Impaired renal function in acute myocardial infarction

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Abstract

Impaired renal function is a risk factor for cardiovascular disease and an adverse prognostic factor in patients with established cardiovascular disease. In addition, with current widespread use of invasive procedures in the treatment of acute myocardial infarction, contrast-induced nephropathy is a growing problem in this patient population. In acute myocardial infarction, impaired renal function may result from underlying kidney disease, acute renal failure, and the effect of drugs and contrast agents used during diagnostic procedures or treatment. These various causes may coexist, resulting in significantly worse outcomes. Prompt recognition of the degree of renal function impairment and institution of appropriate preventive and therapeutic measures are among major goals of in-hospital management of these patients. A commonly used method to evaluate renal function is the determination of glomerular filtration rate. Appropriate nephroprotective treatment should be used in patients at risk of contrast-induced nephropathy. The most commonly used methods include the use of iso-osmotic contrast agents and appropriate hydration in the periprocedural period. Studies are currently under way to evaluate nephroprotective properties of other drugs such as N-acetylcysteine, sodium chloride and sodium bicarbonate solutions, mannitol, and statins. Results of some studies suggest that these measures may effectively reduce the number of renal function deterioration events in patients with acute myocardial infarction.

Regardless of the cause, impaired renal function in acute myocardial infarction is a significant adverse prognostic factor. Thus, despite some inconsistent views regarding the optimal management strategy, intensive diagnostic, preventive, and therapeutic measures are clearly necessary in patients with acute myocardial infarction and impaired renal function. (Cardiol J 2009; 16, 5: 400–406)

Key words: impaired renal function, acute myocardial infarction, contrast induced nephropathy
Introduction

Percutaneous coronary diagnostic and therapeutic procedures require intravascular contrast agent administration that is a major risk factor of contrast-induced nephropathy (CIN) and acute renal failure during the hospitalization.

In Europe, CIN is the third most common cause of acute in-hospital renal failure, leading to prolonged hospitalizations and increased treatment costs.

Impaired renal function (IRF) is a risk factor for cardiovascular disease and an adverse prognostic factor in patients with established cardiovascular disease [1]. Many clinical and population studies demonstrated that IRF is an independent prognostic factor during short- and long-term follow-up of patients with acute coronary syndromes (ACS), including acute myocardial infarction (AMI) [2, 3]. In addition, renal dysfunction was shown to be an adverse predictive factor in AMI regardless of the reperfusion strategy used [2, 4–6].

Currently, percutaneous coronary intervention (PCI) is the preferred treatment strategy also in patients with IRF, as it is associated with a higher rate of effective reperfusion and lower mortality compared to thrombolytic therapy [7]. In some patients, however, PCI carries a risk of CIN. Patients with underlying IRF [8] or IRF secondary to hemodynamic compromise in ACE are at particular risk of this complication. Other risk factors for CIN include large amounts of contrast agent administered during PCI and inability to use appropriate prevention. Thus, identification of patients at risk and institution of appropriate preventive measures are clearly justified.

A registry of patients with ACS in Poland was established in 2003. The rates of various degrees of IRF in patients with ACS are shown in Table 1.

| Table 1. Proportions of patients with acute coronary syndromes and various stages of chronic kidney disease as defined based on impaired glomerular filtration rate. Source: PL–ACS Registry. |
| Glomerular filtration rate | 30–59 mL/min/1.73 m² (Stage III) | 15–29 mL/min/1.73 m² (Stage IV) | < 15 mL/min/1.73 m² (Stage V) |
| UA | 23% | 1.5% | 1% |
| NSTEMI | 28% | 3.9% | 1.8% |
| STEMI | 20% | 2.4% | 0.9% |

UA — unstable angina; NSTEMI — non-ST segment elevation myocardial infarction; STEMI — ST segment elevation myocardial infarction

Definitions

To address the issue of chronic kidney disease (CKD), a group of experts working under the auspices of National Kidney Foundation developed clinical practice guidelines known as Kidney Disease Outcomes Quality Initiative (K/DOQI) [9].

