

University of Groningen

New roles for renin in heart failure and cardio-renal interaction

Schroten, Nicolas

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2015

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Schroten, N. (2015). *New roles for renin in heart failure and cardio-renal interaction*. [Thesis fully internal (DIV), University of Groningen]. [S.n.].

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

**EFFECT OF ADDITIVE RENIN INHIBITION WITH ALISKIREN
ON RENAL HEMODYNAMICS AND NEUROHORMONAL
ACTIVATION IN PATIENTS WITH CHRONIC HEART FAILURE
AND RENAL DYSFUNCTION (ARIANA-CHF-RD)**

Nicolas F. Schrotten¹ MD, Kevin Damman¹ MD PhD,
Marc Hemmelder², MD PhD, Adriaan A. Voors¹, MD PhD,
Gerjan Navis³ MD PhD, Carlo A. J. M. Gaillard³, MD PhD,
Dirk J. van Veldhuisen¹, MD PhD, Wiek H. Van Gilst¹, MD PhD,
Hans L. Hillege¹, MD PhD

¹ University of Groningen, Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands

² Department of Internal Medicine, Medical Center Leeuwarden, Leeuwarden, the Netherlands

³ University of Groningen, Department of Internal Medicine, Division of Nephrology, University Medical Center Groningen, Groningen, the Netherlands

Submitted

ABSTRACT

Objectives – To examine the effect of the renin inhibitor, aliskiren, on renal blood flow in patients with heart failure with reduced ejection fraction (HFREF) LVEF \leq 45% and decreased glomerular filtration rate (GFR) 30-75 mL/min/1.73m² on optimal medical therapy.

Background – Renal blood flow is the main determinant of GFR in HFREF patients. Both reduced GFR and renal blood flow are associated with increased mortality. Aliskiren can provide additional renin-angiotensin-aldosterone-system inhibition and increases renal blood flow in healthy individuals.

Methods – Patients were randomized in a 2:1 ratio to receive aliskiren 300 mg once daily or placebo. Renal function was measured using radioactive labeled ¹²⁵I-iothalamate and ¹³¹I-hippuran at baseline and 26 weeks.

Results – Forty-one patients were included. At baseline the mean age was 68±9 years, 82% male, GFR (49±16 mL/min/1.73m²), renal blood flow (294±77 mL/min/1.73m²), and NT-proBNP 999 (435-2040) pg/mL. There was a non-significant change in renal blood flow after 26 weeks in the aliskiren group compared with placebo (-7.1±30 versus +14±54 mL/min/1.73m²; $P = 0.16$). However, GFR decreased significantly in the aliskiren group compared with placebo (-2.8±6.0 versus +4.4±9.6 mL/min/1.73m²; $P = 0.01$), as did filtration fraction (-2.2±3.3 versus +1.1±3.1%; $P = 0.01$). There were no significant differences in plasma aldosterone, NT-proBNP, urinary tubular markers or adverse events. Plasma renin activity was markedly reduced in the aliskiren group versus placebo throughout the treatment phase ($P = 0.007$).

Conclusions – Adding aliskiren on top of optimal HFREF medical therapy did not improve renal blood flow and was associated with a reduction of GFR and filtration fraction.

INTRODUCTION

The renin-angiotensin-aldosterone-system is activated in patients with heart failure in response to reduced cardiac output and decreased renal blood flow. The purpose of this response is to maintain organ perfusion, but long-term activation appears to be detrimental. (1) (2) Both angiotensin II levels and plasma renin activity (PRA) correlate strongly with glomerular filtration rate (GFR) and renal blood flow. (3) Reduced renal function and high angiotensin II levels and PRA have been associated with increased mortality in patients with chronic heart failure with reduced ejection fraction (HFREF). (4-7) Studies in healthy and hypertensive subjects have shown that renin-angiotensin-aldosterone-system blockade can increase renal blood flow, (8) which may prevent deterioration of renal function. Angiotensin AT1-receptor blockers (ARB) and angiotensin-converting-enzyme inhibitors (ACEi) have shown to reduce both morbidity and mortality, and are a cornerstone in the medical management of HFREF. (9, 10)

However, ACEi and ARB only partially block the renin-angiotensin-aldosterone-system, and high PRA levels have been associated with poor outcome despite treatment with ACEi and ARBs. (11-13) Therefore, direct renin inhibition with aliskiren on top of ACEi or ARBs is a rational treatment option, it reduces angiotensin, aldosterone and NT-proBNP levels in patients with HFREF. (14, 15) Effects of aliskiren on renal hemodynamics have been examined in healthy subjects and demonstrated a more pronounced increase in renal blood flow compared with ACEi, but have not been studied in chronic HFREF. (16)

Considering the high prevalence of renal dysfunction in HFREF patients and the effect of renin-angiotensin-aldosterone-system blockers on kidney function, the effects of aliskiren on renal hemodynamics is of particular interest. The main purpose of this study was to evaluate the effect of aliskiren on renal blood flow, on top of conventional therapy, in symptomatic HFREF patients with reduced GFR.

