CLINICAL RESEARCH STUDY

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Prevalence and Significance of Unrecognized Renal Dysfunction in Patients with Acute Coronary Syndrome

Zach Rozenbaum, MD,[a] Avi Leader, MD,[b,c] Yoram Neuman, MD,[b,d] Meital Shlezinger, MSc,[e] Ilan Goldenberg, MD,[b,e] Morris Mosseri, MD,[b,d] David Pereg, MD[b,d]

[a]*Department of Internal Medicine D, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel;* [b]*Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel;* [c]*Department of Internal Medicine A and* [d]*Department of Cardiology, Meir Medical Center, Kfar Saba, Israel;* [e]*Department of Cardiology, Sheba Medical Center, Tel HaShomer, Israel.*

ABSTRACT

BACKGROUND: Unrecognized renal insufficiency, defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 in the presence of normal serum creatinine, is common among patients with acute coronary syndrome. We aimed to determine the prevalence and clinical significance of unrecognized renal insufficiency in a large unselected population of patients with acute coronary syndrome.

METHODS: The study population consisted of patients with acute coronary syndrome included in the Acute Coronary Syndrome Israeli biennial Surveys during 2000-2013. The estimated glomerular filtration rate was calculated using the simplified Modification of Diet in Renal Disease formula. Patients were stratified into 3 groups: 1) normal renal function (estimated glomerular filtration rates ≥60 mL/min/1/73 m^2); 2) unrecognized renal insufficiency (estimated glomerular filtration rates <60 mL/min/1/73 m^2 with serum creatinine ≤1.2 mg/dL); and 3) recognized renal insufficiency (estimated glomerular filtration rates <60 mL/min/1/73 m^2 with serum creatinine ≥1.2 mg/dL). The primary endpoint was all-cause mortality at 1 year.

RESULTS: Included in the study were 12,830 acute coronary syndrome patients. Unrecognized renal insufficiency was present in 2536 (19.8%). Patients with unrecognized renal insufficiency were older and more frequently females. All-cause mortality rates at 1 year were highest among patients with recognized renal insufficiency, followed by patients with unrecognized renal insufficiency, with the lowest mortality rates observed in patients with normal renal function (19.4%, 9.9%, and 3.3%, respectively, P <.0001). Despite their increased risk, patients with renal insufficiency were less frequently referred for coronary angiography and were less commonly treated with guideline-based cardiovascular medications.

CONCLUSIONS: Acute coronary syndrome patients with unrecognized renal insufficiency should be considered as a high-risk population. The question of whether this group would benefit from a more aggressive therapeutic approach should still be evaluated.

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KEYWORDS: Acute coronary syndrome; Renal insufficiency

Renal insufficiency is a strong predictor of adverse outcomes in patients with various cardiovascular conditions, including acute coronary syndrome.[1-3] A study on 14,527 patients that were enrolled in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) demonstrated that even mild renal disease, as assessed by the estimated glomerular filtration rates, should be considered a major risk factor for cardiovascular complications after a myocardial infarction.[1] Each 10-unit reduction of the estimated glomerular filtration rate was associated

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Requests for reprints should be addressed to David Pereg, MD, Cardiology Division, Meir Medical Center, 59 Tchernichovsky St., Kfar-Saba 44281, Israel.

E-mail address: davidpe@post.tau.ac.il

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with a 10% increase in the risk for death or nonfatal adverse cardiovascular outcomes.

Despite its clinical significance, renal insufficiency is a frequently unrecognized comorbidity in acute coronary syndrome patients. While the assessment of renal function has been routinely based on serum creatinine, a significant proportion of patients with serum creatinine levels slightly above the upper limit of the normal range or even within the normal range have impaired renal function, often even significant renal dysfunction.

It has been demonstrated that among patients with normal serum creatinine undergoing primary percutaneous coronary intervention, up to 30% will be found to have significant renal dysfunction (defined as estimated glomerular filtration rate <60 mL/min).[4] However, the prevalence of this unrecognized renal insufficiency, and even more importantly, its prognostic significance in the general population of acute coronary syndrome patients, has not been studied yet.

CLINICAL SIGNIFICANCE

- Unrecognized renal insufficiency is a common comorbidity in patients with acute coronary syndrome, affecting almost one-fifth of patients.
- Acute coronary syndrome patients with unrecognized renal insufficiency should be considered as a high-risk population.
- Despite their increased risk, patients with unrecognized renal insufficiency are less frequently referred for coronary angiography and less commonly treated with conventional cardiovascular medications.

