z = 0.13	3 (P = 0	).89)				
1.2.2 Mixed Populati	on						
Cleland 2006	56	424	53	426	13.3%	1.07 [0.72, 1.60]	_ <b>_</b>
Edelmann 2013	1	213	0	209	0.7%	2.96 [0.12, 73.02]	
Massie 2008	221	2067	226	2061	16.8%	0.97 [0.80, 1.18]	+
Tsujimoto 2020	207	1216	199	1221	16.6%	1.05 [0.85, 1.30]	+
Yamamoto 2014	18	120	21	125	8.7%	0.87 [0.44, 1.74]	<b>_</b>
Yip 2007	1	101	3	50	1.4%	0.16 [0.02, 1.55]	
Zi 2003	1	36	1	38	0.9%	1.06 [0.06, 17.56]	
Subtotal (95% CI)		4177		4130	<b>58.4</b> %	1.01 [0.88, 1.15]	<b>♦</b>
Total events	505		503				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Cl	hi <sup>2</sup> = 3.	52, df =	6 (P =	0.74); I <sup>2</sup> =	= 0%	
Test for overall effect	z = 0.03	8 (P = 0	).94)				
Total (95% CI)		5410		5474	100.0%	1.02 [0.77, 1.35]	
Total events	840		865				
Heterogeneity: Tau <sup>2</sup> =	= 0.11; Cl	hi <sup>2</sup> = 3	5.84, df =	= 9 (P <	( 0.0001)	; $I^2 = 75\%$	0.01 0.1 1 10 100
Test for overall effect	: Z = 0.1	3 (P = 0)	).90)				0.01 0.1 1 10 100 Favours Meds Favours No Meds
Test for subgroup dif	ferences:	Chi <sup>2</sup> =	0.01, df	= 1 (P	= 0.90), I	$l^2 = 0\%$	ravours meus - ravours no meus

Fig. 2 Association of anti-hypertensive medications with all-cause mortality in patients with HFpEF

subsequent acute myocardial infarction (AMI) (OR 0.53, 95% CI 0.07–3.73; p = 0.5) (Fig. 6).

Use of anti-hypertensive medications was associated with a statistically significant lower risk of MACE (OR 0.90, 95% CI 0.83–0.98; p = 0.02) (Fig. 7).

There was a non-significant trend toward lower risk of worsening HF in patients treated with anti-hypertensive medications with subgroup analysis demonstrating this association to be statistically significant in mixed populations of HFpEF patients with or without HTN but not significant

	Ме	d	No M	ed		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.7.1 ACE							
Cleland 2006	56	424	53	426	17.5%	1.07 [0.72, 1.60]	
Yip 2007	0	45	3	50	0.4%	0.15 [0.01, 2.97]	· · · · ·
Zi 2003	1	36	1	38	0.4%		
Subtotal (95% CI)		505		514	18.3%	1.03 [0.70, 1.54]	<b>•</b>
Total events	57		57				
Heterogeneity: Tau <sup>2</sup> =	, .		,	2 (P =	0.44); I <sup>2</sup> =	= 0%	
Test for overall effect	Z = 0.1	7 (P = 0	).87)				
1.7.2 ARB							
Massie 2008	221	2067	226	2061	47.1%	0.97 [0.80, 1.18]	<b>_</b>
Miura 2016	43	363	46	346	14.8%		
Yip 2007	1	56	3	50	0.6%		
Subtotal (95% CI)	-	2486	5	2457	62.5%		
Total events	265		275				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; C	$hi^2 = 1.$	24, df =	2 (P =	0.54); I <sup>2</sup> :	= 0%	
Test for overall effect	Z = 0.5	8 (P = 0	0.56)				
1.7.3 MRA							
Edelmann 2013	1	213	0	209	0.3%	2.96 [0.12, 73.02]	
Tsujimoto 2020	49	505	74	499	18.8%	0.62 [0.42, 0.91]	
Subtotal (95% CI)		718		708	19.2%	0.63 [0.43, 0.92]	$\bullet$
Total events	50		74				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; C	$hi^2 = 0.$	91, df =	1 (P =	0.34); I <sup>2</sup> =	= 0%	
Test for overall effect	: Z = 2.3	6 (P = 0	0.02)				
Total (95% CI)		3709		3679	100.0%	0.88 [0.73, 1.06]	•
Total events	372		406				
Heterogeneity: Tau <sup>2</sup> =	= 0.01; C	hi <sup>2</sup> = 7.	92, df =	7 (P =	0.34); I <sup>2</sup> :	= 12%	0.01 0.1 1 10 100
Test for overall effect	: Z = 1.3	1 (P = 0)	).19)				0.01 0.1 1 10 100 Favours Meds Favours No Meds
Test for subgroup dif	ferences:	Chi <sup>2</sup> =	4.14, df	= 2 (P	= 0.13),	$l^2 = 51.6\%$	Tavours Meus Favours No Meus