METHODS

The ARIANA-CHF-RD trial was a randomized, double-blind, placebo-controlled trial investigating the safety and efficacy of Additive Renin Inhibition with Aliskiren on renal blood flow and Neurohormonal Activation in patients with Chronic Heart Failure and Renal Dysfunction. The study was conducted at the University Medical Center Groningen and Medical Center Leeuwarden, The Netherlands. Baseline and end-of-treatment visits were all performed at the University Medical Center Groningen. The study protocol complied with the Declaration of Helsinki and was approved by the institutional review board. Written informed consent was obtained from all subjects. The trial was monitored by an independent data

safety monitoring board consisting of a cardiologist, nephrologist and statistician. The trial is registered at www.clinicaltrials.gov (NCT00881439).

PATIENT POPULATION

Patients with chronic HFREF (NYHA Class II-IV), ≥ 18 years of age with a documented left ventricular ejection fraction (LVEF) $\leq 45\%$, were eligible for this study. The primary protocol restricted inclusion to patients with estimated GFR 30-60 mL/min/1.73m², but was amended to allow inclusion of patients with estimated GFR up to 75 mL/min/1.73m² because of slow enrollment. The amendment was approved by the institutional review board and effectuated after 30 patients had been included. Additionally, patients had to be treated with ACEi and beta blockade or, if intolerant to ACEi with ARB, unless contraindicated, at a stable dose for ≥ 4 weeks. Full inclusion and exclusion criteria are listed in Supplement 1. Main exclusion criteria were triple renin-angiotensin-aldosterone-system inhibition, hyperkalemia or acute heart failure at the time of enrollment.

TREATMENT

Patients were randomized to aliskiren or matching placebo in a 2:1 ratio by an automated computer system. Treatment was started at 150 mg daily and, if tolerated, increased to 300 mg daily after one week. Safety visits were performed 2 weeks from baseline and then every 8 weeks, and included physical examination and laboratory tests. Patients were kept at the maximum tolerated dose for the duration of the trial. The protocol specified treatment guidelines in the event of hyperkalemia, worsening renal function or hypotension. The study drug was stopped after 26 weeks of treatment, and a final visit was performed 8 weeks later.

STUDY PROCEDURES

All patients underwent renal function measurements at baseline (3 days before randomization) and after 26 weeks of treatment using radioactive labeled ¹²⁵I-iothalamate and ¹³¹I-hippuran, as described previously. (3) This method has a day-to-day variation coefficient of 2.5% for GFR and 5% for effective renal plasma flow (ERPF). Renal blood flow was calculated as ERPF/1-hematocrit. Patients were supine during measurements. Venous blood samples were collected on ice and at room temperature. Patients provided 2 consecutive 24-hour urine collections. During each follow-up visit, routine laboratory analyses were performed.

Samples for storage were centrifuged and stored at -80°C. Radionuclide ventriculography was performed on the day of randomization and after 26 weeks of treatment. ECGs were made at baseline, 26 weeks and 34 weeks. (Supplement 2)

LABORATORY ANALYSES

Routine laboratory measurements, including serum creatinine, NT-proBNP, urinary albumin excretion rate and serum electrolytes, were performed on the day of the visit. Estimated GFR was calculated using the 4-variable simplified MDRD formula as validated in HFREF patients. (17) Samples for the determination of PRA, plasma renin concentration, angiotensin II, plasma aldosterone, urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary N-acetyl- β -D-glucosaminidase and urinary Kidney Injury Molecule-1 were first stored at -80°C and analysed shortly after the last patient had completed the study, before unblinding. For a more detailed description of the laboratory tests performed please refer to Supplement 3.

OUTCOME

The primary endpoint was the difference in mean change of renal blood flow from baseline to 26 weeks between the aliskiren-treated and placebo group in the intention-to-treat population. Secondary endpoints were the effect of aliskiren on GFR (measured using ^{125}I -iothalamate clearance), filtration fraction (calculated as GFR/ERPF), glomerular and tubular damage markers, (18) circulating plasma markers for renin-angiotensin-aldosterone-system activity, serum NT-proBNP, LVEF and right ventricular ejection fraction (RVEF), NYHA class, patient and physician global assessment scores, heart rate, blood pressure, and adverse events.

STATISTICAL METHODS

Based on a small cohort study in HFREF patients using ^{125}I -iothalamate and ^{125}I -hippuran clearance measurements, (3) we considered an improvement of > 10% in renal blood flow (55 ml/min (standard deviation 90 mL/min)) clinically meaningful. To obtain a power of $\geq 80\%$ at a two-sided significance level of 0.05, a sample size of 67 patients receiving aliskiren and 33 patients receiving placebo would be sufficient.

