Anemia and chronic kidney disease are associated with poor outcomes in heart failure patients

Jean-Christophe Luthi*1,2,3, W Dana Flanders3, Michel Burnier4, Bernard Burnand1 and William M McClellan3,5

Address: 1Institute of Social and Preventive Medicine, University of Lausanne, Switzerland, 2Health Observatory, Canton of Valais, Switzerland, 3Epidemiology Department, Rollins School of Public Health, Emory University, Atlanta, USA, 4Nephrology Department, CHUV, Lausanne, Switzerland and 5Georgia Medical Care Foundation, Atlanta, USA

Email: Jean-Christophe Luthi* - jean-christophe.luthi@chuv.ch; W Dana Flanders - wflande@sph.emory.edu; Michel Burnier - michel.burnier@chuv.ch; Bernard Burnand - bernard.burnand@chuv.ch; William M McClellan - bmcclell@gmcf.org

* Corresponding author

Abstract

Background: Chronic kidney disease (CKD) has been linked to higher heart failure (HF) risk. Anemia is a common consequence of CKD, and recent evidence suggests that anemia is a risk factor for HF. The purpose of this study was to examine among patients with HF, the association between CKD, anemia and inhospital mortality and early readmission.

Methods: We performed a retrospective cohort study in two Swiss university hospitals. Subjects were selected based on the presence of ICD-10 HF codes in 1999. We recorded demographic characteristics and risk factors for HF. CKD was defined as a serum creatinine ≥ 124 956 mol/L for women and ≥ 133 µmol/L for men. The main outcome measures were inhospital mortality and thirty-day readmissions.

Results: Among 955 eligible patients hospitalized with heart failure, 23.0% had CKD. Twenty percent and 6.1% of individuals with and without CKD, respectively, died at the hospital (p < 0.0001). Overall, after adjustment for other patient factors, creatinine and hemoglobin were associated with an increased risk of death at the hospital, and hemoglobin was related to early readmission.

Conclusion: Both CKD and anemia are frequent among older patients with heart failure and are predictors of adverse outcomes, independent of other known risk factors for heart failure.

Background

Heart failure (HF) is a common and serious condition that affects more than four million people in the United States [1]. Approximately 400,000 new cases are diagnosed each year, with mortality 6 years after diagnosis of 80% in men and 65% in women [1]. In Europe, the prevalence of symptomatic heart failure in the general population is estimated to range from 0.4% to 2% [2]. In Switzerland, approximately 210,000 people have HF [3]. Chronic kidney disease (CKD) is also a major health problem resulting in considerably increased morbidity, mortality and in high costs [4]. Furthermore, in the last decade, the prevalence of both CKD[5,6], and HF has been rising steadily [7-9]. Anemia is a frequent complica-
tion of chronic kidney disease, primarily due to failure of erythropoietin production to respond to decreased haemoglobin concentration [10,11]. Anemia has also been found to be a risk factor for cardiovascular disease and in particular for HF [12,13]. In a study conducted in one Swiss university hospital the prevalence of anemia among heart failure patients was 15% [13].

Furthermore, several studies have also shown that anemia with the presence of heart failure was a predictor of poor outcome [14-20] and greater hospital expenses [21]. Moreover, two recent studies have shown that anemia associated with CKD were independent risk factors for one year mortality among patients with HF [22,23]. One study included only patients with left ventricular systolic dysfunction [22], whereas patients with left ventricular diastolic dysfunction were also included in the other [23]. Independent associations between both CKD and anemia with increased risk of one-year mortality were found. In both studies, a 1% decrease in hematocrit was associated with a 2.5% increase in the 12 month risk of death.

The purpose of our study was to examine, among patients with HF, the combined association of CKD and anemia on adverse outcomes. To our knowledge, this is the first study using inhospital mortality and early readmission for this purpose.

**Methods**

**Study design**

This was a retrospective cohort study of patients having a diagnosis of heart failure hospitalized and discharged between January 1- December 31, 1999 from two Swiss university hospitals. All adult patients with heart failure hospitalized in all wards for any reason were included in the study. Outcome measures of interest were inpatient mortality and 30-day readmissions. Follow-up for each patient began on the date of discharge from the hospital and continued for 30 days.

**Population**

Using administrative data, we identified all patients hospitalized with a principal or secondary diagnosis of HF (International Classification of Disease, 10th revision: Table 1: Patients Characteristics at Admission in Patients with Heart Failure and Proportion with Chronic Kidney Disease, N = 955

