Renal insufficiency increases mortality in acute coronary syndromes regardless of TIMI risk score

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Original article

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Abstract

Background: Non ST-segment elevation acute coronary syndromes (NSTE ACS) are the most frequent cause of admission to intensive care units. Early risk assessment and implementation of optimal treatment are of special importance in these patients. Previous studies have demonstrated that renal insufficiency is an independent risk factor in patients with cardiovascular disease.

Aim: To assess the effects of renal function on the course of treatment and prognosis in patients with NSTE ACS admitted to hospitals without on-site invasive facilities but with a possibility of immediate transfer to a reference centre with a catheterisation laboratory.

Methods: Twenty-nine community hospitals without on-site invasive facilities participated in the Krakow Registry of Acute Coronary Syndromes – a prospective, multicentre, web-based, observational registry. Renal insufficiency (RI) was defined as creatinine clearance (CrCl) <60 ml/min.

Results: NSTE ACS was diagnosed in 1396 patients. Renal insufficiency was diagnosed in 34% of all patients. Only 17% of them had been diagnosed with RI prior to admission. Transfer for invasive treatment was undertaken in 10% of RI patients as compared to 16% of patients with CrCl >60 ml/min (NS). In-hospital mortality among patients remaining on conservative treatment in community hospitals was significantly higher among RI patients (4.0 vs. 0.6%; p <0.001). Thienopyridines were less frequently used in RI patients (46 vs. 54%; p <0.05). In-hospital mortality among RI patients remaining in community hospitals and treated conservatively was higher than among non-RI patients in each TIMI risk score group: 7.3 vs. 2.4% (p <0.05) in the high risk group, 4.1 vs. 1.4% (NS) in the moderate and 3.6 vs. 0% (p <0.001) in the low risk group. Multivariate logistic regression analysis identified reduced creatinine clearance and a history of heart failure as independent factors influencing mortality.

Conclusions: Renal insufficiency was present in one-third of NSTE ACS patients. Patients with renal insufficiency had worse clinical risk profile and received less aggressive treatment. Patients with NSTE ACS and renal insufficiency treated conservatively had higher in-hospital mortality. Renal insufficiency modifies mortality irrespective of the TIMI risk score. Creatinine clearance should be considered in modification of the TIMI risk score scale.

Key words: renal insufficiency, acute coronary syndromes, creatinine clearance, TIMI risk score

Introduction

Non ST-segment elevation acute coronary syndromes (NSTE ACS) are the most frequent cause of admission to intensive care units [1, 2]. Early risk assessment, appropriate planning and implementation of optimal treatment are of particular importance in these patients [3].

Epidemiological studies have demonstrated that renal insufficiency (RI) is an independent risk factor in patients with cardiovascular disease, including coronary artery disease [4, 5]. Cardiovascular disease is also a major cause of death in patients with chronic kidney disease (CKD), including end-stage renal failure [6].

The purpose of the present study was to assess the effects of renal function on the course of treatment and prognosis in patients with NSTE ACS admitted to hospitals without on-site invasive facilities but with a possibility of immediate transfer to a reference centre with a catheterisation laboratory.

Methods

Krakow Registry of Acute Coronary Syndromes

The Krakow Registry of ACS was a prospective, multicentre, observational registry designed to examine current epidemiology, in-hospital management and
outcome in patients with ACS in the Krakow Region of Poland with a population of 3.2 million. A total of 29 community hospitals without on-site invasive facilities participated in consecutive enrolment periods of the registry from 2002 until 2006. To minimise selection bias, all consecutive patients with a suspected diagnosis of ACS were included. During the index hospitalisation in the community hospital, data concerning baseline demographics, clinical characteristics, relevant laboratory results, pharmacotherapy and adverse cardiovascular outcomes were recorded on a standardised, electronic, web-based case report form (https://www.cardio.pl/acs/index.php). Standardised definitions were used for adverse events and final diagnosis. Data were collected in a central electronic database. The database was reviewed for completeness by an independent physician and site queries were generated if needed.

Assessment of renal function

Baseline creatinine clearance (CrCl) was calculated using the Cockcroft-Gault formula from serum creatinine [7]. Renal insufficiency was defined as CrCl <60 ml/min (renal insufficiency stage ≥III according to the National Kidney Foundation guidelines) [8].

