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

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Abstract

Background: In-patients 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: Admissions between 1/4/13-30/4/15 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 3-12months before admission.

Results: We identified 1056 admissions of 851 patients (mean age 76 years, 56% Caucasian, 36% with diabetes mellitus, 54% with ischaemic heart disease, 57% with valvular heart-disease). CKD was common; 36%-Stage3a/b, 11%-Stage4/5; 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 Stage0-2. AKI was present in 17.0% (10.4%-stage1, 3.7%-stage2, 2.9%-stage3); these had higher potassium and lower haemoglobin than patients with no AKI. Length of stay was longer in Stage4/5 CKD [11days; p=0.008] and AKI [13days; p=0.006]. Mortality was higher with Stage4/5 CKD (13.8% compared to 7.7% for Stage0-2 CKD (p=0.036)] and increased with AKI (5%-no AKI, 20.9%-stage1, 35.9%-stage2, 48.4%-stage3; p<0.001). Adjusted for age, diabetes and LVSD both AKI and Stage4/5 CKD were independent predictors of in-hospital mortality. In survivors with LVSD, the discharge prescription of ACE Inhibitors/angiotensin receptor blockers decreased with progressive CKD, [84%-no-mild, 59%-moderate, 36%-severe CKD; p<0.001]; this was not purely explained by hyperkalaemia.

Conclusions: In-patients with heart failure and renal impairment, acute and chronic, failed to receive recommended therapy and had poor outcomes.

Key words; Heart Failure, Kidney, Mortality, Epidemiology

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 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 8 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 is 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 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 – 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 HES registered primary HF diagnosis 2013-2014 (18). LVSD was defined by left ventricular ejection fraction of <40%. Loop diuretic doses were converted into furosemide equivalents, for example 1 mg of Bumetinide 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 MDRD formula (19) and converted to Chronic Kidney Disease

Stages (CKD) using KDIGO criteria (20). Severity of Acute Kidney Injury (AKI) was determined by degree of acute change from baseline creatinine to discharge creatinine using KDIGO 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 was 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 Chi-Square 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 ~~shown in Table 1~~. There were marginally more men (55.8%) than women, overall the population was elderly (mean age 75.9year 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/1.73^2. Prevalence and mortality figures for the stages of CKD are shown in Table 1~~2~~. 75.28% of admissions had a baseline eGFR of <90 ml/min/1.73m^2 and 47.35% had an eGFR of<60ml/min/1.73m^2. 10.98% of admissions had an eGFR<30ml/min/1.73m^2.

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~~3~~. The no-mild CKD patients were the youngest (73.84 years) compared to moderate CKD (79.01 years) and severe CKD (78.27 years). Haemoglobin (Hb) levels decreased as CKD severity advanced (no-mild CKD 12.3 g/l, moderate CKD 11.4g/l and severe CKD 10.3g/l) whilst mean serum potassium concentration [K^+] increased as CKD stage advanced (no-mild CKD 4.2 mmol/l, moderate 4.4 mmol/l,

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 (NYHA) 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 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 - ACE-Inhibitors (ACE), 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 ACEorARB, MRA or "triple therapy" (ACEorARB, 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. Diuretic dose was significantly lower in the No-mild CKD group compared to the Moderate group and Severe group, but the difference between the Moderate and Severe groups was non-significant (Table 2~~3~~).

The Influence of Hyperkalaemia on ACEorARB and MRA prescription

The number of cases of survivors to discharge with LVSD being prescribed ACEorARB or MRA was analysed according to serum potassium concentration [K^+], using different thresholds of [K^+] (see Table 34). As the threshold potassium was increased, the percentage of cases not prescribed ACEorARB increased in both patients with eGFR>60ml/min/1.73m^2 and eGFR<60ml/min/1.73m^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^+]>5.0mmol/l. The CKD stage was associated with a statistically significant difference in the percentages of cases prescribed ACEorARB or MRA on discharge only up to a threshold [K^+]>5.0mmol/l. There was a statistically significant difference between the eGFR>60ml/min/1.73m^2 and eGFR<60 ml/min/1.73m^2 groups in the percentage of patients with no ACEorARB or MRA prescription when [K^+]<4.0, >4.0 and >4.5mmol/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 ACEorARB and not; mean [K^+] in the eGFR<60 ml/min/1.73m^2 group prescribed ACEorARB was 4.44mmol/l (SD 0.64) and in the eGFR<60ml/min/1.73m^2 group not prescribed ACEorARB was 4.37mmol/l (SD 0.52) where p=0.353. In the group where eGFR>60 ml/min/1.73m^2, those prescribed ACEorARB had a mean [K^+] of 4.19mmol/l (SD 0.45) compared to 4.38mmol/l (SD 0.62) in those with no ACEorARB was prescribed, where p=0.050.

