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Trajectories of Changes in Renal Function in Patients with Acute Heart Failure

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ABSTRACT

Background: Changes in renal function have been associated with differential outcomes in patients with acute heart failure (HF). However, individual trajectories of changes in renal function are unknown, and it is unclear whether they relate to different clinical characteristics and clinical outcomes. Our aim was to investigate the prognostic importance of individual trajectories of change in renal function in acute HF.

Methods: This was a retrospective, observational analysis from the double-blind, randomized, placebo-controlled PROTECT trial in patients with acute HF. We identified and internally validated 8 different renal trajectories among 1897 patients by visual inspection of inhospital serum creatinine changes. The primary outcome measure was all-cause mortality at 180 days. Mean age was 70 ± 12 years; 70% were male, and mean baseline estimated glomerular filtration rate was 49.0 mL/min/1.73m^2.

Results: A total of 8 different trajectories was established. The most prevalent trajectories were an inhospital bump (19.0%), a sustained increase (17.6%) and a dip (14.5%) in serum creatinine. Overall, the clinical characteristics of patients in different trajectories were remarkably similar. Crude 180-day mortality rates ranged from 12.0% in the trajectory, with no significant changes to 18.3% in the trajectory of sustained increase without significant differences. Overall, after multivariable adjustment, there was no trajectory of changes in renal function that was associated with significantly better or worse outcomes.

Conclusions: Trajectories of changes in renal function in acute HF differ considerably on the patient level. Despite these differences, clinical characteristics and outcomes were similar, therefore, questioning the prognostic importance of changes in renal function in acute HF. (*J Cardiac Fail 2019;25:866–874*)

Key Words: Acute Heart Failure, Individual Renal Patterns, Trajectories of Renal Function.

Introduction

Acute heart failure (HF) is a major health care problem, affecting nearly 1 million new patients per year. It is associated with poor clinical outcomes.[1–4] When chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m^2, is present in acute HF, it is associated with a 2-fold increased risk of mortality.[5] In addition to impaired baseline renal function, deterioration in renal function or worsening renal function (WRF) during hospitalization is commonly observed in patients with acute HF.[5–7] In a meta-analysis, WRF was associated with an increased risk of mortality and HF hospitalization in patients with chronic HF who have both reduced and preserved ejection fraction.[8] In acute HF, in which WRF occurs in 20%–30% of patients, deterioration was also associated with a significantly increased mortality risk.[5,9] On a population level, it has been shown that the mean change in renal function during hospitalization is reflected

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by an increase in serum creatinine that flattens during a longer inhospital stay, which is thought to be related to the great diversity in renal changes in patients.[10]

However, it is questionable whether this analysis was able to capture the individual heterogeneity of patterns of renal function because we hypothesized that individual renal trajectories do not strictly follow the trajectory in a homogeneous population. Therefore, we evaluated the presence of distinct individual trajectories of change in renal function in acute HF and investigated their associations with clinical characteristics and outcomes in an analysis from the Placebo-controlled Randomized Study of Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) study.

Methods

Patients

The main design and findings of the PROTECT trial, a multicenter, randomized, double-blind, placebo-controlled phase III trial, have been published.[11,12]

In short, 2033 patients with acute (decompensated) HF requiring IV diuretic therapy, with mild or moderate renal impairment (estimated creatinine clearance between 20 and 80 mL/min), were randomized to Rolofylline or placebo. The main findings were neutral. Crucial exclusion criteria included a systolic blood pressure < 90 or ≥ 160 mmHg and ongoing or planned treatment with ultrafiltration or dialysis. All patients provided written informed consent.

For the purpose of this analysis, we included all patients in the intention-to-treat population who were still alive at study day 7, had ≥ 3 serum creatinine measurements taken within the first 7 days of the study, had baseline creatinine measurements, and had additional follow-up for death and rehospitalization of ≥ 7 days. Using these criteria, the sample size for the present study was 1897 patients of the total study population (93%). Serum creatinine was assessed in a central laboratory (ICON Laboratories, Farmingdale, New York).

Trajectory establishment and assessment

In a random sample of 200 patients of the population, 3 independent investigators (IB, KS, JTM) identified clusters of different renal trajectories in a blinded (for outcome and other characteristics) fashion. Each investigator looked at the trajectories of individual patients while blinded to the results of the other investigators. This was performed by visual inspection of each patient's individual pattern of serum creatinine when printed on a Y-axis normalized for individual patient absolute creatinine values. Then results were pooled, and inconsistencies were solved by consensus, including assessment by a fourth investigator (KD). This resulted in 8 distinct different renal trajectories.

Subsequently, 2 researchers (IB, KS) individually assigned each patient in the entire study population to 1 of the 8 trajectories in a blinded matter in a similar procedure. Afterwards, results were pooled and inconsistencies were solved by consensus, which again included assessment by a third investigator (KD). To check whether the level of agreement between the investigators was acceptable, interobserver agreement was measured by κ statistics.

Study outcomes

The primary outcome variable of interest was all-cause mortality at 180 days. The secondary outcome included cardiovascular or renal rehospitalization at 60 days and death or rehospitalization for HF at 60 days.

