Prognostic value of renal function in STEMI patients treated with primary PCI: ANIN Registry

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Chronic kidney disease (CKD) adversely affects cardiovascular outcomes and mortality in the general population. We sought to determine the impact of renal function on angiographic and clinical results in ST-elevation myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention (pPCI).

Analyses were based on the prospective 'all-comer' registry of 1,064 consecutive STEMI patients treated with pPCI in our tertiary centre between February 2001 and October 2002. Admission serum creatinine concentration was known in 894 patients (84%). Mean serum creatinine was 105 ± 27 μmol/L and estimated glomerular filtration rate (eGFR) was 67 ± 18 ml/min/1.73 m^2. Thrombolysis in Myocardial Infarction grade 3 (TIMI3) flow was achieved in 751 patients (84%). During hospitalisation, 29 (3%) major bleedings, five (1%) strokes and 12 (1%) re-infarctions occurred. By day 30, two patients were lost to follow-up and 41 (5%) were dead. Renal function was independently associated with 30-day mortality (hazard ratio [HR] 1.6, 95% confidence interval [CI] 1.2–2.1, p=0.003). In CKD patients (eGFR <60 ml/min/1.73 m^2), TIMI3 flow was restored less frequently (79% *vs.* 87%), in-hospital major adverse cardiac and cerebrovascular events (MACCE) were more frequent (15% *vs.* 4%) and 30-day mortality was higher than in non-CKD patients (9% *vs.* 2%). Lower eGFR was associated with increased risk of major bleeding (HR 1.6, 95% CI 1.3–2.1, p<0.0005). In the subgroup of conscious patients with normal serum creatinine, eGFR remained significantly associated with 30-day mortality.

In conclusion, renal function expressed by eGFR is an independent predictor of procedural success and short-term outcomes in STEMI patients treated with pPCI, even in patients with normal serum creatinine. Thus, eGFR should be estimated in all STEMI patients to help identify a high-risk subgroup.

Introduction

Myocardial infarction with persistent ST-elevation (STEMI) continues to be a major public health problem. In a recent report, the incidence of hospital admissions for STEMI in Europe varied between 44 and 142 per 100,000 inhabitants per year, and in-hospital mortality reached 13.5%.[1] More than 30% of STEMI patients have chronic kidney disease (CKD).[2] On the other hand, half of deaths in advanced CKD patients are of cardiovascular causes with myocardial infarction (MI) being the most frequent event.[3]

Patients with CKD are routinely excluded from cardiovascular clinical trials, and certain medications and treatment modalities are less frequently employed in this group;[4] often these patients are treated less aggressively, possibly making proven life-saving therapies underused in this population.[5]

The objective of this study was to evaluate the impact of renal function on angiographic and short-term clinical outcomes in a homogenous, real-life cohort of patients with STEMI treated with primary percutaneous coronary intervention (pPCI), as this has not been extensively studied so far.

Methods

Study design and patient population

This prospective, observational, single-centre study was conducted at the Institute of Cardiology in Warsaw (Anin). All consecutive patients with STEMI (diagnosed according to European Society for Cardiology [ESC]/American College of Cardiology [ACC] guidelines current at the time[6]) treated with pPCI between February 2001 and October 2002 were included in a prospective registry (ANIN Myocardial Infarction Registry). There were no exclusion criteria; in particular, patients with cardiogenic shock, pulmonary oedema, known renal failure or advanced age were not excluded.

The study complies with the Declaration of Helsinki and the ethics committee approved its research protocol.

Clinical setting

The Institute of Cardiology in Warsaw is a tertiary cardiology centre performing about 4,000 coronary angiographies and 2,500 PCIs, including about 700 pPCI for STEMI, per year, where round-the-clock interventional duty for acute coronary syndrome patients was started in February 2001.

The majority of patients were transferred to our centre from non-PCI hospitals. Informed consent for interventional procedures was obtained in the emergency department, and patients were transported directly to the cath lab (not via the cardiac care unit [CCU]). The aim was to reduce door-to-balloon time. Blood samples for baseline serum creatinine were drawn from the arterial sheath prior to contrast administration. The operator was unaware of the lab results while performing the procedure.

