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► **To cite this version:**

Sverre E Kjeldsen, Thomas G von Lueder, Otto A Smiseth, Kristian Wachtell, Nisha Mistry, et al.. Medical Therapies for Heart Failure With Preserved Ejection Fraction. *Hypertension*, 2020, 75 (1), pp.23-32. 10.1161/HYPERTENSIONAHA.119.14057 . hal-03719455

**HAL Id: hal-03719455**

**<https://hal.univ-lorraine.fr/hal-03719455>**

Submitted on 11 Jul 2022

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# **Medical Therapies for Heart Failure With Preserved Ejection Fraction (HFpEF)**

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**Running Head:** Kjeldsen et al. Medical Therapies for HFpEF

**Word count abstract, text and references:** 7373

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## **ABSTRACT**

Current cardiovascular pharmacotherapy targets maladaptive over-activation of the renin-angiotensin-aldosterone system (RAAS), which occurs throughout the continuum of cardiovascular disease spanning from hypertension to heart failure with reduced ejection fraction (HFrEF). Over the past 16 years, four prospective, randomized, placebo-controlled clinical trials using candesartan, perindopril, irbesartan, and spironolactone in patients with heart failure with preserved ejection fraction (HFpEF) failed to demonstrate increased efficacy of RAAS blockade added to guidelines-directed medical therapy. We reappraise these trials and their weaknesses which precluded statistically significant findings. Very recently, dual-acting RAAS blockade with sacubitril-valsartan relative to stand-alone valsartan failed to improve outcome in the Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF) trial. The majority of patients with HFpEF suffer from hypertension, frequently with subclinical left ventricular dysfunction, contributed to by comorbidities such as coronary disease, diabetes, overweight, and atrial fibrillation. Contrasting the findings in HFpEF, trials evaluating RAAS blockade on either side of HFpEF on the cardiovascular continuum in patients with high-risk hypertension and HFrEF, respectively, showed positive outcomes. We do not have a biologically plausible explanation for such divergent efficacy of RAAS blockade. Based on considerations of well-established clinical efficacy in hypertension and HFrEF and the shortcomings of aforementioned clinical trials in HFpEF, we argue that RAAS-blockers including mineralocorticoid receptor antagonists (aldosterone antagonists) should be used in the treatment of patients with HFpEF.

**Key Words:** cardiovascular disease ■ ejection fraction ■ heart failure ■ hypertension ■ mortality

Maladaptive activation of the renin-angiotensin-aldosterone system (RAAS) occurs across the entire continuum of cardiovascular disease from hypertension to heart failure (HF) (1). The RAAS therefore constitutes a prime target in contemporary cardiovascular medicine and is a cornerstone of pharmacotherapy for HF (1). Approximately half of all patients presenting with HF have preserved left ventricular ejection fraction (HFpEF), yet, they are at similar risk of death and recurrent hospitalization as those with reduced left ventricular ejection fraction (HFrEF). In patients with HFpEF, activation of RAAS promotes cardiac fibrosis and stiffness, diastolic dysfunction and associated myocardial systolic functional changes, increased systolic and diastolic arterial pressures, untoward arterial-ventricular coupling regarding pulsatile load and arterial stiffening with reduced arterial compliance, as demonstrated by increased pulse wave velocity (1). Firm recommendations exist in American, Australian and European clinical guidelines on HF with reduced EF (HFrEF). By contrast, specific guidance on medical therapies for HFpEF are lacking or vague at best, reflecting a paucity of scientific evidence. There appears to be consensus to treat symptoms and risk factors for cardiovascular disease in patients with HFpEF, including antihypertensive treatment to achieve blood pressure (BP) targets (2-4). The lack of proven therapies which reduce clinical event rates in HFpEF constitutes a huge unmet public health need. Based on limited evidence supporting specific medical therapies and the limited utility of guidelines, we aim to re-examine the biological underpinnings and clinical evidence on pharmacotherapy for HFpEF.

The simple parameter ejection fraction (EF) has served to provide an estimate of left ventricular (LV) function in HF for several decades (5) though its value to fully capture the phenotype of a failing heart has been questionable. The convenient simplicity and rapid global adoption as a measure of cardiac function explains why most clinical outcome trials have employed EF to study medical therapies for HF with reduced EF (HFrEF; arbitrarily defined as  $EF < 40\%$  or  $< 35\%$ ) and HFpEF ( $EF \geq 50\%$ ). Among numerous limitations of EF is the

confounding effect of LV hypertrophy and increased afterload. Myocardial contractile function in hypertensive hypertrophy may be depressed despite preserved EF (6). Moreover, in concentrically hypertrophied ventricles with small left ventricular cavity, EF may be normal or supra-normal despite considerably reduced myocardial shortening and reduced stroke volume (7) (Fig.1). Furthermore, EF reflects predominantly circumferential fibre shortening and may, therefore, be preserved when there is diminished long-axis shortening, which is often the case in early-stage systolic dysfunction. More recently, speckle-tracking echocardiography-derived LV strain has allowed for more accurate definition of myocardial deformation and thus, improved phenotyping in HF (8).

