CardioRenal Medicine

Cardiorenal Med 2017;7:128–136
DOI: 10.1159/000454933
Received: September 5, 2016
Accepted: November 29, 2016
Published online: January 20, 2017

Original Paper

Spironolactone Treatment and Effect on Survival in Chronic Heart Failure Patients with Reduced Renal Function: A Propensity-Matched Study

Viera Stubnova[a, b] Ingrid Os[a, c] Morten Grundtvig[d] Dan Atar[a, e] Bård Waldum-Grevbo[c]

[a]Institute of Clinical Medicine, University of Oslo, Oslo, [b]Department of Medicine, Finnmark Hospital Trust, Kirkenes, [c]Department of Nephrology, Oslo University Hospital, Ullevål, Oslo, [d]Department of Medicine, Innlandet Hospital Trust, Lillehammer, and [e]Department of Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway

Keywords
Heart failure · Reduced renal function · Spironolactone · Prognosis

Abstract
Background/Aims: Spironolactone may be hazardous in heart failure (HF) patients with renal dysfunction due to risk of hyperkalemia and worsened renal function. We aimed to evaluate the effect of spironolactone on all-cause mortality in HF outpatients with renal dysfunction in a propensity-score-matched study. ***Methods:*** A total of 2,077 patients from the Norwegian Heart Failure Registry with renal dysfunction (eGFR <60 mL/min/1.73 m^2) not treated with spironolactone at the first visit at the HF clinic were eligible for the study. Patients started on spironolactone at the outpatient HF clinics (n = 206) were propensity-score-matched 1:1 with patients not started on spironolactone, based on 16 measured baseline characteristics. Kaplan-Meier and Cox regression analyses were used to investigate the independent effect of spironolactone on 2-year all-cause mortality. ***Results:*** Propensity score matching identified 170 pairs of patients, one group receiving spironolactone and the other not. The two groups were well matched (mean age 76.7 ± 8.1 years, 66.4% males, and eGFR 46.2 ± 10.2 mL/min/1.73 m^2). Treatment with spironolactone was associated with increased potassium (delta potassium 0.31 ± 0.55 vs. 0.05 ± 0.41 mmol/L, p < 0.001) and decreased eGFR (delta eGFR –4.12 ± 12.2 vs. –0.98 ± 7.88 mL/min/1.73 m^2, p = 0.006) compared to the non-spironolactone group. After 2 years, 84% of patients were alive in the spironolactone group and 73% of patients in the non-spironolactone group (HR 0.59, 95% CI 0.37–0.92, p = 0.020). ***Conclusion:*** In HF outpatients with renal dysfunction, treatment with spironolactone was associated with

Viera Stubnova, MD
Department of Medicine, Finnmark Hospital Trust
Postboks 410
NO–9900 Kirkenes (Norway)
E-Mail viera.stubnova@medisin.uio.no

improved 2-year survival compared to well-matched patients not treated with spironolactone. Favorable survival was observed despite worsened renal function and increased potassium in the spironolactone group.

Introduction

Reduced renal function is common in outpatients with chronic heart failure (HF) and an independent predictor of all-cause mortality [1–3]. While the prevalence in the general population is about 4.7% [4], nearly 50% of patients with chronic HF have glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 [1, 2]. Still, patients with kidney disease are underrepresented in randomized controlled trials (RCTs) of cardiovascular interventions [5]. Although RCTs are considered as gold standard when evaluating the effectiveness of therapeutic agents, well-designed observational studies may provide important information in subgroups not addressed in RCTs [6].

The use of spironolactone in addition to ACE inhibitor (ACEi) and β-blocker is recommended in symptomatic patients with reduced left ventricular ejection fraction (LVEF) [7, 8]. Caution is necessary in patients with renal dysfunction, as use of spironolactone may cause hyperkalemia and worsening renal function [9, 10]. Worsening renal function is a strong predictor of increased mortality in HF patients, and the safety of spironolactone in patients with reduced renal function is still a matter of uncertainty [11–14]. Yet, spironolactone is used extensively in HF outpatients with renal dysfunction [2].

The aim of our study was to evaluate the effect of spironolactone on all-cause mortality in chronic HF patients with reduced renal function using a propensity-score-matched model on Norwegian HF outpatients.