Fig. 3 Association of anti-hypertensive medications with all-cause mortality in patients with HFpEF

	Mee	ł	No M	ed		Odds Ratio		Odds Ratio		
Study or Subgroup	udy or Subgroup Events Total		Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl			
Cleland 2006	38	424	40	426	7.2%	0.95 [0.60, 1.51]				
Massie 2008	311	2067	302	2061	53.4%	1.03 [0.87, 1.22]		•		
Tsujimoto 2020	31	505	44	499	6.9%	0.68 [0.42, 1.09]				
Yamamoto 2014	8	120	7	125	1.4%	1.20 [0.42, 3.43]				
Yip 2007	1	101	1	50	0.2%	0.49 [0.03, 8.00]		· · · · ·		
Yusuf 2003	170	1514	170	1509	30.9%	1.00 [0.80, 1.25]		+		
Total (95% CI)		4731		4670	100.0%	0.99 [0.87, 1.12]		•		
Total events	559		564							
Heterogeneity: Tau <sup>2</sup> = Test for overall effect	,		,	5 (P =	0.69); I <sup>2</sup> =	0%	0.01	0.1 1 10 100 Favours Meds Favours No Meds		

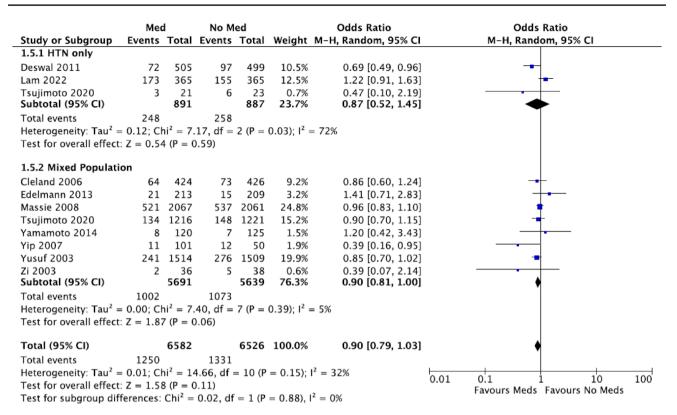
Fig. 4 Association of anti-hypertensive medications with CV mortality in patients with HFpEF

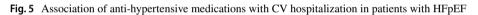
in studies evaluating only HFpEF patients with HTN (OR 0.87, 95% CI 0.78–0.97; p = 0.02 versus OR 0.57, 95% CI 0.18–1.86; p = 0.35) (Fig. 8).

When testing the use of individual antihypertensive medications, they were associated with a lower risk of worsening HF and CV hospitalization (OR 0.86, 95% CI 0.77–0.96; p = 0.01; OR 0.88, 95% CI 0.80–0.96; p < 0.01) (Figs. 9, 10). These associations were primarily driven by use of mineralocorticoid receptor antagonists (MRAs) and angiotensin receptor blockers (ARBs) and

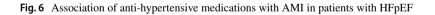
not angiotensin-converting enzyme inhibitors (ACEs). The heterogeneity for these analyses were low (I2 = 0%).

