Effect On Cardiac Function Among Patients With Type 2 Diabetes Following High-Dose Mineralocorticoid Receptor Antagonist Using Echocardiography; Data From The MIRAD Randomized Clinical Trial

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1 Effect on cardiac function among patients with type 2 diabetes following high-dose
2 mineralocorticoid receptor antagonist using echocardiography; data from the MIRAD randomized
3 clinical trial

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1 Background:

2 Early heart failure (HF)-prevention is central in patients with type 2 diabetes, and mineralocorticoid
3 receptor antagonists (MRAs) have shown to improve prognosis. We investigated the effect of high-
4 dose MRA, eplerenone, on cardiac function and structure in patients with type 2 diabetes and
5 established or increased risk of cardiovascular disease but without HF.

6 Methods:

7 In the current randomized, placebo-controlled clinical trial, 140 patients with high-risk type 2 diabetes
8 were randomized to high-dose eplerenone (100-200 mg daily) or placebo as add-on to standard care
9 for 26 weeks. Left ventricular (LV) systolic and diastolic function, indexed LV mass (LVMi), and
10 global longitudinal strain (GLS) were assessed using echocardiography at baseline and after 26 weeks
11 of treatment.

12 Results:

13 Of the included patients, 138 (99%) had an echocardiography performed at least once. Baseline early
14 diastolic in-flow velocity (E-wave) indexed by mitral annulus velocity (e') was mean (SD) 11.1 (0.5),
15 with 31% of patients reaching above 12. No effect of treatment on diastolic function was observed
16 measured by E/e' (0.0, 95%CI [-1.2 to 1.2], P=0.992) or E/A (-0.1, 95%CI [-0.2 to 0.0], P=0.191).
17 Mean LV ejection fraction (LVEF) at baseline was 59.0% (8.0). No improvement in systolic function
18 was observed when comparing groups after 26 weeks (LVEF: 0.9, 95%CI [-1.1 to 2.8], P=0.382;
19 GLS: -0.4%, 95%CI [-1.5 to 0.6], P=0.422), nor in LVMi (-3.8 g/m² 95%CI [-10.2 to 2.7], P=0.246).

20 Conclusion:

21 In the present echo sub-study, no change in cardiac function was observed following high-dose MRA
22 therapy in patients with high-risk type 2 diabetes.

23 Trial registration: Date of registration 25/08/2015 (EudraCT number: 2015-002519-14)

- 1 Key words: Mineralocorticoid receptor antagonist, high-dose eplerenone, global longitudinal strain,
- 2 systolic and diastolic function
- 3

1 BACKGROUND

2 In patients with type 2 diabetes, the risk of heart failure (HF) hospitalization as the first cardiovascular
3 event exceeds myocardial infarction (MI) by approximately a factor four [1]. Undiagnosed
4 cardiovascular disease (CVD), especially HF, in type 2 diabetes is thus, an established risk, which
5 results in severely impaired prognosis. Changes in cardiac structure and diastolic dysfunction,
6 precedes overt HF with preserved ejection fraction (HFpEF), being one of the hallmarks of the first
7 stages in the classification of HF and of cardiac dysfunction [5,6]. While evidence-based preventive
8 treatment options are limited [2–4], in the effort of early prevention and mitigating the risk of
9 subsequent HF, treatment with angiotensinogen converting enzyme-inhibitors (ACEi), angiotensin
10 receptor blockers (ARB), and sodium glucose like transporter-2-inhibitors (SGLT2-i) are now
11 recommended for high-risk type 2 diabetes patients by current guidelines [5,7]. In contrast,
12 mineralocorticoid receptor antagonists (MRAs) remain a fourth-in-line antihypertensive in the
13 absence of overt HF with reduced ejection fraction (HFrEF) [5,7].