Material and Methods

The Norwegian Heart Failure Registry

Since the year 2000, the Norwegian Heart Failure Registry has collected data on outpatients referred to HF clinics in Norwegian hospitals. In 2012, recruitment of patients occurred in 25 HF clinics in the different Norwegian regions with a catchment area representing about half of Norway's population. The recruiting HF clinics are run by cardiologists and specialized nurses. The patients were enrolled successively after being diagnosed with chronic HF of any etiology according to the guidelines of the European Society of Cardiology (ESC) [7, 15], and three visits were recorded. At the first visit (baseline), medical history, physical examination, echocardiography, New York Heart Association (NYHA) functional class, laboratory results, and the medical management of HF were registered. The second visit was registered after the cardiologists had optimized the medical treatment and the patient had participated in an educational program. The third visit, arranged 6 months after visit 2, served as an assessment of the patient's health condition, medication, and laboratory results after intervention at the HF clinic. Mortality data are retrieved yearly from Statistics Norway. A total of 6,779 patients were included by February 2012. HF outpatients with reduced renal function (estimated GFR [eGFR] <60 mL/min/1.73 m^2) not using spironolactone at the first visit were enrolled in the study (n = 2,077).

Definitions

Renal function was expressed as eGFR and calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16].

$eGFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) × 1.159 (if black).

Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males and α is –0.329 for females and –0.411 for males. Renal dysfunction was defined as eGFR <60 mL/min/1.73 m^2.

Based on ESC guidelines on HF [7], LVEF was defined as reduced at ≤35% and as preserved at ≥50%.

Table 1. Baseline characteristics of 2,077 heart failure outpatients with renal dysfunction and no previous use of spironolactone

	Patients with valid data	Total (n = 2,077)	Started on spironolactone (n = 206)	Not started on spironolactone (n = 1,871)	p value
Age, years	2,077 (100)	76.1±8.8	76.1±8.2	76.1±8.9	0.982
Male gender	2,077 (100)	1,356 (65.3)	139 (67.5)	1,217 (65.0)	0.487
Body mass index	1,765 (85.0)	25.8±4.8	27.2±5.3	25.7±4.7	<0.001
Smoking	2,068 (99.6)	225 (10.9)	14 (6.8)	211 (11.3)	0.050
Medical history					
Ischemic heart disease	2,000 (96.3)	1,277 (63.9)	126 (63.3)	1,151 (63.9)	0.869
Hypertension	1,938 (93.3)	750 (38.7)	80 (40.4)	670 (38.5)	0.603
Claudication and/or previous stroke	1,938 (93.3)	386 (19.9)	36 (18.2)	350 (20.1)	0.519
PCI/CABG	1,931 (93.0)	692 (35.8)	67 (34.0)	625 (36.0)	0.573
Physical findings					
Heart rate, beats/min	2,073 (99.8)	71.2±14.9	71.7±14.7	71.1±15.0	0.595
SBP, mm Hg	2,076 (100)	128.0±22.9	128.0±23.6	128.0±22.9	0.979
LVEF groups					0.078
LVEF ≤35%		1,152 (65.5)	102 (58.6)	1,050 (66.3)	
35% < LVEF < 50%		408 (23.2)	45 (25.9)	363 (22.9)	
LVEF ≥50%		198 (11.3)	27 (15.5)	171 (10.8)	
NYHA class III/IV	2,037 (98.1)	1,199 (58.9)	144 (70.9)	1,055 (57.5)	<0.001
Medication					
RAS blockade	2,074 (99.9)	1,780 (85.8)	171 (83.0)	1,609 (86.1)	0.222
ACEi dose/day, % of target dose	2,065 (99.4)	40.0±38.8	47.9±44.0	39.1±38.1	0.002
β-Blocker dose/day, mg	2,044 (98.4)	70.0±66.3	69.2±67.1	70.1±66.2	0.859
Loop diuretics dose/day, mg	2,076 (100)	69.4±65.3	70.7±47.8	69.2±67.0	0.750
RAS + β-blocker use	2,070 (99.7)	1,476 (71.3)	136 (66.3)	1,340 (71.8)	0.098
Acetylsalicylic acid use	2,076 (100)	991 (47.7)	78 (37.9)	913 (48.8)	0.003
Statin use	2,077 (100)	1,108 (53.3)	102 (49.5)	1,006 (53.8)	0.245
Laboratory values					
eGFR, mL/min/1.73 m^2	2,077 (100)	43.7±11.6	45.7±9.9	43.5±11.8	0.010
Serum potassium, mmol/L	2,071 (99.7)	4.39±0.50	4.25±0.48	4.40±0.49	<0.001
Serum sodium, mmol/L	2,075 (99.9)	140.3±3.3	140.1±4.0	140.3±3.3	0.387