Use of antihypertensive medications was associated with a significantly higher risk of hyperkalemia and worsening renal function (OR 3.10, 95% CI 1.57–6.13; p < 0.01; OR 1.81, 95% CI 1.48–2.23; p < 0.01). Use of antihypertensive medications was not associated with a significant risk of hypotension (OR 1.37, 95% CI 0.75–2.52; p-0.31) (Figs. 11, 12, 13).

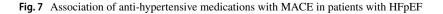




	Me	d	No M	ed		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	om, 95% Cl	
Edelmann 2013	5	213	3	209	30.0%	1.65 [0.39, 7.00]				
Massie 2008	80	2061	73	261	35.5%	0.10 [0.07, 0.15]				
Tsujimoto 2020	20	505	19	499	34.5%	1.04 [0.55, 1.98]		-	<b>-</b>	
Total (95% CI)		2779		969	100.0%	0.53 [0.07, 3.73]				
Total events	105		95							
Heterogeneity: Tau <sup>2</sup> =	= 2.77; C	hi <sup>2</sup> = 49	9.95, df =	= 2 (P <	< 0.00001	l); I <sup>2</sup> = 96%	0.01	0.1	1 10	100
Test for overall effect	Z = 0.6	4 (P = 0	).52)				0.01		Favours No Me	



	Mee	ł	No M	ed		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M–H, Random, 95% Cl	
Cleland 2006	100	424	107	426	7.9%	0.92 [0.67, 1.26]			
Massie 2008	742	2067	763	2061	48.4%	0.95 [0.84, 1.08]			
Tsujimoto 2020	90	505	120	499	8.3%	0.68 [0.50, 0.93]			
Yamamoto 2014	29	120	34	125	2.4%	0.85 [0.48, 1.51]			
Zi 2003	460	1514	497	1509	33.1%	0.89 [0.76, 1.04]		=	
Total (95% CI)		4630		4620	100.0%	0.90 [0.83, 0.98]		*	
Total events	1421		1521						
Heterogeneity: Tau <sup>2</sup> = Test for overall effect	-		-	4 (P =	0.42); I <sup>2</sup> =	0%	0.01	0.1 1 10 1 Favours Meds Favours No Meds	100



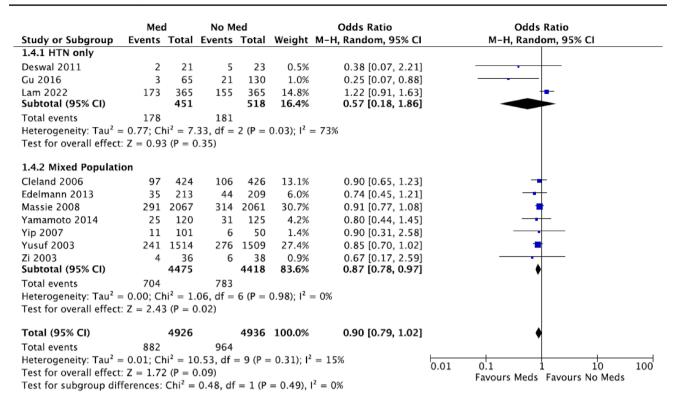


Fig. 8 Association of Anti-Hypertensive Medications with Worsening HF in Patients with HFpEF