Statistical analysis

Symmetrically distributed continuous variables are presented as mean $\pm$ standard deviation; skewed data are presented as median and 25^{th}–75^{th} percentile. Categorical variables are presented as numbers (percentage) (N[%]). Differences in baseline characteristics were evaluated using appropriate statistics, such as ANOVA statistics (normal distribution) or Kruskal-Wallis statistics (skewed data). Differences in proportions were assessed using χ^2 tests. Event rates at the time points of interest are presented using percentages and Kaplan-Meier figures. Logarithmic transformations were applied to model nonlinear relationships. To evaluate the relationships among different trajectories and clinical outcomes, a Cox proportional hazard analysis was performed. For each continuous predictor, the assumption of linearity was checked. Multivariable adjustment was done in 2 steps. First, adjustment for baseline eGFR (calculated by the CKD-EPI formula),[13] and second, a multivariable model based on a previously published 8-item prognostic model in this population, including the variables of age, systolic blood pressure, edema, previous history of hospitalization for HF, baseline serum albumin, blood urea nitrogen, creatinine, and sodium.[14] Estimates are presented as hazard ratios (HR) with 95% confidence intervals (CI). As a sensitivity analysis and internal-validation step, we also evaluated the trajectories of serum creatinine in each of the defined trajectories by using a repeated measures, random effect model. Two-tailed P values < 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics v. 23 (Armonk, New York, USA) and R: a Language and Environment for Statistical Computing, v. 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).[15]

Results

Population

The study population consisted of 1897 patients, of whom 70% were male and had a mean age of 70 ± 12 years, a left ventricular ejection fraction of 32 ± 13% and a baseline eGFR of 49 ± 20 mL/min/1.73m^2. Median diuretic response over 4 days was -0.39 (-0.80 to -0.14) kg/40 mg furosemide.

Trajectories

First, we identified 8 renal trajectories identified by changes in creatinine, as seen in Figure 1. These included a drop followed by a rise (Dip), a rise followed by a drop (Bump), a Dip followed by Bump, a Bump followed by Dip, a Sustained Decrease, a Sustained Increase, an (almost) absence of change (No Change) and, finally, multiple significant fluctuations (Various Changes) that fitted none of the other trajectories.

The κ value for the pilot study (200 patients) was 0.82 (0.77−0.86, 95% CI), correlating with a strong level of agreement. After all 1897 patients were categorized into 1 of the 8 trajectories, the κ value was 0.85 (0.83−0.86, 95% CI). In a sensitivity analysis, we retrospectively evaluated the trajectories of creatinine in each of the defined trajectories. The results of this validation step are shown in Supplementary Figure 1. This confirms the general slope of creatinine on a group level within each trajectory, with the exception of the Various Changes trajectory, which probably represents a mixed bag, with individual changes in creatinine that, on a group level, oppose one another, resulting in a horizontal slope.

The distribution of the prevalence of different trajectories is shown in Figure 1; it ranges from 50 (2.6%) in No Change to 360 (19.0%) in Bump.

Baseline characteristics

Baseline characteristics of the different trajectories are shown in Table 1. Overall, the characteristics of different trajectories were similar, and only small differences were observed. Notably, patients with the trajectory No Change were more likely to be male and had the highest body mass indexes, whereas patients with trajectory Sustained Increase were the oldest. The trajectory Sustained Decrease included patients who had the lowest left ventricular ejection fraction (31% ± 13%) and most commonly were in New York Heart Association class IV (44%). Mean baseline eGFR, was lowest in this group, with a corresponding creatinine value of 1.60 (1.30−2.10) mg/dL. The trajectory Dip followed by Bump included patients who had the highest prescription rates of angiotensin converting enzyme (ACE) inhibitors. Regarding clinical symptoms, severe dyspnea was most commonly present in patients included in trajectory Dip (88.8%). The trajectories of Sustained Increase, Bump and No Change showed the worst diuretic responses: −0.33 (−0.78 to −0.10), −0.33 (−0.70 to −0.11), and −0.26 (−0.47 to −0.14) kg/40 mg furosemide, respectively. The best diuretic response was found in the trajectory Various Changes: −0.46 (−0.97 to 0.16) kg/40 mg furosemide (P value = 0.001). Hemoconcentration, defined as an increase in hemoglobin from admission to day 7 (or discharge) varied between 48% (Drop) and 67% (Pancake) but was not significantly different between trajectories.