With few exceptions (9), early outcome trials evaluating medical therapies for HF enrolled patients on the basis of reduced EF (10,11). Once the efficacy of angiotensin-converting enzyme inhibitors (ACE-I) had been established, positive trials using  $\beta$ -blockers (12-14), angiotensin-receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA) followed, again using “reduced EF” as key entry criteria (15-17). These agents (9-17) have demonstrated robust reductions in mortality and morbidity in HFrEF. A logical extension of the efficacy of RAAS blockade both in patients at risk of HF (hypertension) and with established HF (HFrEF) was to expand such therapies to patients “in between”, i.e. those with HFpEF (2-4). A limited number of trials in HFpEF have been conducted. Since most patients in these trials had known hypertension, RAAS-blockade was expected to be highly effective. Unfortunately, all trials have failed to meet their primary endpoint. Apparently, the trial-based evidence in HFpEF, although limited, contrasts sharply with the central role that the RAAS plays in any cardiovascular disease (1). All those trials exhibit weaknesses which may help to explain their failure.

We have reviewed all HFpEF placebo controlled randomized outcome trials performed with the blockers of RAAS and discussed their strengths and weaknesses, related

mechanisms in play, diagnostic methods and medical treatments. Herein, we review large, well-defined and adequately-powered (“robust”) trials in high-risk hypertension relevant to HFpEF in a reappraisal of the putative beneficial role of RAAS blockade in HFpEF.

Additionally, we will discuss the first outcome trial with angiotensin receptor-neprilysin inhibitor (ARNI) versus valsartan in HFpEF in this context.

## **Review of the prospective placebo-controlled outcome trials in patients with HFpEF**

*Candesartan in heart failure: assessment of reduction in mortality and morbidity study (THE CHARM-PRESERVED STUDY):* In the CHARM studies, patients with HF were allocated to CHARM-Added (18) if HFrEF (randomized to the ARB candesartan vs. placebo added to standard treatment including ACE-I), CHARM-Alternative (19) if intolerant to ACE-I, or CHARM-Preserved (20) if HFpEF. Thus, HF subgrouping took place before randomization. CHARM-Preserved (20) (“CHARM”, n=3,023) included 64% patients with known hypertension and 28% with diabetes (Table 1). The trial had 80% power to detect an 18% benefit. The difference in the primary outcome of composite cardiovascular death and HF hospitalization failed to reach statistical significance (HR=0.89, 95% CIs=0.77-1.03, p=0.12) thus formally the study was “neutral.” Extensive non-randomized use of  $\beta$ -blockers, calcium channel blockers (CCB), ACE-I and spironolactone, and substantial discontinuation rates of allocated study drug, weakened overall findings. CHARM had superiority design without statistical power for further assessment of pre-specified sub-groups or individual components of the composite outcome (20). In a prespecified secondary analysis of CHARM-Preserved, baseline characteristics were used to adjust for imbalances in variables that might affect outcomes. For the primary composite outcome, the resulting *adjusted* hazard ratio (HR) was

0.86 (0.74-1.00; p=0.051) and for first heart failure hospitalization the adjusted HR was 0.84 (0.70-1.00; p=0.047). This finding was similar to results based on events reported by the clinical site investigators (15%) and was close to the results of the other two CHARM component trials (15% and 23% relative risk reductions in the CHARM-Added and CHARM-Alternative trials, respectively) (18-19). A post-hoc analysis of HFpEF (CHARM-Preserved) (21) showed a significant treatment benefit of 7.4 vs. 9.7 primary events per 100 patient-years with HR 0.76 (0.61-0.96; p=0.02) in participants with mid-range EF (40-49%, n=1322). It is therefore very likely that if the CHARM program had employed *one* uniform and consistent protocol and unifying endpoint evaluation (rather than three) across the three CHARM trials, an interaction analysis between HFpEF and HFrEF would not have shown a significant difference in the efficacy of candesartan. In support of this notion, HF hospitalizations in HFpEF were significantly reduced by candesartan despite the numerous limitations outlined above (20).

*Perindopril in elderly people with chronic heart failure study (THE PEP-CHF STUDY):* PEP-CHF randomized 852 HFpEF patients to the ACE-I perindopril vs. placebo (22). Seventy-nine % of patients had preexisting hypertension, and 21% diabetes. Statistical power was low at baseline (Table 1) and fell to 35% (22). The study aimed to recruit 1,000 participants to follow for at least one year. An unexpectedly low event rate and high-rate of open-label ACE-I (Table 1) led to the decision to halt further recruitment due to predicted lack of statistical power for the primary endpoint. All patients were followed until the last patient had completed one-year of follow-up (22). However, subsequent to the 1 year visit, a large proportion of patients ceased blinded treatment and by the end of the study, 35% of patients assigned to perindopril and 37% assigned to placebo were on open-label ACE-I. Therefore, the PEP-CHF trial does not permit conclusions on the clinical efficacy of perindopril in HFpEF. Within the first year, when most patients were on assigned therapy, perindopril



improved symptoms and exercise capacity and reduced hospitalisations for HF. Accordingly, perindopril might be of benefit in a patient population similar to PEP-CHF (22).

*Irbesartan in heart failure with preserved ejection fraction study (THE I-PRESERVE STUDY):*

I-PRESERVE investigated the ARB irbesartan vs. placebo in 4,133 patients with HFpEF, of whom 88% had hypertension (Table 1), and 27% diabetes (23). During the trial, non-randomized medication use reached 73% for  $\beta$ -blocker, 40% for ACE-I, and 28% for spironolactone, while discontinuation of allocated study drug was substantial at 34%. Consequently, I-PRESERVE which was powered for superiority, lacked statistical power. To cite the investigators (23), “the treatment of a large proportion of patients with multiple inhibitors of the RAAS might have left little room for further benefit from the addition of an ARB”. Such a ceiling effect of RAAS inhibition in the medical therapy of HF has also been observed with dual RAAS-blockade in HFpEF (24). No firm conclusion regarding the efficacy of irbesartan in patients with HFpEF can be derived from I-PRESERVE. Indeed, the primary composite outcome in this trial, which was death from any cause or hospitalization for a cardiovascular cause (HF, myocardial infarction, unstable angina, arrhythmia, or stroke), was quite different than other HF trials. Importantly, imbalances in relevant baseline variables were not adjusted for and is still to be performed.

