Spironolactone dose in Heart Failure with Preserved Ejection Fraction: findings from TOPCAT

João Pedro Ferreira[1]; Xavier Rossello[2]; Stuart J. Pocock[3]; Patrick Rossignol[1]; Brian L. Claggett[4]; Jean-Lucien Rouleau[5]; Scott D. Solomon[4]; Bertram Pitt[6]; Marc A. Pfeffer[4]; Faiez Zannad[1]

Affiliations:

[1] Université de Lorraine, Centre d'Investigation Clinique-Plurithématique, CHRU Nancy, INSERM U1116, and FCRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists) , Nancy, France.

[2] Department of Cardiology, Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain; Department of Cardiology, Health Research Institute of the Balearic Islands (IdISBa), University Hospital Son Espases, Palma, Spain

[3] London School of Hygiene and Tropical Medicine, London, United Kingdom.

[4] Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States.

[5] Montreal Heart Institute, Montreal, Quebec, Canada.

[6] Department of Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan.

Contact to:

João Pedro Ferreira, MD, PhD

Centre d'Investigation Clinique-Plurithématique, CHRU Nancy

4 Rue du Morvan, 54500 Vandœuvre-Lès-Nancy

Tel : +33 (0) 3 83 15 73 15

Fax : +33 (0) 3 83 15 73 24

Mail : j.ferreira@chru-nancy.fr

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejhf.1909

Abstract

Background: Spironolactone up-titration may be limited by side effects that could be minimized at lower than target doses, whether lower than target doses remain efficacious is unknown. In TOPCAT, spironolactone (or placebo) were started at 15mg/day, and increased up to a maximum of 45mg/day. The prognostic implications related to spironolactone dose are is yet to be reported.

Aims: To assess the average spironolactone/placebo doses provided during the trial, overall and within "high-risk" subgroups (e.g. elderly, renal dysfunction, high potassium); discontinuation rates; and the efficacy of lower than target doses in HFpEF.

Methods: 1767 patients from "TOPCAT-Americas" were included. Linear, logistic and Cox regressions were applied.

Results: Patients randomized to spironolactone received lower doses than placebo: 22.5 (15.0-27.5)mg/day vs. 27.5 (17.5-27.5)mg/day; $p<0.001$. Patients aged≥75years, with an eGFR≤60ml/min/1.73m^2, and with a K^+>4.5 mmol/L, received lower spironolactone doses (median≈20mg/day). This pattern of dose-differences was not observed in patients taking placebo, where the between-subgroup placebo doses were similar (spironolactone-placebo by subgroup interaction$_p$<0.05). Among patients taking spironolactone, 25.4% discontinued the drug during the first year, compared with 18.3% of the patients taking placebo; $p<0.001$. The discontinuation rates in the aforementioned "high-risk" subgroups reached 30% during the first year. Spironolactone reduced the primary outcome of HFH/CVD without significant heterogeneity between the studied subgroups (interaction$_p$>0.1). Spironolactone discontinuation was associated with a 2 to 4-fold higher risk of subsequent events.

Conclusion: Spironolactone (but not placebo) was used at lower doses among the elderly, those with renal dysfunction and with higher potassium levels. The effect of spironolactone was homogenous across these subgroups. In patients unable to tolerate "target" doses, a low-dose strategy should be preferred to stopping treatment.

Key-words: spironolactone; heart failure with preserved ejection fraction; mean dose; discontinuation; treatment effect.

Introduction

The updated ACC/AHA/HFSA heart failure (HF) guidelines, give spironolactone a class of recommendation IIb ("weak benefit") with a B-R ("moderate-quality randomized evidence") level of evidence for treating patients with heart failure and preserved ejection fraction (HFpEF) in the absence of contra-indication[1]. This recommendation is based upon the results of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, that compared spironolactone with placebo in HFpEF, showing a small reduction in the primary composite outcome of cardiovascular death, aborted cardiac arrest, and HF hospitalization, not reaching statistical significance, but showing a reduction in HF hospitalizations[2]. Importantly, major geographical variations were found in TOPCAT, whereby patients randomized in Eastern Europe had low event-rates, no spironolactone effect on blood pressure or potassium levels, and low or non-detectable levels of spironolactone metabolites in the blood[3-6]. In a *post hoc* analysis with patients from "the Americas", spironolactone effectively reduced the rate of the primary outcome and its individual components including cardiovascular death[3].

In TOPCAT, spironolactone (or placebo) were started at a dose of 15 mg/day, and after 4 weeks, the dose should be increased to 30 mg/day if all safety parameters were acceptable. In the event that the subject continued to have ongoing HF symptoms, the investigator had the option to increase the dose up to 45 mg/day at 4 months[2]. In patients with heart failure with reduced ejection fraction (HFrEF) and based on findings from RALES (The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure)[7], current guidelines recommend spironolactone doses of 25 mg/day, titrated and maintained at 50 mg/day whenever possible. The corresponding

maintenance dose of eplerenone is 50 mg/day[1, 8]. In the EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms) trial, eplerenone dose was stratified according to renal function, where patients with an estimated glomerular filtration rate (eGFR) below 50ml/min/1.73m2 received up to 25mg/day of eplerenone, whereas patients with higher eGFR received up to 50mg/day[9]. This stratified analysis showed that the treatment effect was consistent regardless of the eGFR-dose stratum, still more patients with impaired renal function experienced more side effects, such as hyperkalemia, despite receiving lower eplerenone doses[10].

After TOPCAT, guidelines do not provide specific dose recommendations for HFpEF; however, it may be assumed that the doses should be within the dose-range used in TOPCAT i.e., between 15 and 45 mg/day[1]. These doses are not currently commercialized and in TOPCAT some patient-subgroups might have received low doses and/or have experienced more adverse events.

In this study we sought to assess the spironolactone (and placebo) dose provided during the trial, overall and within subgroups of interest (e.g. elderly, female, those with renal impairment or higher baseline potassium levels). Additionally, we aim to assess the discontinuation rates and treatment effects. The background hypothesis is that if patients in these subgroups of interest took lower spironolactone doses and, despite this, had similar treatment benefit, then one can hypothesize that the minimum tolerated dose is better than stopping treatment or force up-titration, which may increase side-effects and drug discontinuation.

Methods

Study design and participants

The detailed methods of TOPCAT have been previously described[2]. In short, TOPCAT enrolled 3445 patients with symptomatic HF and a left ventricular ejection fraction (LVEF) ≥45% who were randomly assigned to spironolactone (15 to 45 mg daily) or matching placebo. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure[2]. The median (pct_{25-75}) follow-up time was 2.9 (1.9-4.2) years.

TOPCAT was conducted in accordance with the Declaration of Helsinki and approved by all site ethics committees. All participants gave written informed consent to participate in the study.

In TOPCAT the subset patients who both had event rates compatible with HFpEF, had spironolactone side-effects and adequate levels of spironolactone circulating metabolites were those from “the Americas”; hence, consistently with previous reports, this analysis is limited to this subset (n =1767)[3, 4, 11, 12].

Subgroups of interest

The following subgroups were selected for dose comparison: sex was chosen because a recent observational report suggesting that women with HF could respond to lower doses of ACEi/ARBs and beta-blockers compared to men[13]; age, renal function, diabetes, and baseline potassium levels were selected because these are identified "high-risk" subgroups who may be prone to adverse events from mineralocorticoid receptor antagonist (MRA) therapy[14-16]; body mass index, blood pressure and ACEi/ARBs treatment were also selected due to their potential influence on prognosis and MRA dose[17-20].