Renal trajectories and clinical outcomes

During follow-up, 301 (15.9%) of 1897 patients experienced the primary outcome of all-cause mortality at day 180. Among all renal trajectories, differences in mortality were small and not significantly different. In the trajectory with a sustained increase in creatinine, 61 patients (18.3%)

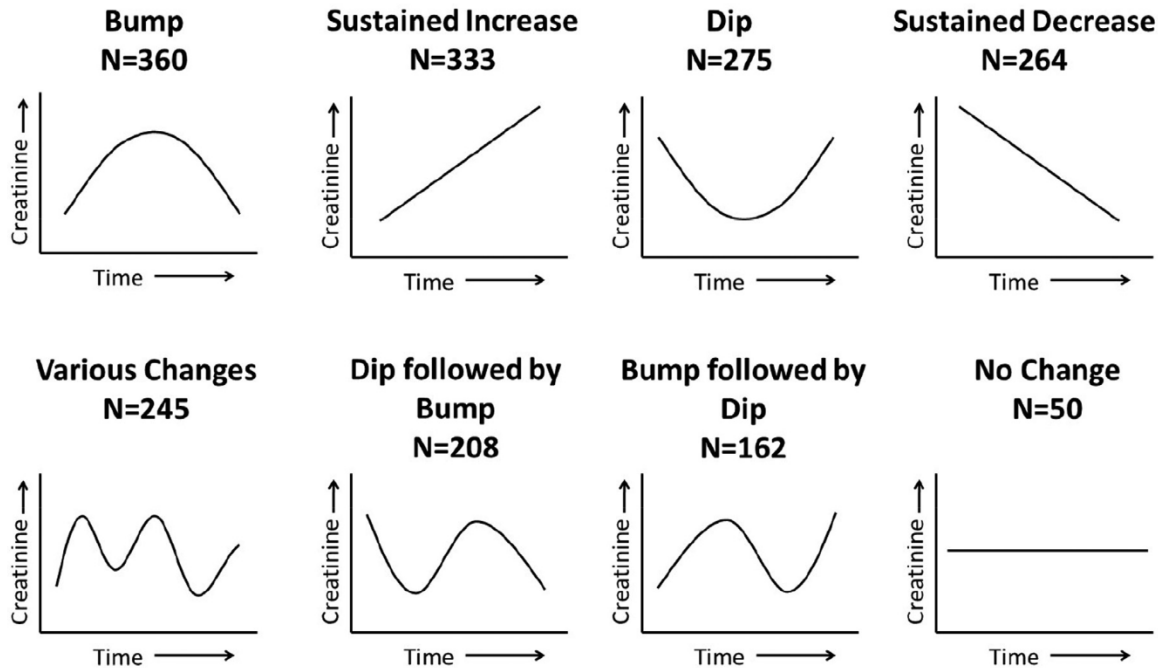

Fig. 1. Prevalence and visual representation of differing trajectories of changes in renal function. Dip: a drop followed by a rise; Bump: a rise followed by a drop; Dip followed by Bump: a drop followed by a rise and subsequent drop; Bump followed by Dip: a rise followed by a drop and a subsequent rise; Sustained Decrease: a continuous decrease; Sustained Increase: a continuous increase; No Change: an (almost) absence of change; Various Changes: multiple significant fluctuations (not fitting other trajectories).