14 Experimental evidence has proven that inhibition of the mineralocorticoid receptor is
15 an important therapeutic target in the prevention of HF in animal models of diabetes, obesity and
16 early HF [8–10]. Further, a large body of evidence from clinical studies have established that MRA
17 improves prognosis in patients with documented HFrEF [11–13], while the available evidence in
18 HFpEF is less clear [4]. The use of MRAs has been suggested to improve cardiac function using
19 echocardiography in patients with varying stages of HF [14,15]. Recently, It has been suggested that
20 the beneficial effects of MRAs may be further amplified with concurrent metabolic disease [16].
21 Therefore, accruing further knowledge on the early prevention of adverse cardiac changes in patients
22 with type 2 diabetes and the possible clinical impact of MRAs is crucial in the prevention of HF
23 among patients with type 2 diabetes.

In this substudy of the Mineralocorticoid Receptor Antagonist in type 2 Diabetes (MIRAD) trial, we aimed to investigate whether high-dose eplerenone as an add-on therapy improves myocardial function evaluated by echocardiography. In the present study we report the prespecified endpoints of left ventricular (LV) systolic and diastolic function, including global longitudinal strain (GLS), after 26 weeks of treatment with the MRA, eplerenone.

METHODS

Trial Design

The presented results are based on data from the MIRAD double-blinded, randomized clinical trial and its design has previously been described in detail while reporting the primary outcome liver fat content [17]. Briefly, the study enrolled 140 patients with type 2 diabetes and a high risk of or established CVD from an outpatient clinic at a university hospital in Copenhagen, Denmark. Patients were randomized using a 1:1 block-randomization (block-size: 10), created by a third party, Glostrup Pharmacy. Patients were randomized to either high-dose eplerenone (100-200 mg) or dose-matched placebo for 26 weeks by primary investigator, MLJ, blinded to treatment, with initial dose of 50 mg and dose increases every 2 weeks until maximal tolerable dose was achieved. The treatment drug and placebo, provided by Glostrup Pharmacy, could not be distinguished from each other. The trial included patients with a diagnosis of type 2 diabetes with a diagnosis of or a high risk of CVD defined by the following key inclusion criteria: previous myocardial infarction, significant stenosis on coronary angiography, previous stroke or transient ischemic attack at least 3 months prior to randomization, presence of peripheral artery disease, NT-proBNP ≥ 70 ng/L, or albuminuria defined as urinary albumin-creatinine ratio ≥ 30 mg/g. Key exclusion criteria were HFrEF (LV ejection fraction (LVEF) $< 40\%$), potassium ≥ 5.0 mmol/L, or impaired kidney function (estimated glomerular filtration rate (eGFR) of ≤ 40 mL/min/1.73 m²).

Acquisition and processing of cardiac images

1 Transthoracic echocardiography was performed by experienced cardiologists using a Vivid E9 (MS,
2 MD, TK) (GE Vingmed Ultrasound, Norway) in accordance with current guidelines [18]. Two-
3 dimensional images were acquired in three apical views (2, 4-chamber and long-axis) and two
4 parasternal views (long and short axis). LV end-diastolic (EDV), end-systolic (ESV), stroke volume
5 (SV), LVEF, and maximal left atrial (LA) volume were derived using the modified Simpson's
6 method. LV diastolic function was assessed using pulsed-wave Doppler to measure E-wave, E-wave
7 deceleration time, and late atrial filling (A-wave). The mean value of measurements at the basis of
8 the interventricular septum and basis of the lateral wall in the 4-chamber view using tissue Doppler
9 were performed to measure e' . GLS was derived from all three apical views. Radial strain and
10 circumferential strain were not performed. All image post-processing was performed offline by a
11 single investigator (NBJ) masked from treatment-group allocation on commercially available
12 software (Echopac BT 12.1.0; GE, Norway). Measures were performed thrice and averaged with the
13 exception of GLS, which was performed once. LVMi was indexed to body surface-area using the
14 formula by Devereux et al. [19], with hypertrophy defined as above 115 g/m^2 for men and 95 g/m^2
15 [18].

16 *Study Outcomes*

17 We report the predefined secondary endpoints of the MIRAD trial: change LV cardiac function by
18 echocardiography (LVEF, EDV, ESV, e' , GLS) with additional measures diastolic function (E/e' ,
19 E/A , LA).