*Treatment of preserved cardiac function heart failure with an aldosterone antagonist trial*

*(THE TOPCAT TRIAL):* TOPCAT investigated the MRA spironolactone versus placebo in 3,445 patients with HFpEF (25). Almost all patients (91%) had preexisting hypertension, and 33% diabetes. Patients were maintained on medical therapy with  $\beta$ -blockers and ACE-I (Table 1). About 40% of the TOPCAT patients were treated with ACE-I which, combined with MRA, is a different form of dual RAAS blockade than ACE-I plus ARB or plus renin

antagonists, and documented to lower mortality in HFrEF (15-17). TOPCAT had 80% power to show a 20% reduction in the primary composite of cardiovascular death, aborted cardiac arrest, and hospitalization for HF, based on an expected event rate of 17.4% through the study duration of 40 months. The overall event rate reached 18.6 vs. 20.4%, resulting in a non-significant trend (HR=0.89, 95% CIs 0.77-1.04, p=0.14) in favor of the primary outcome with spironolactone. Surprisingly, major regional differences for the primary outcome were found: in the Americas 27.3 vs. 31.8% (HR=0.82, 95% CIs 0.69-0.98, p=0.026) whereas in Russia/Georgia merely 9.3 vs. 8.4% (HR=1.10, 95% CIs 0.79-1.51, p=0.576). A number of issues, in particular regarding study conduct are worthy of comment:

Firstly, there were two strata to enter TOPCAT, either based on increased N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels compatible with HF, or on previous hospitalization for HF and clinical diagnosis. Patients in the Americas were largely enrolled by elevated NT-pro-BNP whereas investigators in Russia/Georgia primarily enrolled patients without NT-pro-BNP, and based on clinical judgement.

Secondly, there was marked regional variation in event rates (25), with patients in the placebo group enrolled in Russia/Georgia having a far lower occurrence of the primary outcome than those in the Americas - in fact as low as the healthy population (25). Lower event rates with spironolactone versus placebo were consistent with a treatment benefit in the Americas but not in Russia/Georgia. Despite these shortcomings, several secondary analyses favored treatment with spironolactone, including reduced HF hospitalization (p=0.04).

More disturbingly, striking regional differences in detectable serum concentrations of the spironolactone metabolite canrenone were reported in TOPCAT, with a substantial cohort of subjects in Russia/Georgia randomized to spironolactone who did not receive or take the drug (26). By contrast, TOPCAT showed the superiority of spironolactone in patients in the Americas with proven HFpEF who took their assigned medication, as verified by serum

canrenone levels (26). By contrast, and as expected, spironolactone did not influence the outcome in subjects who presumably neither had HF nor were given or adhered to the study drug. TOPCAT, therefore, exemplifies the destructive force of poor trial conduct and unethical behavior which investigators may exert on the global standard of care for the large patient population of HFpEF. Moreover, spironolactone, as compared with placebo, reduced the composite outcome of hospitalization for HF or cardiovascular mortality among patients randomized in the strata based on elevated baseline NT-pro-BNP. Given the stratified nature of TOPCAT, this result is randomized evidence (27).

There is an urgent moral imperative to re-evaluate the clinical efficacy of MRA in HFpEF in a new randomized clinical trial that meets accepted standards of trial conduct. The addition of elevated NT-pro-BNP as a required entry criterion in contemporary HF trials may be crucial to enroll the targeted patient cohort and to accrue event rates which power calculations are built on. Along these lines we hope and believe that 2 ongoing trials of spironolactone in HFpEF will be useful: the German Heart Foundation Spirit Trial and the Swedish Heart Foundation/NHLBI Spirrit Trial (28).

## **Review of prospective head-to-head outcome trials in patients with high-risk hypertension**

It has been established for decades that antihypertensive treatment vs. placebo (or no treatment) prevents cardiovascular complications. After antihypertensive medications showed their efficacy it was no longer acceptable to allocate patients to a non-active comparator drug, perhaps with the exception of the very old people in which no documentation existed. Thus, in otherwise healthy old people in the range of 80-107 years (on average 83 years), the most striking finding was that a combined diuretic+ACE-I reduced incident HF by 66% (29). In the

late 1990's, in order to design trials with sufficient statistical power, patients with essential hypertension had to qualify by additional cardiovascular risk factors, hypertension mediated organ damage and/or stable cardiovascular disease, while treatment arms had to aim for the same level of BP control. We have reviewed the four key head-to-head outcome trials evaluating ACE-I or ARB in high-risk hypertension with such design, adequate and maintained statistical power and performed in parallel with the HFpEF trials discussed above. Patients with reduced EF or evidence of HF were excluded from these trials. Ejection fraction was not systematically measured in any of these trials in high risk hypertension except for in substudies.

*Losartan intervention for endpoint (LIFE) reduction in hypertension study (THE LIFE STUDY):* LIFE compared the ARB losartan with the  $\beta$ -blocker atenolol on the primary composite of cardiovascular mortality, myocardial infarction and stroke in 9,193 hypertensive patients who entered the study based on electrocardiographic LV hypertrophy (30). Losartan met superiority criteria regarding the primary endpoint ( $p=0.009$ ), whereas incident HF, defined as the need for hospitalization for HF or equivalent quality of treatment, was not different (Table 2).