Table 1. Baseline Characteristics

Trajectory	Bump	Sustained increase	Dip	Sustained decrease	Various changes	Dip followed by Bump	Bump followed by Dip	No change	*P* Value
N = 1897	N = 360	N = 333	N = 275	N = 264	N = 245	N = 208	N = 162	N = 50	
Demographics									
Sex (% male)	242 (67)	217 (65)	176 (64)	182 (69)	167 (68)	138 (66)	106 (65)	42 (84)	0.254
Age (years)	70 ± 12	72 ± 11	70 ± 12	70 ± 11	69 ± 12	68 ± 12	70 ± 11	68 ± 13	0.064
Race (% white)	337 (94)	310 (94)	266 (97)	247 (94)	238 (98)	200 (97)	154 (96)	47 (94)	0.150
Weight (kg)	80 ± 18	83 ± 19	82 ± 20	82 ± 20	83 ± 20	83 ± 18	78 ± 17	91 ± 23	0.002
Height (cm)	168 ± 9	169 ± 9	169 ± 9	169 ± 10	169 ± 9	169 ± 9	167 ± 10	170 ± 8	0.253
Body mass index	29 ± 6	29 ± 6	29 ± 7	29 ± 6	29 ± 6	29 ± 6	28 ± 5	31 ± 7	0.026
LVEF (%)	32 ± 13	33 ± 13	32 ± 12	31 ± 13	32 ± 14	33 ± 13	33 ± 13	31 ± 14	0.638
SBP (mmHg)	125 ± 17	127 ± 19	124 ± 17	121± 17	124 ± 18	124 ± 17	126 ± 19	124 ± 16	0.020
DBP (mmHg)	75 ± 11	73 ± 13	74 ± 11	73± 12	75 ± 12	75 ± 11	73 ± 12	72 ± 11	0.050
Heart rate (beats/min)	80 ± 15	79 ± 15	80 ± 16	81± 17	81 ± 16	82 ± 15	79 ± 16	80 ± 13	0.130
Medication									
ACE inhibitor	234 (65)	181 (54)	165 (60)	174 (66)	158 (65)	139 (67)	103 (64)	27 (54)	0.025
ARB	52 (14)	82 (25)	45 (16)	32 (12)	28 (11)	25 (12)	24 (15)	9 (18)	<0.001
Beta-blocker	273 (76)	254 (76)	219 (80)	199 (75)	184 (75)	165 (79)	121 (75)	43 (86)	0.574
Nitrates	84 (23)	91 (27)	58 (21)	79 (30)	69 (28)	59 (28)	36 (22)	12 (24)	0.199
Ca channel blocker	53 (15)	60 (18)	33 (12)	27 (10)	23 (9)	26 (13)	25 (15)	10 (20)	0.033
MRA	159 (44)	148 (44)	111 (40)	115 (44)	107 (44)	105 (51)	74 (46)	24 (48)	0.607
Medical history									
Angina (N(%))	79 (22)	67 (20)	57 (21)	65 (25)	65 (27)	45 (22)	33 (21)	9 (18)	0.572
AF	185 (51)	166 (50)	160 (59)	160 (61)	131 (54)	107 (52)	87 (55)	28 (60)	0.126
Smoking	71 (20)	81 (24)	53 (19)	52 (20)	54 (22)	37 (18)	32 (20)	14 (28)	0.500
NYHA									<0.001
I/II	64 (19)	81 (26)	46 (18)	26 (10)	42 (18)	30 (15)	25 (16)	6 (12)	
III	174 (51)	169 (54)	139 (54)	116 (46)	120 (52)	94 (47)	79 (51)	28 (56)	
IV	103 (30)	65 (21)	75 (29)	111 (44)	69 (30)	75 (38)	50 (33)	16 (32)	
Diabetes mellitus	153 (43)	157 (47)	138 (50)	115 (44)	115 (47)	92 (44)	68 (42)	25 (50)	0.540
Hypertension	277 (77)	281 (84)	213 (78)	214 (81)	192 (78)	173 (83)	123 (76)	36 (72)	0.090
Ischemic HD	249 (69)	247 (74)	194 (71)	181 (69)	154 (63)	144 (69)	110 (68)	41 (82)	0.092
MI	174 (48)	180 (54)	139 (51)	130 (49)	107 (44)	105 (51)	77 (48)	32 (64)	0.157
PCI	92 (26)	112 (34)	74 (27)	59 (23)	54 (22)	42 (20)	35 (22)	23 (47)	<0.001
Stroke (beyond 2 yrs)	26 (7)	33 (10)	23 (8)	27 (10)	17 (7)	22 (11)	17 (11)	7 (14)	0.521
Biomarkers									
Albumin (g/dL)	3.9 (3.7−4.2)	3.9 (3.6−4.1)	3.9 (3.7−4.1)	3.8 (3.6−4.1)	3.9 (3.6-4.2)	3.8 (3.6−4.15)	3.9 (3.6−4.2)	3.8 (3.6−4.15)	0.005
Chloride (mEq/L)	101 (98−105)	102 (99−105)	101 (99−104)	101 (97-105)	102 (99−104)	102 (99−104)	102 (97−104)	102 (100−106)	0.035
Cholesterol, total (mg/dL)	148 (123−180)	146 (115−176)	141 (117−163)	132 (107−164)	158 (127−188)	147 (122−168)	152 (125−185)	146 (124−171)	0.001
Glucose, random, Serum (mg/dL)	127 (97−164)	123 (103−154)	146 (117−207)	124 (102-167)	133 (106−175)	133 (108−181)	117 (92−138)	133 (121−191)	0.004
Potassium (mEq/L)	4.2 (3.9−4.6)	4.2 (3.8−4.6)	4.3 (3.9−4.7)	4.4 (3.9-4.9)	4.2 (3.9−4.7)	4.2 (3.9−4.7)	4.25 (3.9−4.6)	4.5 (3.95−4.85)	0.097
Sodium (mEq/L)	140 (138−142)	140 (138−143)	140 (137−143)	139 (137-142)	141 (138−143)	140 (138−142)	139 (137−142)	140 (139−143)	0.012
Uric acid (mg/dL)	8.4 (6.8−10.4)	8.8 (7.2−10.3)	8.8 (7.4−10.5)	9.4 (7.6−11.3)	7.9 (6.4-10.1)	8.8 (7.1−10.1)	8.5 (7.2−10.1)	9.1 (6.8−10.3)	<0.001
eGFR (mL/min/1.73m^2)	50.66 ± 20.75	49.14 ± 20.26	50.22 ± 19.59	43.63 ± 16.27	56.47 ± 21.92	51.12 ± 18.57	55.59 ± 20.50	54.06 ± 22.26	<0.001
Creatinine (mg/dL)	1.40 (1.10−150)	1.40 (1.10−1.80)	1.40 (1.10−1.70)	1.60 (1.30−2.10)	1.20 (1.10−1.50)	1.40 (1.10−1.80)	106 (1.00−1.50)	1.50 (1.20−2.00)	<0.001
Hct (%)	40.2 ± 6.2	38.7 ± 5.6	40.5 ± 6.3	40.5 ± 6.2	41.6 ± 6.2	40.9 ± 6.4	40.3 ± 6.2	40.2 ± 5.5	<0.001
Hgb (g/dL)	12.7 ± 1.9	12.2 ± 1.8	12.7 ± 2.0	12.7 ± 2.0	13.2 ± 2.0	12.8 ± 2.0	12.9 ± 2.1	12.6 ± 1.9	<0.001
BUN (mg/dL)	28 (22−39)	31 (22−38)	30 (22-42)	37 (26−50)	27 (21−35)	29 (21−40)	25 (20−35)	29 (22−38)	<0.001
BNP (pg/mL)	406 (248−735)	408 (247−694)	440 (267-860)	612 (296−1007)	432 (253−745)	484 (257−797)	415 (266−780)	443 (219−654)	0.002