20 *Statistical analyses*

21 We used the constrained linear mixed model (cLMM) to evaluate treatment effect (or between-group
22 difference) on all study outcomes. To account for correlation between repeated measurements on the
23 same subject, an unstructured covariance pattern was assumed. Additional echocardiographic
24 measures of LV and right ventricular (RV) function, including RVGLS, are reported as part of the

1 performed echocardiography (Baseline according to treatment group: Supplementary table 1; changes
2 from baseline: Supplementary table 2).

3 Analyses were performed as intention-to-treat. Missing values were deemed to be
4 missing at random and were implicitly imputed by maximum likelihood-estimation in the linear
5 mixed models. Sensitivity analyses using the complete-case cohort did not change conclusions based
6 on the primary analysis (Supplementary table 3). Descriptive characteristics are reported by mean
7 and standard deviation (SD), while changes from baseline and treatment effects are reported using
8 the corresponding means, 95% confidence interval [95%CI] and two-tailed unadjusted p-values. A
9 p-value below 0.05 considered as statistically significant. Data-transformation was used to adhere to
10 model assumptions and results are presented after de-transformation. Statistical analyses and
11 graphical design were performed using SAS Enterprise version 7.15 (SAS Institute Inc., Cary, NC,
12 USA) and GraphPad Prism 8, version 8.1.0 (GraphPad Software, San Diego, CA, USA).

13 RESULTS

14 *Participant characteristics*

15 A total of 140 patients were randomized to eplerenone or placebo between October 2015 and
16 November 2017. At the end of the trial, with the exception of two patients from the eplerenone group,
17 an echocardiography was performed in all patients at least once (99%) (Supplementary figure 1:
18 Flowchart).

19 As summarized in table 1, the patients deemed illegible to be included in the analyses
20 were well-balanced at baseline according to treatment groups. Almost half (44%) of the included
21 patients had established CVD at baseline, with the majority having coronary heart disease (28%). Of
22 the patients included 78% received ACEi or ARB, with 36% and 37% receiving Ca-antagonists or
23 Beta-blockers, respectively. At baseline, patients were fairly well-regulated with a geometric mean
24 (SD) of HbA1c at baseline of 59.5 (14.5), receiving the anti-diabetic standard of care, metformin

being the most prevalent therapy (82%), followed by insulin (51%), glucagon-like peptide 1-receptor agonist (32%), SGLT2-i (23%). Patient prescribed dipeptidyl peptidase IV-inhibitors or sulfonylureas were less common (Table 1). No patients experienced a serious adverse event deemed to be caused by active treatment during the conduction of the trial.

Diastolic function

At baseline, patients with diastolic dysfunction indicated by an E/e' above 12 comprised 31% of the study population, with mean (SD) E/e' was 11.1 (0.5) (Table 1). The maximal diastolic ventricular in-flow peak E-wave and peak A-wave did not change when compared to baseline within the eplerenone group or as an effect of treatment. Similarly, no change was observed in maximal velocity of the mitral annulus, e', within groups or as an effect of treatment. Consequently, no treatment effect of E/e' or E/A was observed when comparing groups at week 26 (E/e': 0.0, 95%CI [-1.2 to 1.2], P=0.992; E/A: -0.1, 95%CI [-0.2 to 0.0], P=0.191) (Table 2, Figure 1). Participants with enlarged indexed atria (>34 mL/m²) at baseline comprised 11% of the study population, with a population-mean at baseline of 53.1 mL (18.0) (Table 1). No change was observed in LA volume from baseline, with an effect of treatment when comparing groups at week 26 of -2.3 mL (95%CI [-6.6 to 1.9], P=0.277) (Table 2, Figure 1).