Statistical analyses

Spironolactone and placebo doses were summarized with medians, means and the respective percentile 25 to 75 range and standard deviations. The average dose was obtained by computing the sum of the spironolactone doses for each patient at each study visit and dividing it by the number of study visits. For the between-group comparison of the doses, Mann-Whitney rank-sum tests were used. To assess if the differences of the doses were different across the subgroups of interest, we performed an interaction test from a linear regression model with the spironolactone-placebo dose as dependent variable and the subgroup plus an interaction term of treatment by subgroup as independent variables. We report the mean doses during the first year of follow-up for each patient as only about 10% of missing dose values were present during this time-period; the doses during the entire follow-up are also presented in the supplement, however the proportion of missing values greatly increased after the first follow-up year (see also the *Supplemental Table 1*). The proportion of spironolactone or placebo discontinuation and the studied sided effects are reported with absolute numbers and proportions and compared using Chi-square tests. To assess if the differences in discontinuation and side effects found between the subgroups of interest were significantly different, we performed an interaction test from a logistic regression model with discontinuation or side effect as dependent variable and the subgroup plus a treatment by subgroup interaction term as independent variables. Logistic regression models were used to assess the determinants of spironolactone up-titration during the first month. Cox proportional hazards' models were used to explore the association between spironolactone treatment and the study primary outcome. The treatment effect estimates are presented with hazard ratios (HRs) and their respective 95% confidence interval (95%CI). To assess whether the treatment effect could vary by subgroup of interest we performed interaction tests between the treatment and the subgroup of interest. Time-updated models were used to study the associations between spironolactone (or placebo) discontinuation and subsequent outcomes. Landmark analyses

were performed to assess the association between spironolactone (or placebo) 4-week up-titration and subsequent outcomes. Statistical analyses were performed using the STATA/SE software, version 16.0 (Stata Corp, College Station, TX, USA).

Results

Spironolactone and placebo doses

As previously reported[3], the median age was 72 (64-79) years, 41% were aged 75 or older, 50% were female, the median body mass index (BMI) was 32 (28-38) kg/m^2, 45% had diabetes, 79% were treated with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker (ACEi/Arb), 48% had chronic kidney disease (CKD), the median eGFR was 61 (49-77) ml/min/1.73m^2, the median potassium (K^+) was 4.2 (3.9-4.5) mmol/L, the median systolic blood pressure (SBP) was 129 (118-138) mmHg, and the median LVEF was 58 (53-64)%.

Patients randomized to spironolactone received lower doses than placebo. Overall, the median (pct_{25-75}) / mean±sd dose during 1-year follow-up was 27.5 (17.5-27.5) / 23.9±8.6 mg/day in the placebo group vs. 22.5 (15.0-27.5) / 21.1±9.3 mg/day in the spironolactone group; p <0.001. *Table 1*, *Figure 1 & Supplemental Figure 1*.

In subgroups, women and men, diabetics and non-diabetics, those with a SBP below or above 120 mmHg, and those taking or not an ACEi/ARBs received similar spironolactone and placebo doses. *Table 1*. Patients with a BMI of 30 kg/m^2 or less received lower spironolactone doses than those with a BMI >30 kg/m^2; but without significant statistical heterogeneity vs. patients receiving a placebo ($interaction_p$ =0.52). Patients, aged 75 years or older, with an eGFR of 60 ml/min/1.73m^2 or less, and those with a baseline K^+ above 4.5 mmol/L, received lower spironolactone doses than patients aged less than 75 years, with an eGFR above 60 ml/min/1.73m^2, and with a K^+ of 4.5 mmol/L or less, respectively; with significant statistical heterogeneity vs. patients receiving the placebo ($interaction_p$ <0.05).

In patients taking the placebo the between-subgroup placebo doses were similar and the dose-difference pattern observed in patients taking spironolactone was not observe in those taking the corresponding placebo. *Table 1* & *Figure 2*.

Similar findings were observed during the first year at equally spaced time-points (4, 8 and 12 months) (*Supplemental Table 2*), and throughout the entire follow-up, where even lower doses were administered. *Supplemental Table 3* (it should be noted that these findings including data from the

entire follow-up period may be biased by a large proportion of missing values and drug discontinuation).

Spironolactone and placebo discontinuation

Among patients taking spironolactone, 25.4% discontinued the drug during the first year of the trial, compared with 18.3% of the patients taking placebo; p <0.001. *Table 2*. Again, patients aged 75 or older, and especially those with an eGFR of 60 ml/min/1.73m^2 or less, and K^+ above 4.5 mmol/L were more likely to permanently stop the drug, with discontinuation rates reaching 30% or more compared with 18% in the placebo group (interaction$_p$ <0.05 for eGFR and K^+). *Table 2*.

The main reported discontinuation reasons were hyperkalemia, worsening renal function and off-label MRA use. *Supplemental Table 4*.

Determinants of treatment up-titration at 4 weeks

During the first month, 531 (30.0%) of the patients were not up-titrated to 30 mg/day. Patients without successful up-titration were more likely to be older, have lower eGFR, a BMI ≤30 Kg/m^2, and a SBP ≤120 mmHg. *Supplemental Table 5*. Patients without successful up-titration did not experience higher event rate, nor the risk was modified by the randomized treatment allocation (spironolactone or placebo). *Supplemental Table 6*.

Treatment effect

As previously reported[3], spironolactone reduced the primary outcome of HF hospitalization or cardiovascular death without significant heterogeneity between the studied subgroups (interaction$_p$ >0.1 for all). *Supplemental Table 7*.

Side effects

Patients taking spironolactone experienced more often WRF and hyperkalemia episodes during the follow-up. Diabetes was a risk factor for both WRF and hyperkalemia. Females also had more WRF episodes; and patients with eGFR ≤60ml/min/1.73m^2, those with baseline K^+ >4.5 mmol/L, those taking ACEi/ARB and with SBP >120 mmHg also had more hyperkalemia episodes. *Table 3*.

Time-updated outcomes after treatment discontinuation

Treatment discontinuation was associated with a 2 to 4-fold higher risk of major cardiovascular events in adjusted models. *Table 4*. Compared with placebo, the risk was higher after spironolactone discontinuation, although the interaction test did not reach statistical significance. Primary outcome example: HR (95%CI) for placebo =1.63 (1.22-2.18) & HR (95%CI) for spironolactone =2.28 (1.72-3.02); interaction p =0.13. *Table 4 (legend)*.

Discussion

The present study shows that spironolactone (but not placebo) was used at lower doses among the elderly, those with impaired renal function and with higher potassium levels at baseline. Most of these patients received around 20 mg of spironolactone per day within the first year of follow-up, and around 15 mg per day if one considers the entire follow-up. These patients had more adverse events and discontinued the treatment more often. Nonetheless, the effect of spironolactone was homogenous across these subgroups. These findings suggest that spironolactone doses inferior to 25 mg/day (around 15 to 20 mg/day) may be used in HFpEF, particularly in "high-risk" patients that may not tolerate higher doses. Keeping the patients on-treatment (even with lower than recommended doses) seems preferable to stopping treatment, as the latter may increase the risk of subsequent events (*Central Illustration*). It should also be highlighted that other subgroups such as men/women, diabetes/no-diabetes, ACEi/ARB treatment/no-ACEi/ARB treatment received similar spironolactone doses.