Values are expressed as n (%) or mean ± SD. ACEi dose/day, percent of daily enalapril equivalent target dose; β-blocker dose/day, daily metoprolol equivalent dose; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI/CABG, percutaneous coronary intervention and/or coronary artery bypass graft; SBP, systolic blood pressure.

Daily doses of ACEi were converted to enalapril equivalent doses (enalapril 20 mg = lisinopril 20 mg = ramipril 10 mg = captopril 100 mg), and then expressed as percent of enalapril target dose. Target dose of enalapril was defined as 20 mg per day. Daily doses of loop diuretics were converted to furosemide equivalent doses (furosemide 40 mg = bumetanide 1 mg). Daily doses of β-blockers were converted to metoprolol equivalent doses (metoprolol 200 mg = bisoprolol 10 mg = carvedilol 50 mg = atenolol 100 mg).

The follow-up time was set to 2 years as data on persistent use of spironolactone after the last registered visit were not available.

Statistical Analysis

Baseline characteristics were presented as mean ± standard deviation for continuous variables and as frequency (percentage) for categorical data. Student t test was used when comparing continuous variables. Similarly, χ^2 test was used when comparing categorical variables.

A multivariate logistic regression model was built to calculate the individual propensity score for being started on spironolactone at the outpatient HF clinic. Spironolactone use at the last visit at the outpatient HF

Table 2. Characteristics of 170 pairs of propensity-matched heart failure outpatients with renal dysfunction and no previous use of spironolactone

	Total (n = 339)	Started on spironolactone (n = 170)	Not started on spironolactone (n = 169)	p value
Age, years	76.7±8.1	76.4±8.0	77.1±8.1	0.445
Male gender	225 (66.4)	113 (66.5)	112 (66.3)	0.969
Body mass index	26.8±5.0	27.0±5.1	26.7±4.9	0.510
Smoking	27 (8.0)	12 (7.1)	15 (8.9)	0.537
Medical history				
Ischemic heart disease	220 (64.9)	107 (62.9)	113 (66.9)	0.449
Hypertension	143 (42.2)	68 (40.0)	75 (44.4)	0.414
Claudication and/or previous stroke	71 (20.9)	35 (20.6)	36 (21.3)	0.872
PCI/CABG	115 (33.9)	58 (34.1)	57 (33.7)	0.940
Physical findings				
Heart rate, beats/min	71.8±15.1	71.4±13.7	72.3±16.4	0.610
SBP, mm Hg	130.4±22.4	129.6±22.7	131.2±22.1	0.502
LVEF groups				0.084
LVEF ≤35%	183 (60.6)	82 (55.0)	101 (66.0)	
35% < LVEF < 50%	76 (25.2)	40 (26.8)	36 (23.5)	
LVEF ≥50%	43 (14.2)	27 (18.1)	16 (10.5)	
NYHA class III/IV	231 (68.1)	118 (69.4)	113 (66.9)	0.615
Medication first visit				
RAS blockade	284 (83.8)	141 (82.9)	143 (84.6)	0.676
ACEi dose/day, % of target dose	46.9±42.6	47.5±44.0	46.3±41.3	0.791
β-Blocker dose/day, mg	69.1±65.0	67.5±65.1	70.7±65.1	0.657
RAS + β-blocker use	224 (66.3)	109 (64.5)	115 (68.0)	0.490
Loop diuretics dose/day, mg	68.1±54.7	71.8±49.1	64.4±60.0	0.215
Acetylsalicylic acid use	142 (41.9)	66 (38.8)	76 (45.0)	0.251
Statin use	173 (51.0)	89 (52.4)	84 (49.7)	0.626
Medication last visit				
RAS blockade	287 (82.5)	137 (78.7)	150 (86.2)	0.067
ACEi dose/day, % of target dose	48.8±44.0	47.8±44.3	49.8±43.9	0.661
β-Blocker dose/day, mg	93.9±75.4	96.4±79.4	91.4±71.3	0.526
RAS + β-blocker use	241 (69.1)	114 (65.1)	127 (73.0)	0.113
Loop diuretics dose/day, mg	65.1±56.1	66.1±53.9	64.0±58.3	0.715
Acetylsalicylic acid use	146 (40.3)	67 (37.0)	79 (43.6)	0.199
Statin use	193 (53.3)	92 (50.8)	101 (55.8)	0.343
Laboratory values				
eGFR, mL/min/1.73 m^2	46.2±10.2	45.6±10.2	46.8±10.2	0.282
Serum potassium, mmol/L	4.27±0.46	4.23±0.47	4.30±0.45	0.164
Serum sodium, mmol/L	140.2±3.7	140.1±4.0	140.3±3.4	0.713

