

Impaired renal function affects clinical outcomes and management of patients with heart failure

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Abstract

Aims Inpatients with heart failure and renal impairment have poor outcomes and variable quality of care. We investigate treatment practice and outcomes in an unselected real-world cohort using historical creatinine measurements.

Methods and results Admissions between 1/4/2013 and 30/4/2015 diagnosed at discharge with heart failure were retrospectively analysed. Stages of chronic kidney disease (CKD) and acute kidney injury (AKI) were calculated from creatinine at discharge and 3–12 months before admission. We identified 1056 admissions of 851 patients (mean age 76 years, 56% Caucasian, 36% with diabetes mellitus, 54% with ischaemic heart disease, and 57% with valvular heart disease). CKD was common; 36%—Stage 3a/b, 11%—Stage 4/5; patients were older, more often diabetic, with higher potassium, lower haemoglobin, and more oedema but similar prevalence of left ventricular systolic dysfunction (LVSD) compared patients with Stages 0–2. AKI was present in 17.0% (10.4%—Stage 1, 3.7%—Stage 2, and 2.9%—Stage 3); these had higher potassium and lower haemoglobin than patients with no AKI. Length of stay was longer in Stage 4/5 CKD [11 days; $P = 0.008$] and AKI [13 days; $P = 0.006$]. Mortality was higher with Stage 4/5 CKD (13.8% compared with 7.7% for Stages 0–2 CKD [$P = 0.036$]) and increased with AKI (5%—no AKI, 20.9%—Stage 1, 35.9%—Stage 2, and 48.4%—Stage 3; $P < 0.001$). Adjusted for age, diabetes, and LVSD, both AKI and Stage 4/5 CKD were independent predictors of in-hospital mortality. In survivors with LVSD, the discharge prescription of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers decreased with progressive CKD, [84%—no-mild, 59%—moderate, and 36%—severe CKD; $P < 0.001$]; this was not purely explained by hyperkalaemia.

Conclusions Inpatients with heart failure and renal impairment, acute and chronic, failed to receive recommended therapy and had poor outcomes.

Keywords Heart failure; Kidney; Mortality; Epidemiology

Received: 19 July 2016; Revised: 15 February 2017; Accepted: 4 May 2017

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Introduction

Heart failure is a significant and growing public health problem. In England, over the year 2014–15, there were 764 977 admissions coded with heart failure as a diagnosis, with 70 890 of them in the first diagnostic position.¹ Whilst progress has been made with prognosis-modifying therapies in heart failure with left ventricular systolic dysfunction (LVSD), cases where ejection fraction is apparently preserved and where patients have multiple comorbidities remain a management challenge. The National Heart Failure Audit for

England and Wales revealed that patients had poor but still highly variable outcomes; patients aged <75 years and those managed on cardiology wards had a lower mortality of approximately 5%, compared with over 15% in other groups.²

Renal impairment on admission in patients admitted with heart failure is common, present in approximately half, and associated with high mortality.^{3–5} Similarly, worsening renal failure during acute admissions with heart failure is associated with increased length of stay, high cost, and up to eight-fold higher mortality.^{6,7} However, the cause of poor outcome associated with renal impairment in heart failure patients is

unclear. The neurohumoral signalling pathways and bidirectional haemodynamic interplay between the heart, the kidney, and therapy for heart failure in the healthy and impaired functional state are complex, and it has been observed that differing degrees, reversibility, and underlying causes of renal impairment have different prognostic implications.^{8,9} Previous studies have had a heterogeneous definition for renal impairment, with few using a historical (pre-admission) creatinine to assess chronicity of renal impairment.

Trials of treatments in heart failure often exclude patients with chronic kidney disease (CKD), leaving the evidence-base in this area relatively poor.¹⁰ Consequently, national and international guidelines and recommendations are required to extrapolate the beneficial impact of disease-modifying therapies and leave a degree of the decision-making in the hands of the clinicians.^{11–14} It has been demonstrated that adherence to recommendations regarding prescription of disease-modifying therapies is variable and is impacted by renal function in trial settings.^{2,15,16} It is not well known what impact renal impairment has on prescribing in current clinical practice, particularly when such patients are managed by non-cardiologists and non-nephrologists. In this study, we examine outcomes and prescribing practices in heart failure patients with and without renal impairment, using historic baseline creatinine measurements, in a hospital-wide cohort of patients from a multi-ethnic, inner-city community.

Methods

Patient identification and data collection

We undertook detailed analysis of data submitted from one hospital trust in England to the National Heart Failure Audit from April 2013 to April 2015 inclusive. These were retrospectively collected data on unscheduled admissions to an inner city UK teaching hospital coded on discharge with a primary diagnosis of heart failure or its accepted equivalents. Data were collected in accordance with the National Heart Failure Audit^{2,17} to which the trust submitted 98% of the Hospital Episodes Statistics (HES) registered primary heart failure diagnosis 2013–14.¹⁸ LVSD was defined by left ventricular ejection fraction of <40%. Loop diuretic doses were converted into furosemide equivalents, for example 1 mg of Bumetanide is equivalent to 40 mg of Furosemide.