(*continued on next page*)

Table 1 (*Continued*)

Trajectory	Bump	Sustained increase	Dip	Sustained decrease	Various changes	Dip followed by Bump	Bump followed by Dip	No change	*P* Value
Clinical symptoms									
Dyspnea on exertion	353 (99.7)	321 (100.0)	275 (99.6)	262 (100.0)	234 (100.0)	203 (100.0)	158 (100.0)	48 (100.0)	0.781
Severe dyspnea	199 (56.2)	161 (50.2)	154 (88.8)	159 (60.7)	149 (63.7)	126 (62.1)	94 (59.5)	25 (52.1)	0.037
JVP (> 10 cm)	123 (37.4)	131 (42.5)	122 (47.7)	99 (41.4)	88 (40.2)	82 (43.4)	41 (27.9)	22 (44.9)	0.012
Orthopnea (> 3 pil)	148 (41.3)	139 (41.9)	129 (46.7)	125 (46.8)	105 (43.4)	88 (43.1)	73 (45.1)	22 (44.0)	0.836
Edema > 3+	90 (24.9)	77 (22.6)	78 (28.1)	89 (33.2)	78 (31.8)	61 (29.3)	37 (22.7)	15 (29.4)	0.045
Rales > 2/3	34 (9.4)	30 (8.8)	25 (9.0)	27 (10.1)	36 (14.8)	21 (10.1)	11 (6.7)	2 (3.9)	0.129
Diuretic response (kg/40 mg Furosemide)	−0.33 (−0.70 to 0.11)	−0.33 (−0.78 to 0.10)	−0.44 (−0.83 to 0.22)	−0.41 (−0.78 to 0.14)	−0.46 (−0.97 to 0.16)	−0.44 (−0.91 to 0.18)	−0.36 (−0.71 to 0.14)	−0.26 (−0.47 to 0.14)	0.001
Outcome									
Death day 180	59 (16.3)	68 (20.0)	43 (15.5)	51 (19.0)	41 (16.7)	25 (12.0)	24 (14.7)	7 (13.7)	0.321
Death or HF rehospitalization day 60	83 (22.9)	82 (24.1)	55 (19.8)	59 (22.0)	36 (14.7)	40 (19.2)	33 (20.2)	15 (29.4)	0.111
Cardiovascular or renal rehospitalization	97 (26.8)	89 (26.2)	61 (21.9)	58 (21.6)	49 (20.0)	45 (21.6)	33 (20.2)	17 (33.3)	0.176

ACE, angiotensin converting enzyme; AF, atrium fibrillation; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; Hct, hematocrit; HD, heart disease; Hgb, hemoglobin; HR, heart rate; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

Values are given as means ± standard deviation, median (interquartile range) or percentage and frequency.

experienced the primary endpoint of all-cause mortality. In the trajectory of sustained decrease, which represents the opposite of the sustained increase trajectory, 48 patients (18.2%) experienced the primary outcome. Notably, the trajectory with almost an absence of change in renal function, No Change, had the lowest mortality rate; 6 patients (12.0%) experienced all-cause mortality at 180 days.

The Kaplan-Meier figure for the primary outcome, mortality at 180 days, among renal trajectories is depicted in Figure 2 (logrank *P* value of 0.51) and showed, in general, similar outcomes for all groups.

In Cox regression analysis, using the trajectory No Change as the reference category (no change in serum creatinine, which showed the best outcome in the Kaplan-Meier survival analysis), the highest mortality risk was observed in both the trajectory Sustained Decrease (HR 1.58, 95% CI 0.68 to 3.70) and the trajectory Sustained Increase (HR 1.59, 95% CI 0.69 to 3.68). However, these differences did not reach statistical significance (*P* value 0.29 and 0.28, respectively) (Table 2). Other trajectories showed a similar pattern, without evidence of increased or decreased risk with any particular trajectory.

In multivariable Cox regression analysis, after adjustment for baseline eGFR, similar findings remained (Table 2). Whereas eGFR at baseline itself was a powerful predictor of mortality, none of the trajectories showed a significant association with increased mortality rates. Even when adjusted for baseline diuretic response, no significant differences were found. Finally, after adjustment for the 8−variable multivariable model previously published from this population, the results remained largely unchanged.

The secondary combined endpoint of death or cardiovascular or renal rehospitalization at day 60 (Figure 3) showed similar results for all trajectories. However, a trend was observed in favor of the fluctuating trajectory Various Changes regarding all the secondary outcomes in unadjusted analyses, whereas the trajectory No Change showed the worst outcomes. However, in Cox regression analysis and after multivariable adjustment, no statistically significant differences among the trajectories were observed.

Discussion

This study was designed to identify patterns of changes in renal function during a hospital admission for acute HF and to relate these patterns to differing clinical characteristics and outcomes. Our results show that despite marked differences in patterns, as determined on an individual patient level, differences in clinical characteristics and clinical outcomes were small.