Values are expressed as n (%) or mean ± SD. ACEi dose/day, percent of daily enalapril equivalent target dose; β-blocker dose/day, daily metoprolol equivalent dose; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI/CABG, percutaneous coronary intervention and/or coronary artery bypass graft; SBP, systolic blood pressure.

clinic was entered as the dependent variable in the model. Baseline variables associated with spironolactone treatment ($p < 0.20$) were entered as independent variables, together with important potential confounding variables associated with mortality in HF patients. As complete data sets are required for the propensity score matching procedure, variables with many missing values (serum cholesterol and LVEF) were excluded from the analyses. The independent variables in the propensity matching procedure were then: age, gender,

BMI, ischemic heart disease, claudication and/or previous stroke, percutaneous coronary intervention and/or coronary artery bypass graft, systolic blood pressure, NYHA functional class 3 and 4, use of RAS-blocking agents, percent of ACEi daily target dose, diuretics dose, use of acetylsalicylic acid, use of statin, eGFR, serum potassium, and serum sodium.

Patients whose optimized HF treatment at the last visit included spironolactone were propensity-score-matched 1:1 with patients not using spironolactone in a randomized case order with match tolerance 0.1 and a priority to exact match.

Kaplan-Meier statistics was used to investigate differences in survival between HF outpatients with reduced renal function that were prescribed spironolactone during HF treatment optimization at HF clinics and patients not on spironolactone. Univariate Cox regression model was utilized to calculate hazard ratio (HR) for spironolactone use on all-cause mortality in HF outpatients with reduced renal function.

Student *t* test was used to assess changes in eGFR and serum potassium from the first to the last visit between the two treatment groups, and paired *t* test was used to assess changes within each treatment group.

Statistical analyses were carried out using SPSS for Windows version 22 (IBM SPSS Statistics, New York, NY, USA). Level of significance was set as p value ≤0.05.

Results

Baseline characteristics of 2,077 HF outpatients with reduced renal function and no prior use of spironolactone at the first visit to HF clinics are presented in Table 1. The mean age was 76.1 ± 8.8 years, 65.3% were males, and the mean eGFR was 43.7 ± 11.6 mL/min/1.73 m^2. Ten percent (n = 206) were registered as using spironolactone at the last visit. Compared to HF outpatients whose optimized medical treatment remained without spironolactone, the future spironolactone users had higher BMI and NYHA class, higher eGFR, and lower serum potassium, and they used higher doses of ACEi (Table 1).

Of a total of 1,814 HF outpatients with no prior use of spironolactone and complete datasets, 170 patients treated with spironolactone at the last visit were propensity-score-matched 1:1 with 169 HF outpatients not treated with spironolactone. Baseline characteristics were well balanced in the two examined groups (Table 2). Two-year mortality rate was 22%. After 48 months, 84% patients were alive in the spironolactone group and 73% patients in the non-spironolactone group. The use of spironolactone was an independent predictor of improved survival in HF outpatients with reduced eGFR (2-year mortality HR 0.59, 95% CI 0.37–0.92, p = 0.020; Fig. 1).

During a mean time of 8.0 ± 6.3 months from the first visit to the last visit, there was a significant change in both eGFR and serum potassium in the spironolactone group compared to the non-spironolactone group (Table 3). Patients treated with spironolactone experienced an increase in serum potassium from 4.24 ± 0.47 to 4.52 ± 0.51 mmol/L (p < 0.001) and a decrease in eGFR from 45.5 ± 10.2 to 41.4 ± 14.6 mL/min/1.73 m^2 (p < 0.001), while there was no significant change in neither serum potassium nor eGFR in patients not using spironolactone.