*Valsartan antihypertensive long-term use evaluation trial (THE VALUE TRIAL):* VALUE compared the ARB valsartan with the CCB amlodipine (31) on the composite of fatal and non-fatal myocardial infarction and HF in 15,245 high-risk hypertensive patients qualifying for study entry according to an algorithm of risk and disease factors; most commonly stable coronary disease and diabetes (Table 2). By request of the US Food and Drug Administration, the study was powered for a non-inferiority analysis including stroke. Non-inferiority between valsartan and amlodipine was fulfilled, and the primary cardiac endpoint did not show superiority for either study drug. As a tertiary endpoint, there was a non-significant trend in favor of valsartan for reduced HF hospitalizations ( $p=0.12$ ).

*Anglo Scandinavian cardiac outcomes trial (THE ASCOT STUDY):* ASCOT investigated an antihypertensive regimen based on amlodipine and add-on ACE-I perindopril if indicated versus the  $\beta$ -blocker atenolol and add-on bendroflumethiazide if indicated (32). To ensure BP control, the  $\alpha$ -blocker doxazosin was given if needed to control BP <140/90 mmHg in both arms, and 19,257 hypertensive patients with additional risk factors, including diabetes and smoking, were randomized (Table 2). Patients with history or evidence of coronary artery disease were excluded because acute myocardial infarction and fatal coronary disease constituted the primary endpoint. The study was stopped prematurely because the amlodipine plus perindopril combination, compared to atenolol plus thiazide, reduced all-cause mortality, a secondary endpoint which then became the study limiting endpoint (Table 2). Due to the premature halt, a trend towards reduction of the primary endpoint did not reach statistical significance (HR=0.90, 95% CIs 0.79-1.02, p=0.11). Various secondary cardiovascular endpoints were significantly reduced by the amlodipine plus perindopril combination, and there was a non-significant trend for reduced HF hospitalization (p=0.13).

*Avoiding cardiovascular events through combination therapy in patients living with systolic hypertension trial (THE ACCOMPLISH TRIAL):* ACCOMPLISH compared fixed combinations of the ACE-I benazepril with either amlodipine or hydrochlorothiazide (33) in 11,506 hypertensive patients with additional risk factors, most notably diabetes and hyperlipidemia (Table 2). The protocol included forced uptitration to reach BP target which was <130/80 mmHg in the patients with concomitant diabetes. The study was stopped early because the benazepril/amlodipine combination showed superiority on the primary composite endpoint of cardiovascular death and various cardiovascular complications to hypertension (20% reduction, p<0.001). There was no difference in HF hospitalizations (p=0.77).

## **Similarities between major outcome trials in HFpEF and high-risk hypertension**

As hypertension is highly prevalent in the HFpEF outcome trials (20,22,23,25), and the study populations in the HFpEF and the high-risk hypertension trials also otherwise appear similar in many aspects, we further discuss possible implications for pharmacotherapy in HFpEF.

*Patient populations* All hypertension trials included patients with preexisting hypertension, and there were substantial rates of known hypertension in the HFpEF cohorts, present in more than 80% of all the patients (20,22,23,25). Limited information was provided regarding LV hypertrophy, which could mask depressed systolic function in hearts with preserved EF (6-8). Hypertensive patients with LV hypertrophy and preserved EF may have extensively reduced systolic function (Fig. 1).

None of the HF studies employed 24-hour ambulatory BP measurements to detect masked hypertension. Masked hypertension is common and occurs in 16% of healthy people (34), associated with increased cardiovascular risk, including the development of unexpected HF and it can only be diagnosed using ambulatory BP measurements. Thus, an even higher percentage of participants in the HFpEF trials may have had hypertension, further supporting the argument that hypertension is an important driver of HFpEF.

A mean body mass index of 28-31 kg/m<sup>2</sup> in all trials (both HFpEF and high risk hypertension) points to overweight as a contributor to both hypertension and HFpEF. A definite causal link remains to be established though patients with visceral obesity have increased serum aldosterone levels (35). It is interesting that in patients with HFrEF in whom

MRAs have been shown to reduce cardiovascular outcomes the greatest effect was in those with visceral obesity defined by an increased waist circumference (17). Thus, in the patients with HFpEF who are hypertensive and overweight MRAs might be particularly effective.

Except for 13% in LIFE (30) and 60% in ACCOMPLISH (33) in all studies, 20-30% of both the HFpEF (20,22,23,25) and high risk hypertension (31, 32) study participants had diabetes, which may predispose to HF (36). Up to 30-40% of study participants in HFpEF trials (20,22,23,25) had coronary disease, and 20-30% had atrial fibrillation (AF); both common findings in hypertension. Among the hypertension trials, VALUE included 46% with coronary artery disease (31) while ASCOT excluded these patients (32). Together, trials in HFpEF and high-risk hypertension comprised patient populations with similar prevalence of hypertension, overweight, diabetes, coronary disease, and AF. It is reasonable to assume that patients with HFpEF, therefore, should have derived similar benefits from RAAS blocking interventions as in the hypertension trials.