Study groups

Patients were divided into two groups according to the level of CrCl: those with CrCl <60 ml/min and those with CrCl >60 ml/min (patients with normal renal function; non-RI). Both groups were then subdivided according to the NSTE ACS TIMI risk score into low (0-2 points), moderate (3-4 points) and high risk (5-7 points) of death [3]. We also analysed demographic and clinical data, treatment modality and in-hospital mortality in patients treated conservatively.

Statistical analysis

Data were analysed according to the established standards of descriptive statistics. Categorical variables are given as percentages and were compared by a maximum likelihood (ML) χ² test. Continuous variables were assessed for normality and are reported as mean ± standard deviation (SD). Continuous variables were compared by t-test or the two-tailed Mann-Whitney U-test as appropriate. In a subsequent step of the analysis, a multivariate logistic regression model was applied to search for independent predictors of in-hospital mortality (including baseline, clinical characteristics and applied pharmacotherapy). All independent variables considered potentially significant were initially included in the model followed by a stepwise deletion of the least significant variable down to a significance level of 0.05 or less. Statistical significance was defined as a p value <0.05.

The study was conducted in accordance with the Declaration of Helsinki and its later revisions.

Results

Of 2382 patients hospitalised for ACS and recorded in the registry database, 1396 were diagnosed with NSTE ACS. Baseline creatinine concentration was measured in 870 of these patients (62%) and further analyses were performed on that patient subset.

Patients with RI defined as CrCl <60 ml/min comprised 34% (n=295) of the NSTE ACS population. Only 17% of them had prior diagnosis of RI. There were significantly more women with reduced CrCl as well as elderly with history of prior angina, myocardial infarction, heart failure and brain stroke. Both groups were similar with respect to the prevalence of arterial hypertension, lipid disorders, percutaneous coronary intervention (PCI) and coronary artery bypass grafting surgery (CABG) in the past (Table I).

Only 10% of RI patients were selected for urgent invasive diagnostic procedures and transferred to a PCI centre in comparison to 16% of those with preserved renal function (p=NS). The overall in-hospital mortality among patients remaining in the community hospitals for conservative treatment was 2%, and was significantly

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Renal insufficiency (n=295)</th>
<th>Normal renal function (n=575)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>69±12</td>
<td>63±10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female gender [%]</td>
<td>55</td>
<td>35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior angina [%]</td>
<td>87</td>
<td>78</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous myocardial infarction [%]</td>
<td>45</td>
<td>32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart failure [%]</td>
<td>43</td>
<td>15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous diagnosis of chronic kidney disease [%]</td>
<td>17</td>
<td>0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Arterial hypertension [%]</td>
<td>82</td>
<td>76</td>
<td>NS</td>
</tr>
<tr>
<td>Past stroke [%]</td>
<td>8</td>
<td>4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetes mellitus [%]</td>
<td>30</td>
<td>22</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hyperlipidaemia [%]</td>
<td>49</td>
<td>49</td>
<td>NS</td>
</tr>
<tr>
<td>Current smokers [%]</td>
<td>18</td>
<td>31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior PCI [%]</td>
<td>6</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Prior CABG [%]</td>
<td>3.4</td>
<td>4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting surgery.

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higher in RI patients than non-RI (4.0 vs. 0.6%, p <0.0001) – Figure 1.

Multivariate logistic regression analysis identified reduced CrCl and a history of heart failure (borderline significance) as independent predictors influencing in-hospital mortality. Renal insufficiency was revealed to modify mortality irrespective of the TIMI risk score (Table III).

Patients with ACS were divided according to the TIMI risk score into low (TIMI risk score 0-2), moderate (3-4) and high risk (5-7) – Figure 2.

Patients with CrCl <60 ml/min in all TIMI risk score groups were less frequently transferred to the reference centre with cathlab facilities (Figure 3). In-hospital mortality among RI patients remaining in community hospitals and treated conservatively was higher in each TIMI risk score subgroup: 7.3 vs. 2.4% (p <0.05) in the high risk group, 4.1 vs. 1.4% (p=NS) in the moderate and 3.6 vs. 0% (p <0.001) in the low risk group (Figure 4).