The aim of our study was to determine the prevalence of unrecognized renal insufficiency in a large unselected population of patients with acute coronary syndrome and to assess its clinical significance compared with recognized renal insufficiency and normal renal function.

METHODS

Study Population

The Acute Coronary Syndromes 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 patients with acute coronary syndrome (ST-elevation and non-ST-elevation myocardial infarction and unstable angina pectoris) included in the ACSIS Surveys during 2000-2013. Excluded were patients with cardiogenic shock at presentation. Demographic, historical, and clinical data were recorded on prespecified forms for consecutive participants by study physicians. The diagnosis of acute coronary syndrome was based on clinical, electrocardiographic, and enzymatic criteria, and eligibility for the study was validated before discharge from the hospital. Patients were managed at the discretion of each center.

Renal Function Assessment

Serum creatinine levels were recorded at presentation to the hospital. Normal values were defined as ≤1.2 mg/dL. The estimated glomerular filtration rate was calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula[5]: estimated glomerular filtration rate = 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.

Normal renal function was defined as estimated glomerular filtration rate ≥60 mL/min/1.73 m^2, according to the guidelines of the National Kidney Foundation.[6] Recognized renal insufficiency was defined as both serum creatinine level above 1.2 mg/dL and an estimated glomerular filtration rate below 60 mL/min/1/73 m^2. Unrecognized renal insufficiency was defined as estimated glomerular filtration rate <60 mL/min/1/73 m^2 in the presence of serum creatinine ≤1.2 mg/dL.

Outcomes

The primary outcome of the 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.

Statistical Analysis

Categorical variables were expressed as percentage, and continuous variables were expressed as mean ± SD. The study cohort was stratified into 3 groups according to the renal function assessment (patients with normal renal function, patients with unrecognized renal insufficiency, and patients with recognized renal insufficiency). Characteristics of study participants were compared using chi-squared test for categorical variables and Student's *t* test or Wilcoxon rank tests as appropriate for continuous variables. The Kruskal-Wallis test was used for comparison of nonnormally distributed continuous variables. Kaplan-Meier survival curves with the Mantel-Haenszel log-rank test was used to compare the probability of all-cause mortality during 1-year. Cox proportional hazards multivariate-adjusted survival models were used to evaluate the independent effects of the different study groups on 1-year all-cause mortality results presented as hazard ratio (HR) and 95% confidence interval (CI). A *P*-value of <.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS statistical software, version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Baseline Characteristics

The 12,830 acute coronary syndrome patients included in the study had a mean age of 63.5 ± 13 years and included 25.8%

females. Of them, 7863 (61.3%) patients had normal renal function (estimated glomerular filtration rate ≥60 mL/min/1.73 m^2), 2431 (18.9%) had recognized renal insufficiency (serum creatinine >1.2 mg/dL and estimated glomerular filtration rate <60 mL/min/1.73m^2), and 2536 (19.8%) had unrecognized renal insufficiency (serum creatinine ≤1.2 mg/dL and estimated glomerular filtration rate <60 mL/min/1.73 m^2). Table 1 compares clinical and demographic baseline characteristics of the 3 groups. Patients with renal dysfunction, either recognized or unrecognized, had significantly higher rates of most of the traditional cardiovascular risk factors as well as a positive history of various cardiovascular conditions compared with patients with normal renal function. Not surprisingly, patients with renal insufficiency were more frequently being treated with guideline-based cardiovascular medications. While most cardiovascular risk factors and prior cardiovascular diseases were more frequent among patients with recognized—compared with unrecognized—renal insufficiency, patients with unrecognized renal insufficiency were more likely to be women and elderly. Similar to patients with normal renal function, almost half of patients with unrecognized renal insufficiency presented to the hospital with an ST-elevation myocardial infarction (Table 2). Prevalence of heart failure at presentation to the hospital was highest among patients with recognized renal insufficiency, followed by unrecognized renal insufficiency, and it was lowest among patients with normal renal function.