Acute Kidney Injury

17.0% of admissions had an AKI (Table 45). 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 in shown in Table 23. More significant AKI (Stage 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^+]

(4.62mmol/l SD 0.84) compared to those without AKI (4.26mmol/l SD 0.64; p<0.001), and lower haemoglobin concentration (11.5g/l SD 2.2) compared to those without AKI (11.8g/l SD 2.0; p=0.046). Those with AKI tended to be older but this did not reach statistical significance (77.6years SD 10.6 with AKI compared to 75.9years SD 13.3 without AKI; p=0.066). There was a trend towards a lower percentage prescription of ACEorARB on discharge (in survivors to discharge with LVSD) where a patient suffered a significant AKI (Stage 2 or 3, 52.2%) compared to 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).

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~~3~~). The presence of an AKI was

associated with a profound increase in mortality correlating to the degree of severity of AKI (Table 4~~5~~).

A logistic regression was performed to ascertain the effects of age, diabetes, LVSD, AKI and Severe CKD (eGFR <30 ml/min/1.73m^2) on the likelihood on in-hospital death. AKI and CKD and remained independent predictors of in-hospital death (see Table 5~~6~~).

Patients with No-mild CKD had a tendency towards a shorter median length of stay of 6 days compared to 8 days for Moderate and 11 days for severe (Table 2~~3~~). Patients with AKI had significantly longer length of hospital stay; 12.68 days (IQR 13) compared to 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~~3~~). The number of total admissions with heart failure for each individual patient during the study timeframe was analysed according to this first presenting CKD stage. There were more readmissions in the more advanced CKD groups compared to No-mild CKD (Table 2~~3~~).

The use of ACEi/ARB in admissions with LVSD ~~HFrEF (heart failure with reduced ejection fraction)~~ was more common than in admissions with no LVSD ~~HFpEF (heart failure with preserved ejection fraction)~~ (70.66% vs. 54.23%; p<0.001). Similarly ~~HFrEF~~ 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 ~~HFrEF and HFpEF~~ admissions with and without LVSD (4.35±0.60 vs. 4.30±0.66 mmol/L; p=.0260). In-patient mortality was also similar between the two groups (10.26% vs. 10.64%; p=0.850).

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 counterintuitive. It is possible that these are milder grades of AKI. It is increasingly recognised 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 failure (9); rising creatinine in response to commencement of ACEorARB has different prognostic implications compared to sepsis related AKI, but these cannot not be distinguished in this retrospective data analysis. Furthermore, the apparently lower mortality in CKD 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 means 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 ACEorARB, 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 recognised 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 over-estimate the severity of CKD, and subsequently under-estimate 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 inter-current illnesses; each could result in previous episodes of AKI recorded as their assumed baseline renal

function. Mortality in AKI may well have been over-estimated 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 (ACEorARB 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/1.73m^2 with a potassium level, at least on discharge, well within the in the normal range were not prescribed an ACEorARB (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 done 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 randomised 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.

~~We have re-established the poor outcomes on a local level associated with both chronic and acute renal impairment in heart failure admissions using a historical pre-admission creatinine reading. We have shown that the prescription of some recommended heart failure medications is impacted by the presence of renal impairment, which is not purely explained by hyperkalaemia or AKI, thus raising the possibility that some patients may be having potentially disease-modifying therapies inappropriately withheld. This warrants further analysis on a wider scale. Randomised controlled trials are necessary to strengthen the evidence base in patients with severe CKD. In the meantime, a specialist multidisciplinary approach may ensure that recommended therapies are being assessed in an appropriate balance of risks and benefits.~~

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Conflicts of Interest

None

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Figures

Figure 1

Title: Use of medications with different stages of Chronic Kidney Disease in patients with ~~heart failure~~ left ventricular systolic dysfunction

Legend: ~~Showing the decreasing use of ACE/ARB, MRA and "triple therapy" (ACE/ARB+BB+MRA) with worsening CKD stages expressed as percentage of patients in the CKD groups; it is not different for beta-blocker use.~~ ACE = Angiotensin Converting Enzyme inhibitor, ARB = Angiotensin receptor blocker, MRA = Mineralocorticoid Receptor Antagonist, CKD=Chronic Kidney Disease. No-Mild CKD = No CKD or CKD stages 1-2, Moderate CKD = CKD stages 3a-3b, Severe CKD = CKD stages 4-5