Differently from ACEi/ARBs and β-blockers in which randomized trials compared different doses of these drugs[21-26], no trials have compared different MRA doses. So far, the best available evidence comes from the EMPHASIS-HF trial, where patients were stratified to different eplerenone-placebo doses according to renal function[10]. Despite receiving lower eplerenone-placebo doses, patients with impaired renal function experience more side-effects; however, the treatment effect was not modified by treatment dose/renal function (interaction$_p$ =0.89). Hence, this stratified evidence strongly support the use of lower (≈25 mg/day) eplerenone doses in patients with HFrEF and impaired renal function. This way, the beneficial effect of the treatment is preserved, while excessive dose-related side-effects can be potentially avoided. Secondary non-stratified analyses of the TOPCAT trial suggest that elderly patients, those with impaired renal function and higher potassium levels experience more adverse events and have higher rates of drug discontinuation without treatment effect heterogeneity between these subgroups[11, 27]. The data depicted in the present report show that the spironolactone doses given to the elderly, to those with impaired renal function and with higher baseline potassium are lower than the doses given to the younger, with better renal function and with lower potassium levels. Importantly, the placebo doses were similar between these subgroups, strongly supporting the inability for titrating spironolactone to higher doses due to side effects and intolerance. During the first follow-up year, the median dose among these "high-risk" subgroups was around 20 mg/day; and, importantly, the treatment discontinuation rates reached nearly 30% for

spironolactone vs. 18% for placebo in these subgroups. Discontinuation rates reaching 30% of the patients may seriously compromise the effect of the treatment that is aimed to improve medium-to-long term outcomes, including repeated hospitalizations[28]. Furthermore, spironolactone discontinuation was associated with a subsequent high rate of adverse cardiovascular events. These findings support the continuation of spironolactone, even at lower doses (15-20 mg/day) if patients cannot tolerate higher doses. Furthermore, patients without successful up-titration during the 4-week optimization period, did not experience higher event rate, nor the risk was modified by the randomized treatment allocation, supporting the notion that lower than target doses may also be effective. Strategies aimed at enabling an adequate drug maintenance and potential up-titration of the inhibitors of the renin-angiotensin-aldosterone system, such as potassium-binders[29], may be important to improve outcomes of HF patients; however, adequately powered outcome trials to assess the efficacy and safety of such a strategy are yet to be performed[30]. Furthermore, newer generation MRAs may be better tolerated than spironolactone[31]. However, these molecules also need to show that they are, at least, non-inferior to spironolactone. Despite these advances, it is likely that spironolactone will remain the most widely used MRA, mainly because it is affordable, widely available, and with a large and long clinical experience[32]. Still, MRAs are generally underused, even in populations who might experience great benefit[33]. With regard to dose adaptations, and until further evidence is available, it seems reasonable to adapt the spironolactone dose according to renal function and potassium levels based on an algorithm that has been used in clinical trials (*Supplemental Table 8*). Notwithstanding, the data suggest that having lower spironolactone dose is better than stopping the drug, and efforts should be placed in order to keep patients` on-treatment.

Limitations

This is a post-hoc analysis of a randomized controlled trial, thus these findings are subject to the bias of observational studies, such as the impossibility to infer causality. From the CRF we could not ascertain the exact reasons for study discontinuation in all patients; however, the provided reasons (e.g. renal dysfunction and hyperkalemia) are expected and consistent with the previous reports. From these data, one cannot infer which spironolactone dose is more adequate; one can only say that many patients did not reach the target of dose of 45 mg/day, especially among those in the aforementioned "high-risk" subgroups that received less than half of the recommended dose. As the treatment effect was consistent in these subgroups, one may suppose that lower doses are probably as efficient and could avoid some side-effects. Contrary to the EMPHASIS-HF trial (that had a prespecified eplerenone dose stratification by renal function)[10], the TOPCAT trial assumed *a priori* that all patients

should achieve similar spironolactone (or placebo) doses, hence the findings reported herein do not represent randomized evidence and should be regarded as hypothesis-generating. The association of spironolactone discontinuation and subsequent outcomes likely reflects the underlying patients` risk rather than the direct treatment effect and, therefore, causality cannot be inferred. This study does not compare "high vs. low" doses, instead it simply reports the "average" doses. To ascertain the optimal spironolactone dose for patients with HFpEF (including the dose for "high-risk" subgroups), prospective, randomized and adequately powered studies will be required.

Conclusions

Spironolactone (but not placebo) was used at lower doses among the elderly, those with impaired renal function and higher potassium levels at baseline. Most of these patients received around 20 mg of spironolactone per day within the first year of follow-up, which was less than half of the target dose. These patients had more adverse events and discontinued the treatment more often. Despite the lower treatment doses and higher discontinuation rates, the effect of spironolactone was homogenous across these subgroups. These findings suggest that patients unable to tolerate target doses of spironolactone may benefit from lower doses that are possibly better tolerated while maintaining efficacy. A low-dose strategy should be preferred to stopping the treatment.

Funding

None.

Disclosures

None.

Acknowledgments

JPF, PR, FZ are supported by the French National Research Agency Fighting Heart Failure (ANR-15-RHU-0004), by the French PIA project "Lorraine Université d'Excellence" GEENAGE (ANR-15-IDEX-04-LUE) programmes, and the Contrat de Plan Etat Région Lorraine and FEDER IT2MP. X.R. has received support from the SEC-CNIC CARDIOJOVEN fellowship program.

References

1. Yancy, C. W.; Jessup, M.; Bozkurt, B.; Butler, J.; Casey, D. E., Jr.; Colvin, M. M.; Drazner, M. H.; Filippatos, G. S.; Fonarow, G. C.; Givertz, M. M.; Hollenberg, S. M.; Lindenfeld, J.; Masoudi, F.

A.; McBride, P. E.; Peterson, P. N.; Stevenson, L. W.; Westlake, C., 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* **2017,** *70* (6), 776-803.

2. Pitt, B.; Pfeffer, M. A.; Assmann, S. F.; Boineau, R.; Anand, I. S.; Claggett, B.; Clausell, N.; Desai, A. S.; Diaz, R.; Fleg, J. L.; Gordeev, I.; Harty, B.; Heitner, J. F.; Kenwood, C. T.; Lewis, E. F.; O'Meara, E.; Probstfield, J. L.; Shaburishvili, T.; Shah, S. J.; Solomon, S. D.; Sweitzer, N. K.; Yang, S.; McKinlay, S. M., Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* **2014,** *370* (15), 1383-92.

3. Pfeffer, M. A.; Claggett, B.; Assmann, S. F.; Boineau, R.; Anand, I. S.; Clausell, N.; Desai, A. S.; Diaz, R.; Fleg, J. L.; Gordeev, I.; Heitner, J. F.; Lewis, E. F.; O'Meara, E.; Rouleau, J. L.; Probstfield, J. L.; Shaburishvili, T.; Shah, S. J.; Solomon, S. D.; Sweitzer, N. K.; McKinlay, S. M.; Pitt, B., Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. *Circulation* **2015,** *131* (1), 34-42.

4. de Denus, S.; O'Meara, E.; Desai, A. S.; Claggett, B.; Lewis, E. F.; Leclair, G.; Jutras, M.; Lavoie, J.; Solomon, S. D.; Pitt, B.; Pfeffer, M. A.; Rouleau, J. L., Spironolactone Metabolites in TOPCAT - New Insights into Regional Variation. *N Engl J Med* **2017,** *376* (17), 1690-1692.

5. Ferreira, J. P.; Girerd, N.; Rossignol, P.; Zannad, F., Geographic differences in heart failure trials. *Eur J Heart Fail* **2015**.

6. Tromp, J.; Ferreira, J. P.; Janwanishstaporn, S.; Shah, M.; Greenberg, B.; Zannad, F.; Lam, C. S. P., Heart failure around the world. *Eur J Heart Fail* **2019**.

7. Pitt, B.; Zannad, F.; Remme, W. J.; Cody, R.; Castaigne, A.; Perez, A.; Palensky, J.; Wittes, J., The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* **1999,** *341* (10), 709-17.

