Relation Between Renal Function and Outcomes in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome

Real-World Data From the European Public Health Outcome Research and Indicators Collection Project

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Background: Clinical trials provide limited information about the outcome of patients with acute coronary syndromes (ACSs) and kidney disease (KD) owing to underrepresentation of this population in most studies.

Methods: To evaluate the outcome of patients with non–ST-segment elevation ACS (NSTE-ACS) and KD in a real-world setting, we compared the risk of in-hospital and 30-day mortality by the presence of KD (defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2) in 13 141 patients with NSTE-ACS enrolled in 3 multinational ACS registries between 2000 and 2006 as part of the European Public Health Outcome Research and Indicators Collection Project.

Results: Patients with KD (n=4181) composed 31.8% of the study population and had significantly higher rates of in-hospital (5.4%) and 30-day (7.2%) case fatality compared with patients without KD (1.1% and 1.7%, respectively; $P<.001$ for both). In multivariate analysis, the presence of KD was independently associated with a significantly higher mortality risk (in-hospital: odds ratio [OR], 2.11; 95% confidence interval [CI], 1.48-3.00; 30-day: OR, 1.95; 95% CI, 1.46-2.61). Patients with KD who underwent coronary angiography experienced a 36% ($P=.05$) and 40% ($P<.001$) lower risk of in-hospital and 30-day mortality, respectively, but this high-risk population still exhibited significantly higher case-fatality rates during hospitalization (3.3%) and at 30 days (4.6%) compared with patients without KD who underwent coronary angiography (0.7% and 1.3%, respectively; $P<.001$ for all).

Conclusions: In a real-world setting, KD was present in approximately one-third of patients with NSTE-ACS and is a powerful independent predictor of subsequent mortality. Patients with NSTE-ACS and KD referred for coronary angiography have a significantly lower risk of death, but this high-risk population continues to exhibit increased mortality rates despite intervention procedures.

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KIDNEY DISEASE (KD) IS DEfined by the National Kidney Foundation as a glomerular filtration rate (GFR) of less than 60.0 mL/min/1.73 m^2 of body surface area.[1] The burden of KD has been estimated to be 13% to 16% in the adult population, and the prevalence of this disorder has increased by approximately 20% to 30% during the past decade.[2] Patients with KD have been shown to be at increased risk for cardiovascular disease[3] and to experience a high complication rate after an acute myocardial infarction.[4,5] Despite this, clinical trials provide limited information regarding the outcome of patients with acute coronary syndrome (ACS) and KD owing to underrepresentation of this population in most studies.[6] Particularly limited are data regarding management strategies in patients with non–ST-segment elevation ACS (NSTE-ACS) and KD. Specifically, the efficacy and the appropriate timing of coronary intervention are unclear in this unique subset of the NSTE-ACS population. Several studies[7-12] have indicated that patients with impaired renal function may have suboptimal long-term outcomes from revascularization strategies, possibly owing to an increased prevalence of coexisting conditions and more severe coronary artery disease, whereas subanalyses of recent clinical trials have suggested that coronary revascularization may improve outcomes in patients with ACS and KD.[13,14]

Table 1. Patients With Available Renal Function (eGFR) Data Included in the Study

Study	Country	Year	Consecutive Patients	Hospitals, No.	University Hospitals, %	Country Representative	Patients, Total No.	NSTE-ACS, No.	eGFR Available, No.
MASCARA study	Spain	2005	Yes	32	75	Yes	7251	4091	3110
EHS-ACS I	Europe	2000	No	84	63	No	10 180	5936	5545
EHS-ACS II	Europe	2005	No	190	54	No	5160	2647	2275
ACSIS 2004	Israel	2004	Yes	25	70	Yes	2094	1121	1089
ACSIS 2006	Israel	2006	Yes	25	70	Yes	2077	1136	1122
Total							**26 762**	**14 931**	**13 141**

Abbreviations: ACSIS, Acute Coronary Syndrome Israeli Survey; eGFR, estimated glomerular filtration rate; EHS-ACS, European Heart Survey on Acute Coronary Syndrome; MASCARA, Manejo del Síndrome Coronario Agudo Registro Actualizado; NSTE-ACS, non–ST-segment elevation acute coronary syndrome.

Data from a real-world setting may provide important information regarding management strategies and outcomes in patients with NSTE-ACS and KD. Accordingly, the present study was performed in 13 141 patients with NSTE-ACS enrolled and prospectively followed up in 3 multinational ACS registries conducted across Europe and the Mediterranean basin as part of the European Public Health Outcome Research and Indicators Collection (EUPHORIC) Project. This study was designed (1) to compare the clinical course of patients with NSTE-ACS and KD with that of patients with NSTE-ACS without KD and (2) to assess in-hospital and 30-day outcomes of patients with NSTE-ACS and KD who underwent coronary angiography during hospitalization.