Renal function data

Creatinine levels on discharge had been recorded routinely using the audit tool.¹⁸ Additionally, a prior baseline creatinine level was obtained from electronic patient notes; the latest reading that was more than 3 months but less than 12 months

prior to admission. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal disease (MDRD) formula¹⁹ and converted to CKD stages using the Kidney Disease Improving Global Outcomes criteria.²⁰ Severity of acute kidney injury (AKI) was determined by degree of acute change from baseline creatinine to discharge creatinine using the Kidney Disease Improving Global Outcomes criteria.²¹

Data clean-up and imputation of missing values

Patients discharged outside the specified time criteria and true duplicate entries were removed (10 admissions total). Special attention was paid to ensure no duplication of in-hospital death was recorded. Where a baseline creatinine was unavailable, there was assumed to be no CKD (Stage 0). In these cases, an AKI was assumed in the presence of a discharge creatinine above the normal range with the stage of AKI estimated based on the degree of elevation. Missing data from other variables were not imputed; if data were transformed to a dichotomous category, missing data points were coded as not being present. Where statistical analysis is made on a subset of the data, this is indicated in the relevant results section.

Statistical analysis

Mean, standard deviation (SD), and interquartile range (IQR) were determined for quantitative variables, frequency, and percentages for categorical variables. The inferential statistical analyses performed were independent samples *t*-tests for quantitative variables comparing two groups, one-way ANOVA tests comparing more than two groups and Pearson χ^2 tests for categorical variables. Two-sided *P*-values were calculated with a value of <0.05 considered statistically significant. Binomial logistic regression was performed for in-hospital mortality.

Results

Demographics and general observations

During the period April 2013–April 2015 inclusive, there were 1056 episodes where patients were discharged with a primary diagnosis of heart failure. These episodes relate to 851 individual patients, revealing a cohort of patients with repeated admissions during the investigated time frame. Baseline data for these individual patients are as follows. There were marginally more men (55.8%) than women, overall the population was elderly (mean age 75.9 years, SD 13.4), and multi-ethnic, with 56.4% White and the remaining 43.6% of non-Whites [a spread of Asian (16.9%), Black

(12.2%), and other (14.5%)]. Over a third of patients had diabetes mellitus (36.2%), and over half of patients had ischaemic heart disease (54.5%), valvular heart disease (57.3%), and hypertension (63.6%). Considering the main place of care for the total number of admissions, the large majority of patients were cared for on General Medical wards (61.7%) with 31.7% on specialist cardiology wards.

Chronic kidney disease

Baseline creatinine readings were available in 954 admissions (90.3%). Those with no recorded baseline were assumed to have CKD Stage 0 or 1 (eGFR > 90 mL/min/1.73m²). Prevalence and mortality figures for the stages of CKD are shown in *Table 1*. Approximately 75.28% of admissions had a baseline eGFR of <90 mL/min/1.73 m², and 47.35% had an eGFR of <60 mL/min/1.73m². Approximately 10.98% of admissions had an eGFR <30 mL/min/1.73m².

Admissions were grouped into three broader categories of CKD; no-mild CKD (Stages 0, 1, and 2), moderate (Stages 3a and 3b), and severe CKD (Stages 4 and 5). Characteristics are detailed in *Table 2*. The no-mild CKD patients were the youngest (73.84 years) compared with moderate CKD (79.01 years) and severe CKD (78.27 years). Haemoglobin levels decreased as CKD severity advanced (no-mild CKD 12.3 g/L, moderate CKD 11.4 g/L, and severe CKD 10.3 g/L), whilst mean serum potassium concentration [K⁺] increased as CKD stage advanced (no-mild CKD 4.2 mmol/L, moderate 4.4 mmol/L, and severe 4.6 mmol/L). The highest proportion of patients with moderate–severe oedema was in the moderate CKD group (61.8%). There was no difference between the three groups regarding worse symptoms of breathlessness (New York Heart Association grading III–IV), or percentage with LVSD. There were fewer patients with diabetes mellitus in the no-mild CKD group (27.1%) compared with the moderate (49.2%) and severe groups (58.6%). Blood pressure parameters were poorly recorded with almost 50% of cases missing, but there was a suggested trend towards higher blood pressure as severity of CKD worsened. There

Table 1 Frequency and in-hospital mortality by chronic kidney disease stage (all admissions)

CKD stage	Number (% of total admissions)	Death in hospital (%)	Age in years (mean and SD)*
0 or 1	261 (24.72)	20/261 (7.66)	70.69 (15.57)
2	295 (27.94)	23/295 (7.80)	76.63 (12.08)
3a	193 (18.28)	21/193 (10.88)	76.79 (11.03)
3b	191 (18.09)	16/191 (8.38)	79.66 (9.20)
4	94 (8.90)	14/94 (14.89)	79.55 (10.87)
5	22 (2.08)	2/22 (9.09)	72.77 (16.12)

CKD, chronic kidney disease; SD, standard deviation.