8. Ponikowski, P.; Voors, A. A.; Anker, S. D.; Bueno, H.; Cleland, J. G.; Coats, A. J.; Falk, V.; Gonzalez-Juanatey, J. R.; Harjola, V. P.; Jankowska, E. A.; Jessup, M.; Linde, C.; Nihoyannopoulos, P.; Parissis, J. T.; Pieske, B.; Riley, J. P.; Rosano, G. M.; Ruilope, L. M.; Ruschitzka, F.; Rutten, F. H.; van der Meer, P., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* **2016**.

9. Zannad, F.; McMurray, J. J.; Krum, H.; van Veldhuisen, D. J.; Swedberg, K.; Shi, H.; Vincent, J.; Pocock, S. J.; Pitt, B., Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* **2011,** *364* (1), 11-21.

10. Ferreira, J. P.; Abreu, P.; McMurray, J. J. V.; van Veldhuisen, D. J.; Swedberg, K.; Pocock, S. J.; Vincent, J.; Lins, K.; Rossignol, P.; Pitt, B.; Zannad, F., Renal function stratified dose comparisons of eplerenone versus placebo in the EMPHASIS-HF trial. *Eur J Heart Fail* **2019,** *21* (3), 345-351.

11. Desai, A. S.; Liu, J.; Pfeffer, M. A.; Claggett, B.; Fleg, J.; Lewis, E. F.; McKinlay, S.; O'Meara, E.; Shah, S. J.; Sweitzer, N. K.; Solomon, S.; Pitt, B., Incident Hyperkalemia, Hypokalemia, and Clinical Outcomes During Spironolactone Treatment of Heart Failure With Preserved Ejection Fraction: Analysis of the TOPCAT Trial. *J Card Fail* **2018,** *24* (5), 313-320.

12. Vaduganathan, M.; Claggett, B. L.; Chatterjee, N. A.; Anand, I. S.; Sweitzer, N. K.; Fang, J. C.; O'Meara, E.; Shah, S. J.; Hegde, S. M.; Desai, A. S.; Lewis, E. F.; Rouleau, J.; Pitt, B.; Pfeffer, M. A.; Solomon, S. D., Sudden Death in Heart Failure With Preserved Ejection Fraction: A Competing Risks Analysis From the TOPCAT Trial. *JACC Heart Fail* **2018,** *6* (8), 653-661.

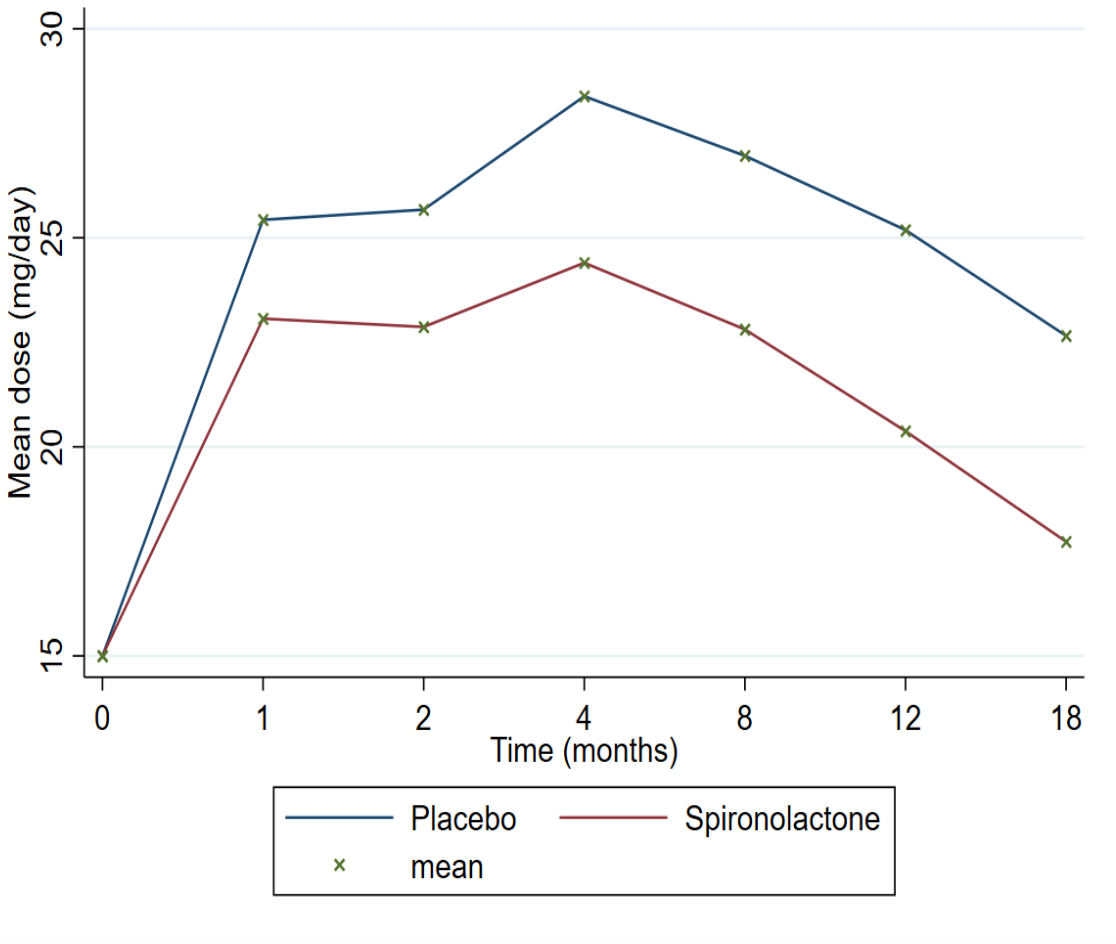
13. Santema, B. T.; Ouwerkerk, W.; Tromp, J.; Sama, I. E.; Ravera, A.; Regitz-Zagrosek, V.; Hillege, H.; Samani, N. J.; Zannad, F.; Dickstein, K.; Lang, C. C.; Cleland, J. G.; Ter Maaten, J. M.; Metra, M.; Anker, S. D.; van der Harst, P.; Ng, L. L.; van der Meer, P.; van Veldhuisen, D. J.; Meyer, S.; Lam, C. S. P.; Voors, A. A., Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *Lancet* **2019,** *394* (10205), 1254-1263.
14. Rossignol, P.; Dobre, D.; McMurray, J. J.; Swedberg, K.; Krum, H.; van Veldhuisen, D. J.; Shi, H.; Messig, M.; Vincent, J.; Girerd, N.; Bakris, G.; Pitt, B.; Zannad, F., Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Circ Heart Fail* **2014,** *7* (1), 51-8.
15. Rossignol, P.; Ferreira, J. P., Balancing Benefits and Risks of Spironolactone in HFpEF and Chronic Kidney Disease Patients: Mind the Gap of Biological Monitoring! *JACC Heart Fail* **2019,** *7* (1), 33-35.
16. Eschalier, R.; McMurray, J. J.; Swedberg, K.; van Veldhuisen, D. J.; Krum, H.; Pocock, S. J.; Shi, H.; Vincent, J.; Rossignol, P.; Zannad, F.; Pitt, B., Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). *J Am Coll Cardiol* **2013,** *62* (17), 1585-93.
17. Rossignol, P.; Masson, S.; Barlera, S.; Girerd, N.; Castelnovo, A.; Zannad, F.; Clemenza, F.; Tognoni, G.; Anand, I. S.; Cohn, J. N.; Anker, S. D.; Tavazzi, L.; Latini, R., Loss in body weight is an independent prognostic factor for mortality in chronic heart failure: insights from the GISSI-HF and Val-HeFT trials. *Eur J Heart Fail* **2015,** *17* (4), 424-33.
18. Stienen, S.; Ferreira, J. P.; Girerd, N.; Duarte, K.; Lamiral, Z.; McMurray, J. J. V.; Pitt, B.; Dickstein, K.; Zannad, F.; Rossignol, P., Mean BMI, visit-to-visit BMI variability and BMI changes during follow-up in patients with acute myocardial infarction with systolic dysfunction and/or heart failure: insights from the High-Risk Myocardial Infarction Initiative. *Clin Res Cardiol* **2019,** *108* (11), 1215-1225.
19. Savarese, G.; Xu, H.; Trevisan, M.; Dahlstrom, U.; Rossignol, P.; Pitt, B.; Lund, L. H.; Carrero, J. J., Incidence, Predictors, and Outcome Associations of Dyskalemia in Heart Failure With Preserved, Mid-Range, and Reduced Ejection Fraction. *JACC Heart Fail* **2019,** *7* (1), 65-76.
20. Olivier, A.; Pizard, A., Effect of eplerenone in patients with heart failure and reduced ejection fraction: Potential effect modification by abdominal obesity. Insight from EMPHASIS-HF trial. *European Journal of Heart Failure* **2017**.
21. Packer, M.; Poole-Wilson, P. A.; Armstrong, P. W.; Cleland, J. G.; Horowitz, J. D.; Massie, B. M.; Ryden, L.; Thygesen, K.; Uretsky, B. F., Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* **1999,** *100* (23), 2312-8.
22. Konstam, M. A.; Neaton, J. D.; Dickstein, K.; Drexler, H.; Komajda, M.; Martinez, F. A.; Riegger, G. A.; Malbecq, W.; Smith, R. D.; Guptha, S.; Poole-Wilson, P. A., Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* **2009,** *374* (9704), 1840-8.
23. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. The NETWORK Investigators. *Eur Heart J* **1998,** *19* (3), 481-9.