#### 4 Discussion

This systematic review and meta-analysis evaluated the role of antihypertensive medications on HFpEF patients with regards to adverse CV outcomes, as well as the impact of these standard medical therapies on potential adverse side effects. The main findings were as follows: (a) antihypertensive medication use was not associated with lower all-cause mortality, CV mortality, CV hospitalization or AMI; (b) use of anti-hypertensive medications was associated with a statistically significant lower risk of MACE; (c) there was a non-significant trend toward lower risk of worsening HF with the use of anti-hypertensive medications however subgroup analysis demonstrated this association to be statistically significant in mixed populations of HFpEF patients with and without HTN; (d) mineralocorticoid receptor antagonists (MRAs) and angiotensin receptor blockers (ARBs) but not angiotensin-converting enzyme inhibitors (ACEs) were associated with a lower risk of worsening HF and CV hospitalization; (e) Use of antihypertensive medications was associated with a significantly higher risk of hyperkalemia and worsening renal function, but not hypotension.

HTN remains one of the leading etiologies for the development of HFpEF [1, 4–6]. The 2015 SPRINT trial further demonstrated that patient's undergoing blood pressure control of at least a target systolic blood pressure of 120mmHg or less had a reduced progression to heart failure compared to those with less intensive control [7]. Thus, current class 1 guidelines recommend titrating antihypertensive medications to attain target blood pressure values in patients with HTN and HFpEF as to prevent worsening HF and/or HF exacerbations [8]. However, little is known on the impact of antihypertensive medications on CV outcomes in HFpEF patients. The traditional pathophysiology behind development of HFpEF in HTN patients emphasizes the role of increased afterload on the LV, resulting in LV hypertrophy. This hypertrophied myocardium not only results in diastolic dysfunction, but also reduced capillary density, increasing risk of ischemia and conduction disorders. Thus, it is theorized LV mass and hypertrophy are predictors of adverse outcomes, and the risk can be reduced with LV hypertrophy regression [9, 10].

Several agents have demonstrated LV hypertrophy regression, with medications targeting the renin-angiotensin-aldosterone system (RAAS) system demonstrating the greatest results [11–14]. However, our results demonstrate antihypertensive agents were associated with reduction in MACE but not associated with reduction in all-cause mortality, CV mortality, CV hospitalization or AMI. Our results demonstrated that there was a trend toward lower risk of worsening HF with the use of anti-hypertensive medications; however, it was nonsignificant. These results have been reaffirmed in several groundbreaking trials, such as I-PRESERVE, CHARM-Preserved, PARAGON-HF, OPTIMIZE-HF and

	Med		No M	ed		Odds Ratio	Odds Ratio
Study or Subgroup	Events '	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.9.1 ACE							
Cleland 2006	64	424	73	426	7.5%	0.86 [0.60, 1.24]	
Yip 2007	5	45	6	50	0.6%	0.92 [0.26, 3.24]	
Zi 2003	2	36	5	38	0.3%	0.39 [0.07, 2.14]	
Subtotal (95% CI)		505		514	8.5%	0.84 [0.59, 1.18]	◆
Total events	71		84				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	$i^2 = 0.3$	82, df =	2 (P =	0.66); l <sup>2</sup> =	= 0%	
Test for overall effect:	Z = 1.02	(P = 0)	.31)				
1.9.2 ARB							
Massie 2008	521			2061	51.4%	0.96 [0.83, 1.10]	•
Yip 2007	6	56	6	50	0.7%	0.88 [0.26, 2.93]	
Yusuf 2003	241		276	1509	27.9%	0.85 [0.70, 1.02]	-
Subtotal (95% CI)		3637		3620	80.0%	0.92 [0.82, 1.02]	•
Total events	768		819				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	$i^2 = 1.0$	05, df =	2 (P =	0.59); l <sup>2</sup> =	= 0%	
Test for overall effect	Z = 1.54	(P=0	.12)				
1.9.3 MRA							
Deswal 2011	3	21	6	23	0.4%	0.47 [0.10, 2.19]	<b>.</b>
Edelmann 2013	21	213	15	209	2.1%	1.41 [0.71, 2.83]	
Tsujimoto 2020	72	505	97	499	9.0%	0.69 [0.49, 0.96]	
Subtotal (95% CI)		739		731	11.5%	0.84 [0.48, 1.46]	➡
Total events	96		118				
Heterogeneity: Tau <sup>2</sup> =		$i^2 = 3.1$		2 (P =	0.15): l <sup>2</sup> =	= 47%	
Test for overall effect	, .		,	- •			
		,					
Total (95% CI)		4881		4865	100.0%	0.89 [0.81, 0.99]	•
Total events	935		1021				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	$i^2 = 6.$	87, df =	8 (P =	0.55); l <sup>2</sup> =	= 0%	0.1 1 10 100
Test for overall effect:	7 2.25	(D 0	0.00	-		0.01	0.1 1 10 100
	2 = 2.25	(P = 0	.02)				Favours Meds Favours No Meds