Epidemiology of renal trajectories

In acute heart failure, 20%−30% of patients experience deterioration or worsening renal function during hospitalization.[5,16] This mean change in renal function in a population with HF is reflected by an increase in serum creatinine that

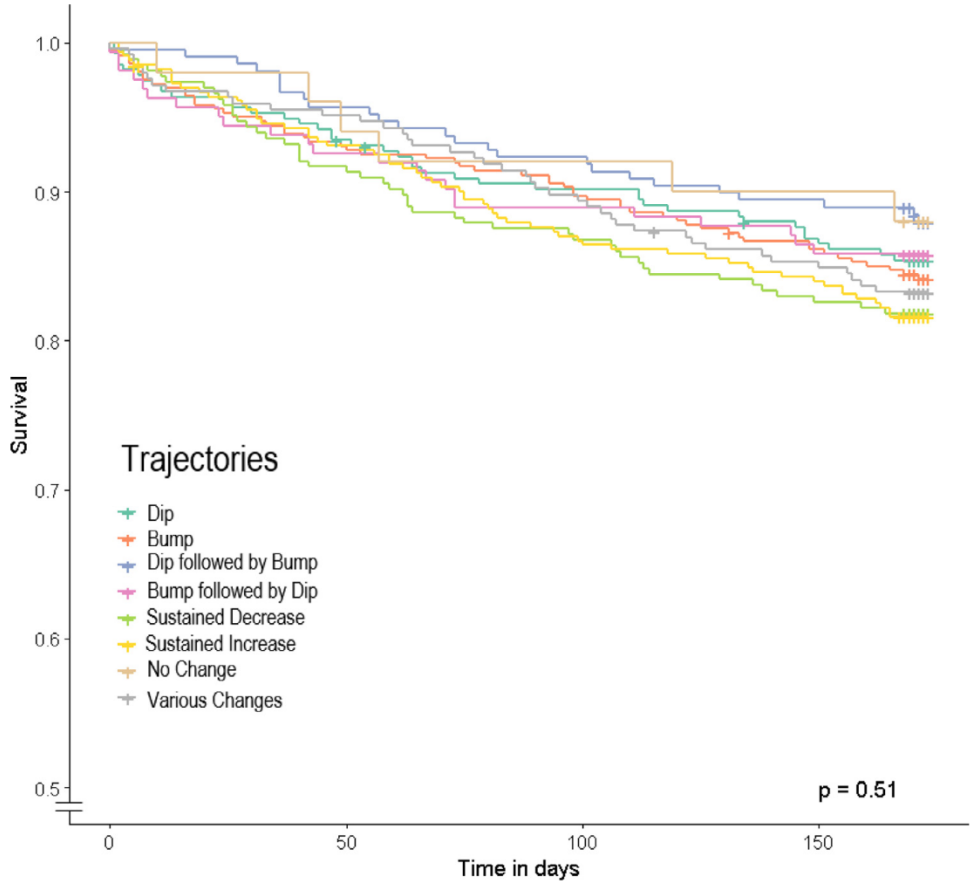

Fig. 2. Differing trajectories and Kaplan-Meier plot of all-cause mortality at 180 days.

reaches a plateau during a longer inhospital stay.[10] However, because the overall characteristics of the population with acute heart failure have great heterogeneity, this may also hold true for patterns of changes in renal function.[17] More evidence of this heterogeneity of the population with HF is also stressed by a recent meta-analysis, in which findings suggest that not only the clinical setting, but also the cause of WRF and associated hemodynamic changes, are of major importance for evaluating the significance of WRF.[5] In a smaller study of 401 patients with with acute decompensated HF, WRF occurred in 21.2% (defined as $\geq$ 20% change in eGFR), while also showing that an improvement in renal function (identified by a decrease in creatinine, similar to the trajectory Sustained Decrease in our study) occurred in 16.2% of the population.[18] Overall, in this small study, the baseline characteristics of both worsening and improving renal function were similar.[19] Despite the innovative comparison of the assessment of 2 opposing renal-function changes, the focus of these particular analyses were still on the change in renal function on a population level. One possible explanation was put forward by Kataoka, suggesting that "paradoxical" improvement of renal function, as reflected by a decrease in serum creatinine despite worsening HF, could be due to interindividual differences in renal function among patients. Moreover, most studies have used merely 2 time points of measurements of serum creatinine to quantify changes in renal function, instead of using several measurements to form a realistic slope.[5,20,21] Therefore, in this present study, we thoroughly evaluated each individual renal trajectory and subsequently identified 8 distinct trajectories of changes of renal function. Of these patterns, a rise in creatinine followed by a drop (trajectory Bump) was most prevalent, whereas almost an absence of change in creatinine (trajectory No Change) was least common. Interestingly, the 2 most opposing trajectories, a sustained increase vs a sustained decrease, had similar baseline characteristics. Overall, baseline differences among all trajectories were remarkably small, despite the great diversity in the individual changes in renal function patterns. Therefore, it might be difficult to establish specific characteristics that identify beforehand which patients will experience similar patterns of change in renal function.