Systolic function and structure

At baseline, mean LVEF at baseline was 59.0% (8.0), with 86% of the population having an LVEF above 50%. Following the addition of eplerenone, neither EDV or ESV changed from baseline in either group or when comparing groups at week 26. There was no change in LVEF when comparing groups at week 26 (0.9, 95%CI [-1.1 to 2.8], P=0.382) (Table 2, Figure 1). Mean GLS (SD) was -15.3% (3.4), with no improvement in the eplerenone group when comparing with baseline (0.06, 95%CI [-0.7 to 0.8], P=0.876). As an effect, no observable treatment effect on GLS was observed when comparing groups at week 26 (-0.4, 95%CI [-1.5 to 0.6], P=0.422, Figure 1). Patients with left

1 ventricular hypertrophy at baseline comprised 16% of the total cohort, with a LVMI population-mean
2 at baseline of 92.8 g/m² (22.7). The addition of eplerenone did not elicit an observable change in
3 LVMI when comparing groups at week 26, with a non-significant treatment effect of -3.8 g/m²
4 (95%CI [-10.2 to 2.7], P=0.246) (Table 2, Figure 1).

5 DISCUSSION

6 In the present echocardiography sub-study of the MIRAD trial no improvement in either cardiac
7 systolic or diastolic function was observed, with no observed change in left ventricular mass
8 following treatment with eplerenone for a duration of 26 weeks in a cohort of high-risk type 2 diabetes
9 patients without known HF.

10 The increased risk of HF following the diagnosis of type 2 diabetes is well-established,
11 with the concomitant diagnose of HF further substantially impairing prognosis [20]. In the present
12 trial, no observable benefit was found using established measures of diastolic cardiac function: E/e'-
13 ratio, E/A-ratio and left atrial volume with an MRA. The absence of an observable effect of an MRA
14 on diastolic function, contrasts previous findings showing an improvement in diastolic function
15 among patients with metabolic syndrome and among patient with early signs of diabetic
16 cardiomyopathy [21,22]. Indeed, summarizing the effects of the addition of MRAs, two meta-
17 analyses on improvements in cardiac function in patients with HFpEF and HFrEF restricted to
18 echocardiography have highlighted improvements in diastolic function, especially, with
19 improvements in E/e', E/A and atrial volume as the most consistent results following MRA treatment
20 [14,15]. Further substantiating these results, a recent publication from the HOMAGE trial,
21 investigating high-dose spironolactone in patients without HF, of whom 42% had diabetes, reported
22 improvements in diastolic function [23]. A plausible explanation to the absence of change is given
23 by the proportion of patients with baseline diastolic dysfunction in the current trial differs markedly
24 from previous reports, with only an abnormal E/e' and LAi of 31% and 11%, respectively. The

1 clinical implication of improvement of diastolic dysfunction has been underlined by a recent report
2 from the PARAGON-trial, elucidating the HFpEF-specific cardiovascular characteristics prior to
3 developing HFrEF. Although the effects of the combination of sacubitril/neprilysin failed to achieve
4 statistical significance on the composite endpoint of cardiovascular death and total HF
5 hospitalizations [24], increased baseline-levels of LVMI, E/e' ratio, atrial size, and pulmonary arterial
6 systolic pressure were found as the greatest predictors of a subsequent cardiovascular event [25].
7 While a cohort with a low proportion of diastolic dysfunction creates a unique opportunity to
8 investigate MRAs ability to mitigate the progression of these traits, a small trial of relatively short
9 duration undoubtedly reduces the expected detectable effect. While we have previously reported the
10 absence of a detectable effect on 24-hour blood pressure [26] and by extension a relatively weak
11 effect on afterload, which could lower the overall expected effect of MRA, evidence of blood
12 pressure-independent effects of MRAs have previously been shown. Experimental studies
13 investigating the potential underlying mechanisms of MRA therapy in HF, demonstrated receptor-
14 mediated effects in cardiomyocytes and vascular endothelial cells, which was independent of simple
15 diuretic effects mediated by mineralocorticoid receptor activation in the kidneys [8–10]. An
16 exploratory analysis from the HOMAGE trial using targeted proteomics has found evidence of the
17 spironolactone exerting pleiotropic effects across multiple mechanistic pathways, spanning the
18 mitigation of fibrosis, thrombosis, congestion, vascular function and inflammation [27].

