Management of Acute Coronary Syndromes in Patients with Renal Insufficiency

Giancarlo Marenzi*, Emilio Assanelli and Antonio L. Bartorelli

FINAL

From the Centro Cardiologico Monzino, I.R.C.C.S., Institute of Cardiology of the University of Milan, Milan, Italy

Abstract: Chronic kidney disease (CKD) is highly prevalent in patients with acute coronary syndromes (ACS) and is associated with poor outcomes. The clinical management of patients with CKD who develop ACS is problematic because of the lack of well-designed randomized trials assessing therapeutic strategies in such patients. The almost uniform exclusion of patients with CKD from randomized studies evaluating new targeted therapies for ACS, and concern about further deterioration of renal function and therapy-related toxic effects, may explain the less frequent use of proven medical therapies in this subgroup of high-risk patients. This could contribute to their excessive mortality. The objective of this review is to discuss the unresolved issues and uncertainties regarding recommended medical therapies and interventional strategies in CKD patients who develop an ACS.

Key Words: Acute coronary syndromes, renal insufficiency, percutaneous coronary intervention, chronic kidney disease.

INTRODUCTION

There is increasing evidence that chronic kidney disease (CKD) is associated with accelerated atherogenesis, and that any degree of renal insufficiency is an independent risk factor for increased cardiovascular events and portends a worsened prognosis in patients with coronary artery disease [1,2]. More recently, the pervasive adverse influence of renal insufficiency has been also demonstrated in the setting of acute coronary syndromes (ACS) [3-11]. Among ACS patients, CKD doubles mortality rates and is third only to cardiogenic shock and congestive heart failure as a predictor of mortality [12]. Antithrombotic agents and percutaneous coronary interventions (PCI) are clearly emerging as the cornerstones of treatment patterns in patients presenting with ACS [13-16]. However, despite the increasing number of CKD patients with a broad range of ACS at presentation, evidence-based data with established or newer drugs and interventional strategies are still lacking in this population. Ideally, these are the patients to whom recent therapeutic advances should be aggressively applied, in order to minimize their increased risk. Ironically, although they may derive the greatest benefit from proven therapies, application of strategies for reducing their cardiovascular morbidity and mortality seem to be limited when compared to patients with normal renal function. The almost uniform exclusion of patients with CKD from randomized studies evaluating new targeted therapies for ACS, and concern about further deterioration of renal function and therapy-related toxic effects, may explain the apparent reluctance of physicians to use these treatments in patients with renal insufficiency. The paradoxical pattern of undertreatment in this subgroup of high-risk patients could contribute to their excessive mortality.

As French and Wright pointed out, the time has come to move beyond the attitude of "therapeutic nihilism" toward patients with renal failure, and develop targeted strategies from well-designed research which will ultimately reduce the burden of risk in this population and achieve improved outcomes [17].

This review outlines the unresolved issues and uncertainties regarding recommended medical therapies and interventional strategies in ACS patients with renal insufficiency. Given the different treatment modalities in patients with ST-elevation myocardial infarction (STEMI) and in those with non-ST-segment elevation acute coronary syndromes (NSTE-ACS), such as unstable angina and non-ST-elevation myocardial infarction, the two clinical conditions will be considered separately.

ST-ELEVATION MYOCARDIAL INFARCTION

Treatment of STEMI in patients with CKD is particularly problematic. Traditionally, patients with advanced renal insufficiency and end-stage renal disease (ESRD) receiving dialysis have not been included in randomized STEMI trials evaluating either medical or interventional therapies. Thus, only scarce data deriving from limited observational studies are available and, to date, no optimal treatment strategy has been defined for this subgroup of patients. This critical deficiency has been addressed by Berger *et al*. [18] who compared the patterns of care and the effect of standard STEMI therapy on 30-day mortality between 1,025 ESRD patients on chronic dialysis (either peritoneal dialysis or hemodialysis) and 145,740 non-ESRD patients. They confirmed that aspirin, beta-blockers, and ACE-inhibitors were less likely to be used in patients on dialysis, even among those considered "ideal candidates" for these medications, than in patients not receiving dialysis. Nevertheless, the authors observed a similar absolute reduction in short-term mortality with aspirin, beta-blocker, and ACE-inhibitor therapy when comparing the dialysis and non-dialysis groups. Aspirin was associated with 20.7% absolute reduction in mortality in dialysis patients, and a 22.8% reduction in non-dialysis patients. Beta-blocker therapy was associated with a 13.6% absolute reduction in

