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Original Paper

The Effect of Admission Renal Function on the Treatment and Outcome of Patients with Acute Coronary Syndrome

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Keywords
Renal function · Acute coronary syndrome · Outcome

Abstract
Background: Chronic kidney disease is a frequent comorbidity among patients with acute coronary syndrome (ACS). We aimed to evaluate treatment characteristics in ACS patients according to their renal function and to assess the effect of differences in therapy on clinical outcomes. ***Methods:*** Included were patients with ACS enrolled in the biennial Acute Coronary Syndrome Israeli Surveys (ACSIS) during 2000–2013. Excluded were patients with cardiogenic shock at presentation. The estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula. The distribution of the eGFRs was divided into 4 categories (<45, 45–59.9, 60–74.9, and ≥75 mL/min/1.73 m^2). The primary endpoint was all-cause mortality at 1 year. ***Results:*** A total of 13,194 patients with ACS were included. Patients with a reduced eGFR were less likely to be admitted to a coronary care unit and had lower rates of coronary angiograms and subsequent percutaneous coronary interventions. Furthermore, as the eGFR was lower, the patients were less frequently treated with aspirin, clopidogrel, β-blockers, and ACE inhibitors/angiotensin receptor blockers. We demonstrated an inverse association between renal function and 1-year mortality, with the highest mortality rates observed in the group with the lowest eGFR (HR = 3.8, 95% CI 2.9–4.9, $p < 0.0001$). Differences in mortality remained significant following a multivariate analysis for all the baseline characteristics as well as for invasive and medical treatment (HR = 2.7, 95% CI 1.9–3.7, $p < 0.0001$). ***Conclusions:*** ACS patients with chronic kidney disease represent a high-

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risk group with an increased mortality risk. Despite this high risk, these patients are less frequently selected for an invasive treatment strategy and are less commonly treated with guideline-based medications. However, reduced renal function was associated with higher mortality regardless of the variations in therapy.

Introduction

Chronic kidney disease is a frequent comorbidity among patients with acute coronary syndrome (ACS) [1–3]. Several studies have demonstrated well that even mild renal disease is an independent risk factor for cardiovascular complications and death after a myocardial infarction. Among the patients included in the VALIANT study, each reduction of the estimated glomerular filtration rate (eGFR) by 10 units was associated with a 10% increase in the risk for death and nonfatal cardiovascular outcomes [1]. Different factors associated with impaired renal function are believed to contribute to adverse outcomes of patients with ACS. These factors include insulin resistance [4, 5], oxidative stress [6], inflammation [7], endothelial dysfunction [8], vascular calcifications [9], and hypercoagulability [10]. Furthermore, the presence of chronic kidney disease is associated with a higher prevalence of baseline cardiovascular comorbidities including diabetes, heart failure, previous myocardial infarction, and stroke [1, 2, 11].

Despite the clear association of renal dysfunction with adverse cardiovascular outcomes, little is known about how ACS patients with impaired renal function are managed. Several studies have demonstrated that ACS patients with chronic kidney disease, compared to patients with normal renal function, are more commonly selected for a conservative rather than an invasive strategy approach with an early coronary angiogram and subsequent angioplasty [1, 2, 12]. It has also been demonstrated that guideline-based medications such as β-blockers, ACE inhibitors, statins, and antiplatelets are underutilized in ACS patients with chronic kidney disease [1, 2, 12]. However, the majority of the available data is related to patients with advanced chronic kidney disease, and it is not clear whether these differences in treatment remain in patients with mild or moderate chronic kidney disease. It is also unclear whether the differences in therapy contribute to the adverse outcomes of patients with renal dysfunction.

The current study aims to evaluate invasive and medical therapy in ACS patients according to their renal function and to assess the effect of differences in therapy on the clinical outcomes of ACS patients.

Subjects and Methods

Study Population

The Acute Coronary Syndrome Israeli Survey (ACSIS) is a biennial, 2-month survey that has been carried out since 1992 in all intensive coronary care units and cardiology departments in Israel. The study population consisted of those patients with ACS (ST- and non-ST-segment elevation myocardial infarction and unstable angina pectoris) included in the ACSIS during 2000–2013. Excluded were patients with cardiogenic shock at presentation. Demographic, historical, and clinical data were recorded by the study physicians on prespecified forms for consecutive participants. The diagnosis of ACS was based on clinical, electrocardiographic, and enzymatic criteria, and eligibility for the study was validated before discharge from the hospital. The patients were managed at the discretion of each center.