Though the HFpEF studies contained a vast majority of patients with background of hypertension, the issue of hypertensive heart disease is a complex one (37, 38). It has been debated for decades whether heart disease is a consequence of high blood pressure *per se* or whether it is caused by concomitant maladaptive mechanisms such as increased activity of the RAAS and/or long-lasting sympathetic over-activity. Thus, patients in the two groups of outcome trials may represent different entities or phenotypes in the sense that the HFpEF patients are selected by developing HF. There is limited information regarding their previous treatment; possibly they developed HF because they did not respond as expected to antihypertensive treatment. Besides pathophysiological mechanisms, there have been important technical, administrative and logistical shortcomings such as lack of statistical power (20, 22, 23) or inclusion of patients without HF (25). Even if different (i.e. lesser) degree of overdrive of the RAAS in HFpEF versus HFrEF occurred, the evidence of largely

underpowered HFpEF trials is insufficient to dismiss potential efficacy of RAAS-blockade in HFpEF.

*The investigational drugs* The beforementioned trials in HFpEF and high-risk hypertension investigated the ARBs candesartan, irbesartan, losartan and valsartan, ACE-Is perindopril and benazepril, the MRA spironolactone and the CCB amlodipine. Treatment of hypertension with various drug classes prevents incident HF including CCBs: amlodipine has also been shown to be well tolerated in patients with HFrEF although without mortality benefit (39). Otherwise, all study drugs showing clinical benefit also have been successful in patients with HFrEF (10-11,15-18,40,41) and in patients post-acute MI with high risk of HF (42,43). Considering the many weaknesses in design, quality, and conduct of the HFpEF trials detailed above, we cannot conclude that RAAS-blockers are ineffective in reducing clinical events in patients with HFpEF. We firmly believe that RAAS blockade may have important beneficial actions in HF across the entire EF spectrum (21,44). These treatment principles are illustrated in Figure 1.

*Risk of cardiovascular events* Risk of events must be considered against the study size and length of follow-up which averaged slightly above three years in the HFpEF studies and four years in the high-risk hypertension studies. The absolute number of patients hospitalized for HF was 1,758 patients in the HFpEF trials (20,22,23,25) and 1,557 patients in the high-risk hypertension trials (30-33). Based on a total number of 11,453 versus 55,201 participants in HFpEF vs. hypertension, the risk of HF hospitalization was on average 8-fold higher in HFpEF trials. It is well known from the placebo controlled trials that all modern antihypertensive drugs lowers the risk of developing HF, on average with approximately 50%, without difference between groups of drugs (30-33). In the HFpEF trials, both candesartan (20) and



spironolactone (25) prevented hospitalization for HF. Though prevention of incident HF is different from preventing hospitalization in patients with known HF, this observation further supports our view that, in the absence of alternatives, RAAS inhibitors for HFpEF should not be restricted on the basis of data from the few underpowered HFpEF outcome trials (20,22,23,25).

*Study entry criteria* The inclusion criteria differed between HFpEF trials. CHARM required patients to be 18 years or older with New York Heart Association functional class II-IV of at least 4 weeks' duration, a history of cardiovascular hospitalization, and EF above 40% (20). In PEP-CHF patients had to be aged  $\geq 70$  years and on diuretics for HF due to left ventricular diastolic dysfunction defined by echocardiographic criteria, and a cardiovascular hospitalization within the previous 6 months (22). I-PRESERVE recruited patients with EF above 45% in addition to clinical and diagnostic criteria for HF (23). In TOPCAT patients 50 years of age or older were eligible if they had at least one predefined sign and one symptom of HF together with EF above 45% measured by either echocardiography or radionuclide ventriculography (25). Accordingly, echocardiography was mandatory in PEP-CHF only (22).

While EF has been a successful (and pragmatic) inclusion criterion in patients with HFrEF, the utility of EF for defining different types of HF is highly questionable. Typically patients with low EF have systolic dysfunction and extensive myocardial damage. Thus, by selecting low EF as an inclusion criterion, the early trials effectively secured enrollment of patients who indeed had heart failure. However, HFpEF may represent a variety of mechanisms impacting on EF. Firstly, preserved EF excludes neither systolic nor diastolic dysfunction. Further, RAAS overactivation remains an important component of the pathophysiology of HFpEF (1). Even with preserved EF, patients with HF may have masked systolic dysfunction due to LV hypertrophy, also associated with a reduction in LV long-axis

function. Limitations herein then apply to CHARM (20), I-PRESERVE (23) and TOPCAT (25), but not to PEP-CHF (22).

## **Prospective comparison of ARNI with ARB on management of HFpEF**

Novel angiotensin receptor antagonist-neprilysin inhibitors (ARNIs) seek to exploit the clinical benefits of combining RAAS antagonism and neutral endopeptidase inhibition. Sacubitril-valsartan comprised of equal molecular moieties of the NEP inhibitor prodrug AHU377 (sacubitril) and the ARB valsartan combined in one compound, is the first-in-class ARNI. The *Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction* (THE PARAGON-HF TRIAL) was a randomized, double-blind, trial that evaluated the safety and efficacy of a dual-acting RAAS blocker (an ARNI) versus a stand-alone ARB on the composite outcome of total hospitalizations for HF and cardiovascular mortality (45). The study drug, sacubitril–valsartan, had been shown to reduce the rate of hospitalization for HF or death from cardiovascular versus enalapril in patients with HFpEF (46). In addition, a phase-II study demonstrated larger reductions in NT-pro-BNP and some clinical parameters with ARNI than the ARB valsartan (47). In PARAGON-HF, almost all patients had hypertension, and additionally, the study cohort exhibits coronary artery disease in 43%, diabetes 43%, AF in 32% and EF  $\geq$ 45% (average 58%), left atrial enlargement and/or LV hypertrophy at baseline and shares thus many similarities with patients in previous HFpEF trials (20,22,23,25) and high-risk hypertension trials (30-33).