*Address correspondence to this author at the Centro Cardiologico Monzino, *Via* Parea 4, 20138 Milan, Italy; Tel: +39.02.580021; Fax: +39.02.58002424; E-mail: giancarlo.marenzi@ccfm.it

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mortality in both the dialysis and non-dialysis patients. The ACE-inhibitor use was associated with a 16.1% absolute reduction in 30-day mortality in dialysis patients and a 5.4% reduction in non-dialysis patients. Beattie *et al*. [5] investigated patients with advanced renal dysfunction who were not on dialysis therapy. They analyzed a prospective coronary care unit registry of 1,724 patients with STEMI admitted over an 8-year period at a single tertiary-care center. Patients were stratified into groups based on different corrected creatinine clearance (CrCl) values. A graded rise in in-hospital complications and death rate, as well as reduction of long-term survival, was observed across increasing renal dysfunction strata. Moreover, the use of mortality-reducing treatments, including primary angioplasty, thrombolysis and β-blockers, decreased with the progressive decline of renal function, suggesting a treatment bias in favor of patients with less advanced renal dysfunction. While the lower rates of PCI may be rationally explained by the fear of an increased risk of contrast-induced nephropathy and of the associated high mortality rate [19,20], the potential risk of bleeding and hemodynamic complications constitutes only a partial justification for the less frequent use of thrombolysis and β-blockers.

Wright *et al*. [6] examined treatment patterns in 3,106 patients with STEMI in relation to their renal function. Reperfusion therapy (intravenous fibrinolysis or primary PCI) was used less frequently (24%) in patients with any degree of renal dysfunction than in patients without renal insufficiency, and was associated with improved long-term survival, but did not reduced the risk of in-hospital mortality. Similarly, the use of aspirin, β-blockers and intravenous heparin during the first 24 hours of hospitalization was less frequent in patients with ESRD and moderate to severe renal insufficiency; these trends persisted with therapies prescribed at hospital discharge, including ACE-inhibitors and β-blockers. Thus, this study confirms less aggressive care in CKD patients with STEMI that parallel the degree of renal dysfunction.

Similar findings were also reported by Shlipak *et al*. [7] in 130,099 elderly patients (age ≥ 65 years) with AMI (about 30% of whom had STEMI). The study demonstrated that patients with normal renal function were treated with aspirin and beta-blockers 20% more often and were more than twice as likely to receive thrombolytic therapy, coronary angiography, and angioplasty as patients with moderate renal insufficiency. Among patients surviving up to hospital discharge, those with no renal insufficiency were most likely to be prescribed aspirin and β-blockers, those with mild renal insufficiency most often received ACE-inhibitors, and those with moderate renal insufficiency most often received calcium channel blockers. All these studies demonstrate that beneficial therapies, such as aspirin, β-blockers, and ACE-inhibitors are underutilized in patients with STEMI and CKD despite increased prevalence of hypertension, congestive heart failure, and coronary artery disease, and despite the fact that these medications are associated with a substantial survival benefit in patients with normal renal function. Similarly, patients with renal insufficiency presenting with ACS are less likely to be treated with statins, despite the evidence of reduced mortality with statins use in patients with or at risk for coronary events [8,21-23]. In addition to the long-term benefit of statin therapy in ACS patients, recent data collected on 300,823 patients of the National Registry of Myocardial Infarction 4, suggest that administration of statins within the first 24 hour of hospitalization for acute myocardial infarction significantly lowers the rate of early complications and in-hospital mortality, possibly due to their pleiotropic effects [24]. Indeed, acute myocardial infarction is associated with a number of abnormalities, including inflammation, endothelial dysfunction, and coagulation disorders, all of which appear to be dampened by statins [25].

