Cardiogenic shock in acute myocardial infarction: clinical outcome and predictors
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Creatinine clearance is independently associated with one year mortality in a primary PCI cohort with cardiogenic shock.

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**ABSTRACT**

**BACKGROUND**
Acute ST-segment elevation myocardial infarction (STEMI) complicated with cardiogenic shock (CS) has still the highest in hospital mortality. Patients with STEMI and increasing creatinine levels within 24 h after admission have a poor prognosis. Data about STEMI complicated with CS and kidney function are sparse. We sought to assess the prognostic value of creatinine clearance on admission in patients with STEMI and CS treated with percutaneous coronary intervention (PCI).

**METHODS AND RESULTS**
Between 1997 and 2005, a total of 3038 patients presented with STEMI and treated with PCI. On admission 292 patients presented with CS. Creatinine clearance (CrCl) could be calculated in 193 patients and classified in tertiles: group I > 96.8 ml/min; Group II between 67.5 and 96.8 ml/min; Group III < 67.5 ml/min. Overall one year mortality was 34%. In group I, II and III mortality was 24%, 30% and 45% respectively ($P$ for trend 0.009). In multivariate logistic regression analysis, the odds for mortality increased with 96% for each tertile of admission CrCl (OR 1.961, 95%CI 1.135–3.385, $P$=0.016).

**CONCLUSION**
Creatinine clearance on admission is strongly associated with one year mortality in STEMI patients with CS on admission and treated with PCI.
INTRODUCTION
Cardiogenic shock occurs in approximately 10% of the patients with ST-segment elevation myocardial infarction (STEMI) and remains the most common cause of death for hospitalized STEMI patients.\(^1\) Even in the era of prompt revascularization as therapy of choice, for patients with delayed cardiogenic shock (CS) as well as for patients with CS on admission, the in-hospital mortality is still approximately 50%.\(^4\) The identification of predictors of mortality is important to direct concomitant therapeutic approaches that can further improve outcome in CS patients.\(^7\]

Kidney dysfunction is independently associated with mortality in patients undergoing elective PCI in a dose dependent manner. Kidney dysfunction is also an established independent predictor of survival after acute myocardial infarction and acute coronary syndromes.\(^8\) Limited data are available about long term mortality in relation to creatinine clearance in patients with STEMI complicated by CS.\(^11\)

Moreover, these data concern patients with a variety of reperfusion modalities. Currently, optimal reperfusion therapy for STEMI is primary PCI and especially when complicated with CS. Therefore, the purpose of this study was to determine the prognostic value of admission creatinine clearance in STEMI patients complicated with cardiogenic shock on admission and treated with primary PCI.

METHODS
STUDY POPULATION
From January 1997 through March 2005 all consecutive STEMI patients treated with primary PCI in our hospital were entered in a dedicated database (n=3038). All patients prospectively registered by the attending cardiologist as being in CS on admission were selected (n=292; 9.6% of total population). From the selected cohort, admission creatinine levels were available of 259 patients. Additionally, from 193 patients, also weight data were available. Subsequently, patients were classified in tertiles of creatinine clearance on admission.

DEFINITIONS
We used the Cockroft-Gault equation to estimate the level of Glomerular Filtration Rate, according to the guidelines for chronic kidney disease in adults.\(^12\) The equation calculates the creatinine clearance by the following formula: \(\text{CrCl (ml/min):}\)
[(140 - age) \times \text{lean body weight [kg]} / 72 \times \text{creatinine (mg/dl)}] (\times 0.85 \text{ for women}). We divided the patients into three groups according to tertiles of creatinine clearance: group I: CrCl $\geq$ 96.8 ml/min (n=64); group II: CrCl $\geq$ 67.5 and $<$ 96.8 ml/min. (n=65); group III: CrCl $<$ 67.5 ml/min. (n=64). The CrCl was found normally distributed and this classification is comparable to the scheme used by the K/DOQI guidelines to classify patients by chronic kidney disease. These latter guidelines classify kidney function in the following manner: normal kidney function (stage I) GFR $\geq$ 90 ml/min, mild kidney dysfunction (stage II) 60-89 ml/min and moderate to severe kidney dysfunction stage (III-V) GFR $<$ 59 ml/min.\textsuperscript{13}