Despite a nominally lower event rate (HR 0.87; 95% CIs 0.75-1.01) PARAGON-HF (45) narrowly missed a significant reduction in its primary endpoint (P=0.059). Prespecified subgroup analysis demonstrated that patients with EF below the median (of 57%) as well as

women derived a significant benefit. However, PARAGON-HF (45) allowed repeated hospitalization in the same patients to count in the primary endpoint. Inasmuch as this is a new type of endpoint which cannot easily be compared with the primary endpoint in the trials we have reviewed, we have also assessed PARAGON-HF by the number of patients who suffered a primary endpoint, 526 and 557 in the two groups, respectively. There is then no difference between ARNI and ARB in patients with HFpEF (45).

It is important to underscore that PARAGON-HF evaluated two distinct RAAS-blocking strategies, one with the addition of neprilysin inhibition. PARAGON-HF is the most contemporary and largest outcomes trial in HFpEF and, given the prevalence of hypertension and high clinical event rate in patients with HFpEF, the investigators considered it problematic to withhold an active (RAAS-blocking) comparator (45). In conclusion, neither PARAGON-HF (nor its precursing phase-II study) can inform the discussion on putative efficacy of RAAS-blockade in HFpEF.

## **Summary regarding medical therapy in HFpEF**

Expanding upon previous work summarizing some of the HFpEF trials (49) we have reviewed all HFpEF placebo controlled randomized outcome trials performed with the blockers of RAAS and discussed their strengths and weaknesses, related mechanisms in play, diagnostic methods and medical treatments.

Multiple guidelines (2-4) recommend control of concomitant risk factors in patients with HFpEF. Firstly, this implies control of hypertension to treatment target <130/80 mmHg. Accumulating evidence from clinical trials, however, suggest that RAAS-blockade in HFpEF with ACE-I, ARBs, and MRAs, may be effective although formal superiority of these drugs over placebo has not been established. ARNI does not have general superiority over ARB (46).

In our opinion, medical therapy of patients with HFpEF firstly should include the use of ACE-I or ARB or ARNI with additional treatment with aldosterone antagonist. Other therapies may be added such as beta-blocker or CCB to reach specific goals such as guidelines (2-4) advised BP targets, heart rates and congestive symptom control.

Taken together, it is questionable whether the use of reduced left ventricular EF entry criteria in initial HF trials (10-17) has advanced medical therapy for the estimated half of HF patients with preserved EF. By including patients with clinical HF, objective findings of heart disease and reduced EF, these early trials ensured inclusion of patients with true systolic dysfunction but left uncertainty for the sizable proportion of the HF population with masked systolic dysfunction and preserved EF. As such, the categorical use of reduced versus preserved EF criteria may be counter-productive for patients with HFpEF, who frequently have signs of systolic dysfunction similar to patients with HFrEF. Refined imaging techniques evaluating left ventricular deformation by speckle tracking echocardiography (7,8) are needed to more appropriately separate the HF populations into those with reduced versus preserved left ventricular function. Such attempts will aid to exclude those with normal function and enrich future HFpEF trials with “reduced LV global strain-preserved EF” patients.

Furthermore, the addition of biomarker entry criteria such as elevated NT-pro-BNP, as in the American cohort of TOPCAT (25) and in PARAGON-HF (45), are supportive to ensure that HFpEF patients truly have HF. Also randomized trials in HFpEF need robust testing of the trial hypothesis by keeping study participants in the trial on randomized study medication and avoiding the addition of concomitant medications to maintain power throughout.

Although EF is suboptimal, this is not necessarily the reason for the HFpEF trials not reaching significance for their primary endpoints; rather study performance as explained above.

However, HFpEF may benefit from further pre-specified sub-classification into patients with systolic dysfunction (strain, longitudinal contractility), diastolic dysfunction (also by

echocardiography), patients with poor rhythm control (paroxysmal or permanent atrial fibrillation), patients with combinations of these cardiac mechanism causing HFpEF or possibly by etiology (hypertension, diabetes, obesity).

## **Conclusions**

Effective medical therapies for patients with HFrEF have been established with ARNI, ACE-I or ARB, MRA/aldosterone antagonist, and  $\beta$ -blockers. By contrast, a limited number of clinical outcome trials investigating RAAS blockade in HFpEF have been unsuccessful. HFpEF patients most often have hypertensive heart disease, typically complicated by obesity, diabetes, AF, coronary artery disease and possibly, left ventricular systolic dysfunction in the absence of reduced EF. Based on an extensive body of science attesting the efficacy of RAAS-blockers and MRAs in hypertension and HFrEF, combination ACE-I (or ARB) and MRAs, or combination ARNI and MRA should be used in every patient with HFpEF.