Clinical outcomes and patterns of change in renal function

In general, WRF in acute HF has been associated with worse clinical outcome because it is independently associated with significantly increased mortality and rehospitalization risks.[5,22] However, this does not directly imply that the likelihood of survival improves if treatment causes improvement in serum creatinine changes. On the contrary, it has been shown that also improved renal function, as shown by a decrease in serum creatinine, is associated with a significant,

Table 2. Cox Survival Analysis for Predicting 180-Day Mortality

Trajectory	Number of patients N (%)	HR (95% CI)	*P* Value	HR (95% CI)*	*P* Value	HR (95% CI)†	*P* Value
No change	50	Ref.	0.52	Ref.	0.57	Ref.	0.46
Bump	360	1.35 (0.58−3.13)	0.48	1.40 (0.60−3.24)	0.43	1.53 (0.66−3.57)	0.32
Sustained increase	333	1.59 (0.69−3.68)	0.28	1.57 (0.68−3.63)	0.29	1.59 (0.68−3.69)	0.28
Dip	275	1.24 (0.53−2.93)	0.62	1.24 (0.52−2.92)	0.63	1.27 (0.54−3.02)	0.58
Sustained decrease	264	1.58 (0.68−3.70)	0.29	1.41 (0.60−3.30)	0.43	1.19 (0.51−2.79)	0.69
Various changes	245	1.43 (0.61−3.36)	0.42	1.67 (0.71−3.93)	0.24	1.74 (0.73−4.13)	0.21
Dip followed by Bump	208	1.00 (0.41−2.44)	1.00	1.02 (0.42−2.49)	0.96	1.11 (0.45−2.73)	0.82
Bump followed by Dip	162	1.22 (0.50−2.99)	0.68	1.38 (0.56−3.40)	0.49	1.45 (0.59−3.59)	0.42

*Model 2. Renal trajectories adjusted for estimated GFR.
†Model 3. Renal trajectories adjusted for age of subject, systolic blood pressure, heart failure hospitalization in past year, severity of edema, baseline albumin (g/dL), sodium (mEq/L), blood urea nitrogen (BUN) (mg/dL), and creatinine (mg/dL).

independent, increased risk of mortality, and WRF in the context of hemoconcentration is not associated with worse outcomes.[7,18,23] Furthermore, the important role of individual risk factors and biomarkers is emphasized; they provide more prognostic information than the sum of population risk factors.[24] Therefore, this present study investigated the prognostic role of the trajectory of serum creatinine as an individual renal marker. Overall, our study found that differences in all-cause mortality were small, even when adjusted for baseline eGFR. The individual renal pattern that is considered to be "true" WRF, a continuous increase in creatinine (Sustained Increase) had unexpectedly similar outcomes when compared to the opposing trajectory, a constant decrease in creatinine (Sustained Decrease), or so-called improved renal function. We were also unable to find other statistically significant differences in clinical outcome for any of the trajectories, for all-cause mortality and the secondary outcomes. Although small differences were observed in crude event rates, it is questionable whether this translates into clinically relevant changes. Overall, we found no significant evidence for an increased or decreased risk with any particular trajectory.

Possible explanations and clinical implications

There are several possible explanations for the present findings. One explanation could be the impact of changes in treatment strategies, which were based on either changes in renal function or actually caused the changes in renal