Acute STEMI was defined as acute myocardial infarction with ST-segment elevation of $>$ 0.1 mV in two or more contiguous leads and chest pain persisting $>$ 30 min and less than 12 h before admission. Cardiogenic shock was defined according to the SHOCK trial as a systolic blood pressure equal or below 90 mmHg for at least 30 min or vasopressors required to maintain blood pressure $>$ 90 mmHg, evidence of end-organ ypoperfusion (e.g.: urine output $<$ 30 ml or cold, diaphoretic extremities or altered mental status) and evidence of elevated filling pressures (e.g. pulmonary congestion on examination or chest radiograph).\textsuperscript{14,15}

Coronary flow was assessed by the attending cardiologist according to the TIMI flow grading system. Left ventricular ejection fraction (LVEF) was assessed by either echocardiography or nuclear scintigraphy, usually performed within the first week after the PCI.

**ENDPOINT**

The primary endpoint was all-cause mortality at one year.

**STATISTICAL ANALYSIS**

Differences between the three admission creatinine clearance groups in categorical variables were tested by chi-square test. Age and left ventricular ejection fraction were dichotomized (age $<$ 60 versus $>$ 60 years and LVEF $<$ 40 versus $>$ 40%). Cumulative survival curves for tertiles creatinine clearance were constructed according to the Kaplan-Meier method and differences were tested for significance by the log-rank statistic. Multivariate logistic regression analysis was performed to assess the relationship between admission creatinine clearance and one year mortality, inclu-
ding all significantly different distributed objective baseline characteristics in the model. In this analysis, according to admission tertile creatinine was used as a continuous variable. All tests were two tailed and a P value of < 0.05 was considered statistically significant. The statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA; version 11.0.1) was used for statistical analysis.

**RESULTS**

**BASELINE CHARACTERISTICS**

Overall one year mortality in the total cohort of 292 patients with CS on admission was 42%. In the described cohort of 193 patients with known creatinine clearance, overall one year mortality was 34%. In patients without known creatinine clearance (n= 99), one year mortality was 59% (FIGURE 1).

One year mortality in patients without creatinine (n =33) levels was 70% and for the cohort without known weight (n=66) it was 23%. Total 30 day mortality was 32%; 21.9% (n=14) in group I, 30.8% (n=20) in group II and 43.8% (n=28) in group III (P =0.029). The study cohort (193 patients) consisted of 127 males (66%) and mean age was 63.7 ± 13.1 years. Left ventricular ejection fraction < 40% was present in 125 patients (77%). Angiographic evidence of multi-vessel disease (MVD) was present in
108 (56%) patients. Furthermore, TIMI 3 flow after PCI occurred in 140 patients (73%). The baseline characteristics of the 193 STEMI patients with CS on admission and treated with PCI are detailed in Table 1.

Patients with decreasing renal function were older (P<0.001) and more often had multi-vessel disease (P=0.028). There was an inverse relationship between achieving TIMI 3 flow after PCI and creatinine clearance (in groups I, II and III [78.1% resp. 75.4% resp. 64.1%, P for trend=0.075]). For the study cohort according to the tert-
<table>
<thead>
<tr>
<th>TABLE 2 Clinical characteristics of 193 STEMI shock patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (n=64) Group II (n=65) Group III (n=64)</td>
</tr>
<tr>
<td>Age &gt;60 years (%)</td>
</tr>
<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>BMI &gt;25.0</td>
</tr>
<tr>
<td>Family history (%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
</tr>
<tr>
<td>Hyperchol (%)</td>
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<tr>
<td>Previous corevent (%)a</td>
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</tbody>
</table>

**Medication**

| Aspirin (%) | 23 (36) | 26 (39) | 29 (46) | 0.72 |
| Beta blocker (%) | 24 (38) | 34 (52) | 29 (46) | 0.50 |
| Ace inhibitor (%) | 17 (26) | 34 (52) | 27 (42) | 0.08 |
| Statin (%) | 31 (48) | 43 (67) | 45 (71) | 0.11 |
| LAD infarction (%) | 35 (54.7) | 35 (53.8) | 27 (42.2) | 0.286 |
| MVD (%) | 28 (43.8) | 37 (56.9) | 43 (67.2) | 0.028 |