The reasons for this "therapeutic nihilism" in patients with advanced renal insufficiency suffering from a STEMI are not clear. Concern about further impairment of renal function and toxic side-effects due to reduced drug clearance are potential explanations. Furthermore, patients with renal insufficiency have more co-morbidities and, as a consequence, more contraindications to these medications. This is in marked contrast to the results of previous studies demonstrating that ACE inhibitors and β-blockers are associated with more beneficial effects in patients with renal insufficiency than in patients with preserved renal function [26,27].

Statins are primarily eliminated by the liver, while the renal route is usually a minor elimination pathway. However, reluctance to prescribe statins in patients with CKD is likely due to remaining uncertainty regarding their clinical effects in patients with renal insufficiency. In particular, no clear evidence of a positive relationship between blood cholesterol and cardiovascular events has been found in these patients. As they approach end-stage renal disease, there appears to be increased oxidation of low-density lipoprotein, with progressive lowering of total cholesterol levels. The influence of dyslipidemia upon cardiovascular outcomes shows a "U"-shaped relationship, with increasing cardiovascular event rate seen among patients with severe renal insufficiency having low cholesterol levels. This "low-cholesterol paradox" has been attributed to the effects of chronic malnutrition and inflammation, which become increasingly important in severe renal insufficiency [28]. This paradox has raised the question of the utility of lipid-lowering therapy, although recent evidence than statin therapy may delay progression of renal dysfunction [29].

Patients with renal insufficiency represent a vulnerable population at higher morbidity and mortality risk; standard medications for secondary prevention (aspirin, beta-blockers, ACE-inhibitors, statins) are justified and their use should be encouraged. However, doubts still exist on how they should be treated in the early phase of STEMI. In particular, there are concerns about the use of aggressive reperfusion strategy (fibrinolytic therapy and primary PCI). Undoubtedly, landmark megatrials, such as the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI), the International Study of Infarct Survival (ISIS), and the Global Utilization of Streptokinase and Tissue Plasminogen for Occluded Coronary Arteries (GUSTO) trials, have shown the benefit of thrombolytic agents in reducing mortality in patients with STEMI [30-32]. However, in all these trials, no