24. Bristow, M. R.; Gilbert, E. M.; Abraham, W. T.; Adams, K. F.; Fowler, M. B.; Hershberger, R. E.; Kubo, S. H.; Narahara, K. A.; Ingersoll, H.; Krueger, S.; Young, S.; Shusterman, N., Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation* **1996,** *94* (11), 2807-16.
25. Marti, C. N.; Fonarow, G. C.; Anker, S. D.; Yancy, C.; Vaduganathan, M.; Greene, S. J.; Ahmed, A.; Januzzi, J. L.; Gheorghiade, M.; Filippatos, G.; Butler, J., Medication dosing for heart failure with reduced ejection fraction - opportunities and challenges. *Eur J Heart Fail* **2019,** *21* (3), 286-296.
26. Lam, P. H.; Dooley, D. J.; Fonarow, G. C.; Butler, J.; Bhatt, D. L.; Filippatos, G. S.; Deedwania, P.; Forman, D. E.; White, M.; Fletcher, R. D.; Arundel, C.; Blackman, M. R.; Adamopoulos, C.; Kanonidis, I. E.; Aban, I. B.; Patel, K.; Aronow, W. S.; Allman, R. M.; Anker, S. D.; Pitt, B.; Ahmed, A., Similar clinical benefits from below-target and target dose enalapril in patients with heart failure in the SOLVD Treatment trial. *Eur J Heart Fail* **2018,** *20* (2), 359-369.
27. Beldhuis, I. E.; Myhre, P. L.; Claggett, B.; Damman, K.; Fang, J. C.; Lewis, E. F.; O'Meara, E.; Pitt, B.; Shah, S. J.; Voors, A. A.; Pfeffer, M. A.; Solomon, S. D.; Desai, A. S., Efficacy and Safety of Spironolactone in Patients With HFpEF and Chronic Kidney Disease. *JACC Heart Fail* **2019,** *7* (1), 25-32.
28. Claggett, B.; Pocock, S.; Wei, L. J.; Pfeffer, M. A.; McMurray, J. J. V.; Solomon, S. D., Comparison of Time-to-First Event and Recurrent-Event Methods in Randomized Clinical Trials. *Circulation* **2018,** *138* (6), 570-577.
29. Pitt, B.; Anker, S. D.; Bushinsky, D. A.; Kitzman, D. W.; Zannad, F.; Huang, I. Z., Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J* **2011,** *32* (7), 820-8.
30. Zannad, F.; Ferreira, J. P.; Pitt, B., Potassium binders for the prevention of hyperkalaemia in heart failure patients: implementation issues and future developments. *Eur Heart J Suppl* **2019,** *21* (Suppl A), A55-a60.
31. Filippatos, G.; Anker, S. D.; Bohm, M.; Gheorghiade, M.; Kober, L.; Krum, H.; Maggioni, A. P.; Ponikowski, P.; Voors, A. A.; Zannad, F.; Kim, S. Y.; Nowack, C.; Palombo, G.; Kolkhof, P.; Kimmeskamp-Kirschbaum, N.; Pieper, A.; Pitt, B., A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J* **2016**.
32. Ferreira, J. P.; Kraus, S.; Mitchell, S.; Perel, P.; Pineiro, D.; Chioncel, O.; Colque, R.; de Boer, R. A.; Gomez-Mesa, J. E.; Grancelli, H.; Lam, C. S. P.; Martinez-Rubio, A.; McMurray, J. J. V.; Mebazaa, A.; Panjrath, G.; Pina, I. L.; Sani, M.; Sim, D.; Walsh, M.; Yancy, C.; Zannad, F.; Sliwa, K., World Heart Federation Roadmap for Heart Failure. *Glob Heart* **2019,** *14* (3), 197-214.
33. Ferreira, J. P.; Mentz, R. J.; Pizard, A.; Pitt, B.; Zannad, F., Tailoring mineralocorticoid receptor antagonist therapy in heart failure patients: are we moving towards a personalized approach? *Eur J Heart Fail* **2017**.

Permission note:

"The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission."

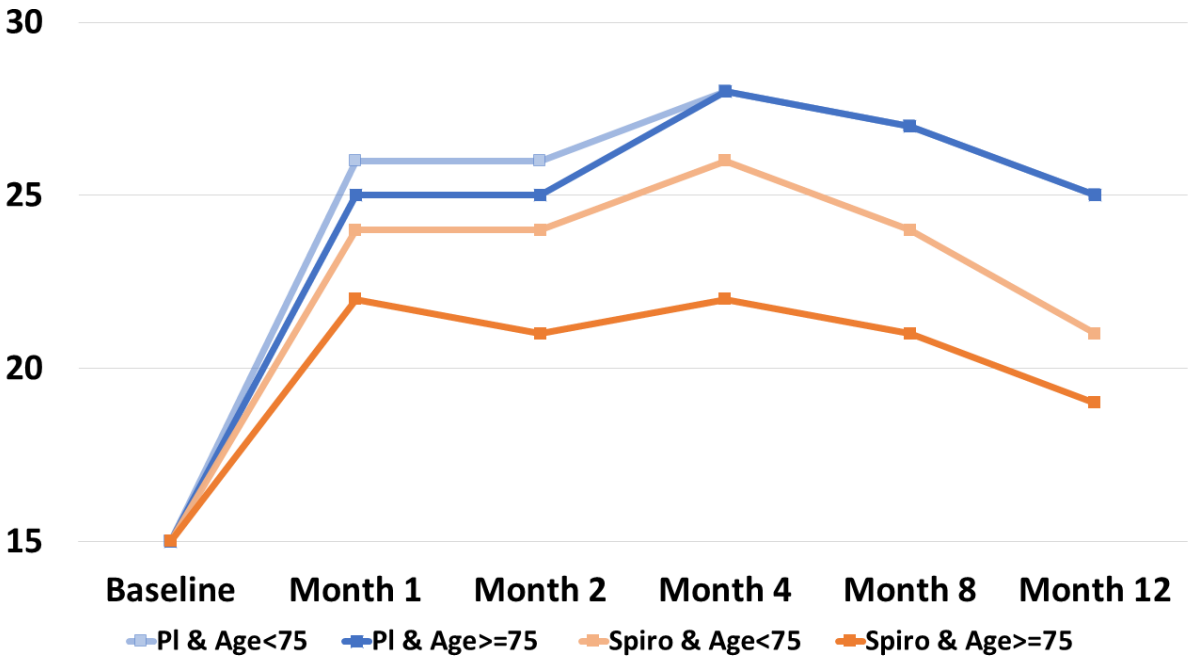
Figure 1. Profile plot of spironolactone vs. placebo dose throughout the follow-up