Fig. 9 Association of anti-hypertensive medications with CV hospitalization in patients with HFpEF

TOPCAT trials, all of which demonstrated no significant difference in the primary adverse CV endpoints with the use of their respectively studied antihypertensive agents [15–19]. Moreover, subgroup analyses with certain antihypertensive agents suggested majority of the benefit may have favored patients with an ejection fraction of 40-49%, and mid-range ejection fractions have shown clinical features resembling heart failure and a reduced ejection fraction (HFrEF) rather than HFpEF [19–22]. Thus, even though our subgroup analysis demonstrated MRAs and ARBs were associated with lower risk of worsening HF and CV hospitalization, the scope of this paper did not further analyze by ejection fraction range, which could limit the generalizability of the results. Nonetheless, the lack of overall improvement in CV outcomes in HFpEF patients with antihypertensive medications questions if the pathophysiology linking HTN and HFpEF is as simplified as hypertrophied myocardium.

An additional emerging model delineating the role HTN plays in HFpEF focuses on systemic inflammation. The inflammation from HTN results in coronary microvascular endothelial dysfunction, resulting in decreased protein kinase G activity, which results in cardiomyocyte hypertrophy and ventricular stiffening [23, 24]. Thus, improving CV

mortality in HFpEF and HTN patients may be due to combating the proinflammatory state of HFpEF. The remarkable EMPEROR-Preserved trial demonstrated the ability of Empagliflozin to reduce the combined risk of CV death or hospitalization in HFpEF patients with/without diabetes [25]. As a sodium–glucose cotransporter 2 inhibitor (SGLT2i), empagliflozin reduces epicardial adipose tissue and alters adipokine signaling, impacts cardiomyocyte ionic homeostasis and reduce myofilament stiffness and extracellular matrix remodeling, all of which further reduces inflammation and oxidative stress [26]. Given SGLT2i are not classified as traditional antihypertensive agents, they were not extensively studied in this paper. However, they demonstrate the need for further investigation on the pathophysiology connecting HFpEF and HTN.

Similar to all medications, antihypertensive agents do not come without their unique adverse side effect profiles. Our results demonstrate the use of antihypertensive medications was associated with a significantly higher risk of hyperkalemia and worsening renal function. Similar results were seen in previous trials [18]. However, these side-effects could be combated with close and frequent monitoring. Thus, it is beneficial