*Reached statistical significance in one-way ANOVA test using Games–Howell *post hoc* test between Stages 2 and 3b ($P = <0.001$) and between Stages 0/1 and 3b ($P = 0.001$).

was no statistically significant difference between the proportions of patients managed on a cardiology ward.

Discharge medications (analysed in survivors to discharge)

Medications that were prescribed on discharge were analysed only in those patients that survived to discharge. The group of medications specifically recommended for patients with LVSD—angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers (ARB), beta-blockers, and mineralocorticoid receptor antagonists (MRA)—were only analysed in those patients known to have LVSD. Diuretic dose (converted to Furosemide dose equivalents) was analysed in all survivors regardless of LVSD. There were a total of 555 admissions comprising survivors to discharge with LVSD, 288 had no-mild CKD, 209 had moderate, and 58 had severe CKD. The percentage of patients prescribed on discharge an ACE/ARB, MRA, or ‘triple therapy’ (ACE/ARB, MRA, and beta-blocker prescribed simultaneously) fell as the degree of CKD worsened, but there was no statistically significant difference between the CKD groups when comparing beta-blocker prescription or digoxin prescription (*Figure 1*). Diuretic dose was significantly lower in the no-mild CKD group compared with the moderate group and severe group, but the difference between the moderate and severe groups was non-significant (*Table 2*).

The influence of hyperkalaemia on ACE or ARB and MRA prescription

The number of cases of survivors to discharge with LVSD being prescribed ACE/ARB or MRA was analysed according to serum potassium concentration [K⁺], using different thresholds of [K⁺] (*Table 3*). As the threshold potassium was increased, the percentage of cases not prescribed ACE/ARB increased in both patients with eGFR > 60 mL/min/1.73m² and eGFR < 60 mL/min/1.73m² (*Figure 2*). With MRA prescription, the percentages of cases not prescribed MRA on discharge were more static with lower thresholds of potassium but an increasing percentage were not prescribed MRAs when [K⁺] > 5.0 mmol/L. The CKD stage was associated with a statistically significant difference in the percentages of cases prescribed ACE/ARB or MRA on discharge only up to a threshold [K⁺] > 5.0 mmol/L (*Figure 3*). There was a statistically significant difference between the eGFR > 60 mL/min/1.73m² and eGFR < 60 mL/min/1.73m² groups in the percentage of patients with no ACE/ARB or MRA prescription when [K⁺] < 4.0, >4.0, and >4.5 mmol/L, with no statistically significant difference found between the two groups at higher thresholds of [K⁺].

There was no significant difference in the mean [K⁺] between the group on ACE/ARB and not; mean [K⁺] in the

Table 2 Comparison of cohorts according to stratified chronic kidney disease

Variable	No-mild CKD	Moderate CKD	Severe CKD	Missing values	Missing P value
Total number of admissions	556	384	116	—	—
Characteristics					
Age, years; mean (IQR)	73.84 (19)	79.01 (12)	78.27 (13)	—	No-mild vs. moderate, $P < 0.001$
Haemoglobin, g/L; mean (IQR)	12.3 (2.7)	11.4 (2.5)	10.3 (2.2)	—	No-mild vs. severe, $P = 0.002$ $P < 0.001$
Potassium, mmol/L; mean (IQR)	4.2 (0.6)	4.4 (0.8)	4.6 (0.9)	—	No-mild vs. moderate, $P < 0.001$ No-mild vs. severe, $P < 0.001$ Moderate vs. severe, $P = 0.001$
Moderate-severe oedema	231/480 (48.1%)	202/327 (61.8%)	54/97 (55.7%)	152 (14.4%)	0.001
NYHA grading III-IV	467/511 (91.4%)	320/348 (92.0%)	99/104 (95.2%)	93 (8.8%)	0.427
LVSD	314/522 (60.2%)	232/363 (63.9%)	66/111 (59.5%)	60 (5.7%)	0.476
Diabetes mellitus	147/543 (27.1%)	187/380 (49.2%)	68/116 (58.6%)	499 (49.3%)	<0.001
Systolic blood pressure on discharge, mmHg; mean (IQR)	116 (29)	117 (25)	126 (42)	—	Not calculated due to missing values
Managed on cardiology ward	183 (32.9%)	121 (31.5%)	31 (26.7%)	—	0.425
Outcomes					
Length of stay, days; median (IQR)	6 (11)	8 (14)	11 (14)	—	No-mild vs. moderate, $P = 0.066$ No-mild vs. severe, $P = 0.008$ Moderate vs. severe, $P = 0.584$
Any AKI	113 (20.3%)	53 (13.8%)	14 (12.1%)	—	0.010
Death in hospital	43 (7.7%)	37 (9.6%)	16 (13.8%)	—	0.106
Individual patients (851)					
Frequency of baseline CKD from first admission	495	272	84	—	—
Readmissions over study period	1.16 (SD 0.48)	1.35 (SD 0.85)	1.36 (SD 1.09)	—	No-mild vs. moderate, $P = 0.002$ No-mild vs. severe, $P = 0.232$ Moderate vs. severe, $P = 0.996$
Survivors to discharge with LVSD (555)	288	209	58	—	—
Discharge medications ^a					
ACE/ARB	241 (83.7%)	124 (59.3%)	21 (36.2%)	—	<0.001
Beta-blockers	246 (85.4%)	172 (82.3%)	47 (81.0%)	—	0.541
MRA	164 (56.9%)	78 (37.3%)	10 (17.2%)	—	<0.001
'Triple therapy' (ACE/ARB, beta-blocker, and MRA)	144 (50.0%)	57 (27.3%)	7 (12.1%)	—	<0.001
Digoxin	50 (17.4%)	49 (23.4%)	9 (15.1%)	—	0.174
Diuretic dose ^b , mg	70.7 (40)	98.4 (120)	94.4 (80)	—	No-mild vs. moderate, $P < 0.001$
Mean all survivors					No-mild vs. severe, $P = 0.021$ Moderate vs. severe, $P = 0.924$