The intention-to-treat population consists of all randomized patients who had taken at least one dose of study medication, and had at least one valid post-baseline renal function measurement. The per-protocol population is defined as pa-

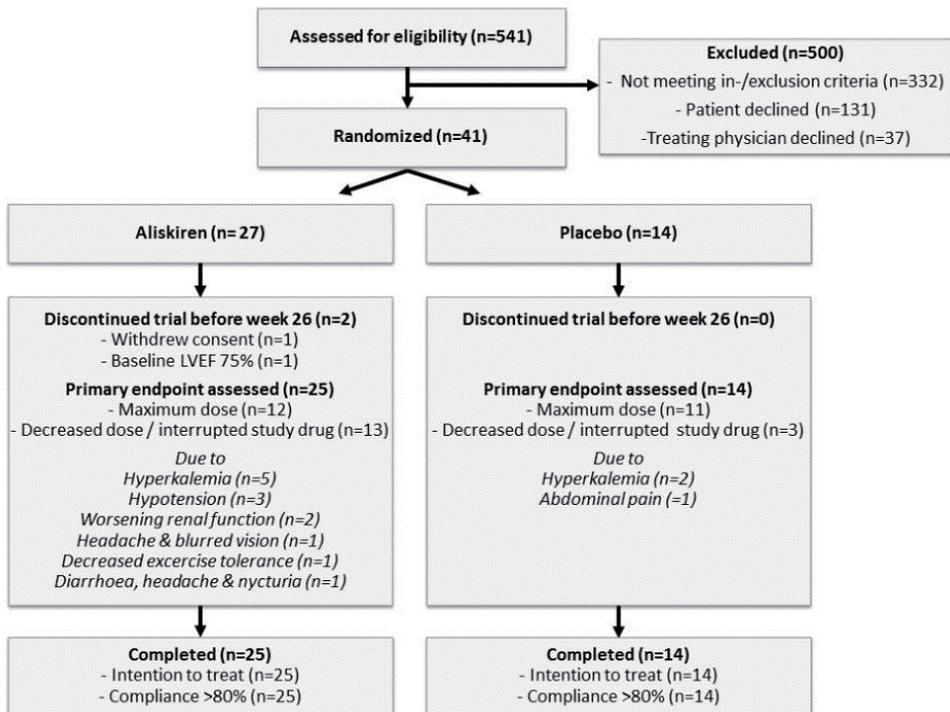
tients in the intention-to-treat population who completed the study at 6 months and were $\geq 80\%$ compliant to study medication. The safety population consists of all randomized patients who received at least one dose of study medication.

Renal blood flow change is expressed as the absolute change from baseline to 6 months. The between-group difference in change from baseline was tested using an analysis of covariance model that included the baseline value as a covariate and factors for treatment and medical center. Change from baseline within the treatment groups was tested using a paired t-test.

For normally distributed secondary outcome parameters, ANOVA was used to test between treatment difference and the Wilcoxon rank-sum test was used for non-normally distributed variables. Changes in parameters were expressed as absolute change from baseline. Skewed variables were log-transformed were appropriate for statistical testing. Differences are presented as percentage change in geometric mean (95% confidence interval). All analyses were done using STATA 12.0.

Between May 2009 and August 2012, 541 HFREF patients were screened and 41 patients included in the ARIANA-CHF-RD trial (Figure 1). Following the early termination of the ALTITUDE trial (19) due to more adverse events in

FIGURE 1: PATIENT DISPOSITION



the aliskiren-treated group, inclusion in the ARIANA-CHF-RD trial was halted and the data safety monitoring board asked to review safety and efficacy data, along with additional information provided by the sponsor of the ALTITUDE trial. Based on the interim efficacy analyses, it was highly unlikely that the primary endpoint (a significant increase in renal blood flow) would be met with 100 patients. The data safety monitoring board advised to a) stop inclusion of new patients in the trial, b) stop study treatment in diabetic patients (no diabetics were receiving study drugs at that time), and c) to complete the study in the remaining subjects. Adverse events in the ARIANA-CHF-RD trial did not raise immediate concerns. The steering committee subsequently endorsed these recommendations.