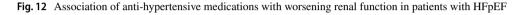
	Med	ł	No M	ed		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.8.1 ACE							
Cleland 2006	97	424	106	426	12.8%	0.90 [0.65, 1.23]	
Yip 2007	5	45	6	50	0.8%	0.92 [0.26, 3.24]	
Zi 2003	4	36	6	38	0.7%	0.67 [0.17, 2.59]	
Subtotal (95% CI)		505		514	14.3%	0.88 [0.66, 1.19]	<b>+</b>
Total events	106		118				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Cł	$1i^2 = 0.$	18, df =	2 (P =	0.92); I <sup>2</sup> =	= 0%	
Test for overall effect:	Z = 0.81	L (P = 0)	).42)				
1.8.2 ARB							
Massie 2008	291	2067	314	2061	42.8%	0.91 [0.77, 1.08]	<b>+</b>
Yip 2007	6	56	6	50	0.9%	0.88 [0.26, 2.93]	
Yusuf 2003	241	1514	276	1509	35.5%	0.85 [0.70, 1.02]	-
Subtotal (95% CI)		3637		3620	79.2%	0.88 [0.78, 1.00]	•
Total events	538		596				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Cł	$ni^2 = 0.$	33, df =	2 (P =	0.85); I <sup>2</sup> =	= 0%	
Test for overall effect:	: Z = 1.95	5 (P = 0	0.05)				
1.8.3 MRA							
Deswal 2011	2	21	5	23	0.4%	0.38 [0.07, 2.21]	
Edelmann 2013	35	213	44	209	5.3%	0.74 [0.45, 1.21]	+
Gu 2016	3	65	21	130	0.8%	0.25 [0.07, 0.88]	
Subtotal (95% CI)		299		362	6.5%	0.53 [0.26, 1.05]	
Total events	40		70				
Heterogeneity: Tau <sup>2</sup> =	= 0.13; Cł	1i <sup>2</sup> = 2.	83, df =	2 (P =	0.24); I <sup>2</sup> =	= 29%	
neterogeneity: rau <sup>-</sup> =	Z = 1.82	? (P = 0	0.07)				
Test for overall effect:							
5 ,		4441		4496	100.0%	0.86 [0.77, 0.96]	•
Test for overall effect:	684	4441	784	4496	100.0%	0.86 [0.77, 0.96]	•
Test for overall effect: <b>Total (95% CI)</b> Total events	684					- 0%	•
Test for overall effect: Total (95% CI)	684 = 0.00; Cł	ni² = 5.	62, df =			- / -	L 0.1 1 10 1 Favours Meds Favours No Meds

Fig. 10 Association of anti-hypertensive medications with worsening HF in patients with HFpEF

	Med	ł	No M	ed		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.10.1 ACE/ARB							
Massie 2008	2	2067	0	2061	4.6%	4.99 [0.24, 104.01]	<b>.</b>
Yusuf 2003	12	1514	9	1509	28.6%	1.33 [0.56, 3.17]	<b>_</b>
Zi 2003	22	36	9	38	24.7%	5.06 [1.86, 13.82]	<b>_</b>
Subtotal (95% CI)		3617		3608	58.0%	2.70 [0.93, 7.79]	
Total events	36		18				
Heterogeneity: $Tau^2 =$	0.43; Cl	ni <sup>2</sup> = 4.	12. df =	2 (P =	0.13); I <sup>2</sup> :	= 51%	
Test for overall effect	Z = 1.83	B (P = 0)	).07)		.,		
1.10.2 MRA							
Deswal 2011	3	21	1	23	7.3%	3.67 [0.35, 38.34]	
Edelmann 2013	4	213	3	209	14.8%	1.31 [0.29, 5.94]	
Gu 2016	2	65	0	130	4.6%	10.28 [0.49, 217.22]	•
Tsujimoto 2020	17	505	2	499	15.3%	8.66 [1.99, 37.67]	
Subtotal (95% CI)		804		861	42.0%	3.90 [1.38, 11.01]	
Total events	26		6				
Heterogeneity: Tau <sup>2</sup> =	0.20; Cl	ni <sup>2</sup> = 3.	62, df =	3 (P =	0.31); I <sup>2</sup> :	= 17%	
Test for overall effect	-		-				
-							
Total (95% CI)		4421		4469	100.0%	3.10 [1.57, 6.13]	$\bullet$
Total events	62		24				
Heterogeneity: Tau <sup>2</sup> =	- 0.23; Cl	1i <sup>2</sup> = 8.	.39, df =	6 (P =	0.21); I <sup>2</sup> :	= 28%	0.01 0.1 1 10 100
Test for overall effect	Z = 3.2	5 (P = 0)	).001)				Favours Meds Favours No Meds
Test for subgroup dif	Foroncori	Ch;2 -	0 24 46	_ 1 /D	0 ( 2)	12 00/	ravours meds ravours no meds