| Characteristics                          | N (%) | Chronic Kidney Disease (%) | N (%) | Mean (SD) serum creatinine µmol/l |
|------------------------------------------|-------|---------------------------|-------|----------------------------------|
| N (%)                                    | 955 (100.0) | 220 (23.0)       | 113.9 (54.0) |
| Hospital A                                | 411 (43.0) | 109 (26.5)         | 116.4 (56.2) |
| Hospital B                                | 544 (57.0) | 111 (20.4)**       | 112.0 (52.3) |
| Age (N = 955)                             |       |                       |       |
| 16 – 60 years                             | 114 (11.9) | 23 (20.2)           | 111.4 (56.2) |
| 61 – 70 years                             | 172 (18.0) | 33 (19.2)           | 110.2 (50.7) |
| 71 – 80 years                             | 282 (29.5) | 61 (21.6)           | 113.2 (56.0) |
| > 80 years                                | 387 (40.5) | 103 (26.6)          | 116.7 (53.5) |
| Sex (N = 954)                             |       |                       |       |
| Male                                     | 518 (54.3) | 131 (25.3)          | 120.1 (55.4) |
| Female                                   | 436 (45.7) | 89 (20.4)           | 106.5 (51.5)** |
| Previous history Heart Failure (N = 876)  | 514 (58.7) | 126 (24.5)          | 115.6 (53.4) |
| Prior MI (N = 945)                        | 322 (34.1) | 84 (26.1)           | 119.2 (50.7)** |
| COPD, bronchitis, Emphysema (N = 944)     | 188 (19.9) | 37 (19.7)           | 107.3 (45.8)** |
| Hypertension (N = 950)                    | 577 (60.7) | 144 (25.0)          | 117.8 (57.7)** |
| Diabetes (N = 952)                        | 221 (23.2) | 57 (25.8)           | 122.3 (58.4)** |
| Current smoker (N = 930)                  | 141 (15.2) | 25 (17.7)           | 104.7 (43.0)** |
| Symptoms and findings                     |       |                       |       |
| PND (N = 608)                             | 163 (26.8) | 37 (22.7)           | 114.1 (50.1) |
| DOE (N = 849)                             | 672 (79.2) | 158 (23.5)          | 113.8 (50.9) |
| Orthopnea (N = 655)                       | 330 (50.4) | 92 (27.9)**         | 111.1 (56.4) |
| Leg edema (N = 791)                       | 438 (55.4) | 117 (26.7)**        | 118.0 (59.0)** |
| Pulmonary rales (N = 815)                 | 508 (62.3) | 124 (24.4)          | 115.0 (53.9) |
| S3 gallop (N = 757)                       | 39 (5.2)   | 8 (20.5)            | 111.4 (32.6) |
| JVD (N = 700)                             | 236 (33.7) | 66 (28.0)**         | 118.2 (62.0) |
| Atrial fibrillation (N = 797)             | 221 (27.7) | 54 (24.4)           | 110.0 (38.9) |

Mi: Myocardial Infarction; COPD: Chronic Obstructive Pulmonary Disease; PND: Paroxystal Nocturnal Dyspnea; DOE: Dyspnea On Exertion; JVD: Jugular Vein Distension

* Chronic kidney disease (CKD) was defined as a serum creatinine > = 124 µmol/L for women and > = 133 µmol/L for men

** p value < 0.05
14 g/dL, and in four groups: <10 g/dL, 10 g/dL to 12 g/dL, 12 g/dL to 14 g/dL, and ≥ 14 g/dL. The final serum creatinine values were ≥ 124 µmol/L for women and ≥ 113 µmol/L for men. Chronic kidney disease (CKD) was defined as a serum creatinine ≥ 124 µmol/L for women and ≥ 133 µmol/L for men. We chose these ranges because they were used previously in an US study, in order to be able to do comparisons of CKD prevalence between countries [23]. We did not calculate creatinine clearance because, in many patients, the information available in our data set did not allow us to calculate it. A random replicate sample of 100 charts was abstracted to assess inter-rater reliability. The Kappa estimate was 0.91 for the determination of the ventricular function (VF) and 1.0 for inhospital mortality.

Information on inhospital mortality and readmission within 30 days was gathered using administrative data provided by the hospitals. We assessed all cause readmission and included only patients from the index hospital. Because these hospitals are university referral centers, each for a different area, we assumed that only few patients could have been readmitted to a different hospital. Indeed, for one provider, we could assess that none of the patients were readmitted to another Swiss hospital using a unique identifier from the Swiss Federal Statistical Office. The determination of the left ventricular function was based on the chart by the presence of a value for a previously measured ejection fraction on echocardiography, cardiac catheterization, radionuclide ventriculography or by a narrative statement in the chart. Patients with left ventricular systolic dysfunction (LVSD) were identified by looking in medical charts for a current (from the index hospitalization) or previous ejection fraction (EF) equal or less than 40%. If no information regarding the EF was found, we searched for a narrative description in the chart. Specifically, the following terms were associated to LVSD: "systolic dysfunction. "dilated cardiomyopathy," "congestive cardiomyopathy," "diffuse global hypokinesis" or "systolic-diastolic dysfunction" (patients reported to have both systolic and diastolic dysfunction by cardiologists). Further, angiotensin converting enzyme inhibitor (ACEI) were identified in the medical charts through generic or trade name, including benazapril, captopril, enalapril, fosinopril, lisinopril, quinalapril, ramipril, perinopril and cilazapril.

The Charlson co-morbidity index, a weighted average of selected co-morbidities, was computed at index hospitalization for each patient as a measure of severity of illness using the Deyo modification [24].

Statistical analysis

Bivariate analyses of the dependent and the primary exposure variables were conducted. We also calculated the crude risk ratio and 95% confidence intervals for inhospital mortality and 30-day readmission. We used chi-square tests, Fisher's exact tests, Student T-tests or ANOVA methods when appropriate. Dichotomous outcome variables were inhospital mortality and readmission within 30 days. Primary exposure variables were hemoglobin and creatinine levels. Other variables, potential confounding factors, included in the bivariate analysis were: hospital, age, sex, history of heart failure, diabetes mellitus, hypertension, prior myocardial infarction, chronic obstructive pulmonary disease, smoking, symptoms and findings at admission (paroxysmal nocturnal dyspnea, dyspnea on exertion (DOE) and orthopnea. Physical findings abstracted included pedal edema, pulmonary rales, S3-gallop and evidence of elevated jugular vein pressure. The presence of atrial fibrillation on the admission electrocardiogram (ECG) was recorded. Hemoglobin levels were distributed in four groups: <10 g/dL, 10 g/dL to 12 g/dL, 12 g/dL to 14 g/dL, and ≥ 14 g/dL. The final serum creatinine values recorded during the hospitalization were also considered. Chronic kidney disease (CKD) was defined as a serum creatinine ≥ 124 µmol/L for women and ≥ 133 µmol/L for men. We choose these ranges because they were used previously in an US study, in order to be able to do comparisons of CKD prevalence between countries [23]. We did not calculate creatinine clearance because, in many patients, the information available in our data set did not allow us to calculate it. A random replicate sample of 100 charts was abstracted to assess inter-rater reliability. The Kappa estimate was 0.91 for the determination of the ventricular function (VF) and 1.0 for inhospital mortality.