RESULTS

BASELINE

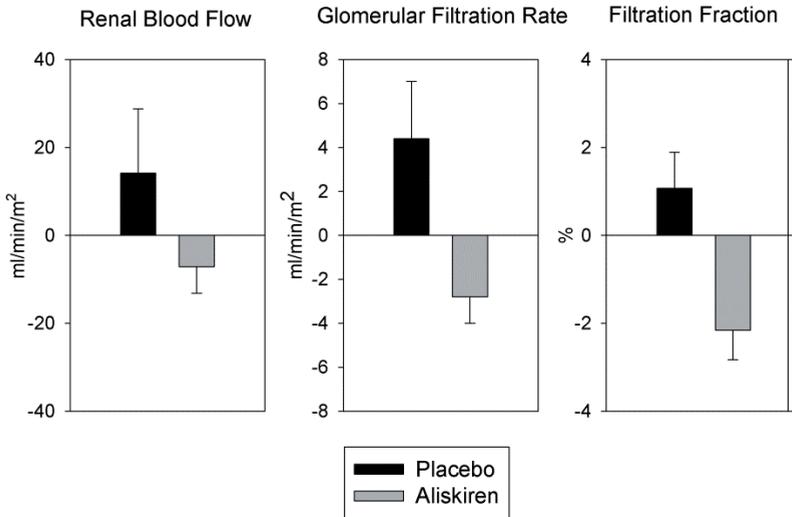
Of the 41 patients included, 14 patients were randomized to placebo and 27 to aliskiren (Figure 1). One patient in the aliskiren group was excluded after the baseline visit, because LVEF was 75% after baseline measurements, while it was $\leq 45\%$ at screening. One patient in the aliskiren group did not attend visits 6 through 8 due to hypotension. This patient stopped the study drug prior to visit 3, after which the complaints resolved. Telephone follow-up was completed, and no other adverse events were reported by this subject. The remaining 39 patients completed the study as planned. Baseline GFR was 49 ± 16 mL/min/1.73m², renal blood flow 294 ± 77 mL/min/1.73m² and LVEF $34 \pm 12\%$, and baseline characteristics were reasonably balanced between the aliskiren and placebo group (Table 1). All patients had $\geq 80\%$ compliance for study medication.

PRIMARY AND SECONDARY OUTCOMES

GFR, RENAL BLOOD FLOW AND FILTRATION FRACTION

Table 2 shows the primary endpoint of the trial. After 26 weeks, there was no significant difference in renal blood flow change between the aliskiren and placebo groups (-7.1 ± 30 versus $+14 \pm 54$ ml/min/1.73m²; $P = 0.16$). However, there was a significant decrease in GFR in the aliskiren versus placebo-treated patients (-2.8 ± 6.0 vs. $+4.4 \pm 9.6$ mL/min/1.73m²; $P = 0.01$) and a greater reduction in filtration fraction (-2.2 ± 3.3 vs. $+1.1 \pm 3.1\%$; $P = 0.01$) (Figure 2). There were no significant differences in tubular damage makers (Table 3).

FIGURE 2: RENAL BLOOD FLOW, GFR, FILTRATION FRACTION CHANGES FROM BASELINE



NEUROHORMONAL CHANGES

102

PRA decreased significantly in the aliskiren group throughout the treatment phase ($P < 0.001$ at week 10 and 26) compared to placebo. Plasma renin concentration increased in the aliskiren group when compared with placebo ($P = 0.033$ at week 10 and $P = 0.039$ at week 26). After washout (treatment withdrawal for 8 weeks) there were no differences between groups in PRA ($P = 0.090$) and plasma renin concentration ($P = 0.836$) (Figure 3). In addition, there were no significant treatment effects on aldosterone, NT-proBNP, plasma and urinary tubular markers, LVEF or RVEF.

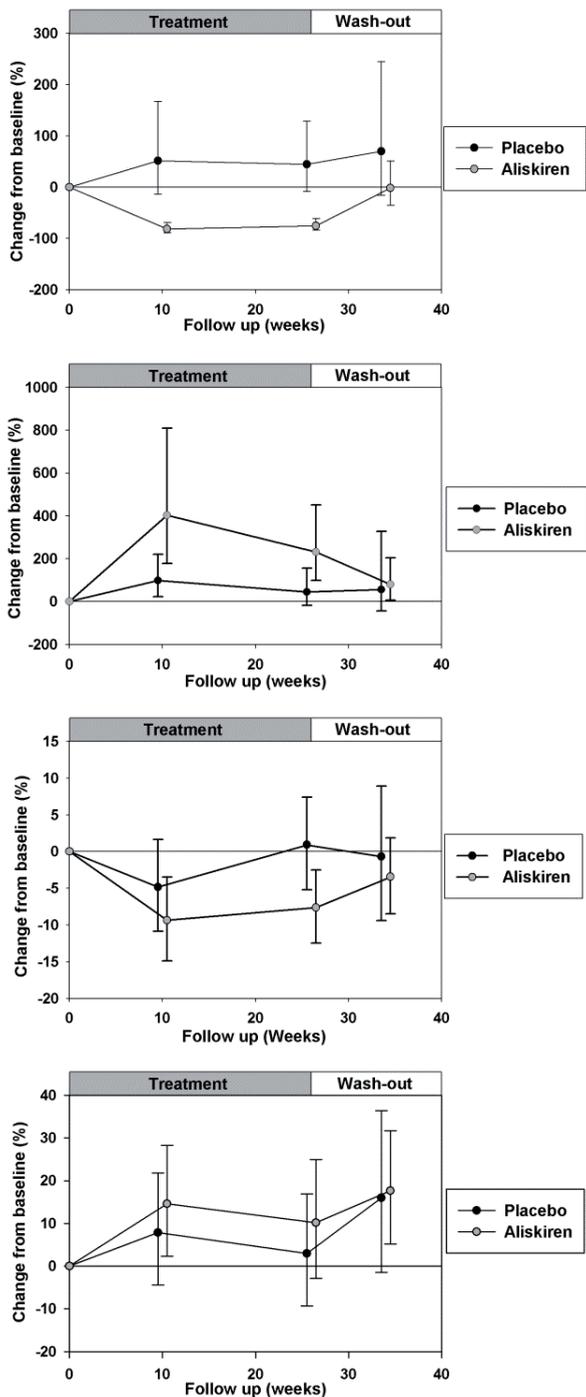
DIABETES

Ten patients with diabetes were included in the trial; two in the placebo and eight in the aliskiren group. There were no significant interactions between treatment and diabetes on the effect on renal blood flow ($P = 0.74$) or change in GFR ($P = 0.75$).