ACE/ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; AKI, acute kidney injury; CKD, chronic kidney disease; IQR, interquartile range; LVSD, left ventricular systolic dysfunction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

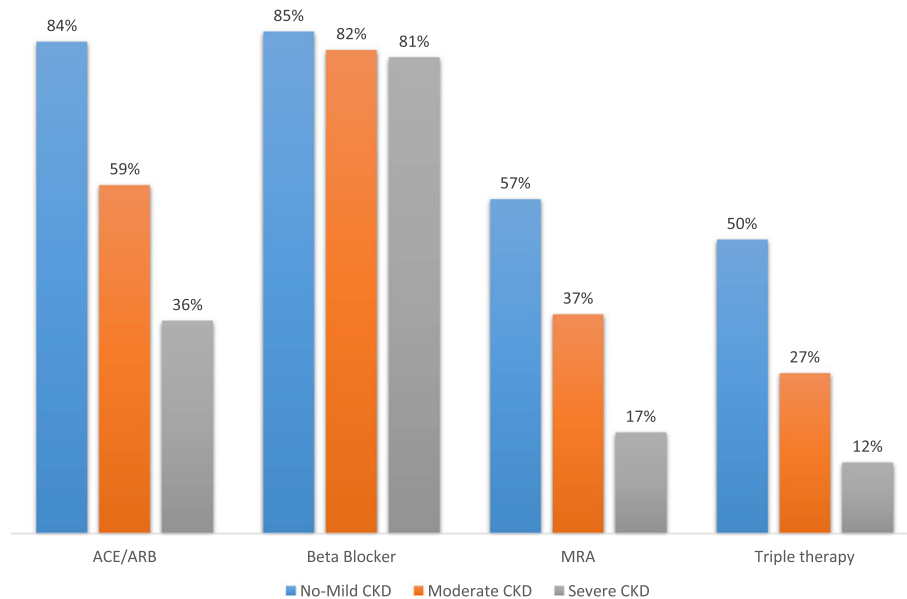
No-mild CKD, Stages 0-2; moderate CKD, Stages 3a and 3b; severe CKD, Stages 4-5.

Quantitative data are expressed as mean value (interquartile range). Categorical data are expressed as absolute numbers/available results for that subset where >5% missing results (percentage of subset of available results).

^aDischarge medications were analysed only in survivors to discharge with known LVSD except diuretics.

^bFurosemide equivalent (frusemide 40 mg = bumetanide 1 mg = torsemide 20 mg) analysed in all survivors to discharge regardless of left ventricular function.

Figure 1 Use of medications with different stages of chronic kidney disease in patients with left ventricular systolic dysfunction. ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; MRA, mineralocorticoid receptor antagonist. No-mild CKD, no CKD or CKD Stages 1–2; moderate CKD, CKD Stages 3a–3b; severe CKD, CKD Stages 4–5.



eGFR < 60 mL/min/1.73m² group prescribed ACE/ARB was 4.44 mmol/L (SD 0.64) and in the eGFR < 60 mL/min/1.73m² group not prescribed ACE/ARB was 4.37 mmol/L (SD 0.52) where $P = 0.353$. In the group where eGFR > 60 mL/min/1.73m², those prescribed ACE/ARB had a mean [K⁺] of 4.19 mmol/L (SD 0.45) compared with 4.38 mmol/L (SD 0.62) in those with no ACE/ARB was prescribed, where $P = 0.050$.