**Angioplasty**

| TIMI 0 flow before (%) | 42 (65.6) | 45 (69.2) | 50 (78.1) | 0.276 |
| TIMI 3 flow after (%) | 50 (78.1) | 49 (75.4) | 41 (64.1) | 0.167 |
| Contrast medium (ml) | 230±101 | 222±144 | 253±253ml | 0.648 |
| LVEF <40% (%) | 40 (71.4) | 41 (83.7) | 44 (75.9) | 0.329 |
| Mortality at 1 year (%) | 16 (25) | 20 (30.8) | 30 (46.9) | 0.026 |

BMI=body mass index; LAD=left anterior descending artery; TIMI=thrombolysis in myocardial infarction; PCI=percutaneous coronary intervention.

aCorevent:previous myocardial infarction, PCI and/or CABG.

Levels of creatinine clearance on admission, baseline characteristics are detailed in TABLE 2. One year mortality was 25%, 31%, 47% respectively in groups I, II and III (P for trend= 0.009). A Kaplan-Meier curve is displayed in FIGURE 2. We also analysed one year mortality when CrCL was categorized in four groups as normal (CrCl >90 ml/min), mild (CrCl 60 to 90 ml/min), moderate (CrCl 30 to 60 ml/min) and...
severe dysfunction (CrCl < 30 ml/min). One year mortality was 26.3% in the normal group (CrCl > 90 ml/min (n=76), 35.3% in the mild dysfunction group (CrCl: 60-90 ml/min (n=68), 53.5% in the moderate dysfunction group (CrCl 30-60 ml/min (n=43)) and 50.0% when CrCl < 30 ml/min (n=6) (P=0.026). Multivariate analysis revealed creatinine clearance in tertiles to be an independent predictor for one year mortality (TABLE 3).

The odds for mortality increased with approximately 100% for each tertile of admission creatinine clearance (OR 1.961, 95% CI 1.135-3.385, P=0.016), even after correction for age > 60 years, male gender, MVD, TIMI < 3 flow after PCI and LVEF < 40%. Admission mere creatinine tertiles were a less strong and not significant predictor (OR 1.359, 95% CI 0.828-2.228, P=0.225, TABLE 4) in the study cohort of 193 patients as well as in the 252 patients with available creatinine levels on admission, but no known weight (OR 1.432, 95% CI 0.938-2.187, p=0.096). As shown above, when mere creatinine levels in tertiles were included in the multivariate model in both 193 patient as well as in the 252 patient cohort, the odds for mortality did not change and these odds for mortality did not change and these odds did not reach significant levels.

**FIGURE 2** Kaplan Meier survival curve according to creatinine tertiles.

*CrCl* denotes creatinine clearance.
TABLE 3  Independent predictors of one-year mortality

<table>
<thead>
<tr>
<th>predictor</th>
<th>OR</th>
<th>95 % CI</th>
<th>p value</th>
<th>Wald</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission creatinine clearance*</td>
<td>1.961</td>
<td>1.135 - 3.385</td>
<td>0.016</td>
<td>5.836</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;0.40</td>
<td>24.686</td>
<td>3.195 - 190.760</td>
<td>0.002</td>
<td>9.445</td>
</tr>
<tr>
<td>No reflow or not achieving TIMI 3 flow</td>
<td>2.635</td>
<td>1.169 - 5.942</td>
<td>0.019</td>
<td>5.457</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.735</td>
<td>0.763 - 3.949</td>
<td>0.189</td>
<td>1.726</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>1.240</td>
<td>0.471 - 3.269</td>
<td>0.663</td>
<td>0.190</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.848</td>
<td>0.368 - 1.953</td>
<td>0.699</td>
<td>0.150</td>
</tr>
</tbody>
</table>

*For the continuous variable, admission creatinine clearance (mmol/L), the odds ratio is noted per tertile