A consequence of CKD is decreased glomerular filtration rate (GFR) [10]. This renal function impairment develops gradually but may be noted already in early stages of CKD, and GFR is the most precise marker of renal function [11]. Thus, a new, five-stage classification of CKD severity was proposed in the K/DOQI guidelines based on the degree of GFR reduction:

— stage I: GFR > 90 mL/min/1.73 m² (a transient increase in GFR may even be noted at this stage);
— stage II: GFR 60–89 mL/min/1.73 m²;
— stage III: GFR 30–59 mL/min/1.73 m²;
— stage IV: GFR 15–29 mL/min/1.73 m²;
— stage V: GFR < 15 mL/min/1.73 m².

The latter stage is, in fact, chronic end-stage renal failure that requires renal replacement therapy.

Normal GFR is approximately 130 ± 20 mL/min/1.73 m² in men, 115 ± 15 mL/min/1.73 m² in women. Thus, CKD is not synonymous with chronic renal failure, as the latter is the terminal stage of CKD as defined in the classification introduced in the K/DOQI guidelines.

Chronic kidney disease

American National Kidney Foundation defined diagnostic criteria of CKD based on both GFR and structural and functional renal kidney changes. According to these criteria, CKD may be diagnosed in two situations [9]:

— if impaired renal function as defined by reduced GFR is sustained for more than three months, and GFR is reduced to less than 60 mL/min/1.73 m², CKD may be diagnosed regardless of any other diagnostic criteria;
— if GFR is normal or exceeds 60 mL/min/1.73 m² (stage I and II), CKD may be diagnosed if sustained structural and functional renal kidney changes are seen for more than three months,
based on abnormal results of additional blood and/or urine testing or morphological abnormalities in imaging studies.

According to this definition, the diagnosis of stage I and II CKD requires additional features of renal damage, while GFR reduced to less than 60 mL/min/1.73 m$^2$ is sufficient to diagnose CKD without the presence of any other diagnostic criteria.

In clinical practice, GFR is most commonly calculated based on creatinine clearance or estimated (so called estimated glomerular filtration rate, eGFR) using the Cockcroft-Gault formula or the Modification of Diet in Renal Disease (MDRD) study formula. Recent data suggest the MDRD formula is the most reliable and objective approach to estimate GFR [12, 13]. The use of the MDRD formula is recommended in the K/DOQI guidelines in all patients except those on a vegetarian diet and subjects with severely reduced body mass. In these groups, renal function evaluation should be based on the determination of creatinine clearance. Four modifications of the MDRD formula have been described, and the simplest of them is as follows:

\[
eGFR \text{[mL/min/1.73 m$^2$]} = 186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times C
\]

where C is a constant equal to 1 in men, 0.762 in women, and 1.21 in Afro-Americans. Online versions of eGFR calculators are widely available in the Internet (see for example http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm).

**Contrast-induced nephropathy**

Contrast-induced nephropathy is defined as acute impairment of renal function that occurs 24–48 hours after an intravenous contrast agent administration and results in an increase in serum creatinine level by at least 25% compared to the baseline values, if no alternative explanation of renal function impairment can be offered [14]. Creatinine level peaks at approximately 2–3 days after the contrast agent administration and returns to the baseline values by 14 days. Unfortunately, some patients may develop acute renal failure requiring dialysis therapy [15].

**Pathophysiology**

Impaired renal function has a negative effect of atherosclerotic vascular lesions, leading to increased production of atherogenic factors, proteinuria, increased inflammatory activity (as manifested by high fibrinogen and C-reactive protein levels), increased level of oxidation products, impaired nitric oxide production, and accelerated vascular calcification [16–18]. All these effects contribute to faster progression of atherosclerosis in patients with IRF, involving both coronary and peripheral vessels. In addition, resulting atherosclerotic plaques are thickened and more calcified [11, 19].