subgroup analysis was performed in patients with renal failure, and scarce data have been published on the use of thrombolytics in CKD patients. In the study by Wright *et al*. [6], 13% of the total population received intravenous fybrinolytic therapy and 10% received PCI as a primary treatment. Reperfusion therapy was used less frequently in patients with any degree of renal insufficiency than in patients without renal insufficiency. However, it was associated with improved long-term survival, but not with reduced risk for in-hospital death. It is conceivable that the potential benefit deriving from early reperfusion could be offset by a morbidity increase, particularly in terms of more bleeding complications after thrombolysis and a higher rate of contrast agent-induced nephropathy after primary PCI. Renal insufficiency should not preclude the success rate of percutaneous or pharmacological reperfusion therapies, but it may be associated with increased incidence of major adverse events. To evaluate the effects of an invasive management with additional early revascularization, the outcome of 352 patients with STEMI, 24.7% with mild-to moderate renal insufficiency (serum creatinine concentration ranging from 1.2 to 2.8 mg/dl), was analyzed in a single-center retrospective study [33]. All patients received aspirin, a thrombin inhibitor and thrombolytic therapy, while early PCI or coronary bypass surgery were performed in 46.8% and 27.6% of patients with normal renal function and 32.2% and 29.9% of those with renal dysfunction. Despite the optimal guideline-based therapy, including invasive management, patients with renal insufficiency showed a significantly higher 30-day and 6-month mortality rate than those with normal renal function (16.1% and 19.5% *vs*. 3.4% and 4.5%, respectively; $p<0.001$). It is noteworthy, however, that the 30-day and 6-month mortality was reduced from 22% to 3.6% ($p<0.03$) and from 25.4% to 7.1% ($p<0.05$) among renal dysfunction patients who underwent PCI during hospitalization. Thus, this study confirms that mild to moderate renal insufficiency in the setting of STEMI is associated with increased mortality, despite extensive use of optimal therapy, but it also suggests that early PCI may be beneficial among such patients. The influence of renal insufficiency in patients with STEMI receiving fibrinolytic therapy was investigated by Gibson *et al*. [34] who analyzed pooled data from 16,710 patients enrolled in four studies (TIMI-10A, -10B, and -14, and the inTIME-2 trial). Again, despite appropriate treatment with thrombo-lytics and adjunctive therapies for acute myocardial infarction (including early PCI in many patients), and even though the epicardial and myocardial reperfusion rates were equivalent, there was a stepwise decrease in survival going from normal to mildly and severely impaired renal function that continued through up to two years of follow-up. The incidence of intracranial hemorrhage was also increased in patients with reduced renal function, suggesting that primary PCI may represent a favorable alternative therapy. Nevertheless, the outcomes of primary PCI in patients with STEMI and renal insufficiency have not been well characterized, because such patients are typically excluded from clinical trials [35,36]. Sadeghi *et al*. [37] evaluated the potential impact of renal insufficiency in patients undergoing primary PCI and enrolled in the Controlled Abcximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. The values of serum creatinine were obtained in 93% of the 1,933 patients at hospital admission, and clinical outcomes were assessed as a function of renal insufficiency by examining CrCl strata. At least moderate renal insufficiency, based on CrCl cutoff of $\leq$60 ml/min, was present in 18% of patients (n=350) who showed a marked increase of the 30-day and 1-year mortality. They had a >9-fold increase in mortality at 30 days, and a 5-fold increase in mortality at 1-year. Interestingly, this study was the first to report the prognostic relevance of contrast-induced nephropathy in STEMI patients undergoing primary PCI. Indeed, these patients represent a population at higher risk for contrast-induced nephropathy than those undergoing elective PCI. Several conditions may contribute to renal injury in this setting. Among them, hypotension or even shock, a large volume of contrast media, and the impossibility of starting a renal prophylactic therapy are the factors most likely involved. In the CADILLAC trial, contrast nephropathy, defined as an absolute serum creatinine increase by >0.5 mg/dl, developed in 4.6% of patients, being 3 times more prevalent in patients with renal impairment, and was associated with a strikingly worse prognosis (30-day mortality of 16.2% and 1-year mortality of 23.3%). However, the incidence of contrast nephropathy in this trial was probably underestimated due to the exclusion of patients with known severe renal insufficiency (serum creatinine > 2.0 mg/dl), and to the lack of routine daily creatinine measurements. Indeed, serum creatinine levels were assessed at admission, 24 hours after PCI, and at discharge. Therefore, transient increase in creatinine that typically occurs 48 to 72 hours after contrast exposure may have been missed in most patients. The prognostic significance of serum creatinine in STEMI patients treated with primary PCI was also confirmed by a retrospective analysis of 1,451 patients drawn from the Heart Institute of Japan Acute Myocardial Infarction (HIJAMI) registry, in which a graded increase of in-hospital death rate (from 3.9% to 17.1% and 34.5%, respectively) was found in the three groups of patients with normal renal function (serum creatinine < 1.2 mg/dl), mild insufficiency (serum creatinine > 1.2 but $\leq$ 2.0 mg/dl) and severe insufficiency (serum creatinine > 2.0 mg/dl) [38].

The impact of contrast-induced nephropathy after primary PCI has been investigated in-depth in a recent study carried out by our institute [39]. In 208 STEMI patients undergoing primary PCI, the incidence, the clinical predictors and the clinical consequences of contrast-induced nephropathy, defined as an absolute increase in serum creatinine > 0.5 mg/dl after PCI, were evaluated. Forty (19%) patients developed contrast-induced nephropathy. When CrCl was estimated, 48 (23%) of the 208 patients had a moderately impaired renal function (CrCl <60 ml/min). Of them, 19 (40%) developed contrast-induced nephropathy. In contrast, of the 160 patients with a base-line CrCl value $\geq$60 ml/min, only 21 (13%) developed contrast-induced nephropathy after primary PCI ($p<0.0001$). Patients with contrast-induced nephropathy experienced a more complicated in-hospital clinical course, and their average length of hospital stay was approximately 1.5 times longer than that of patients without this complication (13±7 *vs*. 8±3 days; $p<0.001$). The overall in-hospital mortality of the