Primary angioplasty was performed in all patients in accordance with generally accepted standards. At the time of this study, the pre-procedure protocol included a loading dose (300–500 mg orally) of acetylsalicylic acid. Unfractionated heparin (bolus intravenous injection of 100 IU per kg body weight or 70 IU if prophylactic abciximab was planned) and a loading dose of clopidogrel (at that time 300 mg orally) were usually given at the start of the procedure. Prophylactic abciximab use was left to the discretion of the operator. Reperfusion success was defined as a Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow.

Data collection

Baseline demographic, clinical, laboratory and angiographic data were collected on admission and angiographic data on completion of the pPCI using pre-printed forms. Data regarding in-hospital course (death, major bleeding, stroke, re-infarction) were obtained from patients' charts. Major adverse cardiac and cerebrovascular events (MACCEs) were defined according to the approved criteria (in particular, major bleeding as in TIMI bleeding score, and re-infarction as in the GUSTO-I trial). Vital status at 30 days was established by telephone calls to patients or their cardiologists. Missing data were obtained from the National Census Registry. A dedicated computerised database was set up and regularly updated.

Estimation of renal function

Renal function was assessed by estimation of glomerular filtration rate (eGFR) using abbreviated Modification of Diet in Renal Disease formula, as recommended by the National Kidney Foundation: eGFR = 32,788 × (serum creatinine)$^{-1.154}$ × age$^{-0.0203}$ × (1.210 if black) × (0.742 if female).

Patients were staged according to Kidney Disease Outcomes Quality Initiative (K-DOQI) guidelines.[7] CKD was defined as eGFR below 60 ml/min/1.73 m^2 with or without evidence of kidney damage. The clinical laboratory at our institution reported creatinine values greater than 133 μmol/L as abnormal for either gender.

Table 1. Baseline characteristics of patients treated with primary percutaneous coronary intervention (pPCI) for ST-elevation myocardial infarction (STEMI) with respect to presence of chronic kidney disease (CKD)

Parameter N (%)	All patients (n=894)	No CKD (n=576)	CKD (n=318)	p value
Female sex	237 (27)	93 (16)	144 (46)	<0.0005
Mean age ± SD (range), years	60 ± 12 (31–96)	57 ± 11 (31–96)	66 ± 11 (39–92)	<0.0005
Diabetes mellitus	116 (13)	55 (10)	61 (19)	<0.0005
Hypertension	419 (47)	241 (42)	178 (56)	<0.0005
Hyperlipidaemia	283 (32)	174 (30)	109 (34)	0.2
Family history of CAD	271 (30)	210 (37)	61 (19)	<0.0005
Current smokers	451 (50)	342 (59)	109 (34)	<0.0005
Prior MI	183 (21)	102 (18)	81 (26)	0.007
Prior PCI	45 (5)	22 (4)	23 (7)	0.04
Mean heart rate ± SD, bpm	80 ± 19	79 ± 18	81 ± 21	0.2
Mean SBP ± SD, mmHg	133 ± 29	134 ± 28	131 ± 32	0.2
Killip class >1	105 (12)	49 (9)	56 (18)	<0.0005
Unconscious patient	34 (4)	12 (2)	22 (7)	<0.0005
Index MI localisation Anterior/ant-lateral Non-anterior or RBBB LBBB	 353 (40) 532 (60) 8 (1)	 234 (41) 337 (59) 4 (1)	 119 (37) 195 (61) 4 (1)	0.7

Key: CAD = coronary artery disease; CKD = chronic kidney disease; LBBB = left bundle branch block; MI = myocardial infarction; PCI = percutaneous coronary intervention; RBBB = right bundle branch block; SBP = systolic blood pressure; SD = standard deviation

Statistics

Typical statistical methods were used. Continuous data were expressed as means ± standard deviation (SD) and categorical data as numeric values and percentages. Additionally, age was expressed as a range. Comparison of continuous variables was performed by means of student *t*-test. Chi square test or Fisher exact test was used for comparison of categorical variables, as appropriate. Time-to-event data were summarised as Kaplan–Meier estimates and compared with log-rank test.