ADVERSE EVENTS

Fifty-six adverse events (4 per patient) occurred in the placebo group and 86 (3.2 per patient) in the aliskiren group ($P = 0.13$) (Table 4). Numerically, more

FIGURE 3: (A) PRA CHANGE FROM BASELINE; (B) PLASMA RENIN CONCENTRATION CHANGE FROM BASELINE; (C) MDRD CHANGE FROM BASELINE; (D) SERUM NGAL CHANGE FROM BASELINE



cases of hypotension, hyperkalemia and worsening renal function occurred in the aliskiren group, and more cases of worsening heart failure, gout and atrial fibrillation or flutter in the placebo group, but none of these difference reached statistical significance. Furthermore, there were no differences in patient global assessments between groups. However, small sample size limits the ability to detect negative treatment effects.

DISCUSSION

We hypothesized that aliskiren, on top of optimal medical therapy including ACEi and/or ARB, would improve renal blood flow in patients with HFREF. However, renal blood flow did not increase, and both filtration fraction and GFR decreased significantly. This confirms additional renin–angiotensin–aldosterone-system inhibiting effects of aliskiren on top of ACEi or ARB, albeit without the expected positive effect on renal blood flow.

Several previous studies have demonstrated that aliskiren can provide additional renin–angiotensin–aldosterone-system blockade on top of an ACEi and/or ARB. (14) In healthy humans and diabetic patients, administration of aliskiren decreased filtration fraction and increased renal blood flow and GFR. (16, 20) It is therefore intriguing that the effects of aliskiren on GFR (and renal blood flow) in our cohort of HFREF patients with moderately decreased GFR seem to point in the opposite direction.

The apparent contrast may have several explanations. First, renal autoregulation is altered in heart failure patients and may become flow-dependent. (21) In our study, a decrease in blood pressure was associated with a decrease in GFR and renal blood flow. This contrasts with findings in healthy subjects, where renal blood flow increased despite a decrease in blood pressure after aliskiren. (16) Normally, when renal blood flow decreases, GFR is preserved by increasing filtration fraction. (2) However, this increase in filtration fraction is limited in the presence of renin–angiotensin–aldosterone-system blockade. (3) Since renal autoregulation itself is often impaired in patients with chronic renal and renovascular disease, (2) additional interference by more stringent renin–angiotensin–aldosterone-system inhibition may have an added deleterious effect on GFR.

It is also possible that the dose of aliskiren was inappropriate; patients were already on maximum tolerated dose of ACEi or ARB when aliskiren was added. The renal effects of aliskiren 300 mg are equivalent to 25 mg captopril or 300 mg irbesartan. (20) This dose may have been too high as add-on therapy. In comparison, add-on spironolactone reduced morbidity and mortality in HFREF patients at doses lower than originally used for treatment of hypertension. (22) In our trial, the drug dose had to be reduced in several patients in the aliskiren group, mostly

because of hyperkalemia, hypotension or worsening renal function. Importantly, these patients remained stable after dose reduction.

It is unclear whether the decrease in renal function is harmful in the long term. A number of ACEi trials have shown that HFREF patients with an initial decrease in GFR show a similar or slower long-term GFR decline, compared to those without. (23-25) Another particularly interesting observation from two trials is that high PRA is associated with increased mortality despite ACEi or ARB treatment. (11) (12) We did observe very pronounced PRA-lowering effects of aliskiren, which may have beneficial extra-renal effects, although no positive effect of aliskiren on clinical endpoints have been demonstrated. Recent studies confirm that administration of a renin inhibitor may worsen renal function in patients with acute heart failure (26) and diabetes, (27) but although increased rates of (reversible) renal dysfunction, hyperkalemia and hypotension were observed, no differences were seen in long-term clinical outcomes so far.

FUTURE DIRECTIONS

Aliskiren provides effective renin–angiotensin–aldosterone-system blockade, even on top of other renin–angiotensin–aldosterone-system blockers, and is currently registered for the treatment of hypertension. The role in HFREF treatment remains unclear. To date, high dose aliskiren on top of ACEi or ARBs has shown disappointing results and considerable side-effects. The ATMOSPHERE trial is currently investigating the effects of aliskiren on clinical outcome in HFREF patients, both as add-on therapy and in head-to-head comparison with enalapril, and may provide a definitive answer. (28) However, even if ATMOSPHERE shows beneficial effects of additive aliskiren therapy, the renal effects of aliskiren demonstrated in our present study need to be recognized.