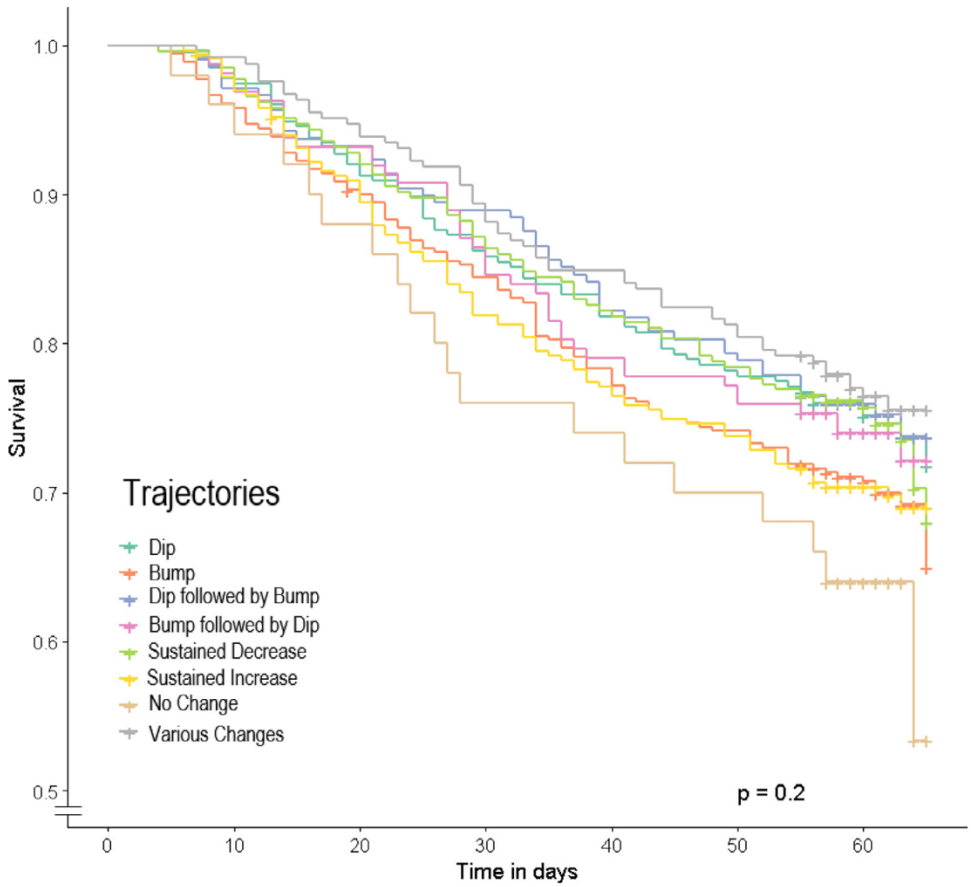

Fig. 3. Differing trajectories and Kaplan-Meier plot of death or cardiovascular or renal rehospitalization at 60 days.

function. Cardiologists routinely assess changes in renal function during treatment of acute HF and probably act on these changes in response to therapy. Our findings are, therefore, a reflection of the general course of creatinine, together with the effect of (changes in) decongestive strategies. In this way, perhaps, by adjusting therapies, physicians may have overcome some of the excess of risk that has been associated with WRF in acute heart failure. Second, it is known that patients with HF commonly experience deterioration in renal function prior to hospital admission, as well as posthospital recurrence of renal dysfunction.[18,25] This means that the observed inhospital changes in creatinine may be only a reflection of a small part of the entire timeframe in which serum creatinine levels may change. Furthermore, renal function changes should always be evaluated together with the clinical course of the patient.[22] However, diuretic response,[26] serving as a surrogate for the clinical course, was not particularly different among trajectories and did not impact the association between trajectories and clinical outcomes.

Strengths and limitations

The novelty of this present study is the use of individual patient data to define the patterns and trajectories of renal function. Individual patient data most accurately reflect real clinical practice. Nevertheless, this is a post hoc analysis, and our findings should, therefore, be considered hypothesis-generating only. Our study was conducted in a cohort of a randomized controlled trial, in which treating physicians were unblinded to serum creatinine values and could have consequently altered their treatment regimes, resulting in altered risks among patients. The inclusion and exclusion criteria of this randomized controlled trial may have resulted in selection bias, possibly inducing type I error. Furthermore, our results are limited by the data available, as our analysis only includes the first 7 days of inhospital events and, therefore, excludes events prior to hospitalization or after discharge. For example, a patient with HF who experiences a continuous decrease in creatinine during the first 7 days after admission might experience a change in renal function after discharge, unknowingly altering the individual risk of mortality. It is still difficult to characterize accurately renal function in acute HF, which could mean that serum creatinine changes in the acute phase do not reflect changes in renal function. Furthermore, trajectory assessment was performed by visual inspection and might result in a different distribution in the trajectory groups when reproduced by different investigators. Additionally, we did not include the magnitude of change in creatinine in our analysis because we focused on the relative change (visual trajectories). The trajectory Various Changes probably represents a mixed bag of differing changes in serum creatinine because the overall changes in creatinine in sensitivity analysis were limited. Given the large number of defined trajectories and the known random variation due to the creatinine assay or random sampling variation, the true changes in creatinine levels in each patient could have been over- or underestimated. Finally, to establish more than 1 fluctuation in creatinine, more than 4 serum creatinine values should be available; therefore, the prevalence of the trajectories Various Changes, Bump followed by Dip and Dip followed by Bump may have been underestimated.

Conclusions

Although there are major differences in patterns of changes in renal function during a hospital admission resulting from acute HF, clinical characteristics and clinical outcomes were similar in the trajectories. Our results, therefore, question the prognostic importance of patterns of changes in renal function in acute HF.

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J.C. was on the Steering Committee for the PROTECT trial, served on the advisory board for MSD, and received payments for both. C.O'C. is a consultant to Merck & Co., Inc., Kenilworth, NJ, USA. P.P. has received honoraria from MSD. B.D. and G.C. are employees of Momentum Research Inc., which was contracted to perform work on the project by Merck & Co., Inc., Kenilworth, NJ, USA. M. M. has received honoraria and reimbursements from NovaCardia, sponsors of the study, and MSD. M.G. has received institutional research support and served on a scientific Advisory Board for Merck & Co., Inc., Kenilworth, NJ, USA. J.T. has received research funds and consulting fees from Merck & Co., Inc., Kenilworth, NJ, USA. D.B. is an employee of Merck & Co., Inc., Kenilworth, NJ, USA. H. D. served as a consultant to Merck & Co., Inc., Kenilworth, NJ, USA. A.V. has received honoraria and reimbursements from NovaCardia, sponsors of the study, and MSD. All other authors declared to have no conflicts of interest. This work was supported by the Netherlands Cardiovascular Research Initiative, an initiative with support of the Dutch Heart Foundation [CVON2014-11 RECONNECT]

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.07.004.

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