entire population was 6.2% (n=13). However, the mortality rate was significantly higher in patients developing contrast-induced nephropathy than in those without it (31% *vs*. 0.6%; p<0.0001). In multivariate analysis, the following variables were significant independent correlates of contrast-induced nephropathy: age ≥ 75 years (OR 5.28, 95% CI 1.98 to 14.05; P=0.0009), anterior STEMI (OR 2.17, 95% CI 0.88 to 5.34; P=0.09), time-to-reperfusion ≥ 6 hours (OR 2.51, 95% CI 1.01 to 6.16; P=0.04), contrast agent volume ≥300 ml (OR 2.80, 95% CI 1.17 to 6.68; P=0.02), and the use of an intra-aortic balloon pump (OR 15.51, 95% CI 4.65 to 51.64; P<0.0001). This study demonstrated that contrast-induced nephropathy is a frequent complication after primary PCI, even in patients without renal insufficiency, and is associated with increased in-hospital morbidity, mortality and prolonged hospitaliz-ation. In consideration of the widespread appli-cation of primary PCI as a reperfusion strategy, innovative preventive approaches aimed at protecting the kidneys from contrast toxicity and ischemic burden during the acute phase of STEMI need to be developed and tested, particularly in high-risk patients, in order to further reduce cardiovascular morbidity and mortality.

NON-ST-ELEVATION ACUTE CORONARY SYND-ROMES

Several observational studies have found that, in the setting of NSTE-ACS, in-hospital outcomes and mid- to long-term mortality are worse among patients with renal insufficiency [8-11,21,40-43]. Management of NSTE-ACS patients with renal insufficiency is challenging due to the increased risk of bleeding and thrombotic events. Data from several clinical trials indicate that new antithrombotic agents and early invasive strategy are of clinical benefit in NSTE-ACS, particularly in high-risk patients, and current practice guidelines recommend an early invasive strategy in most cases [13]. The significant increased mortality of CKD patients suffering from a NSTE-ACS clearly indicates that renal dysfunction represents a strong independent predictor of mortality. Nonetheless, there is still a clear lack of data regarding the optimal management of this complex population, due to the fact that, in most of the NSTE-ACS clinical trials, patients with renal insufficiency were not analyzed separately, or no mention was made of their inclusion or exclusion. Thus, refinement of the antithrombotic strategies among CKD patients in this clinical setting is still a major and unmet need. The challenge is daunting because, on the one hand, renal insufficiency is associated with prolongation of bleeding time and abnormal platelet aggregation and adhesion [44], and, on the other hand, a state of hypercoagulation has been demonstrated with high levels of von Willebrand factor [45], fibrinogen, factors VII, VIII, and XIII and enhanced thrombin generation [44]. The combination of these alterations puts the patient with CKD at risk, simultaneously, for thrombosis and hemorrhage. Thus, use of well-established antiplatelet drugs, such as aspirin and clopidogrel, should be weighed against bleeding risk in renal patients. Based on the benefit demonstrated in NSTE-ACS, it seems advisable to keep CKD patients on aspirin therapy, with a suggestion for low doses. In addition to aspirin, heparin has become the standard of care in patients with ACS. The two preparations generally available are unfractionated heparin (UFH) and low-molecular weight heparin (LMWH). A major difference between these two therapeutic agents is their mechanism of clearance: at low doses, UHF is cleared primarily by macrophages and endothelial cell binding, whereas LMWH is cleared primarily by renal mechanisms [46]. Clinical studies on enoxaparin, the most widely used LMWH in NSTE-ACS, excluded patients with renal insufficiency, so that the optimal dosing for renal patients has not been established [47,48]. A retrospective review showed a significant increase in bleeding events and death in patients with renal insufficiency treated with enoxaparin [49], suggesting that dosage adjustment is needed in these patients to minimize the hemorrhage risk. Reduction in dose to half or reduction in frequency of administration to only once daily may be necessary. However, until conclusive results are available regarding optimal dosing, it may be safer to use UFH in CKD patients presenting with NSTE-ACS. Thus, the pharmacokinetics of aspirin and UHF, although not specifically studied in patients with renal insufficiency, suggest that they are also safe in this population.