Renal Function Assessment

Serum creatinine levels were recorded at presentation to the hospital. The eGFR was calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula [13]:

eGFR = 186 × [serum creatinine (in mg/dL)] − 1.154 × [age (in years)] − 0.203.

For women, the product of this equation was multiplied by a factor of 0.742.

The distribution of the eGFRs was divided into 4 categories (<45, 45–59.9, 60–74.9, and ≥75 mL/min/1.73 m^2), incorporating the guidelines of the National Kidney Foundation [14].

Outcomes

The primary outcome of our study was all-cause mortality at 1 year. Mortality rates were determined for all participants from hospital charts and by matching the identification numbers of the patients with the Israeli National Population Registry. Secondary outcomes included in-hospital mortality and the occurrence of Thrombolysis in Myocardial Infarction (TIMI) major bleeding.

Statistical Analysis

Categorical variables are expressed as percentage and continuous variables are expressed as mean ± SD. The study cohort was stratified into 4 groups according to the renal function assessment (groups 1–4). The comparison of population characteristics was performed by χ^2 test or Fisher exact test for categorical variables and by the Student *t* test or Wilcoxon rank tests, as appropriate, for continuous variables and secondary outcomes. Kaplan-Meier survival curves with the Mantel-Haenszel log-rank test were used to compare survival. We conducted a Cox proportional-hazards analysis to estimate the HRs and 95% CIs for all-cause mortality at 1 year.

To adjust for differences in baseline clinical characteristics and comorbidities, invasive coronary procedures during hospitalization, and medical therapy at discharge, a step-wise multivariable logistic regression analysis (for age, body mass index, gender, diabetes mellitus, hypertension, smoking status, prior myocardial infarction, prior percutaneous coronary intervention [PCI], prior coronary artery bypass graft, congestive heart failure, cerebrovascular accident or transient ischemic attack, peripheral vascular disease, cholesterol levels, coronary angiography and revascularization during hospitalization, and medical therapy with aspirin, clopidogrel, β-blockers, ACE inhibitors or angiotensin receptor blockers [ARBs], and statins at hospital discharge) was used to examine prognostic factors for the outcomes.

A *p* value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS statistical software version 9.1.

Results

Baseline Characteristics

The 13,194 patients that were included in the study had a mean age of 63.5 ± 13 years and included 25.8% females. The mean (±SD) eGFR was 82.83 ± 51 mL/min/1.73 m^2. A total of 5,506 (41.7%) of the patients had an eGFR of ≥75 mL/min/1.73 m^2, 2,444 (18.6%) had an eGFR of 60–74.9 mL/min/1.73 m^2, 1,639 (12.4%) had an eGFR of 45–59.9 mL/min/1.73 m^2, and 3,605 (27.3%) had an eGFR of <45 mL/min/1.73 m^2. Patients with reduced renal function were older and more frequently female. The prevalence of most of the coexisting conditions at baseline – including hypertension, diabetes, and prior cardiovascular disease including prior myocardial infarction, congestive heart failure, and coronary revascularization, as well as cerebrovascular and peripheral arterial disease – increased with decreasing eGFRs (Table 1). Accordingly, the proportion of patients who were receiving cardiovascular pharmacotherapies (antiplatelets, statins, β-blockers, and ACE inhibitors/ARBs) at baseline increased with decreasing eGFRs.

Table 1. Baseline characteristics of the study population according to eGFR (mL/min/1.73 m^2)