Acute kidney injury

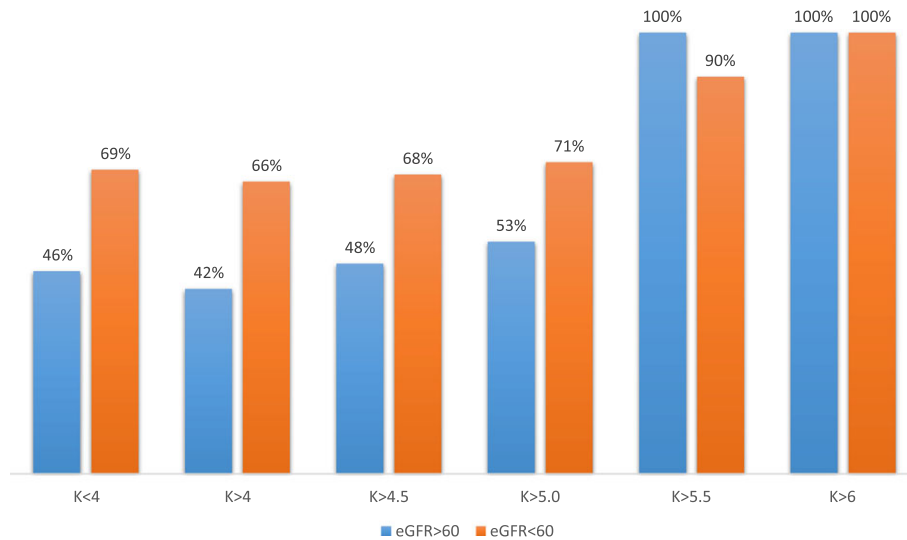
Approximately 17.0% of admissions had an AKI (Table 4). Severe AKI was not common overall (10.4% of total admissions had Stage 1 AKI, 3.7% had Stage 2 AKI, and 2.9% Stage 3 AKI). The presence of any AKI stratified by CKD grouping is shown in Table 2. More significant AKI

Table 3 Percentage of patients with estimated glomerular filtration rate above and below 60 mL/min/1.73m² not prescribed angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and mineralocorticoid receptor antagonist according to serum potassium threshold cut-off

	eGFR > 60 mL/min/1.73m ² (Stage 0–2 CKD)	eGFR < 60 mL/min/1.73m ² (Stage 3–5 CKD)	P value
[K ⁺] < 4.0 mmol/L			
Not on ACE/ARB	12/85 (14.1%)	28/61 (45.9%)	$P < 0.001$
Not on MRA	39/85 (45.9%)	42/61 (68.9%)	$P = 0.006$
[K ⁺] > 4.0 mmol/L			
Not on ACE/ARB	35/203 (17.2%)	93/204 (45.6%)	$P < 0.001$
Not on MRA	85/203 (41.9%)	135/204 (66.2%)	$P < 0.001$
[K ⁺] > 4.5 mmol/L			
Not on ACE/ARB	21/84 (25.0%)	60/121 (49.6%)	$P < 0.001$
Not on MRA	40/84 (47.6%)	82/121 (67.8%)	$P = 0.004$
[K ⁺] > 5.0 mmol/L			
Not on ACE/ARB	8/19 (42.1%)	27/51 (52.9%)	$P = 0.420$
Not on MRA	10/19 (52.6%)	36/51 (70.6%)	$P = 0.159$
[K ⁺] > 5.5 mmol/L			
Not on ACE/ARB	3/4 (75.0%)	8/10 (80.0%)	$P = 0.837$
Not on MRA	4/4 (100.0%)	9/10 (90.0%)	$P = 0.512$
[K ⁺] > 6.0 mmol/L			
Not on ACE/ARB	1/1 (100.0%)	1/1 (100.0%)	N/A
Not on MRA	1/1 (100.0%)	1/1 (100.0%)	N/A

ACE/ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; [K⁺], serum potassium concentration; MRA, mineralocorticoid receptor antagonist; N/A, not applicable.

Figure 2 Lack of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy with increasing serum potassium in patients with left ventricular systolic dysfunction. Showing percentage of patients not on angiotensin-converting enzyme inhibitor/angiotensin receptor blocker with rising levels of serum potassium, separately in patients above and below estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73m². K, serum potassium in mmol/L.



(Stages 2 and 3) was present in 46 (8.3%) of admissions with no-mild CKD, 18 (4.7%) with moderate CKD, and 6 (5.2%) of admissions with severe CKD ($P = 0.074$). Those with any AKI had a higher mean $[K^+]$ (4.62 mmol/L SD 0.84) compared with those without AKI (4.26 mmol/L, SD 0.64; $P < 0.001$), and lower haemoglobin concentration (11.5 g/L, SD 2.2) compared with those without AKI (11.8 g/L, SD 2.0; $P = 0.046$). Those with AKI tended to be older, but this did not reach statistical significance (77.6 years, SD 10.6 with AKI compared with

75.9 years, SD 13.3 without AKI; $P = 0.066$). There was a trend towards a lower percentage prescription of ACE/ARB on discharge (in survivors to discharge with LVSD) where a patient suffered a significant AKI (Stage 2 or 3, 52.2%) compared with no or Stage 1 AKI (70.3%), but this did not reach statistical significance ($P = 0.064$). Similarly with MRA prescription on discharge, 46.1% with no or Stage 1 AKI had MRA prescription of discharge, whereas 30.4% with Stage 2 or 3 AKI had MRA on discharge ($P = 0.141$).