LIMITATIONS AND STRENGTHS

Our study has several limitations. First, the trial has been stopped before reaching the predetermined sample size. Calculations by two independent statisticians, however, have shown that it is highly unlikely that the outcome would be different had 100 patients been included. Second, many patients had to decrease or interrupt their study drug dose due to adverse events. This may have led to a smaller treatment effect. However, analysis of PRA showed a substantial decrease in all patients receiving aliskiren, despite many subjects receiving less than the maximum dose. Third, no conclusions can be drawn regarding the long-term effects of treatment.

The study also has a number of strengths. Radioactive labeled tracers provide very accurate measurements of renal function. Furthermore, we were able to measure renal blood flow and filtration fraction as well as tubular damage markers in 24h urine and plasma, allowing investigation of many aspects of kidney function and damage. Finally, key measurements were all performed at a single center, avoiding any inter-laboratory differences.

CONCLUSION

In this small phase II trial, addition of aliskiren on top of optimal medication did not improve renal blood flow and resulted in a significant reduction of GFR and filtration fraction in patients with HFREF and reduced GFR.

ACKNOWLEDGEMENTS

We would like to thank the members of the data safety monitoring board dr MP van den Berg, dr N.J.G.M. Veeger, dr R.T. Gansevoort and dr E.R. van den Heuvel for their critical appraisal of the trial.

106

DISCLOSURES

This trial was sponsored by an investigational grant of Novartis AG. AV received consultancy fees and research grants from Novartis Pharma AG. WG received funding and speakers fee from Novartis Pharma AG. DV has received Board membership fees from Novartis Pharma AG. The remaining authors report no disclosures with regards to this manuscript.

REFERENCES

1. Braam B, Cupples WA, Joles JA, Gaillard C. Systemic arterial and venous determinants of renal hemodynamics in congestive heart failure. *Heart Fail Rev.* 2012;17:161-75.
2. Palmer BF. Renal dysfunction complicating the treatment of hypertension. *N Engl J Med.* 2002;347:1256-61.
3. Smilde TD, Damman K, van der Harst P, et al. Differential associations between renal function and “modifiable” risk factors in patients with chronic heart failure. *Clin Res Cardiol.* 2009;98:121-9.
4. Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation.* 2000;102:203-10.
5. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation.* 1986;73:257-67.

6. Swedberg K, Eneroth P, Kjeksus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS trial study group. *Circulation*. 1990;82:1730-6.
7. Damman K, Valente MAE, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: An updated meta analysis. *Eur Heart J*. 2013.
8. Braam B, Koomans HA. Renal responses to antagonism of the renin-angiotensin system. *Curr Opin Nephrol Hypertens*. 1996;5:89-96.
9. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. collaborative group on ACE inhibitor trials. *JAMA*. 1995;273:1450-6.
10. Lee VC, Rhew DC, Dylan M, Badamgarav E, Braunstein GD, Weingarten SR. Meta-analysis: Angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. *Ann Intern Med*. 2004;141:693-704.
11. Latini R, Masson S, Anand I, et al. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in val-HeFT. *Eur Heart J*. 2004;25:292-9.
12. Szymanski MK, Damman K, van Veldhuisen DJ, van Gilst WH, Hillege HL, de Boer RA. Prognostic value of renin and prorenin in heart failure patients with decreased kidney function. *Am Heart J*. 2011;162:487-93.
13. de Boer RA, Schrotten NF, Bakker SJ, et al. Plasma renin and outcome in the community: Data from PREVEND. *Eur Heart J*. 2012;33:2351-2359.
14. McMurray JJ, Pitt B, Latini R, et al. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail*. 2008;1:17-24.
15. Seed A, Gardner R, McMurray J, et al. Neurohumoral effects of the new orally active renin inhibitor, aliskiren, in chronic heart failure. *Eur J Heart Fail*. 2007;9:1120-7.
16. Fisher ND, Jan Danser AH, Nussberger J, Dole WP, Hollenberg NK. Renal and hormonal responses to direct renin inhibition with aliskiren in healthy humans. *Circulation*. 2008;117:3199-205.
17. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. *Circulation*. 2006;114:1572-80.
18. Damman K, Masson S, Hillege HL, et al. Clinical outcome of renal tubular damage in chronic heart failure. *Eur Heart J*. 2011;32:2705-12.
19. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367:2204-13.
20. Hollenberg NK, Fisher ND, Nussberger J, Moukarbel GV, Barkoudah E, Danser AH. Renal responses to three types of renin-angiotensin system blockers in patients with diabetes mellitus on a high-salt diet: A need for higher doses in diabetic patients? *J Hypertens*. 2011;29:2454-61.
21. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure. relationship of cardiac index to kidney function. *Drugs*. 1990;39 Suppl 4:10,21; discussion 22-4.
22. Batterink J, Stabler SN, Tejani AM, Fowkes CT. Spironolactone for hypertension. *Cochrane Database Syst Rev*. 2010; (8):CD008169. doi:CD008169.
23. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. *Circ Heart Fail*. 2011;4:685-91.