	Group 1 ≥75 (*n* = 5,506)	Group 2 60–74.9 (*n* = 2,444)	Group 3 45–59.9 (*n* = 1,639)	Group 4 <45 (*n* = 3,605)	*p* value
Creatinine, mg/dL	0.9±0.15	1.1±0.13	1.3±0.19	3.2±1.9	<0.0001
eGFR, mL/min/1.73 m^2	112.6±44.4	67.9±4.3	53.2±4.3	30.2±11.4	0.00044
Age, years	57.9±11.61	65.3±11.5	70.8±10.8	68.2±13.3	<0.0001
BMI	28.2±13.2	27.7±7.3	27.8±8.6	28.4±16.2	0.65226
Female gender	15.4	23	33.3	31.1	<0.0001
Diabetes	30.2	31.7	40.5	41.4	<0.0001
Hypertension	48.2	61	74.8	63.2	<0.0001
Current smoker	49.88	31.32	22.33	26.92	<0.0001
Myocardial infarction	24	28.4	37.1	35.7	<0.0001
PCI	25	28.9	31.7	26.4	<0.0001
CABG	6.2	10.9	15.4	13.4	<0.0001
CHF	2.9	5.6	11.8	15.1	<0.0001
CVA/TIA	5	7.6	11.5	11.1	<0.0001
PVD	4.8	7.6	10.7	14.4	<0.0001
Cholesterol, mg/dL	189.1±45.7	184.7±42.1	180±48	187.2±47.4	<0.0001
HDL, mg/dL	39.8±12.4	41.6±12.4	42±13.4	41.2±13.1	<0.0001
LDL, mg/dL	115.6±39	112.9±37.1	106.6±39.5	101.76±39	<0.0001
Triglycerides, mg/dL	174.1±129.5	240.2±360.1	150.5±104.2	149.8±111.5	<0.0001
Medications[a]					
Aspirin	39.7	49.9	56.1	61.7	<0.0001
Clopidogrel	7	7.8	10.3	12.4	<0.0001
Anticoagulants	1.6	3.4	5.4	8.2	<0.0001
β-Blockers	28.2	36.6	45.2	51.2	<0.0001
ACE-Is/ARBs	28.9	37.2	49.5	50	<0.0001
Statins	38.3	44	48.9	51.9	<0.0001

Values are presented as percentage or mean ± SD. eGFR, estimated glomerular filtration rate; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CHF, congestive heart failure; CVA, cerebrovascular accident; TIA, transient ischemic attack; PVD, peripheral vascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. [a] Chronic prehospitalization medical therapy.

Treatment Characteristics

Table 2 compares the treatment characteristics of the patients according to their renal function. Patients with a reduced eGFR were less likely to be admitted to a coronary care unit or a cardiology ward and less commonly underwent an echocardiographic assessment for left ventricular ejection fraction. As the eGFR was lower, the patients were more frequently selected for a conservative approach with significantly lower rates of coronary angiograms and subsequent PCIs during the index hospitalization. Conversely, patients with lower eGFRs were more commonly referred for surgical revascularization with coronary artery bypass grafting. Interestingly, patients with chronic kidney disease were less frequently treated with guideline-based cardiovascular medications including antiplatelets, statins, and β-blockers. In contrast, these patients more commonly received antianginal medication and anticoagulants.

Outcomes

Lower eGFRs were associated with higher mortality rates (Fig. 1). The unadjusted Kaplan-Meier estimates of survival at 1 year were 97% in the group with an eGFR of ≥75 mL/min/

Table 2. In-hospital treatment according to eGFR (mL/min/1.73 m^2)

	Group 1 ≥75 (n = 5,506)	Group 2 60–74.9 (n = 2,444)	Group 3 45–59.9 (n = 1,639)	Group 4 <45 (n = 3,605)	p value
Procedure					
Coronary angiography	91	88.2	82.3	66.7	<0.0001
PCI	74	73.8	66.1	53.6	<0.0001
CABG	4.3	4.3	5.7	5.7	0.00391
Echocardiography	79	77.5	78.2	74.3	<0.0001
Admission ward					
CCU/cardiology	86.11	85.24	80.72	80.67	<0.0001
Internal	12.56	13.28	17.5	17.5	<0.0001
Other	1.33	1.48	1.78	1.84	<0.0001
Medical therapy[a]					
Aspirin	96.8	95.4	92.3	89.9	<0.0001
Clopidogrel	76.5	75.1	65.3	47.3	<0.0001
Anticoagulants	2.6	4.2	6.3	7.6	<0.0001
β-Blockers	81.4	81.1	78.8	73.9	<0.0001
Nitrates	9.9	16.4	19.5	34.9	<0.0001
ACE-Is/ARBs	74.6	77.5	77.7	59.6	<0.0001
Diuretics	11.2	20.7	33.6	34	<0.0001
Statins	89.6	87.6	84.2	65.7	<0.0001

Values are presented as percentage. eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CCU, coronary care unit; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. [a] Medical therapy at discharge from hospital.