Information on inhospital mortality and readmission within 30 days was gathered using administrative data provided by the hospitals. We assessed all cause readmission and included only patients from the index hospital. Because these hospitals are university referral centers, each for a different area, we assumed that only few patients could have been readmitted to a different hospital. Indeed, for one provider, we could assess that none of the patients were readmitted to another Swiss hospital using a unique identifier from the Swiss Federal Statistical Office. The determination of the left ventricular function was based on the chart by the presence of a value for a previously measured ejection fraction on echocardiography, cardiac catheterization, radionuclide ventriculography or by a narrative statement in the chart. Patients with left ventricular systolic dysfunction (LVSD) were identified by looking in medical charts for a current (from the index hospitalization) or previous ejection fraction (EF) equal or less than 40%. If no information regarding the EF was found, we searched for a narrative description in the chart. Specifically, the following terms were associated to LVSD: "systolic dysfunction." "dilated cardiomyopathy," "congestive cardiomyopathy," "diffuse global hypokinesis" or "systolic-diastolic dysfunction" (patients reported to have both systolic and diastolic dysfunction by cardiologists). Further, angiotensin converting enzyme inhibitor (ACEI) were identified in the medical charts through generic or trade name, including benazapril, captopril, enalapril, fosinopril, lisinopril, quinalapril, ramipril, perinopril and cilazapril.

The Charlson co-morbidity index, a weighted average of selected co-morbidities, was computed at index hospitalization for each patient as a measure of severity of illness using the Deyo modification [24].

Statistical analysis

Bivariate analyses of the dependent and the primary exposure variables were conducted. We also calculated the crude risk ratio and 95% confidence intervals for inhospital mortality and 30-day readmission. We used chi-square tests, Fisher's exact tests, Student T-tests or ANOVA methods when appropriate. Dichotomous outcome variables were inhospital mortality and readmission within 30 days. Primary exposure variables were hemoglobin and creatinine levels. Other variables, potential confounding factors, included in the bivariate analysis were: hospital, age, sex, history of heart failure, diabetes mellitus, hypertension, prior myocardial infarction, chronic obstructive pulmonary disease, smoking, symptoms and findings at admission (paroxysmal nocturnal dyspnea, dyspnea on exertion, orthopnea, leg edema, pulmonary rales, jugular vein distension, S3-gallop), atrial fibrillation, left ventricular function, ejection fraction, ACEI prescription at discharge, Charlson co-morbidity index, as well as inospital length of stay.

We then performed multivariate analyses using logistic regression to adjust for potential confounding factors. Logistic regression was used to calculate adjusted odds ratio with associated 95% confidence intervals. Covariates were initially selected using a priori considerations as well as strength of association and statistical significance in bivariate analyses. We included the variable "Left ventricular function" in the starting model in order to control
for the heterogeneity of the study population between diastolic and systolic HF. We first looked if interaction between hemoglobin and creatinine was significant. After defining the starting model as above, we assessed, by backward elimination, which confounding factors should remain in the model. We first looked to see if the least significant variable was a confounding factor by dropping it and refitting the model. We then assessed if the odds ratio changed by more than 10% compared to odds ratio of the starting model. If the odds ratios changed by more then 10%, the variable was considered as a potential confounding factor and remained in what became the final model. If a variable did not meet these criteria, it was removed from the model and the same procedures were reapplied until the best final model was found. Fit of the models was assessed using the Hosmer-Lemeshow goodness of fit test. For all models, we checked for any potential collinearity problems between the variables. All analyses were implemented with the SAS software, version 8.02 (SAS Institute Inc. Cary, NC, USA).

Results

Baseline characteristics

Our sample included 955 eligible patients with HF available for analysis. Among those 411 (43.0%) were admitted to hospital A and 544 (57.0%) in hospital B. The mean (SD) age was 75.4 years (12.8), 45.7% were female. A history of HF was present in 58.7% of the patients. A history of myocardial infarction was reported for 34.1%, hypertension for 60.7%, diabetes for 23.2%, and COPD or bronchitis or emphysema for 19.9%. At discharge, anticoagulants were prescribed in 28.7% of the patients, beta-blockers in 12.8%, calcium blockers in 13.3%, digoxin in 32.2%, diuretics in 59.9%, nitrates in 30.3%, angiotensin receptor blockers in 8.1% and spironolactone in 11.1%.

In our sample, based on a value of left ventricular ejection fraction or a narrative statement, 28.9% had their left ventricular function not determined, 28.0% had a left ventricular systolic dysfunction (LVSD), and 43.1% a left ventricular diastolic dysfunction.