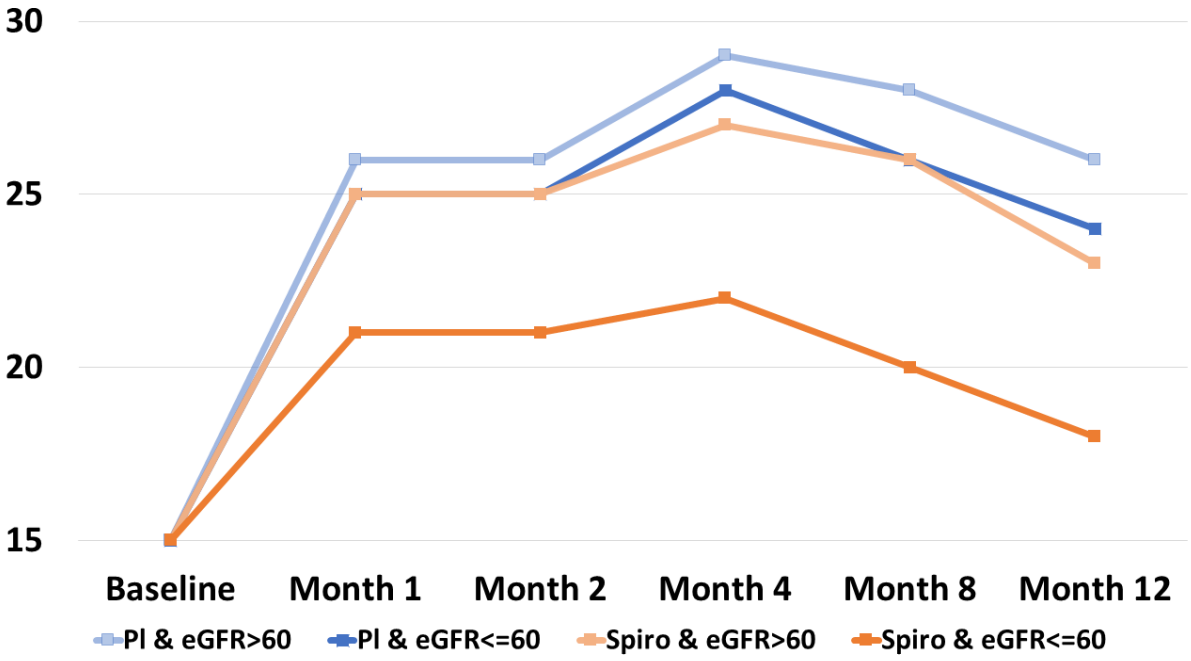
Legend: representation of the spironolactone and placebo doses (in mg/day) over time

Figure 2. Spironolactone dose in mg/day (y-axis) by subgroups over time

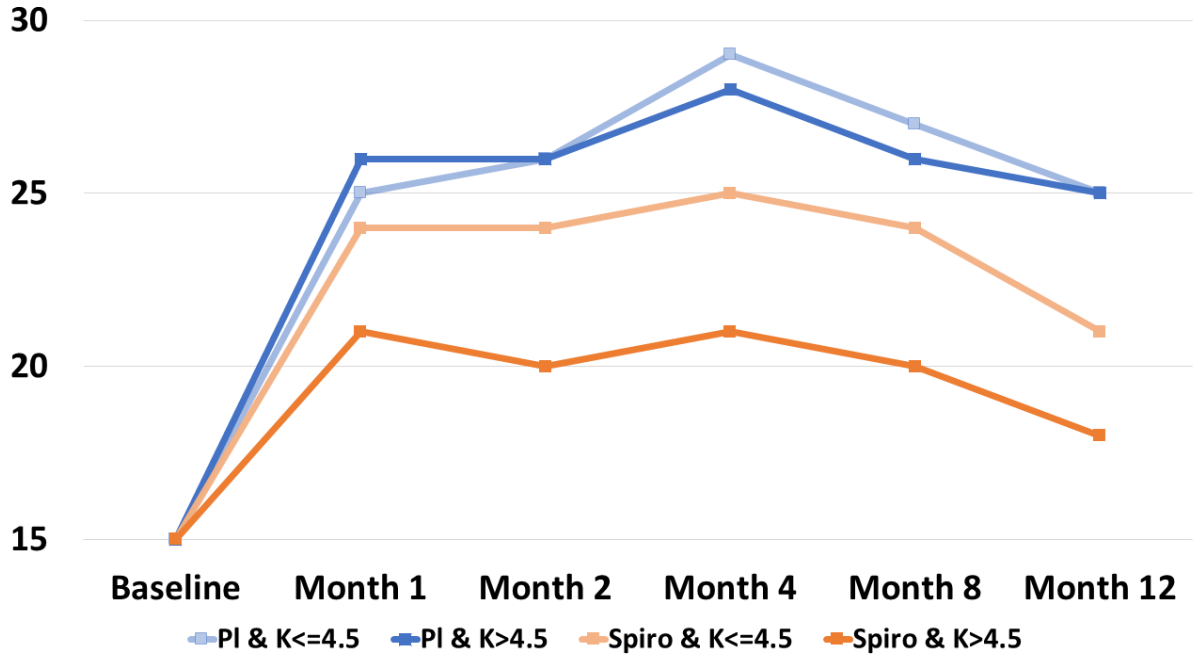
(A) Age



(B) Estimated glomerular filtration rate (eGFR)