Figure 3 Lack of mineralocorticoid use with increasing serum potassium in patients with left ventricular systolic dysfunction. Showing percentage of patients not on mineralocorticoid receptor antagonist with rising levels of serum potassium in patients above and below an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73m². K, serum potassium in mmol/L.

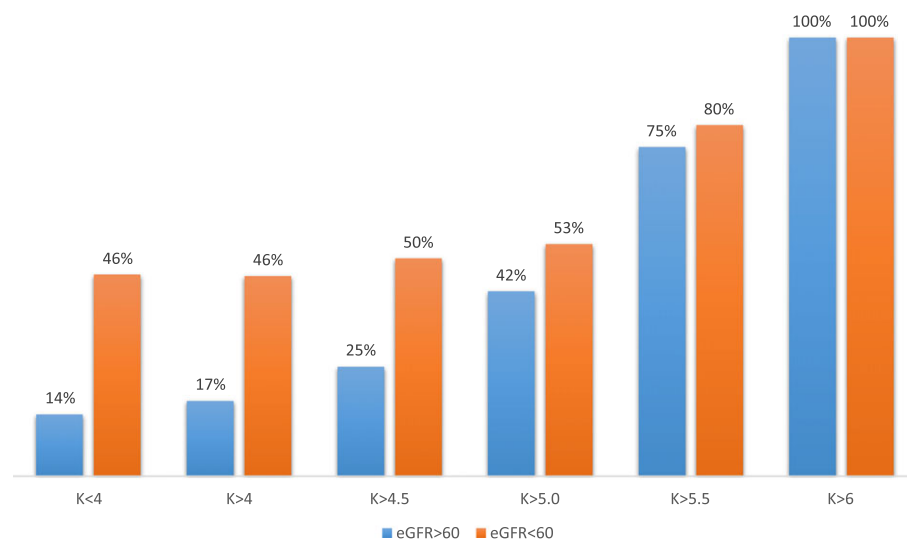


Table 4 Incidence and in hospital mortality of stages of acute kidney injury in all admissions

Stage of AKI	Frequency (%)	Mortality $P < 0.001$
No AKI	876 (83.0)	44/876 (5.0%)
1	110 (10.4)	23/110 (20.9%)
2	39 (3.7)	14/39 (35.9%)
3	31 (2.9)	15/31 (48.4%)

AKI, acute kidney injury.

Mortality, length of stay, and readmissions with renal impairment

The total number of recorded deaths during the same hospital admission was 96 (9.1% of admissions). The death rate increased as CKD stage advanced (Table 2). The presence of an AKI was associated with a profound increase in mortality correlating to the degree of severity of AKI (Table 4).

A logistic regression was performed to ascertain the effects of age, diabetes, LVSD, AKI, and severe CKD (eGFR < 30 mL/min/1.73m²) on the likelihood on in-hospital death. AKI and CKD remained independent predictors of in-hospital death (Table 5).

Patients with no-mild CKD had a tendency towards a shorter median length of stay of 6 days compared with 8 days for moderate and 11 days for severe (Table 2). Patients with AKI had significantly longer length of hospital stay; 12.68 days (IQR 13) compared with 9.91 days (IQR 12) without AKI $P = 0.006$.

The baseline CKD stage was analysed in the individual patients (851) from their first admission (Table 2). The number of total admissions with heart failure for each individual patient during the study time frame was analysed according to this first presenting CKD stage. There were more readmissions in the more advanced CKD groups compared with no-mild CKD (Table 2).

The use of ACE-I/ARB in admissions with LVSD was more common than in admissions with no LVSD (70.66% vs. 54.23%; $P < 0.001$). Similarly, admissions with LVSD were more likely to be on beta-blockers (84.27% vs. 64.52%; $P < 0.001$) and MRA (46.23% vs. 14.59%; $P < 0.001$) at discharge. Serum potassium was similar between admissions with and without LVSD (4.35 ± 0.60 vs. 4.30 ± 0.66 mmol/L; $P = 0.0260$). Inpatient mortality was also similar between the two groups (10.26% vs. 10.64%; $P = 0.850$).

Table 5 Binomial logistical regression for in-hospital mortality

Variable	<i>B</i>	S.E.	Wald	<i>P</i> value	EXP(<i>B</i>)	95% CI for EXP (<i>B</i>)
Systolic dysfunction	0.105	0.249	0.178	0.673	0.900	0.553 1.466
Any AKI	2.029	0.242	70.244	<0.001	0.131	0.082 0.211
Diabetes mellitus	0.135	0.012	10.576	0.583	0.874	0.540 1.414
Severe CKD (eGFR < 30 mL/min/1.73m ²)	0.677	0.331	4.173	0.041	0.508	0.265 0.973
Age	0.040	0.012		0.001	1.040	1.016 1.065
Constant	3.312	1.021	10.518	0.001	0.036	

AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Discussion

This observational analysis of a large real-world cohort of patients with heart failure using pre-admission creatinine readings demonstrates adverse outcomes in the presence of renal impairment, both acute and chronic, particularly mortality. Both severe CKD and AKI were independent predictors of mortality. The length of stay was longer in severe CKD and AKI patients. Readmission rates were higher in patients with moderate CKD. Detailed analysis of medications on discharge highlights the lack of use of evidenced-based therapy in LVSD and in a significant proportion of cases these therapies were not used despite the levels of potassium being safe.