Table 2: Hospital Characteristics in Patients with Heart Failure and Proportion with Chronic Kidney Disease, N = 955

| Characteristics | N (%) | Chronic Kidney Disease (%) | Mean (SD) serum creatinine µmol/L |
|-----------------|-------|-----------------------------|----------------------------------|
| N (%)           | 955 (100.0) | 220 (23.0) | 113.9 (54.0) |
| Ejection fraction in % (N = 446) |       |             |                       |
| < = 20          | 77 (17.3) | 20 (26.0) | 121.3 (45.1) |
| 20–30           | 128 (28.7) | 29 (22.7) | 115.9 (65.2) |
| 30–40           | 108 (24.2) | 28 (25.9) | 116.8 (49.2) |
| > 40            | 133 (29.8) | 37 (27.8) | 120.2 (63.5) |
| Left ventricular function (N = 955) |       |             |                       |
| Diastolic dysfunction | 412 (43.1) | 98 (23.8) | 115.7 (51.1) |
| Systolic dysfunction | 267 (28.0) | 61 (22.9) | 116.6 (64.6) |
| Undetermined    | 276 (28.9) | 61 (22.1) | 108.5 (46.3) |
| Discharged with ACEI (N = 884) | 541 (61.2) | 109 (20.2) | 108.1 (36.2)** |
| Charlson comorbidity index (N = 955) |       |             |                       |
| 0–1             | 398 (41.7) | 55 (13.8) | 102.4 (38.5) |
| 2               | 216 (22.6) | 28 (13.0) | 102.2 (40.0) |
| >2              | 341 (35.7) | 137 (40.2)** | 134.6 (69.1)** |
| Inhospital mortality (N = 955) | 89 (9.3) | 44 (49.4)** | 159.3 (106.1)** |
| 30 days readmissions (N = 866) | 116 (13.4) | 26 (22.4) | 107.7 (38.7) |
| Length of stay (days) (N = 955) |       |             |                       |
| 0–6             | 247 (25.9) | 58 (23.5) | 118.3 (55.1) |
| 7–12            | 321 (33.6) | 69 (21.5) | 112.6 (53.6) |
| >12             | 387 (40.5) | 93 (24.0) | 112.0 (53.7) |

ACEI: Angiotensin Converting Enzyme Inhibitors
* Chronic kidney disease (CKD) was defined as a serum creatinine ≥ 124 µmol/L for women and ≥ 133 µmol/L for men
** p value < 0.05
Previous or current value of left ventricular ejection fraction was found in 46.7% of the patient’s charts. The mean (SD) ejection fraction was 36.0% (15.0%) with a 25th to 75th intraquartile range from 25 to 45%. An ACEI was prescribed at discharge in 61.2% of the patients. The mean (SD) Charlson comorbidity index was 2.2 (1.4). The median length of stay was 10 days, with a 25th to 75th intraquartile range from 6 to 17 days.

Prevalence of CKD

The mean (SD) value of the last serum creatinine value reported during the hospitalization was 113.9 (54.0) µmol/L, with a range from 32 to 545 µmol/L and a 25th to 75th intraquartile range from 84 to 126 µmol/L. Chronic kidney disease was defined as a serum creatinine ≥124 µmol/L in women and ≥133 µmol/L in men. Men (25.3%) were more likely than women (20.4%) to have CKD. In total, 220 (23.0%) patients of the entire cohort had CKD. The mean serum creatinine value was statistically significantly higher in patients with a history of myocardial infarction, hypertension, diabetes or leg edema (Table 1). Higher creatinine values were also observed in patients with a Charlson comorbidity index larger than 2 (Table 2).

Prevalence of anemia

Hemoglobin level was recorded for 920 members (96%) of the cohort. The mean (SD) hemoglobin was 13.0 g/dL (2.2) with a 25th to 75th intraquartile range from 11.8 g/dL to 14.6 g/dL. On admission, an hemoglobin of ≥14 g/dL was found in 36.1% of the patients, 36.3% had a hemoglobin between 12 g/dL and 14 g/dL, 19.6% between 10 g/dL and 12 g/dL, and 8% ≤10 g/dL.

The proportion of patients with CKD was associated with increasing anemia (Table 3). The mean serum creatinine was increasing with severity of anemia (Table 3) from 102.0 µmol/L among patients with no anemia, up to 141.0 µmol/L for severe anemia (p < 0.0001). Patients with severe anemia were more likely not to be discharged with ACEI (Table 3).

Mortality and readmission

Eighty-nine (9.3%) patients died during their hospitalization, 20% among those with CKD and 6.1% among those without CKD (p < 0.0001). Among patients who died in the hospital, 49.4% had CKD, and their mean (SD) serum creatinine value was 159.3 µmol/L (106.1) (p < 0.0001). Anemia on admission to the hospital was associated with increased risk of death. In-hospital mortality was 5.4% for patients with a hemoglobin of ≥14 g/dL, 9.3% for a hemoglobin between 12 g/dL and 14 g/dL, 10.0% for a hemoglobin between 10 g/dL and 12 g/dL, and 18.9% for a hemoglobin <10 g/dL (p = 0.002) (Table 3). In-hospital mortality rates were also higher in patients with COPD (Table 4) and in patients with a Charlson comorbidity index over 2. Individuals with left ventricular diastolic and systolic dysfunction, as well as those with undetermined ventricular function, had comparable risk of hospital death (Table 5).

Among 866 patients discharged alive, 116 (13.4%) were readmitted within 30 day, 14.0% of patients with CKD, and 12.9% of those without CKD. Early readmission occurred in 11.5% of patients with a hemoglobin of ≥14 g/dL, 12.5% for a hemoglobin between 12 g/dL and 14 g/dL, and 10.0% for a hemoglobin between 10 g/dL and 12 g/dL, 19.6% between 10 g/dL and 12 g/dL, and 8% ≤10 g/dL.