24. Hillege HL, van Gilst WH, van Veldhuisen DJ, et al. Accelerated decline and prognostic impact of renal function after myocardial infarction and the benefits of ACE inhibition: The CATS randomized trial. *Eur Heart J*. 2003;24:412-20.
25. Lesogor A, Cohn JN, Latini R, et al. Interaction between baseline and early worsening of renal function and efficacy of renin-angiotensin-aldosterone system blockade in patients with heart failure: Insights from the val-HeFT study. *Eur J Heart Fail*. 2013.
26. Gheorghiade M, Bohm M, Greene SJ, et al. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: The ASTRO-NAUT randomized trial. *JAMA*. 2013;309:1125-35.
27. Parving HH, Brenner BM, McMurray JJ, et al. Aliskiren trial in type 2 diabetes using cardio-renal endpoints (ALTITUDE): Rationale and study design. *Nephrol Dial Transplant*. 2009;24:1663-71.
28. Krum H, Massie B, Abraham WT, et al. Direct renin inhibition in addition to or as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: Rationale and design of the aliskiren trial to minimize OutcomeS in patients with HEart failuRE (ATMOSPHERE) study. *Eur J Heart Fail*. 2011;13:107-14.

SUPPLEMENTARY MATERIALS

SUPPLEMENT 1. INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

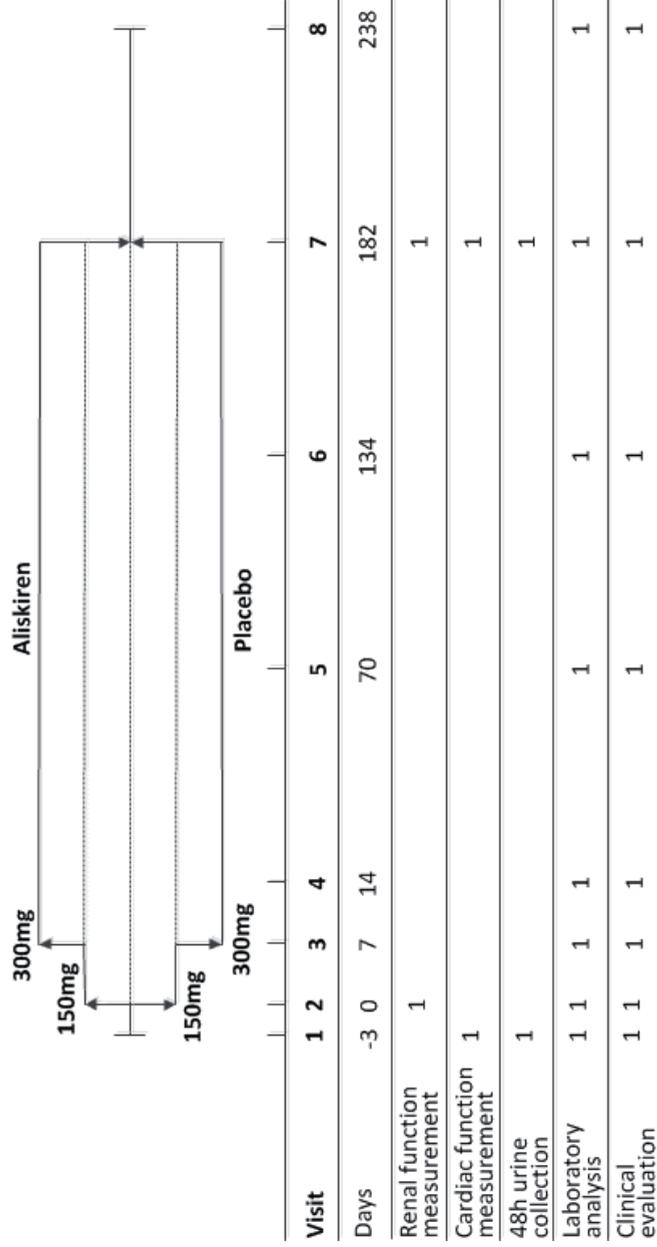
- Outpatients ≥ 18 years of age, male or female.
- Patients with a diagnosis of chronic heart failure (NYHA Class II-IV)
- LVEF $\leq 45\%$ at visit 1 (local measurement, measured within the past 6 months assessed by echocardiogram, MUGA or ventricular angiography)
Amendment (June 2011): LVEF $\leq 45\%$ at visit 1 (local measurement, measured within the past 6 months assessed by echocardiogram, MUGA or ventricular angiography)
Or, if more than 6 months ago, in a stable phase and at least 6 months after myocardial infarction)
- Estimated GFR between 30 and 60 ml/min/1.73m² as measured by the MDRD formula
Amendment (June 2011): Estimated GFR between 30 and 75 ml/min/1.73m² as measured by the MDRD formula
- Patients must be treated with an ACE inhibitor at a stable dose (enalapril 10 mg daily at least or any other ACE inhibitor, e.g. ramipril, quinapril, lisinopril, fosinopril, perindopril, trandolapril on equivalent doses, or maximum tolerated dose) or, if intolerant to ACE inhibitors, with ARB therapy (candesartan 32 mg daily or any other ARB in equivalent dose, or maximum tolerated dose) for at least 4 weeks prior to visit 1.
Amendment (June 2011): Patients must be treated with an ACE inhibitor at a stable dose (enalapril 10 mg daily at least or any other ACE inhibitor, e.g. ramipril, quinapril, lisinopril, fosinopril, perindopril, trandolapril on equivalent doses, or maximum tolerated dose) or, if intolerant to ACE inhibitors, with ARB therapy (candesartan 16 mg daily or any other ARB in equivalent dose, or maximum tolerated dose) for at least 4 weeks prior to visit 1.
- Patients must be treated with a beta blocker unless contraindicated or not tolerated at a stable dose for at least 4 weeks prior to visit 1 (for patients not on target dose or in absence of that medication, the reason should be documented).