**Table II.** In-hospital treatment in NSTE ACS patients stratified by renal function

<table>
<thead>
<tr>
<th>Medication</th>
<th>Renal insufficiency (n=295)</th>
<th>Normal renal function (n=575)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates [%]</td>
<td>96.3</td>
<td>95</td>
<td>NS</td>
</tr>
<tr>
<td>Beta-blockers [%]</td>
<td>65</td>
<td>83</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acetylsalicylic acid [%]</td>
<td>92.5</td>
<td>95</td>
<td>NS</td>
</tr>
<tr>
<td>Thienopyridines [%]</td>
<td>46</td>
<td>54</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Heparins (LMWH+UFH) [%]</td>
<td>85</td>
<td>85.6</td>
<td>NS</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitors [%]</td>
<td>0.3</td>
<td>0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics [%]</td>
<td>54</td>
<td>31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACE inhibitors [%]</td>
<td>74</td>
<td>76</td>
<td>NS</td>
</tr>
<tr>
<td>Statins [%]</td>
<td>64</td>
<td>74</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Abbreviations: LMWH – low molecular weight heparin, UFH – unfractionated heparin

**Figure 1.** Transfer for invasive diagnosis and in-hospital mortality in entire registry population stratified by renal function; CrCl <60 ml/min – black bars, CrCl >60 ml/min – white bars

**Figure 3.** Transfer of NSTE ACS patients for invasive treatment to PCI centre in TIMI risk score subgroups; CrCl <60 ml/min – black bars, CrCl >60 ml/min – white bars

**Table III.** Multivariate analysis for factors potentially influencing in-hospital mortality in NSTE ACS patients remaining for conservative treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance &lt;60 ml/min</td>
<td>4.9949</td>
<td>1.1201-22.2739</td>
<td>0.035**</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.6504</td>
<td>0.1931-2.1901</td>
<td>0.487</td>
</tr>
<tr>
<td>Age (per 1 additional year)</td>
<td>1.0060</td>
<td>0.9378-1.0781</td>
<td>0.861</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3.0848</td>
<td>0.9039-10.5272</td>
<td>0.072*</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>1.6063</td>
<td>0.4722-5.4645</td>
<td>0.448</td>
</tr>
<tr>
<td>Prior angina</td>
<td>0.9734</td>
<td>0.1038-9.1260</td>
<td>0.981</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2.0627</td>
<td>0.6044-7.0393</td>
<td>0.248</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.4894</td>
<td>0.4555-4.8697</td>
<td>0.510</td>
</tr>
<tr>
<td>TIMI risk score (per additional point)</td>
<td>1.3540</td>
<td>0.8399-2.1829</td>
<td>0.213</td>
</tr>
</tbody>
</table>

Abbreviations: OR – odds ratio, CI – confidence interval, * p <0.1, ** p <0.05
Discussion

The number of patients with RI is ever increasing [4]. In our Registry every third patient had renal function impairment. We also need to take into account that only one in seven of these patients had been diagnosed with RI prior to hospitalisation for NSTE ACS. Patients with RI were older, more often female and had more co-morbidities, thus confirming the findings of other investigators [9, 10]. This is probably associated with the fact that renal function and consequently CrCl declines with age [9]. The higher percentage of older women among those with reduced CrCl reflects the higher survival rate among women and consequently the higher proportion of women in the study group.

The optimal methods for the assessment of renal function in everyday clinical practice remain controversial. Glomerular filtration rate (GFR) is considered to be the best measure of kidney filtering capacity [10]. The level of GFR <60 ml/min is selected as the cut-off value for definition of RI because it represents a reduction by more than half of the normal value of ≈125 ml/min in young adults and this level is associated with the development of symptoms characteristic of RI [11, 12]. The National Kidney Foundation recommends estimating GFR from CrCl taking into account age, body weight and gender in order to avoid misclassification based on creatinine concentration alone [8].

Studies are continued to clarify the increased cardiovascular risk in patients with abnormal renal function. Decreased GFR may be associated with the prevalence of such traditional risk factors as arterial hypertension or dyslipidaemia, but also with other less understood factors such as hyperhomocysteinaemia. Decreased GFR is thought to be a marker of undiagnosed vascular disorders, especially in high-risk populations, and simultaneously an indicator of progressive remodelling and ventricular dysfunction [13]. Decreased GFR also strongly predisposes to the development of acute renal failure (ARF), which may per se increase mortality [12]. Diabetes mellitus (DM) is another important risk factor for the development of RI. In our study DM was significantly more frequent in patients with reduced CrCl.