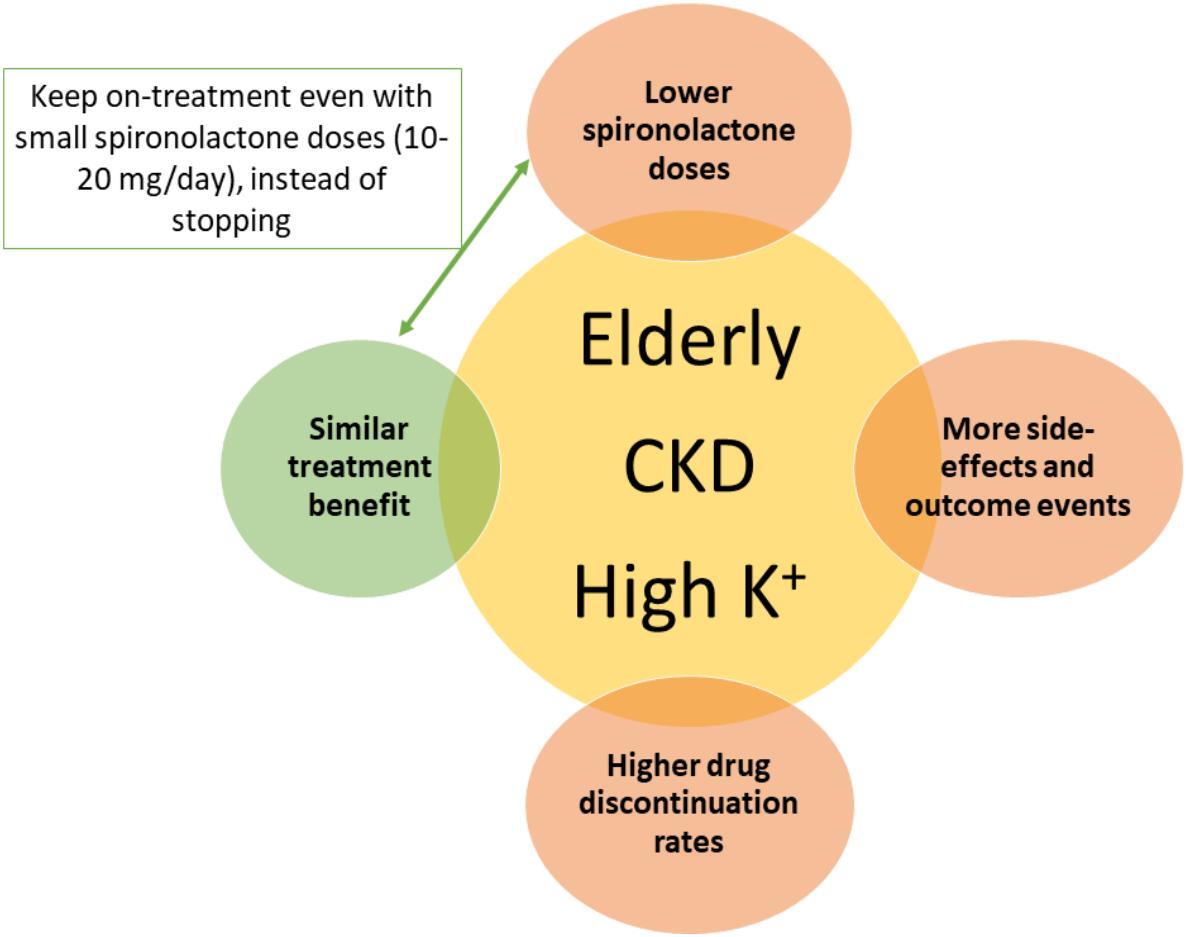


(C) Potassium (K+)



Legend: the y-axis represents the mean treatment dose in mg/day; the treatment by subgroup interaction$_p$ is <0.05 for all the represented subgroups (see also the Table 1)

Central Illustration. Main findings of the study



Legend: CKD, chronic kidney disease; K^+, serum potassium.

Table 1. Drug dose during 1-year follow-up

Group	Placebo dose (mg/day)		Spironolactone dose (mg/day)		P inter.
	Median (pct_{25-75})	Mean ± SD	Median (pct_{25-75})	Mean ± SD	
Overall (n=1767)	27.5 (17.5-27.5)	23.9 ± 8.6	22.5 (15.0-27.5)	21.1 ± 9.3	-
Placebo vs. Spironolactone P-value	<0.001				
Sex					
Male (n=885)	27.5 (17.5-27.5)	23.6 ± 8.7	22.5 (15.0-27.5)	21.4 ± 9.1	0.23
Female (n=882)	27.5 (20.0-27.5)	24.2 ± 8.5	22.5 (15.0-27.5)	20.9 ± 9.5	
Male vs. Female P-value	0.40		0.51		
Age					
Age <75yr (n=1020)	27.5 (17.5-27.5)	24.0 ± 8.3	25.0 (15.0-27.5)	22.1 ± 9.0	0.016
Age ≥75yr (n=747)	27.5 (17.5-27.5)	23.8 ± 9.0	20.0 (15.0-27.5)	19.9 ± 9.6	
Age <75 vs. ≥75 P-value	0.99		<0.001		
Renal function/eGFR					
eGFR ≤60ml/min (n=854)	27.5 (17.5-27.5)	23.3 ± 8.6	20.0 (12.5-27.5)	19.1 ± 9.1	0.002
eGFR >60ml/min (n=912)	27.5 (20.0-30.0)	24.5 ± 8.5	26.6 (15.0-27.5)	23.0 ± 9.2	
eGFR ≤60 vs. >60 P-value	0.027		<0.001		
Diabetes					
No Diabetes (n=788)	27.5 (20.0-27.5)	24.1 ± 8.6	22.5 (15.0-27.5)	21.3 ± 9.3	0.81
Diabetes (n=977)	27.0 (17.5-27.5)	23.7 ± 8.6	22.5 (15.0-27.5)	20.9 ± 9.5	
No diabetes vs. Diabetes P-value	0.17		0.48		
Potassium (K^+)					
K^+ ≤4.5mmol/L (n=1389)	27.5 (17.5-27.5)	24.0 ± 8.7	24.0 (15.0-27.5)	21.7 ± 9.1	0.011
K^+ >4.5mmol/L (n=377)	27.5 (17.5-27.5)	23.6 ± 8.3	17.5 (12.5-27.5)	18.7 ± 10.0	
K^+ ≤4.5 vs. >4.5 P-value	0.60		0.001		
Body mass index (BMI)					
BMI ≤30Kg/m2 (n=623)	27.5 (17.5-27.5)	23.1 ± 8.5	20.0 (15.0-27.5)	20.1 ± 9.1	0.52
BMI >30Kg/m2 (n=1135)	27.5 (20.0-30.0)	24.4 ± 8.6	25.0 (15.0-27.5)	21.7 ± 9.4	
BMI ≤30 vs. >30 P-value	0.039		0.004		
Systolic blood pressure (SBP)					
SBP ≤120mmHg (n=615)	27.0 (16.3-27.5)	23.4 ± 8.8	22.5 (15.0-27.5)	21.1 ± 9.4	0.34
SBP >120mmHg (n=1149)	27.5 (18.8-27.5)	24.2 ± 8.5	22.5 (15.0-27.5)	21.1 ± 9.3	
SBP ≤120 vs. >120 P-value	0.10		0.95		
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker treatment					
No ACEi/ARB (n=381)	27.5 (17.5-27.5)	23.6 ± 8.6	22.5 (15.0-27.5)	21.3 ± 9.3	0.60
ACEi/ARB (n=1385)	27.5 (18.8-27.5)	24.0 ± 8.6	22.5 (15.0-27.5)	21.1 ± 9.4	
No ACEi/ARB vs ACEi/ARB P-value	0.74		0.81		

The results are presented as median (percentile 25-75) and mean ± standard deviation; the p-values are derived from a Mann-Whitney rank-sum test (with similar results from the Student t-test); the interaction test is derived from a linear regression model.

Table 2. Drug discontinuation during 1-year follow-up

Group	Placebo discontinuation	Spironolactone discontinuation	Interaction P
Overall (n=1767)	161 (18.3)	225 (25.4)	-
Placebo vs. Spironolactone P-value	-	<0.001	
Sex			
Male (n=885)	85 (19.3)	114 (25.7)	0.65
Female (n=882)	76 (17.3)	111 (25.1)	
Male vs. Female P-value	0.44	0.85	
Age			
Age <75yr (n=1020)	96 (18.3)	114 (23.1)	0.25
Age ≥75yr (n=747)	65 (18.3)	111 (28.1)	
Age <75 vs. ≥75 P-value	0.98	0.075	
Estimated glomerular filtration rate (eGFR)			
eGFR ≤60ml/min (n=854)	77 (17.8)	125 (29.6)	0.036
eGFR >60ml/min (n=912)	84 (18.9)	100 (21.6)	
eGFR ≤60 vs. >60 P-value	0.72	0.006	
Diabetes			
No Diabetes (n=788)	84 (17.4)	118 (23.8)	0.82
Diabetes (n=977)	77 (19.4)	107 (27.4)	
No diabetes vs. Diabetes P-value	0.45	0.23	
Potassium (K^+)			
K^+ ≤4.5mmol/L (n=1389)	126 (18.6)	167 (23.5)	0.043
K^+ >4.5mmol/L (n=377)	35 (17.3)	58 (33.1)	
K^+ ≤4.5 vs. >4.5 P-value	0.69	0.009	
Body mass index (BMI)			
BMI ≤30Kg/m2 (n=623)	59 (18.5)	82 (27.0)	0.59
BMI >30Kg/m2 (n=1135)	102 (18.4)	141 (24.3)	
BMI ≤30 vs. >30 P-value	0.97	0.39	
Systolic blood pressure (SBP)			
SBP ≤120mmHg (n=615)	54 (17.1)	71 (23.8)	0.99
SBP >120mmHg (n=1149)	107 (19.0)	153 (26.1)	
SBP ≤120 vs. >120 P-value	0.48	0.44	
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker treatment			
No ACEi/ARB (n=381)	36 (19.5)	43 (21.9)	0.23
ACEi/ARB (n=1385)	125 (18.0)	182 (26.4)	
No ACEi/ARB vs ACEi/ARB P-value	0.65	0.21	

The results are presented as numbers and proportions (%); the p-values are derived from a Chi2 test; the interaction test is derived from a logistic regression.