19 The current study observed no significant effect of high-dose MRA on LVMI, as a
20 marker of direct receptor-mediated remodeling when using echocardiography [28]. However, in
21 recent years a shift towards using cardiac MRI to determine LVM regression has proven useful in
22 studies using SGLT2-i [29,30]. Indeed, LVM regression was demonstrated as an effect of add-on
23 high-dose MRA therapy using cMRI in a subset of patients in the current cohort (Accepted for
24 publication in JACC-HF). Even though a direct comparison between methods restricted to the cMRI-
25 cohort revealed overlapping estimates of the treatment effect, the increased variance when using

1 echocardiography did not make it possible to detect a significant difference given the current size of
2 the study population (Results not shown). The presence of cardiac-specific remodeling as an effect
3 of MRA therapy has, however, previously been substantiated in a selective hypertensive population,
4 further indicating beneficial effects specific to cardiac structure and function [31].

5 We did not observe an effect on systolic measures of cardiac function as indicated by
6 LVEF or GLS in this cohort without overt HF, which might be expected from a cohort of patients in
7 stable antidiabetic and antihypertensive treatment without overt systolic dysfunction. In line with
8 previous publications, trials have yet to observe a consistent improvement in LVEF in patients
9 without HFrEF following MRA therapy [14,15]. However, in contrast to LVEF, previous reports
10 have shown a beneficial effect on GLS among patients with metabolic syndrome [21]. Following
11 previous suggestions of a GLS below 17-18% indicating abnormal function [18], the addition of GLS
12 may capture additional markers of risk not easily detected using conventional echocardiographic
13 measures alone. The addition of strain has previously provided incremental prognostic information
14 in patients with type 2 diabetes [32]. Therefore, further studies are warranted investigating the
15 potential of GLS to further stratify the cardiac phenotype of patients with type 2 diabetes despite the
16 present study observed no change in this measure.

17 Even though an improvement was not evident in the present trial, previous results have
18 suggested the benefit of MRA to standard care prior to the development of HF [33,34], with the
19 ongoing SPIRRIT trial re-investigating the role of spironolactone in HFpEF (ClinicalTrial.gov:
20 NCT02901184). Interestingly, recent results from the FIDELIO-trial, investigating the third-
21 generation, dihydropyridine-based MRA, finerenone, has provided new evidence in line with these
22 findings, and may provide evidence of clinically relevant effects of MRAs in the context of prior to
23 patients developing HF. Both the primary and secondary endpoint, a renal and cardiac composite
24 endpoint, respectively, reached statistical significance [35]. The related, ongoing FIGARO trial
25 (ClinicalTrial.gov: NCT02545049) and the recently initiated FINEARTS-HF (ClinicalTrial.gov:

1 NCT04435626) combined, investigating the width of the HFpEF phenotype, are powered to detect
2 changes in incidence of first and recurrent hospitalization due to heart failure and cardiovascular
3 mortality, with results expected to highlight the potential of MRAs as preventive of HFrEF and
4 possibly as a therapeutic in HFpEF.

5 *Limitations*

6 The present study is a relatively small, single-center study with a duration of only 6 months, and thus,
7 with restricted ability to predict long-term changes in risk. Although the inability to reproduce
8 previous data reported across various clinical modalities is, undoubtedly, a consequence of the
9 underlying effect size, it may also be an effect of the inherent limitations of echocardiography as
10 compared to cMRI when investigating a cohort focusing on prevention rather than changes in a
11 population of overt HF. Using echocardiography to measure of systolic and diastolic function,
12 however, is established as the reference standard in its ability to predict long-term risk of
13 cardiovascular events. Consequently, it must be acknowledged the inability unable to reproduce and
14 extrapolate results produced using cMRI on a subset of the current cohort (e.g., LVM regression) may
15 weaken implication on long-term risk (Manuscript accepted in JACC-HF). The present study
16 contained a large proportion of patients with no signs of either overt systolic or diastolic function,
17 with a long-standing stable clinical condition, which lowers the expected effects size of treatment.
18 Considering the results of the recently-published PARAGON-trial, a population based on inclusion-
19 criteria based on measured, which were highlighted as the greatest predictors of cardiovascular event
20 in patients with HFpEF (e.g., higher LVMi, E/e' ratio, left atrium size or pulmonary arterial systolic
21 pressure) may provide a better framework to detect the absolute changes caused by treatment in study
22 designs in the future.