**Sources of Funding** None

## **Disclosures**

Dr. Kjeldsen has received lecture and/or consultancy honoraria from Merck KGaA, MSD, Sanofi, and Takeda. Dr. von Lueder has received lecture and/or consultancy honoraria from Astra-Zeneca, Vifor, Pharmacosmos, Novartis, Pfizer, and Boehringer-Ingelheim. Dr. Wachtell has received honoraria from MSD. Dr. Westheim has received lecture honoraria from Novartis. Dr. Devereux has received honoraria from MSD. Dr Zannad has received

lecture and/or steering committee/consultancy fees from Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer, Boston Scientific, Cardior, Cereno Scientific, CEVA, Cirius therapeutics, CVRx, G3 Pharmaceuticals, J&J, LivaNova, Merck, Mitsubishi, Mundipharma, Nestlé Health Science, Novartis, NovoNordisk, Pfizer, Quantum Genomics, Relypsa, ResMed, Vifor Fresenius and ZS Pharma . The other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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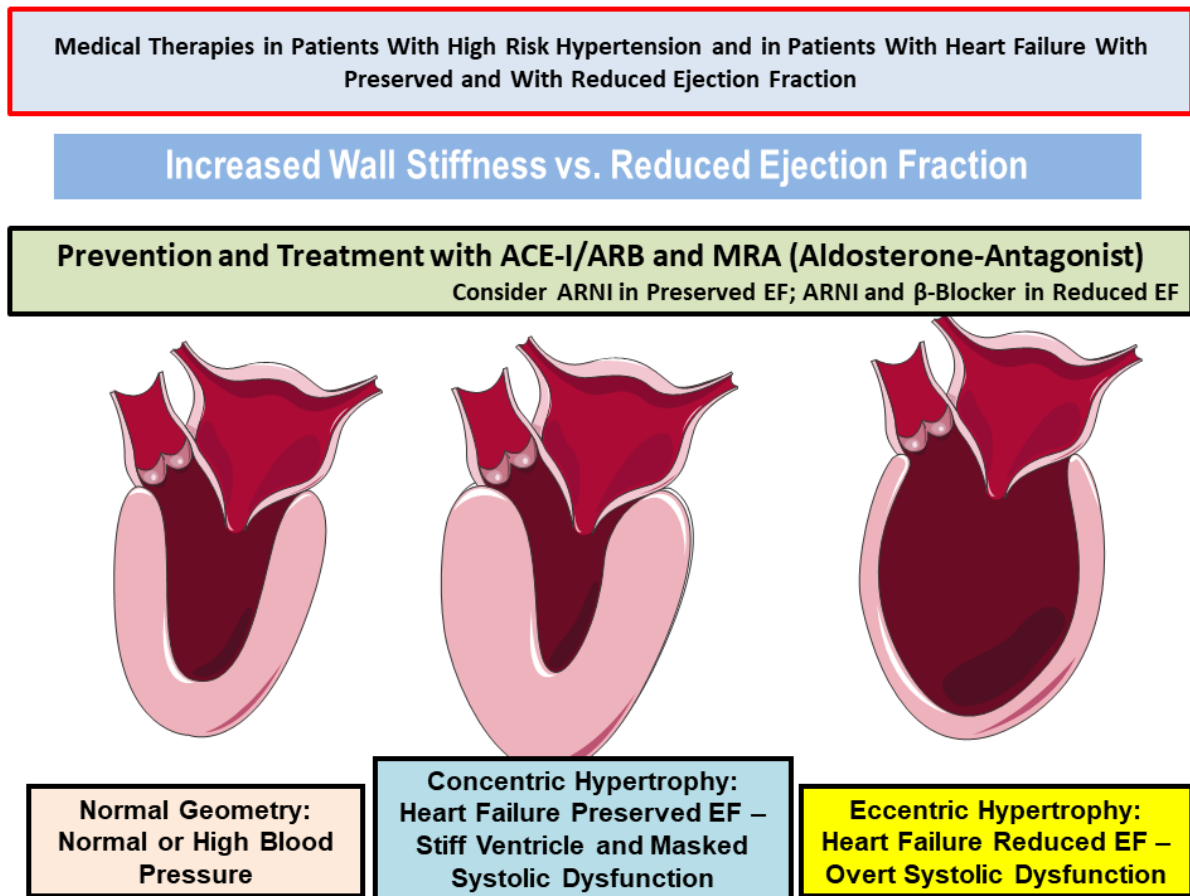
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## Legends



**Fig. 1**

Heading:

Medical Therapies in Patients With High Risk Hypertension and in Patients With Heart Failure With Preserved and With Reduced Ejection Fraction

Footnote:

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker;