Table 3. Worsening renal function and hyperkalemia occurrence at any time-point during the trial

Group	Placebo side-effect	Spironolactone side-effect	Interaction P
Overall (n=1767)			
Worsening renal function	289 (32.8)	389 (43.9)	
Placebo vs. Spironolactone P-value	-	<0.001	-
Hyperkalemia	46 (5.2)	141 (15.9)	
Placebo vs. Spironolactone P-value	-	<0.001	
Sex			
Worsening renal function			
Male (n=885)	129 (29.3)	175 (39.4)	
Female (n=882)	160 (36.4)	214 (48.5)	0.81
Male vs. Female P-value	0.025	0.006	
Hyperkalemia			
Male (n=885)	22 (5.0)	73 (16.5)	
Female (n=882)	24 (5.5)	68 (15.4)	0.63
Male vs. Female P-value	0.76	0.66	
Age			
Worsening renal function			
Age <75yr (n=1020)	179 (34.0)	217 (43.9)	
Age ≥75yr (n=747)	110 (31.0)	172 (44.0)	0.48
Age <75 vs. ≥75 P-value	0.35	0.99	
Hyperkalemia			
Age <75yr (n=1020)	27 (5.2)	74 (15.0)	
Age ≥75yr (n=747)	19 (5.4)	67 (17.2)	0.73
Age <75 vs. ≥75 P-value	0.90	0.38	
Estimated glomerular filtration rate (eGFR)			
Worsening renal function			
eGFR ≤60ml/min (n=854)	147 (34.0)	188 (44.7)	
eGFR >60ml/min (n=912)	141 (31.5)	201 (43.3)	0.76
eGFR ≤60 vs. >60 P-value	0.42	0.69	
Hyperkalemia			
eGFR ≤60ml/min (n=854)	30 (6.9)	97 (23.0)	
eGFR >60ml/min (n=912)	16 (3.6)	44 (9.5)	0.35
eGFR ≤60 vs. >60 P-value	0.026	<0.001	
Diabetes			
Worsening renal function			
No Diabetes (n=788)	141 (29.3)	198 (40.1)	
Diabetes (n=977)	147 (37.0)	191 (48.9)	0.98
No diabetes vs. Diabetes P-value	0.015	0.009	
Hyperkalemia			
No Diabetes (n=788)	20 (4.2)	64 (13.0)	
Diabetes (n=977)	26 (6.6)	77 (20.0)	0.94
No diabetes vs. Diabetes P-value	0.12	0.006	
Potassium (K^+)			
Worsening renal function			
K^+ ≤4.5mmol/L (n=1389)	215 (31.7)	323 (45.5)	
K^+ >4.5mmol/L (n=377)	73 (36.1)	66 (37.7)	0.032
K^+ ≤4.5 vs. >4.5 P-value	0.24	0.063	
Hyperkalemia			
K^+ ≤4.5mmol/L (n=1389)	22 (3.3)	90 (12.7)	
K^+ >4.5mmol/L (n=377)	24 (11.9)	51 (29.3)	0.35
K^+ ≤4.5 vs. >4.5 P-value	<0.001	<0.001	

Body mass index (BMI)			
Worsening renal function			
BMI ≤30Kg/m2 (n=623)	94 (29.5)	131 (43.2)	0.40
BMI >30Kg/m2 (n=1135)	191 (34.4)	258 (44.5)	
BMI ≤30 vs. >30 P-value	0.13	0.72	
Hyperkalemia			
BMI ≤30Kg/m2 (n=623)	13 (4.1)	51 (16.8)	0.25
BMI >30Kg/m2 (n=1135)	32 (5.8)	90 (15.6)	
BMI ≤30 vs. >30 P-value	0.28	0.65	
Systolic blood pressure (SBP)			
Worsening renal function			
SBP ≤120mmHg (n=615)	88 (27.9)	117 (39.1)	0.80
SBP >120mmHg (n=1149)	200 (35.5)	272 (46.5)	
SBP ≤120 vs. >120 P-value	0.020	0.037	
Hyperkalemia			
SBP ≤120mmHg (n=615)	16 (5.1)	47 (15.7)	0.95
SBP >120mmHg (n=1149)	30 (5.3)	94 (16.1)	
SBP ≤120 vs. >120 P-value	0.87	0.88	
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker treatment			
Worsening renal function			
No ACEi/ARB (n=381)	61 (33.0)	77 (39.3)	0.28
ACEi/ARB (n=1385)	227 (32.7)	312 (45.3)	
No ACEi/ARB vs ACEi/ARB P-value	0.94	0.13	
Hyperkalemia			
No ACEi/ARB (n=381)	13 (7.1)	22 (11.2)	0.027
ACEi/ARB (n=1385)	33 (4.8)	119 (17.3)	
No ACEi/ARB vs ACEi/ARB P-value	0.21	0.040	

The results are presented as numbers and proportions (%); the p-values are derived from a Chi2 test; the interaction test is derived from a logistic regression.

Worsening renal function defined as any eGFR drop >30% from the baseline value during the follow-up; Hyperkalemia defined as any K^+ measurement >5.5 mmol/L during the follow-up.

Table 4. Time-updated models to assess the risk of events after spironolactone or placebo discontinuation (Total n =1767)

Outcome	N. (%) events before discont. (12549 observations)	N. (%) events after discont. (4345 observations)	HR (95%CI)	p-value	Inter. p*
CVD or HFH (n =522)	348 (2.9)	174 (5.1)	1.88 (1.55-2.29)	<0.001	0.13
CVD (n =223)	106 (0.8)	117 (2.7)	2.76 (2.08-3.66)	<0.001	0.15
ACM (n =387)	154 (1.2)	233 (5.4)	3.76 (3.02-4.67)	<0.001	0.32

Legend: CVD, cardiovascular death; HFH, heart failure hospitalization; ACM, all-cause mortality; discount., spironolactone discontinuation; HR, hazard ratio; 95%CI, 95% confidence interval.
All models adjusted on age, sex, body mass index, systolic blood pressure, diabetes, atrial fibrillation, previous myocardial infarction, estimated glomerular filtration rate, potassium, and use of ACEi/ARBs.
*P-value for interaction between drug discontinuation and spironolactone or placebo allocation.
HR (95%CI) for the placebo and spironolactone groups:
CVD or HFH: HR (95%CI) for placebo =1.63 (1.22-2.18) & HR (95%CI) for spironolactone =2.28 (1.72-3.02).
CVD: HR (95%CI) for placebo =2.45 (1.69-3.56) & HR (95%CI) for spironolactone =3.60 (2.29-5.65).
ACM: HR (95%CI) for placebo =3.56 (2.64-4.77) & HR (95%CI) for spironolactone =4.38 (3.13-6.12).