Table 3: Hospital Characteristics in Patients with Heart Failure According to Hemoglobin Level, N = 955

| Hemoglobin in g/dL | <10 N (%) or Mean (SD) | 10–12 N (%) or Mean (SD) | 12–14 N (%) or Mean (SD) | ≥14 N (%) or Mean (SD) |
|-------------------|------------------------|--------------------------|--------------------------|------------------------|
| N (%) (N = 920)   | 74 (8.0)               | 180 (19.6)               | 334 (36.3)               | 332 (36.1)             |
| CKD (N = 920)*    | 28 (37.8)              | 61 (33.9)                | 78 (23.4)                | 48 (14.5)              |
| Mean (SD) serum creatinine (N = 920)* (µmol/L) | 141.0 (91.0) | 131.6 (76.5) | 110.3 (42.5) | 102.0 (30.7) |
| Left ventricular function (N = 920)* | 26 (35.1) | 57 (28.9) | 109 (32.6) | 81 (24.4) |
| Diastolic dysfunction | 19 (25.7) | 70 (38.9) | 136 (40.7) | 171 (51.5) |
| Systolic dysfunction | 29 (39.2) | 58 (32.2) | 89 (26.7) | 80 (24.1) |
| Undetermined | 26 (35.1) | 52 (28.9) | 109 (32.6) | 81 (24.4) |
| Mean (SD) ejection fraction in % (N = 429)* | 41.8 (14.7) | 39.7 (14.7) | 35.9 (15.5) | 34.1 (14.3) |
| Discharged with ACEI (N = 854)* | 31 (45.6) | 108 (63.2) | 196 (63.2) | 193 (63.2) |
| Hospital A (N = 406) | 27 (6.7) | 72 (17.7) | 153 (37.7) | 154 (37.9) |
| Hospital B (N = 514) | 47 (9.1) | 108 (21.0) | 181 (35.2) | 178 (34.6) |
| Inhospital mortality (N = 920)* | 14 (18.9) | 18 (10.0) | 31 (9.3) | 18 (5.4) |
| 30 days readmissions (N = 839) | 8 (13.3) | 29 (17.9) | 38 (12.5) | 36 (11.5) |
| Mean (SD) length of stay (days) (N = 920)* | 18.8 (21.3) | 16.8 (16.4) | 13.8 (17.0) | 12.4 (9.5) |

CKD: Chronic Kidney Disease; ACEI: Angiotensin Converting Enzyme Inhibitors
*p value < 0.05
Table 4: Patients Characteristics at Admission in Patients Hospitalized with Heart Failure by Outcome Indicators, N = 955

| Patients Characteristics | N  | N dead (%)  | N  | N Readmitted (%) |
|--------------------------|----|-------------|----|------------------|
| Hospital A               | 411| 41 (10.0)   | 370| 43 (11.6)        |
| Hospital B               | 544| 48 (8.8)    | 496| 73 (14.7)        |
| Age (N = 955)            |    |             |    |                  |
| 16 – 60 years            | 114| 7 (6.1)     | 107| 18 (16.8)        |
| 61 – 70 years            | 172| 12 (7.0)    | 160| 20 (12.5)        |
| 71 – 80 years            | 282| 23 (8.2)    | 259| 43 (16.6)        |
| > 80 years               | 387| 47 (12.1)   | 340| 35 (10.3)        |
| Sex (N = 954)            |    |             |    |                  |
| Male                     | 518| 49 (9.5)    | 469| 64 (13.7)        |
| Female                   | 436| 40 (9.2)    | 396| 52 (13.1)        |
| Previous history HF (N = 876) | 514| 50 (9.7)    | 464| 51 (11.0)        |
| Prior MI (N = 945)       | 322| 29 (9.0)    | 293| 35 (12.0)        |
| COPD, bronchitis, emphysema (N = 944) | 188| 26 (13.8)*  | 162| 32 (19.8)*       |
| Hypertension (N = 950)   | 577| 49 (8.5)    | 528| 68 (12.9)        |
| Diabetes (N = 952)       | 221| 20 (8.9)    | 201| 34 (16.9)        |
| Current smoker (N = 930) | 141| 13 (9.2)    | 128| 24 (18.8)*       |
| Symptoms and findings    |    |             |    |                  |
| PND (N = 608)            | 163| 9 (5.5)     | 154| 24 (15.6)        |
| DOE (N = 849)            | 672| 49 (7.3)    | 623| 80 (12.8)        |
| Orthopnea (N = 655)      | 330| 22 (6.7)    | 308| 43 (14.0)        |
| Leg edema (N = 791)      | 438| 39 (8.9)    | 399| 55 (13.8)        |
| Pulmonary rales (N = 815)| 508| 35 (6.9)    | 473| 53 (11.2)        |
| S3 gallop (N = 757)      | 39 | 2 (5.1)     | 37 | 3 (8.1)          |
| JVD (N = 700)            | 236| 20 (8.5)    | 216| 31 (14.4)        |
| Atrial fibrillation (N = 797)| 221| 9 (4.1)      | 212| 24 (11.3)        |

HF : Heart Failure; MI: Myocardial Infarction; COPD: Chronic Obstructive Pulmonary Disease; PND: Paroxystal Nocturnal Dyspnea; DOE: Dyspnea On Exertion; JVD: Jugular Venous Distension
*p value < 0.05

dL, 17.9% for a hemoglobin between 10 g/dL and 12 g/dL, and 13.3% for a hemoglobin < 10 g/dL. Patients who were current smokers and with COPD were also more likely to be readmitted (Table 4).