Study Outcomes

All-cause mortality rate at 1 year for the entire study population was 7.7%. Mortality rates were highest in patients with recognized renal insufficiency, followed by patients with unrecognized renal insufficiency, and were lowest in patients

Table 1 Baseline Characteristics of Patients According to Renal Function

	Normal Renal Function	Unrecognized Renal Insufficiency	Recognized Renal Insufficiency	
	eGFR ≥60 n = 7863	sCr >1.2 eGFR <60 n = 2536	sCr ≤1.2 eGFR <60 n = 2431	*P* Value
Creatinine	0.95	1.1	2.4	
eGFR	99 (35)	53.6 (4.3)	40.7 (14.4)	
Age (SD), y	60.1 (12)	72.2 (11)	65.4 (13.2)	<.0001
BMI	28 (11.3)	28.9 (14.1)	28.1 (12)	.09
Weight (SD), Kg	80.3 (15.2)	74.9 (15.9)	77.9 (14.6)	<.0001
Female sex, %	17.6	40.1	22.5	<.0001
Comorbidities, %				
Diabetes	30.6	34.8	47.4	<.0001
Hypertension	52.1	55.8	78.2	<.0001
Family history of CAD	15.1	21.4	28.6	<.0001
Current smokers	44.3	31.8	20.2	<.0001
Prior MI	25.3	38.6	40.4	<.0001
Past PCI	26.2	21.6	35.7	<.0001
Prior CABG	7.6	9.2	19.3	<.0001
Prior CHF	3.8	8.3	19.1	<.0001
Past CVA/TIA	5.8	8	14.1	<.0001
Prior PVD	5.5	8.6	17.5	<.0001
Medications				
Aspirin	42.8	51.9	62.2	<.0001
Clopidogrel	7.2	9.2	12.5	<.0001
Statins	40	47.4	52.1	<.0001
ACE-I/ARB	31.3	47.9	50.9	<.0001
B-blockers	30.8	42.8	51	<.0001
Laboratory tests				
Total cholesterol	188	196	174	<.0001
LDL-C	114.9	110.5	102.5	<.0001
HDL-C	40.3	44.1	40.9	<.0001
Triglycerides	194.7	157.1	148.9	<.0001
Hemoglobin	13.9	13.2	12.5	<.0001

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blockers; B-blockers = beta-blockers; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral artery disease; Scr = serum creatinine; TIA = transient ischemic attack.

Table 2 Clinical Presentation and Admission Data According to Renal Function

	Normal Renal Function	Unrecognized Renal Insufficiency	Recognized Renal Insufficiency	
	eGFR ≥60	sCR >1.2 eGFR <60	sCR ≤1.2 eGFR <60	*P* Value
Clinical presentation, %				
Admission Killip 2+3	8.4	16.7	31.5	<.0001
Admission Killip 3	2.4	5.6	12	<.0001
Typical CP	79.1	80.6	68.5	<.0001
Syncope/aborted SCD	2.1	2.6	3.9	<.0001
Anterior MI	29.9	33.6	27	<.0001
STEMI	47.8	49.5	33.3	<.0001

CP = chest pain; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; SCD = sudden cardiac death; sCR = serum creatinine; STEMI = ST-elevation myocardial infarction.

with normal renal function (19.4%, 9.9%, and 3.3%, respectively, P <.0001) (Figure 1). Following a multivariate analysis that included all the baseline characteristics listed in Table 1, patients with unrecognized renal insufficiency had significantly higher 1-year mortality risk compared with patients with normal renal function (HR 1.92; 95% CI, 1.5-2.3, P <.0001) and lower mortality risk compared with patients with recognized renal insufficiency (HR 0.75; 95% CI, 0.3-0.85, P = .003).

Differences in 1-year mortality rates of the 3 groups remained similar following sub-group analysis for sex, age, diabetes status, and acute coronary syndrome type (Figure 2).

Hospitalization Characteristics

Table 3 presents the hospitalization characteristics of the 3 groups. Patients with renal insufficiency, recognized or not, were less frequently admitted to an intensive coronary care unit or a cardiology department and had significantly longer hospitalization compared with patients with normal renal function. While the vast majority of acute coronary syndrome patients with normal renal function underwent coronary angiogram during hospitalization, patients with unrecognized and recognized renal insufficiency were less frequently referred for an invasive approach (90.3%, 79.6%, and 72%, respectively, P <.0001). Furthermore, both groups of patients with renal dysfunction were less