To adjust for baseline differences between study groups, all variables associated with the clinical end points at univariate analysis (p<0.1 for selection) were tested in multivariate analyses; Cox proportional hazards model and logistic regression were used to identify independent predictors of mortality and final TIMI grade 3 flow, respectively (tested variables were sex, age, history of hypertension, diabetes mellitus, smoking status, prior MI or PCI, heart rate [HR] and systolic blood pressure [SBP] on admission, eGFR, Killip class, localisation of MI, abciximab usage, multi-vessel disease [MVD], initial TIMI grade flow and final TIMI grade flow exclusively for mortality). Final models were built by forward stepwise variable selection, with a p value <0.05 used as a criterion for entry and p >0.1 for removal of variables. Results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

All reported p values are two-tailed, and a p value <0.05 was considered statistically significant unless otherwise specified. All statistical analyses were carried out using the Statistical Package for Social Sciences version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

In 894 of 1,064 consecutive patients enrolled in the registry, blood samples for baseline serum creatinine (SCr) were taken before the administration of the contrast media, and they formed the study group. The baseline characteristics of studied patients are shown in **table 1**.

Mean SCr was 105 ± 27 μmol/L and eGFR was 67 ± 18 ml per minute per 1.73 m^2, following a normal distribution. A total of 97 patients (11%) had abnormal serum creatinine. The prevalence of CKD was 36%.

Compared with the non-CKD group, patients with CKD were older and more likely to be female. They were less likely to be current smokers or to have a family history of coronary artery disease (CAD). However, they were more likely to have a history of MI, diabetes and hypertension. They were also more likely to be in a higher Killip class or unconscious post-cardiac arrest on admission.

Angiographic and procedural characteristics and outcomes

Angiographic characteristics and procedural results were typical for a cohort of STEMI patients treated with pPCI. Most often the infarct-related artery (IRA) was the right coronary artery. More than half of patients had multi-vessel disease (MVD). On the initial angiography, TIMI 0 or 1 flow in the IRA was observed in 732 patients (82%).

In most patients, only the IRA was treated, and the majority of procedures (78%) included stent implantation. Abciximab was given in almost 50% of patients, mostly prophylactically. Final TIMI grade 3 flow was achieved in 751 cases (84%).

CKD patients had MVD more often (60% *vs.* 48%, p=0.004), and received stents less often (73% *vs.* 80%, p=0.03). They required intra-aortic balloon pump (IABP) more frequently (3% *vs.* 1%, p=0.02) and had a lower procedural success rate (79% *vs.* 87%, p=0.004) when compared with patients with normal renal function.

The independent predictors of procedural failure (final TIMI grade <3), after adjustment for covariates, were decreased eGFR (HR 1.1, 95% CI 1.0–1.3, p=0.01), initial TIMI flow <2 (HR 2.9, 95% CI 1.6–5.6, p=0.001) and history of smoking (HR 2.5, 95% CI 1.7–3.3, p<0.0005).

Table 2. Angiographic and short-term clinical outcomes by stages of CKD

Stage of CKD, n (%)	All patients (n=894)	I (n=87)	II (n=489)	III (n=305)	IV (n=13)	p value
Final TIMI 3 flow	751 (84)	80 (92)	419 (86)	243 (80)	9 (69)	0.009
In-hospital re-infarction	12 (1)	0 (0)	6 (1)	5 (2)	1 (8)	0.1
In-hospital stroke	5 (1)	2 (2)	1 (0)	2 (1)	0 (0)	0.1
In-hospital major bleeding	29 (3)	0 (0)	8 (2)	20 (7)	1 (8)	<0.0005
In-hospital MACCE	46 (5)	2 (2)	15 (3)	27 (9)	2 (15)	<0.0005
30-day mortality	41 (5)	1 (1)	11 (2)	24 (8)	5 (38)	<0.0005

Key: CKD = chronic kidney disease; MACCE = major adverse cardiac and cerebrovascular event; TIMI = Thrombolysis in Myocardial Infarction

Clinical outcomes

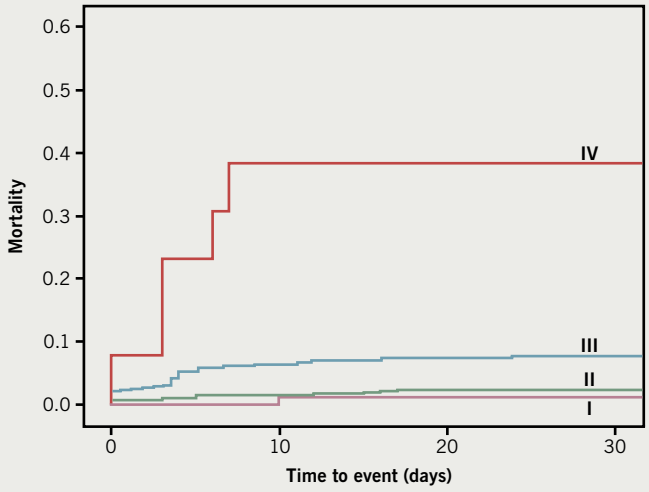
During a mean of 8 ± 7 days of hospitalisation, MACCEs occurred in 69 patients (8%). Vital status at day 30 was known in 892 out of 894 patients. Forty-one patients (5%) died by day 30.