23 CONCLUSION

1 In conclusion, the addition of high-dose eplerenone to standard therapy in patients with type 2
2 diabetes and high risk of or established CVD for a duration of 26 weeks was not associated with a
3 detectable improvement in cardiac systolic or diastolic function when measured using
4 echocardiography.

5 DECLARATIONS

6 *Ethics approval and consent to participate*

7 The study protocol was approved by the Regional Scientific Ethics Committee (H-15009313), the
8 Danish Data Protection Agency (2012-58-0004), participants supplied written and verbal informed
9 consent, and the study was completed in accordance with the Declaration of Helsinki. The trial was
10 conducted and monitored by an independent unit from Copenhagen, Denmark, in accordance with
11 the International Conference on Harmonization Guidelines for Good Clinical Practice. The trial was
12 registered at the European Clinical Trials Register (Date of registration: 25/08/2015, EudraCT
13 number: 2015-002519-14).

14 *Consent for publication*

15 Not applicable

16 *Availability of data and materials*

17 The datasets generated and/or analysed during the current study are not publicly available due to
18 national restrictions in sharing patient-sensitive material, but are available from the corresponding
19 author on reasonable request.

20 *Competing interests*

21 C.K. has served on scientific advisory panels and/or received speaker fees from Boehringer
22 Ingelheim, Merck Shape and Dome, Astra Zeneca, Amgen, Novartis, Novo Nordisk and Shire. P.R.
23 reports personal fees from Ablative Solutions, AstraZeneca, Bayer, Boehringer-Ingelheim, Corvidia,

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5 Bristol Meyer Squibb, Bayer, and J.F. has served on scientific advisory boards at Merck Shape and
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7 declare.

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12 funders have no role in the design and conduct of the trial, the analysis of data, or the writing of
13 manuscripts.

14 *Author contributions*

15 NBJ executed and planned the study, contributed to data collection, conducted statistical analyses,
16 and wrote the manuscript. MLJ executed the study and contributed to data collection. JR collected
17 data, contributed to patient referrals, and revised the manuscript. MS, MD and TK performed the
18 echocardiographies and critically revised the manuscript. MS designed and planned the trial, collected
19 and interpreted the data. PR designed the trial, analyzed and interpreted the data, and critically revised
20 the manuscript. JF planned the trial and critically revised the manuscript. CK conceptualized and
21 planned the trial, wrote grant applications, and wrote the manuscript. CK, the guarantor of this work,
22 has access to all the data and takes responsibility for the integrity of the data and the accuracy of the
23 data analyses.

24 *Acknowledgements*

1 Not applicable

2 LIST OF ABBREVIATIONS

3	HF	Heart failure
4	MRA	Mineralocorticoid Receptor Antagonist
5	LV	Left Ventricular
6	LVMi	Left Ventricular Mass indexed to body surface area
7	GLS	Global Longitudinal Strain
8	E-wave	Early Diastolic in-flow velocity
9	e'	Mitral annulus velocity
10	LVEF	Left Ventricular Ejection Fraction
11	CVD	CardioVascular Disease
12	MI	Myocardial Infarction
13	HFpEF	Heart Failure with Preserved Ejection Fraction
14	ACEi	Angiotensinogen Converting Enzyme-Inhibitor
15	ARB	Angiotenin Receptor Blocker
16	SGLT2-i	Sodium-Glucose Like Transporter-2-Inhibitor
17	HFrEF	Heart Failure with Reduced Ejection Fraction
18	MIRAD	Mineralocorticoid Receptor Antagonist in type 2 Diabetes
19	eGFR	Estimated Glomerular Filtration Rate
20	EDV	End Diastolic Volume
21	ESV	End-Systolic Volume
22	SV	Stroke Volume
23	LA	Left Atrial
24	A-wave	Late Atrial Filling velocity
25	cLMM	Constrained Linear Mixed Model
26	RV	Right Ventricular
27	SD	Standard deviation
28	GLP1-RA	Glucagon-Like Peptide1-Receptor Agonist