**Multivariate analysis**

Both hemoglobin and serum creatinine were independently associated with poor outcomes after controlling for confounding factors (Table 6). For in-hospital mortality, the model controlled for length of stay and COPD. For each g/dL increase in hemoglobin, the in-hospital mortality rate declined by 39% (p = 0.0008). For each one µmol/L increase in serum creatinine, in-hospital mortality rate decreased by 1% (p = 0.166). Further, the interaction term between hemoglobin and serum creatinine was statistically significant (p = 0.008). At the mean creatinine level, increasing hemoglobin levels were associated with lower mortality (RR = 0.86, for each unit increase in hemoglobin). Effect modification, suggested a weaker association of hemoglobin with mortality as creatinine levels increased. Further, at the mean level hemoglobin, increasing creatinine levels were associated with higher mortality (RR = 1.015, for each unit increase in creatinine).

In the multivariate analysis using 30 days readmission as dependent variable, we controlled for age, COPD and history of heart failure. The interaction term between hemoglobin and serum creatinine was not statistically significant. Results showed that for each one g/dL increase in hemoglobin, readmission rate declined by 13% (p = 0.009). Further, for each one µmol/L increase in serum creatinine, readmission rate increased by 0.08% (p = 0.744).

After controlling for all other risk factors, the odds ratio related to inhospital mortality associated with the presence of anemia defined as hemoglobin less than 12 g/dL, was 1.47 (95% CI 0.89 to 2.42) in all heart failure patients and 4.04 (95% CI 2.46 to 6.66) in patients with additional CKD compared with HF patients who had a hemoglobin level ≥ 12 g/dL and no CKD. Similarly, the odds ratio for early readmissions were 1.60 (95% CI 1.00 to
2.58) for anemia and 1.14 (95% CI 0.67 to 1.93) for CKD. In these models, the interaction terms between anemia and CKD lacked statistical significance.

Discussion

In this study, both anemia and chronic kidney disease were highly prevalent among HF patients discharged from two university hospitals and independently associated with an increased risk of dying in the hospital or of being readmitted within 30 days. The association between CKD, anemia and these outcomes (in hospital mortality and readmission) in HF patients has not been reported previously. Most studies have focused only on survival after hospital discharge as an outcome.

One study, in the framework of the SOLVD study, included only patients with left ventricular dysfunction. The risk of increased mortality associated with a 1% reduction in hematocrit was 2.7% [22]. These results were comparable to another study conducted among Medicare beneficiaries in community hospitals in the US. In this latest study, patients with left ventricular diastolic dysfunction were also included as patients with left ventricular systolic dysfunction. The risk of death associated with a 1% reduction in hematocrit was 2% [23]. In a new large recent study, among HF patients, chronic kidney disease and anemia were found independently to confer a two-fold increased risk of death [25]. Silverberg et al. recently reported that, in a randomized trial of 32 ambulatory HF patients with NYHA class III and IV and an hemoglobin < 12 g/dL, the correction of anemia was associated with an improved functional status and decreased hospitalization. However, the major limitation of this study was its small sample size and the fact that the randomization was not blinded [26]. These observations suggest that anemia is a clinically important risk factor for death and readmission among heart failure patients, with or without CKD. The clinical implication of these findings for patients with HF is that failure to correct severe anemia among patients with CKD confers a preventable burden of reduced quality of life, while clinical trials have demonstrated that correction of anemia improved these measures. HF patients should be carefully examined for presence of CKD and anemia and, if present, treated according to current evidence [27]. Treating anemia among inpatients with HF and CKD may then reduce inhospital mortality and early readmission. However, currently no large clinical trials have been conducted to evaluate the effect of erythropoietin therapy on survival or readmission among patients suffering from HF and CKD.

Table 5: Hospital Characteristics in Patients with Heart Failure by Outcome Indicators, N = 955

| Patients Characteristics | Inhospital mortality N = 955 | 30 day readmission N = 866 |
|--------------------------|-----------------------------|---------------------------|
| Ejection fraction in % (N = 446) | | |
| <= 20 | 77 | 8 (10.4) | 69 | 7 (10.1) |
| 20–30 | 128 | 13 (10.2) | 115 | 20 (17.4) |
| 30–40 | 108 | 5 (4.6) | 103 | 12 (11.7) |
| > 40 | 133 | 14 (10.5) | 119 | 23 (19.3) |
| Left ventricular function (N = 955) | | |
| Diastolic dysfunction | 412 | 35 (8.5) | 377 | 54 (14.3) |
| Systolic dysfunction | 267 | 24 (9.0) | 243 | 37 (15.2) |
| Undetermined | 276 | 30 (10.9) | 246 | 25 (10.2) |
| Discharged with ACEI (N = 836) | NA | NA | 532 | 76 (14.3) |
| Charlson comorbidity index (N = 955) | | |
| 0–1 | 398 | 26 (6.5) | 372 | 47 (1.6) |
| 2 | 216 | 20 (9.3) | 196 | 24 (12.2) |
| >2 | 341 | 43 (12.6)* | 298 | 45 (15.1) |
| Length of stay (days) (N = 955) | | |
| 0–6 | 247 | 32 (13.0) | 215 | 26 (12.1) |
| 7–12 | 321 | 17 (5.3) | 304 | 36 (11.8) |
| >12 | 387 | 40 (10.3)* | 347 | 54 (15.6) |

ACEI: Angiotensin Converting Enzyme Inhibitor; CHF: Congestive Heart Failure; NA: not applicable because relates only to patients discharged alive.

*p value < 0.05
In our study we found that, among HF patients, the prevalence of CKD was 25% among males and 20% among females respectively. However, by using this cut-point of a serum creatinine of ≥124 µmol/L for women and ≥133 µmol/L for men for defining CKD, we underestimated the true prevalence of CKD especially among elderly people. We choose these cut-points based on previous studies implemented in the USA [23]. Reduced kidney function occurred frequently in patients with HF. Two studies have shown that creatinine clearance less than 60 ml/minute was present in 20 to 50% of HF patients [28,29]. In another study, which included Medicare beneficiaries with heart failure hospitalized in community hospitals, 38% had CKD. In this cohort, the prevalence of CKD was 33% in females and 46% in males [23]. Our results are similar to those found in these studies and show that CKD is highly prevalent among HF patients.