Figure 2:

Title: Lack of ACE/ARB therapy with increasing serum potassium in patients with ~~heart failure~~ left ventricular systolic dysfunction

Legend: Showing percentage of patients not on ACE/ARB with rising levels of serum potassium, separately in patients above and below eGFR of 60 ml/min/1.73m^2. ~~For all levels of serum potassium use of ACE/ARB is less in patients with eGFR<60ml/min/1.73m^2.~~ K = serum potassium in mmol/L, ACE = Angiotensin Converting Enzyme inhibitor, ARB = Angiotensin receptor blocker

Figure 3:

Title: Lack of Mineralocorticoid use with increasing serum potassium in patients with ~~heart failure~~ left ventricular systolic dysfunction

Legend: Showing percentage of patients not on MRA with rising levels of serum potassium in patients above and below a eGFR of 60 ml/min/1.73m^2. ~~More patients are not on MRA when eGFR<60ml/min/1.73m^2.~~ K=serum potassium in mmol/L, MRA=mineralocorticoid receptor antagonist

Tables

Table 1. Clinical characteristics of the population (individual patients n=851)

Characteristic	
Gender	55.8% Male 44.25 Female
Ethnicity	56.4% White 16.9% Asian 12.2% Black 14.5% Other
Age	Mean age 75.9 years (SD 13.4)
Co-morbidities	54.5% Ischaemic heart disease, 57.3% valvular heart disease, 63.6% hypertension, 36.2% Diabetes mellitus
Place of care (all admissions)	31.7% Cardiology 61.7% General Medicine 2.2% Elderly Care 4.4% Other

SD standard deviation

Table 12 – Frequency and in-hospital mortality by CKD 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 Stage 2 and 3b (p=<0.001) and between Stage 0/1 and 3b (p=0001).

Table 23 - Comparison of cohorts according to stratified CKD.

Variable	No-mild CKD	Moderate CKD	Severe CKD	Missing Values	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 No-mild vs. severe p=0.002
Haemoglobin g/l Mean (IQR)	12.3 (2.7)	11.4 (2.5)	10.3 (2.2)		<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%)		<0.001
Systolic blood pressure on discharge mmHg Mean (IQR)	116 (29)	117 (25)	126 (42)	499 (49.3%)	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 1st 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*				
ACEorARB	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" (ACEorARB, beta-blocker, 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† mg Mean all survivors	70.7 (40)	98.4 (120)	94.4 (80)	No-mild vs. Moderate p<0.001, No-mild vs. Severe

		p=0.021 Moderate vs. Severe p=0.924

CKD Chronic Kidney Disease IQR Interquartile Range NYHA New York Heart Association LVSD Left Ventricular Systolic Dysfunction AKI Acute Kidney Injury ACEorARB Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker MRA Mineralocorticoid Receptor Antagonist

No-mild CKD: Stage 0-2, Moderate CKD: Stage 3a and 3b, Severe CKD: Stage 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). [*]Discharge medications were analysed only in survivors to discharge with known LVSD except diuretics. [†]Furosemide equivalent (frusemide 40mg = bumetanide 1mg = torsemide 20mg) analysed in all survivors to discharge regardless of LV function.

Table 34. – Percentage of patients with eGFR above and below 60ml/min/1.73m^2 not prescribed ACEorARB and MRA 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$^+$]<4.0mmol/l			
not on ACEorARB	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$^+$]>4.0mmol/l			
not on ACEorARB	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$^+$]>4.5mmol/l			
not on ACEorARB	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$^+$]>5.0mmol/l			
not on	8/19 (42.1%)	27/51 (52.9%)	P=0.420

ACEorARB			
not on MRA	10/19 (52.6%)	36/51 (70.6%)	P=0.159
[K$^+$]>5.5mmol/l			
not on ACEorARB	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$^+$]>6.0mmol/l			
not on ACEorARB	1/1 (100.0%)	1/1 (100.0%)	N/A
not on MRA	1/1 (100.0%)	1/1 (100.0%)	N/A

ACEorARB Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker

MRA mineralocorticoid receptor antagonist eGFR estimated glomerular filtration rate

[K^+] serum potassium concentration N/A not applicable

Table 45: 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

Table 56. Binomial Logistical regression for in-hospital mortality

Variable	B	S.E.	Wald	P value	EXP(B)	95% CI for EXP (B)	
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		