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Figure 1: Change from baseline according to treatment group (Panel A-E)

Figure caption:

Values shown as mean with corresponding upper/lower 95%CI-limit using a constrained linear mixed model. Patients exhibited same tendency towards a decrease in E/e' (A) and left atrial volume (B), with only the eplerenone group showing a decrease in left atrial volume when compared to baseline, but no overall improvement in diastolic function. No improvement was found in systolic function using LVEF (C) or GLS (D) (shown in percentage points) nor was an overall treatment effect found in structure (E). * Significant decrease from baseline. ** Significant decrease when comparing group after 26 weeks.

1 Table 1: Baseline characteristics according to treatment group

	Placebo	Eplerenone
Demographics	70	68
Age, years	64.1 (8.7)	62.8 (10.0)
Sex, Male (%)	50 (71)	52 (76)
BMI, kg/m ²	30.8 (4.6)	30.5 (3.9)
BSA, m ²	2.1 (0.2)	2.1 (0.2)
Duration of diabetes, years*	11 (5 to 16)	12 (7 to 16)
HbA1c, mmol/mol	59.0 (14.9)	59.5 (13.6)
eGFR, mL/min/1.73m ²	83.4 (16.6)	86.9 (20.6)
24h-blood pressure, mmHg	129/77 (12.9/10.1)	129/78 (12.8/8.5)
Cardiovascular disease, n (%)	32 (46%)	30 (44%)
Chronic heart disease**	20 (29%)	18 (26%)
Stroke	4 (6%)	8 (12%)
Peripheral arterial disease	11 (16%)	5 (7%)
UACR, mg/g***	19.2 [13.3 to 27.7]	17.2 [12.0 to 24.5]
proBNP, ng/L***	83.7 [66.0 to 106.2]	69.5 [55.6 to 86.9]
Echocardiography		
EF, %	58.3 (8.5)	59.2 (7.4)
GLS, %	-15.5 (3.7)	-15.1 (3.1)
LVM, g	194.4 (43.9)	195.7 (54.9)
LVMi, g/m ²	93.9 (19.7)	92.6 (25.7)
LVH, n (%)	12 (17)	10 (15)
E/e'	11.3 (4.9)	10.9 (3.9)
E/e' >12, n (%)	22 (33)	20 (29)
e', cm/s	6.9 (1.6)	7.4 (1.7)
LA volume, mL	53.0 (19.4)	53.2 (16.6)
LAi, <34 mL/m ² , n (%)	8 (12)	7 (10)
Medication, n (%)		
RAS-inhibitors	56 (80%)	52 (76%)
Ca-antagonist	29 (41%)	21 (31%)
Beta blockers	25 (36%)	24 (35%)
Diuretics	38 (54%)	33 (49%)
Metformin	56 (80%)	58 (85%)
GLP1-RA	25 (36%)	19 (28%)
SGLT2-inhibitors	9 (13%)	13 (19%)
Insulin	38 (54%)	33 (49%)
SU or DPP-IV	16 (23%)	22 (32%)
Cholesterol lowering	63 (90%)	63 (93%)

Values are reported as mean (SD) unless otherwise specified. *Median (interquartile range). ** Established chronic heart disease was defined as previous cardiovascular/coronary stenosis requiring intervention (e.g. by MI, PCI or CABG) or previous myocardial infarction. ***Geometric mean [95%CI]. Abbreviations: BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; UACR, urine-albumin-creatinine-ratio; NT-proBNP, N-terminal proBrain Natriuretic Peptide; EF, left ventricular ejection fraction; GLS, global longitudinal strain; LVM, left ventricular mass; LVMi, left ventricular mass indexed to surface area; LVH, left ventricular hypertrophy; E/e', early diastolic inflow velocity indexed to mitral annulus velocity; e', mitral annulus velocity; LA volume, left atrial volume; LAi, left atrium indexed to body surface area; RAS, renin-angiotensin-system; Ca-antagonist, Calcium-antagonist; GLP1-RA, Glucagon-Like-Peptide 1 receptor agonist; SGLT2, sodium-glucose cotransporter-2; SU or DPP-IV, sulfonylurea or dipeptidyl peptidase-IV