Major bleeding was significantly associated with renal function. Any decrease in eGFR by 10 ml/min/1.73 m^2 increased the risk of major bleeding (HR 1.6, 95% CI 1.3–2.1, p<0.0005). Frequency of re-infarction or stroke was not statistically different with regard to eGFR. Both mortality and MACCE rates increased in higher stages of CKD (**table 2**). Cumulative mortality was higher in higher stages of CKD as demonstrated by Kaplan–Meier method (**figure 1**).

Prognostic factors for short-term mortality

After adjustment for covariates, 30-day mortality was significantly associated with eGFR (HR 1.6, 95% CI 1.2–2.1, p=0.001 for each 10 ml/min/1.73 m^2), age (HR 1.1, 95% CI 1.0–1.1, p=0.005 for each 10 years), prior PCI (HR 5.8, 95% CI 1.7–20.0, p=0.005), unconscious state (HR 18.6, 95% CI 6.7–

Figure 1. Kaplan–Meier curves of cumulative mortality by CKD stages (log-rank p<0.0005)



Stage of CKD	Number of patients at risk, n (%)			
	Day 0	Day 10	Day 20	Day 30
I	87 (100)	87 (100)	86 (99)	86 (99)
II	489 (100)	483 (99)	478 (98)	478 (98)
III	305 (100)	285 (93)	281 (92)	281 (92)
IV	13 (100)	8 (62)	8 (62)	8 (62)

51.8, p<0.0005) and use of IABP (HR 40.0, 95% CI 9.7–166.7, p<0.0005).

After exclusion of unconscious patients from the analyses, eGFR continued to demonstrate statistically significant independent association with short-term mortality (HR 1.6, 95% CI 1.2–2.3, p=0.004).

Estimated GFR remained an independent predictor of short-term mortality in conscious patients with serum creatinine within normal range (HR 1.8, 95% CI 1.16–2.75, p=0.009 for each 10 ml/min/1.73 m^2).

Discussion

The main finding of our study was that every decrease in kidney function as measured by eGFR in STEMI patients was associated with adverse outcomes, even if serum creatinine was within normal range. Thus, eGFR should be considered a continuous parameter, which influences prognosis without any specific cut-off value.

Over one-third of our STEMI patients were in stage 3 or 4 of renal disease. Prevalence of CKD (particularly stage 4) among our patients was higher than in randomised clinical trials,[8] in which patients with CKD were systematically excluded, and was similar to that found in registries.[2,9] One must, however, bear in mind significant variability of definitions of renal dysfunction employed by different studies.[10] Of note, many authors used serum creatinine rather than the eGFR recommended by the National Kidney Foundation.[7]

In the whole cohort of patients, the 30-day mortality rate was relatively low (5%). This could be due to short 'door-to-balloon time', which is a recognised prognostic factor.[11] This was achieved through round-the-clock presence of an interventional cardiologist on the premises, as opposed to on-call duty, and direct transfer of patients from admissions to the cath lab rather than via CCU. Despite the fact that we included all consecutive patients, regardless of haemodynamic status and renal function, angiographic success was obtained in more than 80% of patients. As a result, prevalence of in-hospital MACCEs was low. This could be an explanation for no significant difference in re-infarction and stroke between groups in different CKD stages.

The adverse impact of renal impairment on mortality in various cardiovascular diseases has been previously published by several authors.[12] Coronary revascularisation procedures, both surgical and percutaneous, were also shown to have worse results in CKD patients than in patients with normal renal function.[13] This might be partly explained by the relatively common co-existence of CKD and atherosclerosis, as most of the classical risk factors for these conditions are shared, e.g. age, diabetes, hypertension, obesity, smoking and dyslipidaemia.[14] To make it even worse, kidney failure speeds up development of atherosclerosis; such patients have more extensive coronary and peripheral artery disease, e.g. more often have MVD.[15] In our study, it was shown that CKD need not be severe or even mild, as demonstrated in a recent study,[16] to worsen the prognosis. Mild decrease of eGFR, even within normal range, was also of importance and, actually, any drop in this parameter worsened the prognosis without a specific cut-off value.