Discussion

In the present study of Norwegian HF outpatients with renal dysfunction, patients treated with spironolactone had improved 2-year survival compared to the propensity-matched patients not treated with spironolactone. The survival benefit was observed despite decrease in renal function and increase in serum potassium levels in patients treated with spironolactone.

Table 3. Change in eGFR and serum potassium in heart failure outpatients with renal dysfunction during follow-up at the heart failure clinic (no spironolactone use at baseline)

	Patients with valid data	Total (n = 339)	Started on spironolactone (n = 170)	Not started on spironolactone (n = 169)	p value
eGFR change	330 (97.3)	–2.57±10.4	–4.12±12.2	–0.98±7.9	0.006
Serum potassium change	327 (96.5)	0.18±0.51	0.31±0.55	0.05±0.41	<0.001

Values are expressed as n (%) or mean ± SD. eGFR, estimated glomerular filtration rate.

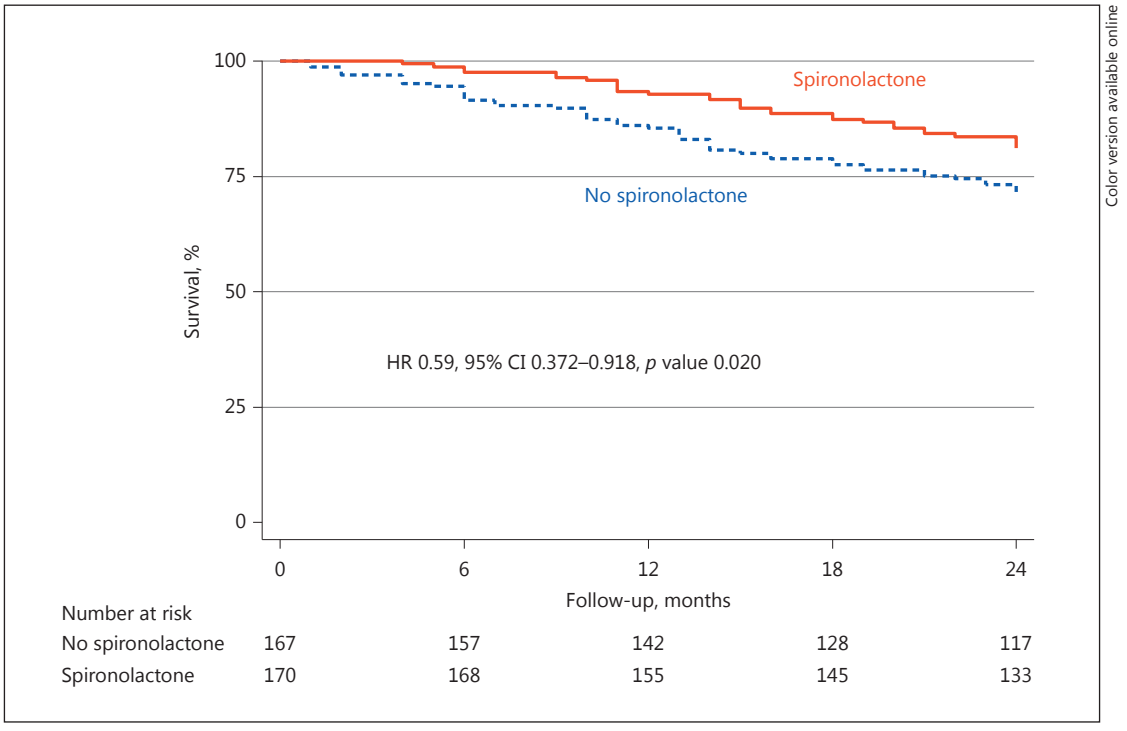

Fig. 1. Kaplan-Meier survival plot of heart failure outpatients with renal dysfunction propensity-matched by spironolactone treatment at the last visit at the heart failure clinic.