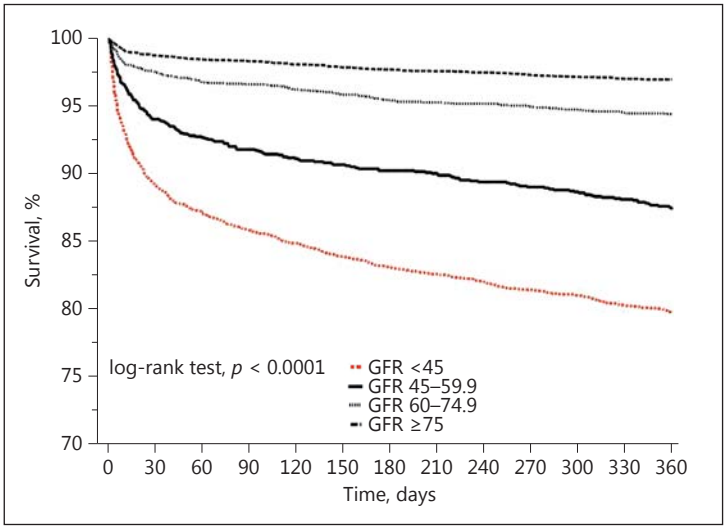

Fig. 1. Kaplan-Meier curves for 1-year all-cause mortality according to renal function. GFR, glomerular filtration rate.

1.73 m^2, 94.5% in the group with an eGFR of 60–74.9 mL/min/1.73 m^2, 87.3% in the group with an eGFR of 45–59.9 mL/min/1.73 m^2, and 80% in the group with an eGFR <45 mL/min/1.73 m^2.

Using the group with an eGFR of ≥75 mL/min/1.73 m^2 as the reference group yielded unadjusted HRs for all-cause death that increased as the degree of renal impairment increased (Table 3). In the adjusted model (for all the baseline characteristics listed in Table 1), groups

Table 3. HRs for 1-year all-cause mortality according to renal function (eGFR, mL/min/1.73 m^2)

	Group 1 ≥75	Group 2 60–74.9	Group 3 45–59.9	Group 4 <45
Unadjusted HR (95% CI)	1	2 (1.6–2.5)	4.4 (3.6–5.4)	7.6 (6.4–9)
p value		<0.0001	<0.0001	<0.0001
HR adjusted for baseline characteristics[a] (95% CI)	1	1.3 (0.9–1.8)	2 (1.5–2.7)	3.8 (2.9–4.9)
p value		0.07	<0.0001	<0.0001
HR adjusted for baseline characteristics[a] and treatment[b] (95% CI)	1	1.4 (1–1.9)	1.9 (1.4–2.7)	2.7 (1.9–3.7)
p value		0.05	0.0002	<0.0001

[a] Age, body mass index, gender, diabetes mellitus, hypertension, smoking status, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft, congestive heart failure, cerebrovascular accident or transient ischemic attack, peripheral vascular disease, and cholesterol levels. [b] Coronary angiography and revascularization during hospitalization, and medical therapy with aspirin, clopidogrel, β-blockers, ACE inhibitors or angiotensin receptor blockers, and statins at hospital discharge.

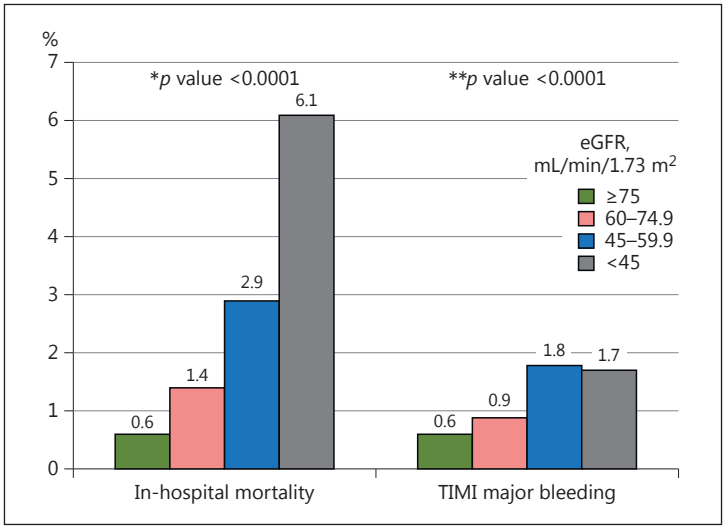

Fig. 2. Secondary outcomes of the study population according to renal function. * *p* value for the trend of in-hospital mortality according to renal function. ** *p* value for the trend of Thrombolysis in Myocardial infarction (TIMI) major bleeding. eGFR, estimated glomerular filtration rate.