**Clinical aspects of renal failure in acute myocardial infarction**

Renal function should be promptly evaluated in all patients admitted due to AMI. The major laboratory parameter is serum creatinine level which allows eGFR calculation. Values below 60 mL/min/1.73 m$^2$ are associated with markedly worse prognosis, because these patients are significantly more likely to develop CIN [14]. Thus, management of these patients should be modified accordingly and this issue is discussed in more detail below. As highlighted in the K/DOQI guidelines, risk assessment should be based on eGFR evaluation using the MDRD formula [9]. If serum creatinine level is not available promptly, thorough history should be taken regarding past renal function and/or kidney disease. This evaluation of renal function may be omitted only if even short delay in the use of contrast agent for diagnostic or therapeutic purposes would pose more risk for the patient than any future complications of the contrast agent administration [9].

Renal function may deteriorate after AMI. This may result from both hemodynamic compromise affecting glomerular perfusion and diagnostic and/or therapeutic procedures requiring the use of a contrast agent. The degree of renal function impairment resulting from these factors may vary from mild reduction in GFR to the occurrence of acute renal failure. The latter develops most frequently in patients with AMI complicated by a cardiogenic shock or with underlying renal function impairment. Important prognostic factors include time to reperfusion, infarct location, and coexisting conditions, particularly diabetes.

Renal function impairment or CIN may occur in any patient with AMI or undergoing any diagnostic and/or therapeutic procedures involving an intravenous contrast agent administration. However, some subsets of patients require higher level of diagnostic vigilance or even appropriate management modifications.

The major predictive factor for CIN is GFR, with the increase in risk being proportional to the degree of IRF [15]. Thus, CKD is the major concomi-
tant clinical condition contributing to the development of CIN. The risk of CIN is also increased in patients with diabetes, anemia or heart failure, patients above 75 years of age, and patients in cardiogenic shock. The occurrence of CIN is in turn associated with higher risk of acute renal failure.

Impact of IRF on the prognosis in AMI treated with PCI

The effect of IRF on the management and prognosis in patients with AMI treated with PCI was studied by many researchers. For example, the group of Suchetry Vasu analyzed the effect of impaired renal function on in-hospital prognosis in patients with AMI treated with PCI. The patients were divided in two groups, with less severe (stage 0–II) or more severe (stage III–V) CKD. The cutoff serum creatinine was 2.5 mg/dL. In this study, patients with more severe CKD were much more likely to suffer from coexisting conditions such as diabetes, hypertension, and peripheral vascular disease. These patients were also at significantly higher risk of developing cardiogenic shock or cardiac failure, with significantly increased in-hospital mortality (23.4% vs. 4.2%, p < 0.001) [16]. Worse outcomes in patients with more severe CKD may be largely explained by more severe coronary artery disease in this group, leading to less beneficial effects of PCI compared to patients without IRF [20]. However, more advanced CKD remained an independent prognostic factor affecting in-hospital mortality even after controlling for confounders [16]. An analysis of HIJAMI registry demonstrated that long-term outcomes in patients with AMI treated with PCI were similar to the results reported by Vasu et al. [21]. This worse prognosis may be related to specific biochemical and physiological features of CKD, as periprocedural bleeding events and strokes are much more likely in these patients. In addition, CKD affects metabolism of drugs used in the treatment of AMI, such as aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors. All these factors result in a higher risk of complications and worse outcomes [17]. As mentioned above, reduced survival of patients with IRF was highlighted in the HIJAMI registry analyses that showed that impaired renal function is associated with a higher likelihood of unsuccessful PCI [22]. Eijkelkamp et al. [23] evaluated more than 6000 patients with AMI who were followed for approximately 27 years. Average yearly increase in serum creatinine level in patients who suffered an AMI was 3.1% compared to 0.4% in the control group of patient with no history of AMI (p = 0.005). This resulted in a significantly higher age-related fall in GFR (2.2 vs. 0.5 mL/min/1.73 m² per year, p = 0.006) [23]. These results may perhaps be explained by accelerated glomerulosclerosis in patients who suffered an AMI but the exact determination of the pathomechanism and any therapeutic possibilities in this regard awaits further studies. Many observations suggest bidirectional pathogenetic interactions between IRF and AMI, as impaired renal function seems to increase the risk of AMI, but the AMI itself is a risk factor for IRF.