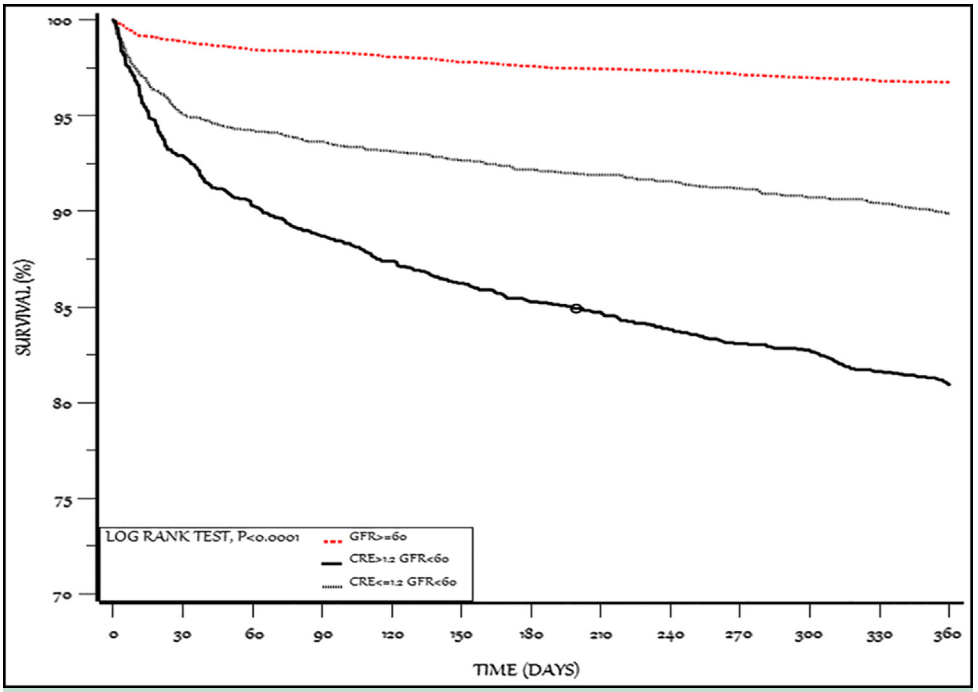

Figure 1 Kaplan-Meier for 1-year all-cause mortality according to renal function. CRE = creatinine; GFR = glomerular filtration rate.