Interest in the relationship between HF and anemia is growing. Anemia commonly complicates HF (14–28% of patients depending on the cut off used) [30] and is a potential exacerbating factor [31]. In our study the prevalence of anemia (hemoglobin < 12 g/dL) among HF patients was 28%. In another study performed in one Swiss university hospital, the prevalence of anemia was 15% [13]. Silverberg et al. showed that the prevalence of anemia increased with the severity of HF and reached almost 80% in those patients with a NYHA class IV [26]. Anemia observed among individuals with HF is highly multi-factorial, but, a decreased renal function is a cause in numerous patients [32].

Anemic patients with chronic renal failure should receive treatment with recombinant human erythropoietin (r-HuEPO, Ééotin) to maintain hemoglobin levels over 11 g/dL with an acceptable target of 12 to 12.5 g/dL, according to recommendations from the European practice guideline for management of anemia in patients with chronic renal failure [33] and the National Kidney Foundation K/DOQI clinical practice guidelines for anemia of chronic kidney disease [27]. Benefits of adequate hemoglobin levels had been established in patients undergoing dialysis, and are supposed to be relevant also in CKD patients. In addition, anemic patients should receive iron supplementation in order to maintain serum ferritin levels above 100 µg/L and transferrin saturation above 20%.

This study had a number of limitations. It is an observational study based on information available in medical records. The chart abstraction process was implemented in each hospital by different persons with different education and backgrounds, although with similar training. Then, in one hospital the entire medical chart was available to the abstractors, whereas in the other only the electronic discharge letter, laboratory findings and reports from cardiology testing were available. In addition, the quality of medical records and completeness of information may also vary between centers. Incorrect information may have led to some misclassification bias. Further this study was conducted on an opportunity sample of two hospitals, making the generalisibility of results uncertain. Then, we excluded patients with valvular heart disease and acute myocardial infarction, because it was our intent to focus on a homogenous group of individuals with established heart failure. However, we agree that the issue of anemia and outcomes in both of these patient groups is important. Further, we were not able to exclude other causes of anemia, including the presence of iron, folate and vitamin B12 deficiencies, dilutional anemia, and the anemia of chronic diseases different from CKD, as explanations for anemia observed in this population and perhaps, to account for some potential confounders.
given the relative high number of elderly patients in the study population and that these patients may have CKD even with normal creatinine value; we underestimated the true prevalence of CKD. Finally, we acknowledge that we were not able to measure others risk factors associated with epo-resistance such as immune activation. We will consider measuring it in future studies. However, we would like to emphasis that the concerns about ACEI and anemia should not keep physicians from using ACE inhibitors in their management of heart failure.

Conclusion
In conclusion, we found further evidence that the concomitant presence of either CKD or anemia increased the risk of dying in the hospital or of being readmitted within 30 days among patients hospitalized with heart failure. The association persisted after controlling for other factors associated with adverse outcomes in these patients.

Competing interests
This study was supported by a grant from the coalition of the five Swiss University Hospitals and grants from the Fonds du 450ème anniversaire de l’Université et la Fondation Mottat. It was also sponsored by MSD Switzerland and Roche Switzerland. These sponsors were however not involved in the analysis of the results neither in writing nor in correcting the manuscript.

Authors' contributions
JCL participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, as well as drafting the manuscript. WDF participated in the design of the study, supervised the statistical analysis, and revised critically the article. MB and BB participated in the conception and design of the study, interpretation of data and revised critically the manuscript. WMM conceived of the study, participated in its interpretation of data and revised critically the manuscript, and revised critically the article. All authors read and approved the final manuscript.