More transient renal function impairment also seems to have an adverse prognostic effect in patients who suffered an AMI. In the PREVEND study, Lathamsetty et al. [24] demonstrated that in-hospital rise in creatinine level was associated with significantly worse outcomes regardless of any further improvement in renal function. In this population, even a short-lasting rise in creatinine level resulted in significantly increased mortality compared to patient who did not experience renal function impairment (7.4% vs. 27%). In addition, this increase in mortality was similar to patients in whom creatinine level remained permanently elevated (27% vs. 23%). A short-term rise in creatinine level was shown to be an independent predictor of mortality at six months [24]. Again, mechanisms of these worse outcomes remain to be determined.

The degree of post-infarction GFR reduction is largely related to the mechanism of renal damage. Kowalczyk et al. [25] evaluated prognostic differences between patients with IRF due to underlying CKD or induced by an administration of a contrast agent. The most important independent adverse prognostic factor in this study was the occurrence of cardiogenic shock. Although the least favorable long-term outcomes were noted in patients with CKD, controlling for confounders (including cardiogenic shock) revealed that CIN was even stronger adverse prognostic factor than CKD, particularly in patients with diabetes. High mortality among patients with CKD in this study may be explained by a higher rate of cardiogenic shock in this group.

Other common factors than cardiogenic shock and CKD that increase the risk of CIN include diabetes, time to reperfusion exceeding six hours, and the anterior wall infarct location [26]

Prevention and treatment

The current management of ST segment elevation ACS is discussed in the regularly updated
European Society of Cardiology (ESC) guidelines and American guidelines. The latest 2008 ESC guidelines on ST segment elevation ACS recommend that patients with renal dysfunction should be treated in a similar way to the general population of AMI patients, but renal disease should be taken into account when choosing reperfusion strategy and considering specific pharmacotherapy due to worse outcomes in this patients group [27]. Both European and American guidelines do not provide separate recommendations for a growing population of patients with CKD and chronic renal failure. These guidelines are generally based on the results of randomized clinical trials and registry studies performed in wide populations of AMI patients. For the purpose of the present review, we analyzed studies on which the 2005 PCI guidelines were based [28]. Inclusion criteria in these studies show significant heterogeneity in terms of acceptable renal function. In approximately half of the studies on which level of evidence A or B recommendations were based, the exclusion criteria included any renal failure or elevated serum creatinine (> 1.7–3.5 mg/dL) [29]. In this regard, published recommendations on the invasive treatment in AMI may be considered of limited value in patients with AMI and coexisting IRF. Studies are currently under way to determine the optimal management strategy in these patients. As mentioned above, even a transient rise in creatinine level is an adverse prognostic factor in AMI [24]. This increase in risk is mainly related to the occurrence of CIN. The Canadian Radiological Society published guidelines on prevention of CIN in patients undergoing diagnostic and therapeutic procedures requiring an intravenous contrast agent administration and recommended, particularly in patients at high risk of CIN (i.e., with GFR < 30 mL/min), the use of iso-osmolar and low-osmolar contrast agents which are less nephrotoxic compared to the high-osmolar contrast media [15]. However, Aspelin et al. [30] demonstrated advantage of an iso-osmolar over a low-osmolar contrast agent in high-risk patients with diabetes. Due to large differences in osmolality between particular agents, further studies are necessary to establish the optimal choice of a contrast agent. According to the Canadian Radiological Society guidelines, the use of 100–140 mL of a contrast agent per procedure is associated with a minimal risk of CIN. These guidelines also recommend routine hydration with 0.9% NaCl or NaHCO₃ solution to increase volemia [15]. In patients undergoing acute coronary interventions, Masuda et al. [31] demonstrated a lower rate of CIN with the use of sodium bicarbonate compared to sodium chloride (7% vs. 35%, p = 0.01). A free radical scavenger, N-acetylcysteine, has also been recommended, particularly in patients with GFR < 60 mL/min [32]. Nallamothu et al. [33] performed a metaanalysis of 20 randomized studies evaluating the effect of acetylcysteine on the incidence of CIN and showed a non-significant trend toward a lower rate of CIN in patients receiving acetylcysteine. In a randomized REMEDIAL study in 326 medium- and high risk patients undergoing coronary or peripheral angiography and/or angioplasty procedures, Briguori et al. [34] demonstrated an advantage of sodium bicarbonate and acetylcysteine combination over both sodium chloride with acetylcysteine and sodium chloride with acetylcysteine and ascorbic acid in terms of reduction of the incidence of CIN (1.9% vs. 9.9% vs. 10.3%). Recently, Kelly et al. [35] published a metaanalysis of 41 randomized studies including 3622 patients undergoing various diagnostic and therapeutic procedures requiring the use of a contrast agent and demonstrated an advantage of N-acetylcysteine, mannitol and theophyllin over periprocedural fluid administration only in terms of the effectiveness of CIN prevention.