with a lower eGFR had worse outcomes than the reference group, with the worst outcomes in the group with the lowest eGFR (HR = 3.8, 95% CI 2.9–4.9, $p < 0.0001$) (Table 3). In order to evaluate the effect of differences in therapy on the outcome, we conducted a second multivariate analysis with adjustment for all the baseline characteristics with the addition of coronary angiograms and PCIs during hospitalization and medical therapy at discharge with aspirin, clopidogrel, β-blockers, and ACE inhibitors/ARBs until hospital discharge. Following this analysis, the 1-year mortality risk of patients with low eGFRs dropped slightly but still remained significantly higher than in the reference group (HR = 2.7, 95% CI 1.9–3.7, $p < 0.0001$) (Table 3).

Similar to the primary endpoint, decreasing eGFRs were associated with increased in-hospital mortality. An eGFR <60 mL/min/1.73 m^2 was associated with a 3-fold increased risk for TIMI major bleeding during hospitalization (Fig. 2).

Discussion

The current study demonstrated an inverse association between the eGFR and 1-year mortality risk of patients admitted with ACS. While the association of impaired renal function with adverse clinical outcome in ACS patients has been demonstrated previously, our study is the first to include a comprehensive analysis of treatment characteristics according to renal function. We demonstrated that despite their high risk for adverse outcomes, patients with chronic kidney disease were less frequently referred for coronary angiography and subsequent angioplasty and were less commonly treated with guideline-based medical therapy. However, differences in outcomes between the 4 renal function groups remained significant even following multivariate adjustment for all clinical and demographic baseline characteristics as well as for coronary angiography and revascularization during hospitalization and medical therapy at discharge.

Chronic kidney disease is a very strong predictor of adverse clinical outcomes in patients with ACS [2–4]. The mechanism of this association is not fully understood and seems to be multifactorial [5–10, 15–19]. Several studies have demonstrated significant differences in the treatment of ACS patients according to their renal function. A Canadian cohort of 5,549 consecutive patients admitted with ACS between 1997 and 1999 demonstrated that medical interventions with β-blockers, acetylsalicylic acid, lipid-lowering therapy, and thrombolysis were significantly less likely to be used in patients with eGFRs <60 mL/min/1.73 m^2 [15]. Similar findings were made in another study on 3,106 patients with acute myocardial infarction. Patients with moderate or severe chronic kidney disease received adjunctive and reperfusion therapies less frequently than those with normal renal function [2]. Not surprisingly, postdischarge death was less likely in patients who received acute reperfusion therapy, aspirin, and β-blocker therapy. These findings were supported by several other studies on patients with ACS [12, 20].

However, most of these studies were conducted almost 2 decades ago, when fibrinolytic therapy was commonly used and treatment with several guideline-based medications such as ACE inhibitors, statins, and clopidogrel was not well established. Moreover, most of the available data are related to patients with advanced chronic kidney disease, and it is not clear whether these differences in treatment remain in patients with mild or moderate renal dysfunction. It is also unclear whether the differences in therapy contribute to the adverse outcomes of patients with renal dysfunction. In the current study, we demonstrated that differences in treatment are present even among patients with moderate chronic kidney disease (eGFR <60 and >45 mL/min/1.73 m^2). Furthermore, following adjustment for in-hospital coronary procedures and medical therapy at discharge, the 1-year mortality risk decreased but remained significant.