Table 2: Changes in cardiac function from baseline at week 26 and effect of treat

	Baseline			Placebo			P	Eplerenone			P	Treatment effect			P
Diastolic function															
E-wave, cm/s	0.8	[0.7 to	0.8]	0.0	[0.0 to	0.0]	0.530	0.0	[0.0 to	0.0]	0.855	0.0	[0.0 to	0.1]	0.752
A-wave, cm/s	0.8	[0.7 to	0.8]	0.0	[0.0 to	0.0]	0.448	0.0	[0.0 to	0.1]	0.180	0.0	[0.0 to	0.1]	0.131
e'-wave, cm/s	7.1	[6.8 to	7.4]	0.0	[-0.3 to	0.4]	0.944	0.1	[-0.2 to	0.5]	0.521	0.1	[-0.4 to	0.6]	0.669
E/e'-ratio	11.2	[10.4 to	11.9]	0.2	[-1.4 to	1.8]	0.802	1.1	[-0.5 to	2.7]	0.191	0.0	[-1.2 to	1.2]	0.992
E/A-ratio	1.1	[1.0	1.2]	0.0	[-0.1	0.1]	0.682	-0.1	[-0.1	0.0]	0.162	-0.1	[-0.2	0.0]	0.191
Deceleration, ms	264.0	[251.6	276.4]	2.8	[-13.8	19.3]	0.742	14.4	[-2.3	31.1]	0.089	11.7	[-9.7	33.1]	0.282
Atrial volume, mL	53.2	[50.1 to	56.2]	-2.1	[-5.2 to	1.0]	0.187	-4.4	[-7.6 to	-1.3]	0.006	-2.3	[-6.6 to	1.9]	0.277
Systolic function															
EF, %*	58.7	[57.4 to	60.1]	0.2	[-1.4 to	1.8]	0.802	1.1	[-0.5 to	2.7]	0.191	0.9	[-1.1 to	2.8]	0.382
EDV, mL	87.5	[83.6	91.4]	1.9	[-2.3	6.0]	0.379	-2.1	[-6.2	2.1]	0.319	-4.0	[-9.6	1.7]	0.166
ESV, mL	36.6	[34.4	38.9]	0.1	[-2.2	2.4]	0.938	-1.9	[-4.2	0.4]	0.113	-2.0	[-5.0	1.1]	0.201
GLS, %*	-15.3	[-15.8 to	-14.7]	0.5	[-0.3 to	1.3]	0.220	0.06	[-0.7 to	0.8]	0.876	-0.4	[-1.5 to	0.6]	0.422
LVMi, g/m ²	92.9	[89.1	96.8]	1.8	[-2.9	6.6]	0.449	-2.0	[-6.8	2.9]	0.426	-3.8	[-10.2	2.7]	0.246

Values reported are mean with corresponding 95%CI using a constrained linear mixed model *Change reported in percent points. Abbreviations: E-wave, early diastolic inflow velocity; A-wave, late diastolic inflow velocity; e', mitral annulus velocity; GLS, global longitudinal strain; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; LVMi, left ventricular mass indexed to body surface area.

Figures

Figure 1

Change from baseline according to treatment group (Panel A-E) Values shown as mean with corresponding upper/lower 95%CI-limit using a constrained linear mixed model. Patients exhibited same tendency towards a decrease in E/e' (A) and left atrial volume (B), with only the eplerenone group

showing a decrease in left atrial volume when compared to baseline, but no overall improvement in diastolic function. No improvement was found in systolic function using LVEF (C) or GLS (D) (shown in percentage points) nor was an overall treatment effect found in structure (E). * Significant decrease from baseline. ** Significant decrease when comparing group after 26 weeks.

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