Large doses of statins were also reported to have nephroprotective properties in AMI patients treated with PCI, and this effect is probably associated with the antioxidant activity of these drugs [36]. Patti et al. [37] prospectively studied more than 4000 patients undergoing PCI and found a lower rate of CIN among statin-treated patients compared to controls (3% vs. 27%, p < 0.0001). However, subgroup analysis showed no nephroprotective effect of statins in patients with baseline creatinine clearance < 40 mL/min. Similar results in AMI patients treated with primary PCI were reported by Zhao et al. [38] who noted a significantly lower rate of CIN in patients who were pre-treated with statins (7.1% vs. 20.6%, p < 0.01). In contrast, a randomized, double-blind PROMISS study showed no benefit of simvastatin (in a total dose of 160 mg) in terms of reduction of the incidence of CIN in patients with renal failure (creatinine clearance < 60 mL/min or serum creatinine > 1.1 mg/dL) undergoing coronary angiography (2.5% vs. 3.4%, p = 1.00) [39]. Nephroprotective properties of many other treatments during invasive cardiac procedures including those used in the treatment of AMI were also evaluated, but no clear and reliable evidence of their effectiveness exist to date [40].

General recommendations of the Canadian Radiological Society regarding prevention of CIN
Table 2. The Canadian Radiological Society guidelines on the prevention of contrast-induced nephropathy.

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<tr>
<th>General recommendations in patients with GFR &lt; 60 mL/min/1.73 m²</th>
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<tbody>
<tr>
<td>Avoid, if possible, iodine contrast agents.</td>
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<tr>
<td>Avoid nephrotoxic drugs during the last 48 hours before contrast agent administration.</td>
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<tr>
<td>Avoid high-osmolar contrast agents. Instead, use iso-osmolar and low-osmolar contrast agents.</td>
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<tr>
<td>Use minimal amounts of the contrast agent and avoid repeated administration within 72 hours.</td>
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<tr>
<td>Consider administration of N-acetylcysteine. Further studies on the use of N-acetylcysteine are warranted.</td>
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<tr>
<th>Specific recommendations in patients with GFR 30–60 mL/min/1.73 m²</th>
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<tr>
<td>Avoid patient dehydration. Consider administration of oral or intravenous fluids.</td>
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<tr>
<td>Consider follow-up GFR determination 48 hours after the contrast agent administration.</td>
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<tr>
<th>Specific recommendations in patients with GFR &lt; 30 mL/min/1.73 m²</th>
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<tr>
<td>Administer intravenous fluids to increase intravascular volume (normal saline or sodium bicarbonate).</td>
</tr>
<tr>
<td>Perform follow-up GFR determination 48 hours after the contrast agent administration.</td>
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GFR — glomerular filtration rate

Summary

As highlighted in the present review, IRF has a significant effect on the management and prognosis in patients with AMI. Worse renal function is associated with a significantly higher risk of complications, including adverse cardiovascular events and mortality, both in hospital and during long-term follow-up. Review of the literature demonstrates significant heterogeneity in the approach to the evaluation of renal function and the definition of IRF, resulting in discrepant data on the rate of various degrees of IRF in patients with ACS. In addition, many studies were performed in populations with only milder degree of renal function impairment, excluding patients with more advanced kidney disease.

However, regardless of these methodological issues and different definitions, renal dysfunction is undoubtedly a major prognostic factor in AMI, and it appears that efforts to diagnose, prevent and treat this condition became a part of routine management in this patient population.

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References