Exclusion criteria

- History of hypersensitivity to any of the study drugs.
- Patients treated concomitantly with both ARB and aldosterone antagonist.
Amendment (November 2009) Treatment with triple RAAS blockade (ACEi, ARB and aldosterone antagonist) or strong P-gp inhibitors.

- Current acute decompensated heart failure (HF).
 - Symptomatic hypotension at randomisation.
 - Acute cardiovascular events within the past 3 months.
 - Coronary or carotid artery disease likely to require surgical or PCI.
 - Right heart failure due to severe pulmonary disease.
 - Diagnosis of peripartum or chemotherapy induced cardiomyopathy within the last year.
 - Patients with a history of heart transplant or who are on a transplant list or with a left ventricular assistance device.
 - Untreated ventricular arrhythmia with syncope episodes within past 3 months.
 - Documented history of ventricular tachycardia or ventricular fibrillation without ICD.
 - Symptomatic bradycardia, second or third degree heart block without a pacemaker.
 - Implantation of a cardiac resynchronization therapy device within prior 3 months.
 - Presence of a hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to left ventricular dilatation.
 - Presence of hemodynamically significant obstructive lesions of left ventricular outflow tract.
 - Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs.
 - Serum potassium ≥ 5.2 mEq/L at the randomisation visit.
 - Presence of a disease with a life expectancy of < 5 years.
 - Current double-blind treatment in an investigational drug study within the past 30 days.
 - Any surgical or medical condition that in the opinion of the investigator or medical monitor would jeopardize the evaluation of efficacy or safety.
 - History of noncompliance and patients who are considered potentially unreliable.
 - Pregnant or nursing (lactating) women and women of child-bearing potential.
 - Long-term NSAIDs or COX2 inhibitor use, except aspirin at doses used for CV prophylaxis.
 - Treatment with a direct renin inhibitor, intravenous vasodilators and/or inotropic drugs
-

SUPPLEMENT 2 – STUDY DIAGRAM



SUPPLEMENT 3 – LABORATORY ANALYSES

PRA is expressed as ng/mL/h of generated Angiotensin-I and was measured using an enzymatic assay with radioactive tracers (Sigma-Aldrich Life Science Products, St. Louis, MO). The detection limit is 0.1 ng/ml/h, with an interassay coefficient of variation (CV) 16.6% at pH 6.0 and 37°C. PRC was measured using a radioimmunometric assay kit for the quantitative determination of renin mass/volume (Cisbio, Codolet, France) with a detection limit of 1.0 ng/L; interassay CV 5.7%. Plasma aldosterone concentration was measured using a solid phase ¹²⁵I radioimmunoassay (Siemens Medical Solutions USA, Inc, Malvern, PA) intra-assay CV below 5.4%, interassay CV below 15.7%. NGAL was determined by means of ELISA (R&D systems, Minneapolis, MN). Urine samples were diluted 100 times in 0.1% BSA-PBS buffer. The median CV of the NGAL ELISA was 9.3%.

KIM-1 was determined in urine samples by means of ELISA (R&D systems, Minneapolis, MN). Urine samples were diluted two times in 0.1% BSA-PBS buffer. The median CV of the KIM-1 ELISA was 9.0%. NGAL was determined in urine samples by means of ELISA (R&D systems, Minneapolis, MN). Urine samples were diluted 100 times in 0.1% BSA-PBS buffer. The median CV of the NGAL ELISA was 9.3%. NAG was determined by means of a substrate assay in urine samples diluted six times in substrate solution. The enzyme NAG converts substrate p-nitrophenyl N-acetyl-β-D-glucosaminidase at pH 4.5. After 60 minutes at 37°C, 1 M Na₂CO₃ was added to the mixture to terminate the reaction and to develop a yellow colour released from the converted substrate. This colour was measured at 400 nm by a microtiter plate reader. The median CV of the NAG assay was 17.5%. All urinary kidney injury markers were corrected for urinary creatinine levels.