Fig. 11 Association of anti-hypertensive medications with hyperkalemia in patients with HFpEF

	Me	ł	No M	ed		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cleland 2006	3	424	1	426	0.8%	3.03 [0.31, 29.23]	
Edelmann 2013	77	213	43	209	18.4%	2.19 [1.41, 3.38]	
Massie 2008	69	2067	57	2061	25.4%	1.21 [0.85, 1.73]	
Miura 2016	54	363	30	346	16.0%	1.84 [1.15, 2.95]	
Yamamoto 2014	1	120	0	125	0.4%	3.15 [0.13, 78.10]	
Yusuf 2003	72	1514	36	1509	20.6%	2.04 [1.36, 3.07]	
Zi 2003	77	213	43	209	18.4%	2.19 [1.41, 3.38]	
Total (95% CI)		4914		4885	100.0%	1.81 [1.48, 2.23]	•
Total events	353		210				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect					0.33); I <sup>2</sup> :	= 13%	0.01 0.1 1 10 100 Favours Meds Favours No Meds



	Me	ł	No M	ed		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl	
Cleland 2006	1	424	1	426	4.4%	1.00 [0.06, 16.12]				
Massie 2008	2	36	3	38	9.0%	0.69 [0.11, 4.37]				
Yamamoto 2014	60	2067	62	2061	46.0%	0.96 [0.67, 1.38]		-	-	
Yusuf 2003	37	1514	17	1509	36.7%	2.20 [1.23, 3.92]				
Zi 2003	3	120	0	125	3.9%	7.48 [0.38, 146.30]				
Total (95% CI)		4161		4159	100.0%	1.37 [0.75, 2.52]		•	•	
Total events	103		83						-	
Heterogeneity: Tau <sup>2</sup> =	= 0.18; C	hi <sup>2</sup> = 7.	47, df =	4 (P =	0.11); I <sup>2</sup> :	= 46%	0.01	0.1		100
Test for overall effect	z = 1.02	2 (P = 0	0.31)				0.01	÷·-	1 10 Favours No Me	100 ds

Fig. 13 Association of anti-hypertensive medications with hypotension in patients with HFpEF

to adopt an individualized and patient-centered approach in the management of patients with HFpEF.

# **5** Conclusion/Future Direction

Our present systematic review and meta-analysis has important clinical implications. HFpEF remains a challenging entity to treat, and the use of antihypertensive medications are not associated with overall reduction in adverse CV outcomes, with the exception of MACE and a trend toward reduction in worsening HF. Lastly, standard medical therapy with antihypertensive agents do pose significant side effects and require close monitoring. Despite the results of this recent meta-analysis, several questions regarding HFpEF remain unanswered with regards to subgroup analysis of various antihypertensive agents across CV outcomes and ejection fraction ranges, and we need more evidence before we can extend these findings (and recommendations) to patients.

# **6** Limitations

Our review has several limitations. First, not all studies specified the type of antihypertensive agent. Second, not all studies specified the etiology of HFpEF or ejection fraction range.

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Third, there was heterogenicity with regard to long-term follow-up period. Forth, only a few studies distinguished between all-cause and CV mortality. Additional high-quality studies are required to elucidate the association of the use of antihypertensive agents in HFpEF patients with other cardiovascular outcomes.

### Declarations

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Conflict of interest The authors report no relevant conflicts of interest.

**Compliance with ethical standards (guidelines statement)** The systematic review was conducted with a protocol in accordance with the Preferred Reporting of Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

**Ethical approval** The study is a systematic review and meta-analysis; no ethical approval was required.

Data availability Not applicable.

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