We noted more bleeding events in the CKD group. Correlation of renal impairment with bleeding disorders is a well-recognised issue.[17] Renal failure may be associated with uraemic platelet dysfunction and decreased thrombopoiesis.[18] It also causes impaired aggregability in response to such thrombogenic triggers as adenosine diphosphate (ADP), collagen and epinephrine.

In addition to traditional cardiac risk factors, which are highly prevalent in patients with CKD, CKD patients exhibit marked nephroangiosclerosis (intimal hyperplasia, hyalinosis, smooth muscle cell hypertrophy),[19] abnormal coronary flow reserve, inflammation, oxidative stress, insulin resistance, accelerated vascular calcification, activation of the renin–angiotensin system, anaemia and vitamin D deficiency, which might contribute directly to adverse outcomes. Moreover, endothelial dysfunction and chronic inflammation, which play an important role in atherothrombosis, are present even with mild impairment of renal function. This may lead to a worse prognosis, not only in patients with early stages of CKD,[16]

but also in patients with normal renal function, as was demonstrated in our study.

The available data on immediate angiographic results of pPCI in STEMI patients with different degrees of kidney failure is inconclusive. However, in some studies, similar to ours, angiographic success rate has been shown to differ between stages of kidney disease.[20] It may be related to the combined effect of endothelial dysfunction and higher extent of atherosclerosis. Both *in vivo* and *in vitro* studies performed on microvessels obtained from patients with advanced CKD confirmed dysfunction of their endothelium.[21]

Adverse outcomes in MI patients associated with depressed renal function have already been reported.[22] However, there are three features that, taken all together, differentiate our study from the previous. First, it was conducted in a homogenous, single centre cohort of STEMI patients that received uniform treatment. Therefore, the potential influence of some confounding factors (such as diagnosis: non-ST-segment elevation MI [NSTEMI] *vs.* STEMI, type of treatment: interventional *vs.* fibrinolytic, experience of the centre, volume of procedures, different algorithms of management of STEMI patients) was avoided. Furthermore, and in opposition to most other studies,[7] our population is unselected and represents a high prevalence of kidney disease. It reflects frequency of CKD among acute coronary syndrome in real-life practice.[23] All patients received modern reperfusion therapy, without any pre-selection based on renal function or other variables (pPCI with high rate of stenting and abciximab usage). Finally, some prior studies,[24] have used serum creatinine rather than the eGFR to detect renal function. The accuracy of serum creatinine level as a marker of renal function is limited, owing to nonlinear associations with eGFR that vary according to age, sex and race.[25] We found that the prognostic significance of renal function expressed by eGFR was also present in a subgroup of patients with serum creatinine within the normal range. Thus, eGFR should be determined in all patients with STEMI.

Several limitations should be considered when interpreting our results. This was a single-centre study, which may cause an unrecognised bias normally avoided in multi-centre analyses. We had no information about baseline serum creatinine in 170 patients, however, mortality in this excluded subgroup was not significantly different from the study population.

We also had no knowledge about renal function before index STEMI, therefore, we were not able to distinguish between the types of renal dysfunction (acute *vs.* chronic). We were not able to demonstrate the association between renal function and incidence of re-infarction or stroke due to low numbers of events. Adjunctive therapy used at the time of the study differed from the present routine. Although acetylsalicylic acid was given pre-hospital, most of the patients received heparin and clopidogrel only during the procedure and not in the ambulance or in the referring hospital.

The loading dose of clopidogrel was 300 mg, and not 600 mg as later recommended in STEMI patients. For obvious reasons newer antiplatelet agents (e.g. prasugrel, ticagrelor), drug-eluting stents or thrombectomy were not used at that time.

In conclusion, renal function expressed by eGFR is an independent predictor of procedural success and short-term outcomes in STEMI patients treated with pPCI, even in patients with normal serum creatinine. Thus, eGFR should be estimated in all STEMI patients to help identify a high-risk subgroup

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Conflict of interest

None declared.

Key message

- Renal function expressed by eGFR is an independent predictor of procedural success and short-term outcomes in STEMI patients treated with pPCI.

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