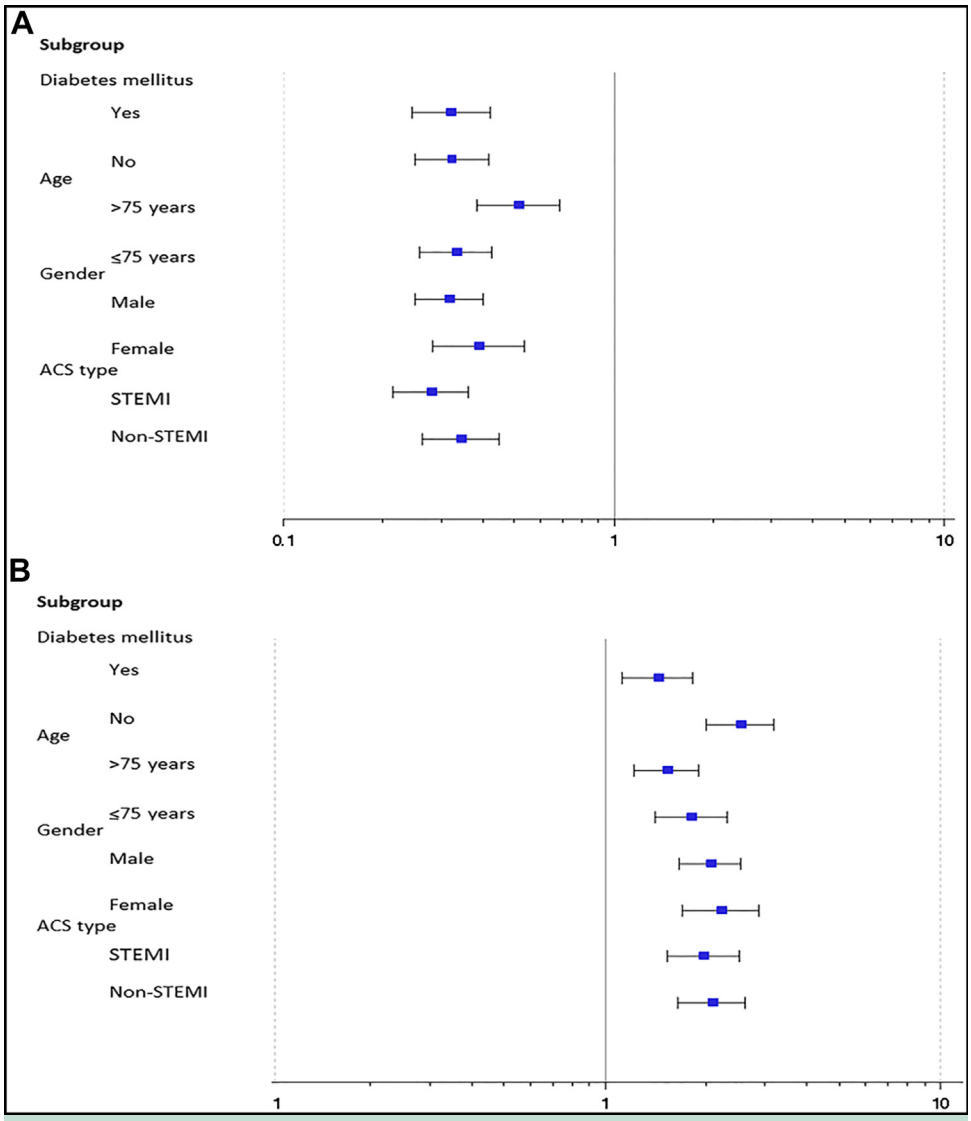

Figure 2 Subgroup analysis of 1-year mortality according to renal function group. (**A**) Subgroup analysis of 1-year mortality for patients with normal renal function compared with patients with unrecognized renal insufficiency (unrecognized renal insufficiency represented as HR = 1). (**B**) Subgroup analysis of 1-year mortality for patients with recognized renal insufficiency compared with patients with unrecognized renal insufficiency (unrecognized renal insufficiency represented as HR = 1). ACS = acute coronary syndrome; STEMI = ST-elevation myocardial infarction.

frequently treated with guideline-based cardiovascular medications including antiplatelets, statins, beta-blockers, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

DISCUSSION

The current study demonstrated that unrecognized renal insufficiency is a common comorbidity in acute coronary syndrome, affecting almost one-fifth of patients. We showed that, similar to patients with recognized renal insufficiency, unrecognized renal insufficiency represents a high-risk group with increased mortality risk compared with patients with normal renal function. Nevertheless, despite their increased risk, patients with unrecognized renal insufficiency are less frequently being referred for coronary angiography and are less commonly being treated with guideline-based cardiovascular medications.

It has been well established that renal failure is a poor prognostic factor in patients with acute coronary syndrome.[7-9] Even mild renal dysfunction is associated with increased short- and long-term adverse cardiovascular outcomes.[10-12] While serum creatinine is still the most commonly used mode for renal function assessment, it is an unreliable proxy influenced by various factors including age, sex, race, and lean body weight.[13-15] Interestingly, in our study, more than 50% of patients with significant renal dysfunction (defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2) had

Table 3 Hospitalization Characteristics According to Renal Function

	Normal Renal Function	Unrecognized Renal Insufficiency	Recognized Renal Insufficiency	
	eGFR ≥60	sCr >1.2 eGFR <60	sCr ≤1.2 eGFR <60	*P* Value
Admission department, %				
CCU/Cardiology	85.8	82.1	79.5	<.0001
Internal Medicine	12.8	16.5	18.4	<.0001
Other	1.4	1.4	2.1	<.0001
Hospitalization duration (d)	5.7 (5)	7.5 (6.4)	7.9 (6.9)	<.0001
Medical treatment, %				
Aspirin	97.5	95.9	94	<.0001
Plavix	78	72	70.2	<.0001
Statins	87.7	80.8	65.1	<.0001
ACE-I/ARB	75.2	74.3	61.2	<.0001
B-blockers	82.8	81.7	73.8	<.0001
Procedures, %				
Coronary angiography	90.3	79.6	72	<.0001
PCI	74	63.9	57.5	<.0001
CABG	4.3	6	5.5	.0006
DC shock	2	3	3.2	.0004
CPR	1	2.5	3	<.0001
Mechanical ventilation	1.2	5.3	7	<.0001
IABP	2.2	2.2	3.2	.017

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blockers; B-blockers = beta-blockers; CABG = coronary artery bypass graft; CCU = coronary care unit; CPR = cardiopulmonary resuscitation; DC = direct current; eGFR = estimated glomerular filtration rate; IABP = intra-aortic balloon pump; PCI = percutaneous coronary intervention; sCR = serum creatinine.