ARNI = angiotensin receptor neprilysin inhibitor; EF = ejection fraction; MRA =

mineralocorticoid receptor antagonist/aldosterone antagonist





**Table 1 Heart Failure with Preserved Ejection Fraction: Superiority Designed, Placebo Controlled RCTs**

<b>Trial, Year (Ref. #), N Mean Duration</b>	<b>Study Drug Mean Dose Discontinued</b>	<b>Study Participants (Means)</b>	<b>Baseline BP and HR (Means)</b>	<b>Composite Primary Endpoint</b>	<b>A priori Statistical Power</b>	<b>Main Outcome Results</b>	<b>N Heart Failure Hospital.</b>	<b>Concomitant Open Label Medication</b>
CHARM, 2003 (1), N = 3023 37 months (3 yr. +)	Candesartan 25 mg 20%	EF 54 % Age 64 yr. Men 60 % BMI 29 kg/m <sup>2</sup> HT 64 % DM 28 %	136/78 mmHg 71 beats/min	CV death, HF hospital- ization Risk 9 % (expected 11 %)	80 % for 18% reduction	HR = 0.89 CI=0.77-1.03 p = 0.12	Active 230 Placebo 279 p = 0.017	Diur 77% β-block. 50% CCB 31% ACE-I 20% spiro 11 %
PEP-CHF, 2006 (3), N = 852 26 months (2 yr. +)	Perindopril 4 mg 38%	EF 64 % Age 75 yr. Men 44 % BMI 28 kg/m <sup>2</sup> HT 79 % DM 21 %	139/80 mmHg 73 beats/min	Death, HF hospital- ization Risk 13 %	90 % for 26 % reduction	HR = 0.92 CI=0.70-1.21 p = 0.55	Active 64 Placebo 73 p = 0.375	Diur 100% β-block 55% CCB 33% ACE-I 36% spiro 10 %
I-PRESERVE, 2008, (4) N = 4133 50 months (4 yr. +)	Irbesartan 300 mg 34%	EF 59 % Age 72 yr. Men 40 % BMI 30 kg/m <sup>2</sup> HT 88 % DM 27 %	136/79 mmHg 71 beats/min	Death, CV hospital- ization Risk 18 % (expected 18 %)	90 % for 14.5 % reduction	HR = 0.95 CI=0.86-1.05 p = 0.35	Active 325 Placebo 336 p = 0.50	Diur 90% β-block 73% CCB 40% ACE-I 40% spiro 28%
TOPCAT, 2014 (5), N = 3445 40 months (3 yr. +)	Spiro- lactone 25 mg 33%	EF 56 % Age 69 yr. Men 48 % BMI 31 kg/m <sup>2</sup> HT 91 % DM 33 %	130/80 mmHg 68 beats/min	CV death, aborted cardiac arrest, HF hospitalization Risk 19.5 % (expected 17.4 %)	80 % for 20 % reduction	HR = 0.89 CI=0.77-1.04 p = 0.14	Active 206 Placebo 245 p = 0.04	Diur 82% β-block 78% CCB 37 ACE-I 84% spiro N/A

RCT = randomized controlled trial; BP = blood pressure; HR = heart rate *or* hazard ratio; EF = ejection fraction; CV = cardiovascular; CI = 95% confidence intervals; CCB = calcium channel blocker; HF = heart failure; BMI = body mass index; ACE-I = angiotensin converting enzyme inhibitor; HT = hypertension; DM = diabetes mellitus; LVH = left ventricular hypertrophy; MI = myocardial infarction; CHD = coronary heart disease.

**Table 2 High Risk Hypertension without Heart failure: Superiority and Non-Inferiority Designed RCTs**

<b>Trial, Year (Ref. #), N Mean Duration</b>	<b>Study Drugs Mean Dose Discontinued</b>	<b>Study Participants (Means)</b>	<b>Baseline BP and HR (Means)</b>	<b>Composite Primary Endpoint</b>	<b>A priori Statistical Power</b>	<b>Main Outcome Results</b>	<b>N Heart Failure Hospital.</b>	<b>Concomitant Open Label Medication</b>
LIFE, 2002 (6), N = 9,193 4.8 Yr.	Losartan v. Atenolol 82 vs. 79 mg 23 vs. 27 %	Age 67 yr. Men 46 % BMI 28 kg/m <sup>2</sup> DM 13 % LVH (all)	174/98 mmHg 74 beats/min	CV death, MI, stroke Los 11 % Aten 13 %	80 % for 15 % reduction	HR = 0.85 CI=0.76-0.96 p = 0.009	Los 153 Aten 161 p = 0.62	Diur 90 % CCB 40 % α-block 10 % Vasodil 10% (other)
VALUE, 2004 (7), N = 15,245 4.2 Yr.	Valsartan v. Amlodipine 152 vs. 8.5 mg 26 vs. 25 %	Age 67 yr. Men 57 % BMI 29 kg/m <sup>2</sup> DM 32 % CHD 46 %	155/88 mmHg 72 beats/min	Cardiac event, MI, HF, fatal, non-fatal Val 10.6 % Amlo 10.4 %	90 % for 15 % reduction	HR = 1.04* CI=0.94-1.15 p = 0.49	Val. 354 Amlo 400 p = 0.12	Diur 18 % β-block 46 % ACE-I 20 % α-block 21%
ASCOT, 2005 (8), N = 19,257 5.5 Yr.	Amlodipine+ Perindopril v. Atenolol+ Thiazide 25 %	Age 63 yr. Men 77 % BMI 29 kg/m <sup>2</sup> DM 27 % Smoking 33 %	164/95 mmHg 72 beats/min	All cause mortality Amlo+P 8 % Aten+T 9 %	80 % for 16 % reduction (of primary)	HR = 0.89 <sup>†</sup> CI=0.81-0.99 p = 0.02	Amlo+Perindo 134 Aten+Thiazide 159 p = 0.13	
ACCOMPLISH, 2008 (9), N=11,506 3 Yr.	Amlodipine+ Benazepril v. Benazepril+ Thiazide	Age 68 yr. Men 60 % BMI 31 kg/m <sup>2</sup> DM 60 % Dyslipidemia 74%	145/80 mmHg 70 beats/min	CV death, stroke, coronary events Benaz+Amlo 9.6% Benaz+Thiazide 11.8	90 % for 15 % reduction	HR = 0.80 CI=0.72-0.90 p < 0.001	Amlo+Benaz 100 Benaz+Thiazide 96 p = 0.77	

RCT = randomized controlled trial; BP = blood pressure; HR = heart rate *or* hazard ratio; EF = ejection fraction; CV = cardiovascular; CI = 95% confidence intervals; CCB = calcium channel blocker; HF = heart failure; BMI = body mass index; ACE-I = angiotensin converting enzyme inhibitor; HT = hypertension; DM = diabetes mellitus; LVH = left ventricular hypertrophy; MI = myocardial infarction; CHD = coronary heart disease.

\*non-inferiority with cerebral stroke included; <sup>†</sup>all-cause mortality