Mineralocorticoid receptor antagonists have been shown to improve survival in patients with advanced HF with reduced ejection fraction [17–19]. A recent study from the Swedish Heart Failure Registry reported an interaction between spironolactone use and renal function concerning all-cause mortality, indicating a relatively more favorable effect of spironolactone in patients with reduced renal function compared to patients with preserved GFR [20]. In a subgroup analysis of RALES (Randomized Aldactone Evaluation Study), individuals with reduced eGFR had similar reduction in relative risk of all-cause mortality as individuals with eGFR >60 mL/min/1.73 m^2 [21]. However, study populations in RCTs are highly selected and patients with reduced renal function are underrepresented. Coca et al. [5] found that individuals with renal disease were excluded in 56% of cardiovascular RCTs. Furthermore, only 13–25% of individuals from observational studies were estimated to be eligible for HF RCTs [22]. Patients included in our study were unselected patients treated in Norwegian outpatient

HF clinics. Compared to the subgroup of RALES patients with reduced kidney function [21], patients in the present study were older and had lower eGFR and higher serum potassium.

The use of mineralocorticoid receptor antagonists in HF patients with reduced renal function has been debated due to safety concerns. Extended use of spironolactone after publication of RALES resulted in increased rate of hospitalization for hyperkalemia [7–9]. In our study, the beneficial effect of spironolactone on survival was observed despite decrease in renal function and increase in serum potassium during follow-up at the outpatient HF clinics. It is well accepted that worsening renal function has a negative impact on survival in HF patients [11, 12, 23]. However, the prognostic effect of worsening renal function might depend on the HF medication used. A meta-analysis showed that improved survival associated with use of RAAS inhibitors was greatest in patients with worsening renal function [11]. Likewise, Vardeny et al. [21] demonstrated a favorable effect of spironolactone on survival in HF patients with reduced eGFR despite worsening renal function. On the other hand, worsening renal function following the use of high-dose loop diuretics was associated with increased mortality [24]. Given the beneficial effect of spironolactone on survival in HF patients despite decreased eGFR, one could hypothesize that some reduction in renal function with spironolactone should be accepted and should not lead to discontinuation of treatment. However, the degree of worsening renal function and hyperkalemia that should be tolerated needs to be further investigated.

We used propensity-score-matched analysis to correct for differences between baseline characteristics of patients treated and not treated with spironolactone. Propensity score matching makes it possible to design an observational study so that it mimics some of the characteristics of RCTs by balancing the baseline differences between the study and control group. It is an increasingly used method that might be superior to multivariate Cox regression when correcting for confounding variables in observational studies [25]. Based on 16 predefined measured variables in the present study, patients prescribed spironolactone were matched 1:1 with patients not prescribed spironolactone. However, neither propensity score matching nor multivariate Cox regression can correct for unmeasured confounding variables. Yet, the large number of variables used for the estimation of propensity score may back the reliability of our findings.

There are some important limitations. Although the study population consists of unselected outpatients attending HF clinics, some degree of selection might be present. The patients that were prescribed spironolactone were not selected at random, but rather after careful evaluation by the cardiologist. Therefore, we cannot conclude that spironolactone use would be beneficial for all patients with reduced kidney function. Furthermore, the majority of the included individuals had moderately reduced kidney function with eGFR 30–59 mL/min/1.73 m^2 and only 10% had eGFR <30 mL/min/1.73 m^2. It is likely to assume that patients with severely reduced kidney function would most probably be treated by nephrologists rather than cardiologists, and therefore would not be included in the Heart Failure Registry.

Only mortality data were available after the last registered visit at the outpatient HF clinic. Data on doses of spironolactone and other medication, hospital admissions for decompensated HF, or adverse events would have strengthened the study. Such data were not available. The follow-up time was restricted to 2 years because of lack of data on persistent use of spironolactone.

In conclusion, spironolactone improved the 2-year survival in HF outpatients with reduced renal function compared to propensity-score-matched patients not treated with spironolactone. Favorable survival was observed despite the fact that patients treated with spironolactone experienced a decrease in renal function and an increase in serum potassium. Reluctance to prescribe spironolactone owing to fear for adverse renal events may deprive HF patients with reduced renal function of possibly lifesaving treatment.

Acknowledgements

We gratefully acknowledge all contributors to the Norwegian Heart Failure Registry as the registry is critically dependent on high-quality data from the participating heart failure clinics. The first author is a research fellow and funded by the South-Eastern Norway Regional Health Authority.