References
1. Williams JF, Bristow MR, Fowler MB, Francis GS, Garson A, Gersh BJ, Hammer DF: Guidelines for the Evaluation and Management of Heart Failure: Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure). J Am Coll Cardiol 1995, 26:1376-1398.
2. Remme WJ, Swedberg K, Task Force for the Diagnosis and Treatment of Chronic Heart Failure European Society of Cardiology: Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001, 22:1527-1560.
3. Bailly AS, Periat M Le: coût du petit débit cardiaque: une approche médocïcométrique. Med et Hyp 1997, 35:1153-9.
4. NIH Consensus Statement: Consensus Development Conference Panel. Morbidity and Mortality of Renal Dialysis. Ann Intern Med 1994, 121:62-67.
5. Rossert JA, Wauters JP: Recommendation for the screening and management of patients with chronic kidney disease. Nephrol Dial Transplant 2002, 17:19-28.
6. US Renal Data System 2001 (USRDS 2001) Annual Data Report. National Institute of Diabetes and Digestive and Kidney Diseases 2001.
7. Cleland JGF, Khand A, Clark AL: The Heart Failure Epidemic: Exactly how big is-it? Eur Heart J 2001, 22:623-626.
8. Petrie MC, Berry C, Stewart S, McMeray JY: Failing Airing Hearts. Eur Heart J 2001, 22:1978-1990.
9. Miller LW, Nussod ED: Epidemiology of Heart Failure. CardioClinics 2001, 19:547-555.
10. Erslav Aj, Besarab A: Erythropoietin in Pathogenesis and Treatment of Anemia of Chronic Renal Failure. Kid Intern 1997, 51:622-130.
11. Valderramano F: Anemia Management in Chronic Kidney Disease Patients: an Overview of Current Clinical Practice. Nephral Dial Transplant 2002, 17:13-18.
12. Ezekowitz JA, McAlister FA, Armstrong PW: Anemia Is Common in Heart Failure and Is Associated With Poor Outcomes. Insights From a Cohort of Patients With New-Onset Heart Failure. Circulation 2003, 107:223-225.
13. Tanner H, Moschovitis G, Kuster GM, Hullin R, Piffnner D, Hess OM, Mohacsi P: The prevalence of anemia in chronic heart failure. International Journal of Cardiology 2002, 86:115-121.
14. Felker GM, Garris WA, Linder J, Kraut KH, Cuffe MS, Gheorghe M, O’Connor CM: Usefulness of Anemia as a Predictor of Death and Re-Hospitalization in Patients with Decompensate Heart Failure. Am J Cardiol 2003, 92:625-628.
15. Kosiborod M, Smith GL, Radford MJ, Foyy JM, Krumholz HM: The Prognostic Importance of Anemia in Patients with Heart Failure. Am J Med 2003, 114:12-119.
16. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J: Anemia is Associated with Worth Symptoms, Greater in Permanent Functional Capacity and Significant Increase in Mortality in Patients with Advanced Heart Failure. J Am Coll Cardiol 2002, 39:1780-1786.
17. Mozaffarian D, Nye R, Levi WC: Anemia Predicts Mortality in Severe Heart Failure. The Prospective Randomized Am Iodipin Survival Evaluation (PRAISE). J Am Coll Cardiol 2003, 41:1933-1939.
18. Nordsyke Rj, Kim Jj, Goldberg GA, Vendiola R, Batsa D, Maciamish M, Thomasson Jv: Impact of Anemia on Hospitalization Time, Charges, and Mortality in Patients with Heart Failure. Value in Health 2004, 7:64-69.
19. Anand I, McMurray Jj, Whitmore J, Warren M, Pham A, McCamish MA, Burton PB: Anemia and its Relationship to Clinical Outcome in Heart Failure. Circulation 2004, 110:149-154.
20. Kyan E, Devlin M, Prendiville TE, Ledwidge M, McDonald K: The prevalence and natural history of anemia in an optimally treated heart failure population. Br J Cardiol 2003, 11:369-375.
21. Gregory DD, Sarnak MJ, Konstam MA, Pereira B, Salem D: Impact of Chronic Kidney Disease and Anemia on Hospitalization Expense in Patients With Left Ventricular Dysfunction. Am J Cardiol 2003, 92:1300-1305.
22. Ai-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, Sarnak MJ: Reduced Kidney Function and Anemia as Risk Factors for Mortality in Patients With Left Ventricular Dysfunction. J Am Coll Cardiol 2001, 38:953-962.
23. McClellan WM, Flanders WD, Langston RD, Jurkowitz EC, Presley R: Anemia in Renal Insufficiency are Independent in Risk Factors for Death among Patients with Congestive Heart Failure admitted to Community Hospitals: A Population-based Study. J Am Soc Nephrol 2002, 13:1928-1936.
24. Deyo RA, Cherkin DC, Cella MA: Adapting a clinical comorbidity index for use with ICD-9 CM administrative databases. J Clin Epidemiol 1992, 45:613-619.
25. Herzog CA, Li S, Collins AJ: The impact of congestive heart failure (CHF), chronic kidney disease (CKD), and anemia on survival in the Medicare population. Circulation 2002, 106(suppl):471-2.
26. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, Shapia J, Gavish D, Baruch R, Kofman B, Kaplan C, Steinbruch S; Iaina A: The Use of Subcutaneous Erythropoietin and Intravenous Iron for the Treatment of Severe, Resistant Congestive Heart Failure Improved Cardiac and Renal Function and Functional Cardiac Class, And Markedly Reduces Hospitalization. J Am Coll Cardiol 2000, 35:1737-1744.
27. National Kidney Foundation K/DOQI clinical practice guidelines for anemia of chronic kidney disease: update 2000. Am J Kidney Dis 2001, 37(suppl 1):S182-S238.
28. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW: The Prognostic Implications of Renal Insufficiency in Asymptomatic Patients with Left Ventricular Systolic Dysfunction. J Am Coll Cardiol 2000, 35:681-689.
29. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton J, van Veldhuisen DJ: Renal Function, Neuro-hormonal Activation, and Survival in Patients with Chronic Heart Failure. Circulation 2000, 102:203-210.
30. Crommie N, Lee C, Struthers AD: Anemia in Chronic Heart Failure: What is its frequency in the UK and its underlying causes? Heart 2002, 87:377-378.
31. Coletta AP, Niktin N, Clarc AL, Cleland IJGF. Clinical Trials Updates from the American Heart Association Meeting: PROSPER, DIAL, Home Care Monitoring Trials, Immuno-Modulation Therapy, COMPANION and Anemia in Heart Failure. European Journal of Heart Failure 2003, 5:95-99.
32. Silverberg DS, Wexler D, Blum M, Tchebiner J, Sheps D, Keren G, Schwartz D, Baruch R, Yachnin T, Shaked M, Zubkov A, Steinbruch S, Iaina A: The Correction of Anemia in Severe Resistant Heart Failure with Erythropoietin in Intravenous Iron Prevents the Progression of Both the Heart and the Renal Failure and Markedly Reduces Hospitalization. Clinical Nephrology 2002, 58(suppl 1):S37-S45.
33. European Best Practice Guidelines for the Management of Anemia in Patients with chronic Renal Failure. Nephrol Dial Transplant 1999, 14(suppl 5):1-50.

Pre-publication history
The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2369/7/3/prepub