Some unexpected results merit discussion. To see higher rates of AKI in no CKD is counter-intuitive. It is possible that these are milder grades of AKI. It is increasingly recognized that the relationship between acute renal impairment and outcomes is more complex than first thought. Prognosis does not simply depend on a single time-point creatinine above the normal range but has been shown to be complex than this.⁷ Similarly, it has been suggested that not all episodes of AKI confer the same poor outcomes on a population with heart failure⁹; rising creatinine in response to commencement of ACE/ARB has different prognostic implications compared with sepsis-related AKI, but these cannot be distinguished in this retrospective data analysis. Furthermore, the apparently lower mortality in CKD Stage 5 is unanticipated. Low mortality in CKD Stage 5 may represent a population of dialysis-dependent patients admitted for fluid removal and discharged, though the mortality is higher in the long run.²² Those with CKD Stage 5 are also younger, and many fewer numbers mean the statistical influence of individual patients is much greater. The blood pressure findings with progressive CKD are also unexpected. One traditional explanation for renal impairment in heart failure is hypoperfusion of the renal parenchyma due to low systolic blood pressures. This study has shown the blood pressures are greater in worse CKD, which could be related to the lower proportion taking an ACE/ARB or may suggest that a more complex pathogenic mechanism is at work.

Some important points must be made about the limitations of these data, such as absence of data on blood pressure at admission. In addition to the recognized inherent

limitations in datasets collected retrospectively for audit purposes and limited to a single hospital database, specific factors must be considered relating to the collection of renal function data. Our estimations of CKD and AKI are crude and subject to bias generated by time-point collections. Firstly, by interpreting creatinine results at discharge, we are likely to have underestimated the incidence of AKI; few patients are likely to have been discharged home with an evolving AKI or at peak creatinine. Secondly, a single measurement of baseline renal function captured purely using time-defined criteria may overestimate the severity of CKD and subsequently underestimate AKI. A proportion of the patients in this cohort have repeated admissions to hospital capture in this audit alone, and the possibility remains of other intercurrent illnesses; each could result in previous episodes of AKI recorded as their assumed baseline renal function. Mortality in AKI may well have been overestimated using a discharge time-point creatinine. It is worth noting that discharge creatinine readings are what is collected routinely on a national level using the audit dataset.¹⁹

What is highly significant is the poorer take-up in prescription of some potentially disease-modifying medicines (ACE/ARB and MRA) for LVSD in patients with increasing CKD. Clearly, given that the evidence base for these medications in this subgroup of patients is poorer and there is a real risk of significant side-effects, notably hyperkalaemia, prescribing practices in individual cases may well deviate from best practice guidelines. However, this study demonstrates that a significant proportion of patients with eGFR < 60 mL/min/1.73m² with a potassium level, at least on discharge, well within the normal range were not prescribed an ACE/ARB (45.9%) or MRA (65.6%). The possibility is raised that in cases of moderate–severe CKD, potentially beneficial medications may be being inappropriately withheld. This analysis needs repeating on a larger scale to ensure these findings are representative of wider practice. In addition, further qualitative work needs to be performed to assess the reasons for non-prescription of recommended therapies, which may include, as well as predictable clinical contra-indications, non-documented ‘contextual factors’²³ as well as physician factors such as lack of expertise in non-specialists.¹⁶ Additionally, further randomized controlled trials are needed

that include patients with more advanced CKD to ascertain the benefit of potentially disease-modifying therapies,²⁴ and there is a potential role for the novel potassium binders in those cases where hyperkalaemia is preventing their use.²⁵ Meanwhile, consideration should be given to augmenting national audit datasets with more details on renal function to capture temporal variation. The routine inclusion of nephrologists in the specialist heart failure multidisciplinary team may allow a more nuanced assessment of the risks and benefits of different management strategies in this group of patients that continue to represent a very real management challenge.

Conclusions

In conclusion, this study in multi-ethnic, inner-city, heart failure patients re-established association of chronic and acute renal impairment with poor outcome and suboptimal medical therapy, highlighting the need for multidisciplinary approach and better evidence for treatment, to improve morbidity and mortality.

Acknowledgement

This study was partly presented at the ASN Kidney Week November 2015 and BRS/RA UK Kidney Week 2016.

Conflict of interest

None declared.

Funding

R.J. holds a Clinical Research Fellowship funded by St George’s Hospital Charity.