Statement of Ethics

All enrolled patients had given written informed consent prior to inclusion in the database. The study was approved by the National Data Inspectorate and the Regional Committee of Medical Research Ethics.

Disclosure Statement

B.W.-G. reports personal fees from Novartis Pharma, outside the submitted work. M.G. reports personal fees from Novartis Pharma and Vifor Pharma, outside the submitted work. D.A. reports personal fees from Novartis Pharma, St. Jude Medical, and Vifor Pharma, outside the submitted work. The other authors have no conflict of interest related to the work to disclose.

References

1 Damman K, Valente MA, 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 2014;35:455–469.
2 Waldum B, Westheim AS, Sandvik L, Flonaes B, Grundtvig M, Gullestad L, Hole T, Os I: Renal function in outpatients with chronic heart failure. J Card Fail 2010;16:374–380.
3 van Deursen VM, Urso R, Laroche C, Damman K, Dahlstrom U, Tavazzi L, Maggioni AP, Voors AA: Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail 2014;16:103–111.
4 Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, Hallan HA, Lydersen S, Holmen J: International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J Am Soc Nephrol 2006;17:2275–2284.
5 Coca SG, Krumholz HM, Garg AX, Parikh CR: Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. JAMA 2006;296:1377–1384.
6 Klungel OH, Martens EP, Psaty BM, Grobbee DE, Sullivan SD, Stricker BH, Leufkens HG, de Boer A: Methods to assess intended effects of drug treatment in observational studies are reviewed. J Clin Epidemiol 2004;57:1223–1231.
7 McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, et al: ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803–869.
8 Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, et al: 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128:1810–1852.
9 Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA: Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. New Engl J Med 2004;351:543–551.
10 Svensson M, Gustafsson F, Galatius S, Hildebrandt PR, Atar D: How prevalent is hyperkalemia and renal dysfunction during treatment with spironolactone in patients with congestive heart failure? J Card Fail 2004;10:297–303.
11 Clark H, Krum H, Hopper I: Worsening renal function during renin-angiotensin-aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction. Eur J Heart Fail 2014;16:41–48.
12 Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, van Veldhuisen DJ, Hillege HL: Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. J Card Fail 2007;13:599–608.
13 Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW: The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35:681–689.

14 Maeder MT, Rickli H, Pfisterer ME, Muzzarelli S, Ammann P, Fehr T, Hack D, Weilenmann D, Dieterle T, Kiencke S, et al: Incidence, clinical predictors, and prognostic impact of worsening renal function in elderly patients with chronic heart failure on intensive medical therapy. Am Heart J 2012;163:407–414, 414.e401.
15 Remme WJ, Swedberg K, Task Force for the D, Treatment of Chronic Heart Failure ESoC: Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527–1560.
16 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al: A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612.
17 Pitt B, Zannad F, Remme WJ, 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. New Engl J Med 1999;341:709–717.
18 Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B: Eplerenone in patients with systolic heart failure and mild symptoms. New Engl J Med 2011;364:11–21.
19 Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M: Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. New Engl J Med 2003;348:1309–1321.
20 Lund LH, Svennblad B, Melhus H, Hallberg P, Dahlstrom U, Edner M: Association of spironolactone use with all-cause mortality in heart failure: a propensity scored cohort study. Circ Heart Fail 2013;6:174–183.
21 Vardeny O, Wu DH, Desai A, Rossignol P, Zannad F, Pitt B, Solomon SD: Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). J Am Coll Cardiol 2012;60:2082–2089.
22 Niederseer D, Thaler CW, Niederseer M, Niebauer J: Mismatch between heart failure patients in clinical trials and the real world. Int J Cardiol 2013;168:1859–1865.
23 Rossignol P, Cleland JG, Bhandari S, Tala S, Gustafsson F, Fay R, Lamiral Z, Dobre D, Pitt B, Zannad F: Determinants and consequences of renal function variations with aldosterone blocker therapy in heart failure patients after myocardial infarction: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. Circulation 2012;125:271–279.
24 Brunner-La Rocca HP, Knackstedt C, Eurlings L, Rolny V, Krause F, Pfisterer ME, Tobler D, Rickenbacher P, Maeder MT: Impact of worsening renal function related to medication in heart failure. Eur J Heart Fail 2015;17:159–168.
25 Austin PC: An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399–424.