Despite their increased mortality risk, patients with chronic kidney disease were less frequently selected for an invasive strategy with an early coronary angiogram and subsequent angioplasty and were less commonly treated with guideline-based medications. This observation, referred to as the "treatment risk paradox," has been described before in different populations of ACS patients that underwent early risk stratification using various risk scores [21, 22]. In these studies, rates of coronary angiography, revascularization, and medical treatment decreased with increasing patient risk. Both patient-related factors (frailty, mental and functional status, and patient preference) and physician-related factors (misjudgment of a patient's risk at baseline) appear to contribute substantially to this phenomenon. Other factors that may explain differences in therapy among patients with chronic kidney disease include the risk of contrast-induced nephropathy and the potential risk of bleeding. It was previously shown that the risk of contrast-induced nephropathy is higher in patients with chronic kidney disease even among nondiabetics and may occur in up to 40% of patients with

an eGFR <60 mL/min/1.73 m^2 [23, 24]. Consequently, contrast-induced nephropathy was strongly associated with in-hospital complications and increased mortality risk.

ACS patients who develop major bleeding are a well-recognized high-risk population for death and cardiovascular complications [25, 26]. A large study on 17,421 ACS patients who were included in the ACUITY and the HORIZON MI studies demonstrated that even moderate chronic kidney disease is a strong and independent predictor of major bleeding during the first year [27]. These findings, which were supported by further reports [28, 29], may partially explain the more conservative approach that was more frequently selected for patients with chronic kidney disease. Furthermore, a meta-analysis of 9 trials involving 9,969 ACS patients with chronic kidney disease demonstrated that the benefits from antiplatelet therapy among these patients are potentially outweighed by bleeding hazards [30]. Similarly, in the current study we demonstrated that an eGFR <60 mL/min/1.73 m^2 was associated with a 3-fold increased risk for TIMI major bleeding. Patients with advanced chronic kidney disease are usually excluded from major ACS clinical trials, and therefore data regarding the efficacy and safety of the different medications and interventions are frequently derived from post hoc analyses of trials of broader populations. Therefore, the clinical evidence is often unsatisfactory and in some cases even contradictory. For example, while several studies have demonstrated the clinical benefit of primary PCI to patients with STEMI (ST-segment elevation myocardial infarction) regardless of their renal function [31, 32], data from the GRACE registry demonstrated similar in-hospital mortality rates for patients with STEMI and severe chronic kidney disease, regardless of whether coronary revascularization was achieved [33]. Other possible explanations for the lower utilization of guideline-based pharmacotherapy in ACS patients with chronic kidney disease may include the higher prevalence of comorbidities and, as a consequence, more contraindications and side effects of medications, such as the increased risk of statin induced-myopathy [34] or renal functional deterioration and hyperkalemia with ACE inhibitors and ARBs.

The present study has several limitations. First, previous serum creatinine levels were not available to us, and therefore some patients may have presented with acute rather than chronic kidney disease. Second, all the equations that are used for GFR estimation – including the MDRD formula – are based on serum creatinine levels. Since creatinine is secreted in the renal tubules, these equations may overestimate the measured GFR. Nevertheless, the creatinine-based eGFR is still the most common mode for renal function assessment in clinical practice. Cystatin C is an alternative serum measure of kidney function that approximates direct measures of GFR and is less influenced by age, sex, or muscle mass. Therefore, the association between renal function and cardiovascular outcomes of patients with ACS may be more accurately assessed using cystatin C measurements rather than the eGFR. However, cystatin C was not measured in our study. Third, the primary endpoint of our study was all-cause mortality, and specific causes of death were not available. Nevertheless, it is reasonable to assume that in a population of patients with ACS, the majority of fatalities during the first year following hospital discharge would be due to cardiovascular causes. Finally, given the extreme differences in baseline characteristics between the 4 groups, even the most appropriate multivariate analysis may fail to isolate baseline renal function.

In conclusion, our findings support the available data regarding the association of chronic kidney disease with adverse outcomes in ACS patients. We demonstrated that despite their high risk, patients with chronic kidney disease are less frequently selected for an invasive strategy and are less commonly treated with guideline-based medical therapy. However, reduced renal function was associated with higher mortality regardless of the variations in therapy. The question whether a more invasive strategy and a more frequent administration of the conventional medical therapy can improve the outcomes of these patients should be investigated in future studies.

Disclosure Statement

The authors have no conflict of interest regarding this paper.

Statement of Ethics

The study has been approved by the local ethics committee. The authors have no ethical conflicts regarding this paper.

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