What is even more pronounced is the fact that patients at higher risk are often treated less aggressively [14]. Although modern pharmacological and invasive treatment, so effective in the general population, may be safely and equally successfully used in patients with elevated risk, we may talk about therapeutic nihilism. The proportion of RI patients receiving appropriate pharmacological treatment that modifies the risk of death and referred for invasive therapy is lower than in the general population. Recent guidelines have mandated more aggressive lipid (statins) therapy, especially in patients with microalbuminuria, categorised as a high risk group.

The patients in the Krakow Registry of ACS with reduced CrCl were less often given beta blockers, thienopyridines and statins, but more frequently diuretics. This confirms the finding that patients with low level of GFR less often receive aggressive treatment with ACE inhibitors, beta-blockers, aspirin, platelet inhibitors or invasive procedures [13-16]. This trend is especially strong in the elderly over 65 years of age [17]. A similar tendency occurs in patients with end-stage renal disease, of whom less than half receive multi-drug treatment with ASA, beta-blockers, ACE inhibitors and statins [18]. It is important to modify this approach, especially for beta-blockers and statins, which have been found to have beneficial effects in patients with chronic renal disease [18, 19].

Patients with reduced CrCl are less often referred to invasive cardiology centres irrespective of TIMI risk score. The unwillingness to transfer patients for invasive treatment is probably a result of concern about increased risk of death and complications, including ARF associated both with invasive cardiology procedures (contrast medium usage) and CABG. However, it is high-risk patients that derive most benefit from aggressive invasive treatment [20-22].

Renal insufficiency in patients with NSTE ACS is an independent risk factor for mortality. In patients with reduced CrCl, mortality rate is significantly higher irrespective of stratification by TIMI risk score. It is of particular importance that in-hospital mortality in all TIMI risk score groups is significantly higher among RI patients, which further emphasises that renal function is an independent predictor in NSTE ACS. Therefore, CrCl should be considered in modification of the widely applied Antman’s TIMI risk score scale [3]. The multivariate models confirm this association. In-hospital mortality in patients with ACS is higher if they have RI at presentation and depends on its severity; an increased mortality rate is also observed at long-term follow-up [11, 23].

The widely used TIMI risk score does not take into account reduced CrCl as a factor influencing final outcome in patients with NSTE ACS. There is probably an urgent need to establish a new scheme or modify the
existing one, paying special attention to RI in NSTE ACS patients when estimating the risk of death and other serious ischaemic complications, because current studies confirm the unfavourable effect of reduced CrCl on outcomes in these patients, leading to a paradoxical situation in which mortality for NSTE ACS through low, moderate and high risk TIMI score is similarly high.

Over recent years, equations estimating GFR on the basis of serum creatinine concentration and other obtainable patient data have been developed and validated. The widely used Cockcroft-Gault formula incorporates serum creatinine, gender, age and body weight [7]. However, weight measurements or estimations make calculation and reporting of Cockcroft-Gault results by laboratories problematic. In our analysis the body weight was precisely measured at admission to community hospitals, either by the nurse or by the doctor in the emergency room.

Study limitation

Use of the Cockcroft-Gault formula may be considered a limitation of the study due to the fact that new American Heart Association guidelines for detection of CKD in patients with or at increased risk of cardiovascular disease advise the use of a novel model – MDRD [24]. The Cockcroft-Gault formula was advised at the time of our registry and was the most popular method for the assessment of kidney function [8].

The major limitation in the interpretation of the results is the fact that it was a registry, with all the very well known disadvantages and drawbacks of registries. However, there seems to be positive acceptance of and a need for high quality registry results as they are certainly complimentary to the results of randomised clinical trials, and convey a message that is sometimes omitted in the latter. Nevertheless, we tried to avoid group selection potential bias by applying statistical tools like multivariate regression analysis.

Conclusions

Every third patient with NSTE ACS had RI only one in seven of these patients had prior diagnosis of CKD. Patients with NSTE ACS treated conservatively and RI had higher in-hospital mortality. In patients with NSTE ACS renal function provides valuable information about prognosis and may supplement the widely used TIMI risk score. The combination of the two may be a useful tool for genuine estimation of risk of death and complications in NSTE ACS.

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Niewydolność nerek zwiększa śmiertelność w ostrych zespołach wieńcowych niezależnie od skali ryzyka TIMI

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Słowa kluczowe: niewydolność nerek, ostre zespoły wieńcowe, klirens kreatyniny, skala ryzyka TIMI

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