TIMI=thrombolysis in myocardial infarction

DISCUSSION

The main finding of this study is the independent association between creatinine clearance in STEMI patients with CS on admission treated with PCI and one year mortality. The relation between admission creatinine clearance and mortality has not been reported before in this subset of patients. The odds for mortality at one year increased with almost 100% for every tertile of creatinine clearance. Several mechanisms are proposed in trying to explain the association between decreasing renal function and mortality. Hypertension, diabetes mellitus or other metabolic derangements have been associated with decreasing renal function and mortality. Surprisingly, these risk factors were of no influence in our cohort since they were equally distributed in all groups. Poor LVEF is an independent predictor of one year mortality. This confirms the results of a sub analysis of the SHOCK trial, which particularly addressed the prognostic importance of early post infarction LVEF in STEMI patients with CS. However, reduced LVEF after PCI was equally distributed amongst tertiles of creatinine clearance. Poor LVEF alone cannot explain the high mortality in STEMI patients with CS. In the group with the lowest creatinine clearance, multi-vessel disease was more pronounced. This extensive atherosclerosis seen in the coronary arteries may be generalized and also seen in the kidney arteries, therefore, this may partially explain a low creatinine clearance on admission. Decreasing renal function can worsen from microcirculatory hypoperfusion, resulting in a severe decrease of diuresis. In addition, the need for inotropes and or vasopressors may further reduce microcirculation of the kidney and thus the vicious
circle is complete. Moreover, the compensating mechanism of increasing left ventricular filling pressures to achieve the same cardiac output can more easily result in the formation of pulmonary oedema. This end organ hypoperfusion in the presence of hypervolemia may lead to further clinical deterioration.

Additionally, we studied the prognostic value of creatinine levels on admission. In patients with chronic heart failure, formulae estimating kidney function had previously shown to predict prognosis more accurately compared with mere creatinine levels. In acute heart failure this has not been described before. In our study the value of creatinine levels in tertiles was less strong and not a significant predictor. In the entire patient cohort of 259 patients with known creatinine levels as well as in the patient cohort with also known weight, the odds for mortality did not change. Therefore, we conclude that the predictive value of creatinine levels is lower and that the predictive value of creatinine clearance in the excluded patients would be an equally strong predictor as in the cohort under study. The formula to compute creatinine clearance is available and can easily be used in clinical practice. Therapeutic approaches during PCI may focus on prevention of further kidney damage. Systemic pharmacologic therapy with administration of Nacetylcysteine in combination with sodium bicarbonate therapy or more selective target renal therapy (TRT) may reduce contrast medium induced nephropathy. Additionally, increasing cardiac output with a left ventricular assist device in these patients may reduce ongoing kidney failure. The newly available percutaneous left ventricular assist devices have shown a reduction in the need for vasopressors.

Education, screening and treatment in an early phase of kidney failure may importantly impact survival. On the basis of the present study we can conclude that patients with kidney failure, undergoing primary PCI for acute myocardial infarction complicated with cardiogenic shock have a poor prognosis. Furthermore, creatinine clearance rather than just considering creatinine levels is a stronger predictor for clinical outcome. These conclusions warrant further research in how to interfere in these extremely ill patients.

LIMITATIONS

There are several limitations to our study. First, our study is a prospective observa-
tional single centre study. However, it reflects a representative population as it concerns a homogenous population over a long study period (1997-2005). Second, selection bias could have played a role in our study. Patients without available admission laboratory data were excluded from the study cohort. It could be hypothesized, that in this group of CS patients' blood sampling did not have priority or was not performed at all, because of deplorable patient status. Acetylcysteine (ACC) or bicarbonate infusion can be administered before or during PCI on the catheterization laboratory or afterwards on the intensive care unit. We did not administer either of these medications before and during PCI in STEMI patients admitted with cardiogenic shock. Additionally, on the intensive care unit, we are only recently considering implementing ACC after primary PCI. Therefore, our data are not likely to be hampered by an occasional administration of ACC on the intensive care unit. Furthermore, antithrombotic therapy has improved over time and could have played a role in lower mortality described in this cohort. These issues could partly explain the relatively lower overall mortality (34%) in our study cohort. Cardiogenic shock has been defined according to the shock trial definition. However, it does not provide a grading scale and cardiogenic shock is likely to be a gradual phenomenon. It is conceivable that the results of our study may be influenced by the grade of cardiogenic shock the patients were in. However, such a scale is currently not available.
REFERENCES