References

1. Hospital Episode Statistics Analysis, Health and Social Care Information Centre. Hospital episode statistics admitted patient care, England – 2014–5. 2015. <http://www.hscic.gov.uk/searchcatalogue?productid=19420&q=title%3a%22Hospital+Episode+Statistics%2c+Admitted+patient+care+-+England%22&sort=Relevance&size=10&page=1#top> (6 June 2016).
2. Cleland JG, McDonagh T, Rigby AS, Yassin A, Whittaker T, Dargie HJ. National Heart Failure Audit Team for England and Wales. The national heart failure audit for England and Wales 2008–2009. *Heart* 2011; **97**: 876–886.
3. Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiadu M, Greenberg BH, O’Connor CM, Sun JL, Yancy CW, Young JB, OPTIMIZE-HF Investigators and Coordinators. Predictors of in-hospital mortality in patients hospitalized for heart failure: insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized

- Patients with Heart Failure (OPTIMIZE-HF). *J Am Coll Cardiol* 2008; **52**: 347–356.
4. 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.
 5. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J, ADHERE Scientific Advisory Committee and Investigators. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail* 2007; **13**: 422–430.
 6. Palmer JB, Friedman HS, Waltman Johnson K, Navaratnam P, Gottlieb SS. Association of persistent and transient worsening renal function with mortality risk, readmissions risk, length of stay, and costs in patients hospitalized with acute heart failure. *Clinicoecon Outcomes Res* 2015; **7**: 357–367.
 7. Reid R, Ezekowitz JA, Brown PM, McAlister FA, Rowe BH, Braam B. The prognostic importance of changes in renal function during treatment for acute heart failure depends on admission renal function. *PLoS One* 2015; **10**: e0138579.
 8. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J* 2015; **36**: 1437–1444.
 9. Damman K, McMurray JJ. Why and when should we worry about worsening renal function? *Eur J Heart Fail* 2014; **16**: 4–5.
 10. Damman K, Tang WH, Felker GM, Lassus J, Zannad F, Krum H, McMurray JJ. Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. *J Am Coll Cardiol* 2014; **63**: 853–871.
 11. National Institute for Health and Clinical Excellence. Chronic heart failure in adults: management (Clinical Guideline 108). 2010. <https://www.nice.org.uk/guidance/cg108> (6 June 2016).
 12. National Institute for Health and Clinical Excellence. Acute heart failure: diagnosis and management (Clinical Guideline 187). 2014. <https://www.nice.org.uk/guidance/cg187> (6 June 2016).
 13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members. 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 Heart J* 2016; **37**: 2129–2200.
 14. WRITING COMMITTEE MEMBERS, ACC/AHA TASK FORCE MEMBERS. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an 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 Card Fail* 2016; **22**: 659–669.
 15. Calvin JE, Shanhag S, Avery E, Kane J, Richardson D, Powell L. Adherence to evidence-based guidelines for heart failure in physicians and their patients: lessons from the Heart Failure Adherence Retention Trial (HART). *Congest Heart Fail* 2012; **18**: 73–78.
 16. Peters-Klimm F, Laux G, Campbell S, Muller-Tasch T, Lossnitzer N, Schultz JH, Remppis A, Junger J, Nikendei C. Physician and patient predictors of evidence-based prescribing in heart failure: a multilevel study. *PLoS One* 2012; **7**: e31082.
 17. National Institute for Cardiovascular Outcomes Research. National Institute for Cardiovascular Outcomes Research Dataset and user guides for National Heart Failure Audit. <https://www.ucl.ac.uk/nicor/audits/heartfailure/datasets> (6 June 2016).
 18. National Institute for Cardiovascular Outcomes Research. National Institute for Cardiovascular Outcomes Research, Annual Reports for National Heart Failure Audit. <https://www.ucl.ac.uk/nicor/audits/heartfailure/reports> (6 June 2016).
 19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130**: 461–470.
 20. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney International Supplements* 2012; **3**: 1–150.
 21. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International Supplements* 2012; **2**: 1–138.
 22. Banerjee D, Ma JZ, Collins AJ, Herzog CA. Long-term survival of incident hemodialysis patients who are hospitalized for congestive heart failure, pulmonary edema, or fluid overload. *Clin J Am Soc Nephrol* 2007; **2**: 1186–1190.
 23. Steinman MA, Dimaano L, Peterson CA, Heidenreich PA, Knight SJ, Fung KZ, Kaboli PJ. Reasons for not prescribing guideline-recommended medications to adults with heart failure. *Med Care* 2013; **51**: 901–907.
 24. Kannan A, Poongkunran C, Balamuthusamy S. Effect of spironolactone in CV mortality in hemodialysis patients. *J Am Coll Cardiol* 2014; **64**: 528–529.
 25. Pitt B, Bakris GL, Bushinsky DA, Garza D, Mayo MR, Stasiv Y, Christ-Schmidt H, Berman L, Weir MR. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. *Eur J Heart Fail* 2015; **17**: 1057–1065.