normal serum creatinine values. The fact that this group of patients with unrecognized renal insufficiency had significantly higher mortality rates compared with patients with normal renal function underlines the importance of the more accurate renal function assessment using equations estimating the glomerular filtration rate. It is becoming increasingly common for formal laboratory reports to routinely include the estimated glomerular filtration rate, and our results should encourage this trend. Indeed, the 2014 American Heart Association/American College of Cardiology Guidelines for the Management of Patients with non-ST-elevation acute coronary syndromes recommend that glomerular filtration rate should be estimated initially and throughout care for all patients.[16]

Several factors associated with impaired renal function are believed to contribute to the adverse outcome of patients with acute coronary syndrome. These factors include insulin resistance,[17,18] alterations in the extracellular matrix,[19] oxidative stress,[20] inflammation,[21] endothelial dysfunction,[22] renin-angiotensin-aldosterone system activation,[23] vascular calcifications,[24] and increased plasma levels of fibrinogen and homocysteine.[23,25,26] Furthermore, the presence of chronic renal failure is associated with a higher prevalence of baseline cardiovascular comorbidities including diabetes, heart failure, previous myocardial infarction, and stroke and coronary interventions.[16,27] In our study, all these conditions were significantly more common among patients with renal failure (either recognized or not) compared with patients with normal renal function. In addition, patients with renal dysfunction and especially those with unrecognized renal insufficiency were older and more frequently female. This can be explained by the frailty and lower muscle mass of these patients that may result in significant renal dysfunction with normal serum creatinine levels. All these conditions have been associated with adverse prognosis of patients with acute coronary syndrome.[28,29] However, in the current study, differences in outcomes remained significant even following a multivariate analysis that included all comorbidities.

Several studies, including the SWEDEHEART 2010,[30] have demonstrated that despite their high-risk features and poor outcome, acute coronary syndrome patients with renal insufficiency are less frequently referred to an invasive revascularization approach. In our study, both groups of patients with renal insufficiency were less frequently admitted in cardiology units and were more frequently referred for a conservative rather than an invasive approach compared with patients with normal renal function. Interestingly, patients with renal dysfunction were also less frequently treated with the conventional cardiovascular medications recommended by the guidelines. Similar findings have been demonstrated in a few previous studies.[31-33] The almost uniform exclusion of patients with severe renal dysfunction from randomized studies evaluating new targeted therapies for acute coronary syndrome, coupled with concerns 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. It is therefore possible that some of the increased risk associated with renal insufficiency may be related to differences in treatment.

Several limitations of this study warrant consideration. First, the evaluation of renal function was based on a single serum creatinine measurement taken at hospital admission. It is possible that some patients present to the hospital with acute renal failure and therefore, admission creatinine levels may not reflect their baseline renal function. In order to minimize this limitation, patients who presented to the hospital with cardiogenic shock were excluded. Second, our cohort did not undergo urine collection for protein or albumin. Even very mild microalbuminuria has clearly been shown to be a risk factor for both cardiovascular morbidity and mortality,[34-36] particularly among patients with diabetes mellitus, but also among nondiabetics. Third, our database included the prevalence of hypertension, but blood pressure values were not available. Although blood pressure measurement during hospital admission for acute coronary syndrome may not be representative for baseline values, this is still an important limitation given the well-known association between high blood pressure and renal dysfunction. Fourth, all the equations that are used to estimate the glomerular filtration rate, including the MDRD equation, are based on serum creatinine. Due to the tubular secretion of creatinine, these equations mildly overestimate the measured glomerular filtration rate. However, they are still considered accurate and are by far the most commonly used mode for glomerular filtration rate assessment. Cystatin C is an alternative serum measure of kidney function that approximates direct measures of glomerular filtration rate and is less influenced by age, sex, race, and muscle mass.[37] Studies have shown that the combined creatinine−cystatin C equation performed better than equations based on either of these markers alone.[37] Thus, the association between renal function and cardiovascular outcomes in our cohort may be more accurately assessed using cystatin C measurements rather than the estimated creatinine clearance. However, cystatin C was not measured in our cohort. Finally, the primary endpoint of our study was all-cause mortality, and we did not have any data on specific causes of death, most importantly regarding cardiovascular death.

The current study demonstrated that unrecognized renal insufficiency is very common among patients with acute coronary syndrome and is associated with adverse short- and long-term outcomes. Despite their poor prognosis, acute coronary syndrome patients with unrecognized renal insufficiency are less frequently being referred for an invasive approach and receive suboptimal medical therapy compared with patients with normal renal function. The specific causes for the adverse outcome and whether a more aggressive therapeutic approach can improve the prognosis of these patients should be assessed by future studies.

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