Use of newer antithrombotic agents, such as platelet glycoprotein (GP) IIb/IIIa receptor inhibitors, has become the standard of care for the higher-risk NSTE-ACS patients, mainly for those undergoing PCI [50]. However, patients with renal insufficiency were also excluded from entry into most randomized trials investigating GPIIb/IIIa antagonists. Thus, it is not clear if they may derive the same therapeutic benefit with equivalent safety from these pharmacological agents as do patients with normal renal function. This question is not surprising given that renal insufficiency is associated with numerous and well-recognized qualitative platelet abnormalities and coagu-lation disorders [44,45,51]. Moreover, because agents such as tirofiban and eptifibatide are largely cleared through the kidneys, moderate to severe renal insufficiency would be expected to increase the mean plasma concentration of these drugs, producing a greater inhibition of platelet aggregation. Since platelet-bound abcximab is eliminated by the reticuloendothelial system [52], its use in patients with renal insufficiency should not be associated with greater impairment of platelet function. Thus, unlike tirofiban and eptifibatide, abciximab does not require dosing adjustment in CKD patients. Although all major randomized GPIIb/IIIa trials excluded CKD patients, particularly those with severe renal insufficiency, some data about the impact of these agents in this difficult population may be derived from retrospective trial analysis. It is noteworthy that data extrapolated from the GUSTO-IV ACS study indicate that, in patients with a serum creatinine concentration over 2 mg/dL, abcximab bolus with infusion was associated with a reduction of the combined end-point of death or myocardial infarction when compared to placebo (15.1% *vs*. 26.8%) [53]. However, the relationships between renal function and ischemic and hemorrhagic complications among ACS patients receiving an intracoronary stent and treated with either tirofiban or abcximab in the TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Trial) trial was assessed [54]. Although patients with a serum creatinine concen-tration > 2.5 mg/dL were excluded, those with the lowest CrCl quartile (CrCl < 70 mL/min) had a higher

bleeding complication rate. Significant differences between patients receiving tirofiban and those receiving abcximab were not detected for major bleeding or transfusions, but minor bleeding rates were lower for patients who received tirofiban treatment (2.8% *vs*. 4.3%; p=0.006).

In a recent retrospective subanalysis of the Second Randomized Evaluation in PCI Linking Bivalirudin to Reduced Clinical Events trial (REPLACE-2) [55], within the total randomized population of 5,710 patients undergoing PCI (43% of whom because of NSTE-ACS), 886 patients with moderate or severe renal insufficiency showed, as expected, an increased burden of early and late morbidity and mortality. However, bivalirudin (a direct thrombin inhibitor) use among those with renal impairment proved no inferiority when compared to heparin and GPIIb/IIIa inhibition, with respect to ischemic events. In addition, in the overall population, as well as in patients who had a CrCl <60 ml/min, bivalirudin was associated with fewer bleeding events. These results are in line with a previous meta-analysis of trials evaluating bivalirudin administration in patients undergoing PCI that showed a reduction of bleeding and ischemic events, with a greater absolute benefit among patients with renal failure [56]. In consideration of the important clinical implications of antithrombotic therapy in this clinical setting, additional randomized trials are warranted to further evaluate the effect of bivalirudin, in terms of ischemic and bleeding complications prevention, in NSTE-ACS patients with renal insufficiency.

CONCLUSIONS

Chronic renal insufficiency - of any degree - is present in a substantial proportion of patients with ACS, and represents a potent and independent risk factor for adverse outcome. Although the mechanisms underlying the poor prognosis of this vulnerable population are not fully understood, it is conceivable that the interplay between extensive comorbidities, paradoxical patterns of less aggressive treatment, excess toxicity from conventional therapies, and unique pathobiology of CKD has a considerable role. Unfortunately, data are still limited regarding the value of most therapeutic interventions, because CKD patients with ACS have typically been excluded from randomized trials. Thus, our current challenge is to further study these high-risk patients in prospective randomized trials in order to identify adjunctive pharmacological therapies and newer interventional strategies that may favorably affect their otherwise poor prognosis. Nevertheless, as long as evidence-based data are not provided to guide clinical practice, all attempts must be made to promote the use of more aggressive therapies, when they can be applied with an acceptable level of safety.

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