METHODS

STUDY POPULATION

The EUPHORIC Project (http://www.euphoric-project.eu) is a consortium of 15 institutions from 10 European countries and Israel that aims to define and test outcome indicators in relevant areas of pathology and to produce protocols to collect, harmonize, and analyze data by integrating the European Community Health Indicators list of outcome indicators. The cardiovascular aspect of the project comprises 3 main large-scale registries of patients with ACS: the Acute Coronary Syndrome Israeli Survey (ACSIS), which contributed 2094 patients from 2004 and 2077 patients from 2006 to the EUPHORIC Project; the Spanish Manejo del Síndrome Coronario Agudo Registro Actualizado (MASCARA) study, which contributed 7251 patients from 2005; and the European Heart Survey on Acute Coronary Syndrome (EHS-ACS), with 10 180 patients from 2000 and 5160 patients from 2005. The 3 respective registries have been described in detail previously.[15-19] Briefly, the ACSIS is a biennial 2-month national ACS survey conducted in all 25 operating cardiac departments in Israel since 1992; the MASCARA study is a nationwide prospective cohort study that included consecutive patients hospitalized for ACS in 32 randomly selected Spanish hospitals in 2004-2005; and in the EHS-ACS, 30 to 50 consecutive patients were enrolled in each of 203 participating medical centers from 31 countries across Europe.

The 3 registries collected data about patients with ACS using similar case report forms and the same definitions for ACS: (1) admission for anginal chest pain (or the equivalent) with no significant or assessable changes in the electrocardiogram but with elevated markers of myocardial necrosis or a positive screening test for ischemia during admission or a history of known coronary heart disease; (2) admission for anginal chest pain or the equivalent and changes on electrocardiography compatible with myocardial ischemia; and (3) the absence of chest pain but with elevated markers and changes on electrocardiography compatible with ischemia or positive screening test results for ischemia during admission. Patients were followed up throughout their hospitalization and 30 days after hospital discharge. Informed consent for participation in the survey was acquired when necessary.

The present study population comprises 13 141 patients with NSTE-ACS included in the MASCARA study (n=3110); the ACSIS 2004 (n=1089) and the ACSIS 2006 (n=1122); and the EHS-ACS I (n=5545) and the EHS-ACS II (n=2275) who had a discharge diagnosis of non–ST-segment elevation myocardial infarction or unstable angina and for whom data regarding serum creatinine concentration during hospitalization were available (**Table 1**). Patients with a hospital discharge diagnosis of ST-segment elevation myocardial infarction were excluded from the study. Advanced age, any degree of renal dysfunction, and the presence of additional comorbidities did not constitute exclusion criteria.

DEFINITIONS AND OUTCOME MEASURES

Blood analysis was performed in the local laboratory of each enrolling center. Baseline serum creatinine level was recorded for all patients included in the present study (composing 71% of the NSTE-ACS population enrolled in the surveys [Table 1]) and was used for the assessment of renal function. The GFR is considered most suitable for quantifying renal function.[20] Estimated GFR (eGFR) was assessed using the 4-component Modification of Diet in Renal Disease equation incorporating age, race, sex, and serum creatinine level: $eGFR = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$. The product of this equation was multiplied by a correction factor of 0.742 for women and 1.21 for black individuals.[20] Using the guidelines of the National Kidney Foundation,[1] study patients were categorized as having KD (eGFR, <60 mL/min/1.73 m^2) or not having KD (eGFR, ≥ 60 mL/min/1.73 m^2). To evaluate the consistency of the results in patients with different levels of renal function, patients with KD were further categorized as having moderate (eGFR, 30-59 mL/min/1.73 m^2) or severe (eGFR, <30 mL/min/1.73 m^2) renal dysfunction.[1]

The primary outcome measures of the present study were in-hospital and 30-day mortality. Secondary outcome measures included the occurrence of recurrent angina or reinfarction during hospitalization.

STATISTICAL ANALYSIS

Univariate analysis was performed using the χ^2, t, Mann-Whitney, or Kruskal-Wallis test or 1-way analysis of variance

Table 2. Baseline Characteristics and Outcomes of Study Patients by Survey

Characteristic	MASCARA Study (n = 3110)	EHS-ACS I (n = 5545)	EHS-ACS II (n = 2275)	ACSIS 2004 (n = 1089)	ACSIS 2006 (n = 1122)	*P* Value
Women, No. (%)	931 (29.9)	1934 (34.9)	779 (34.2)	293 (26.9)	261 (23.3)	<.001
Age, mean (SD), y	68.1 (11.9)	66.1 (12.0)	65.8 (12.3)	65.1 (13.2)	64.5 (12.8)	<.001
Diabetes mellitus, No. (%)	1075 (34.6)	1330 (24.0)	569 (25.0)	399 (36.6)	414 (36.9)	<.001
Hypertension, No. (%)	2050 (65.9)	3486 (62.9)	1452 (63.8)	687 (63.1)	744 (66.3)	.07
Current smokers, No. (%)	1736 (55.8)	2745 (49.5)	1205 (53.0)	467 (42.9)	657 (58.6)	<.001
History of CVD, No. (%)	1860 (59.8)	4578 (82.6)	1313 (57.7)	651 (59.8)	807 (71.9)	<.001
eGFR, median (first-third quartiles)	70.2 (52.4-87.9)	70.5 (56.7-85.2)	72.2 (56.7-86.0)	70.1 (52.3-86.8)	73.9 (57.3-89.3)	.003
KD (eGFR, <60 mL/min/1.73 m^2), No. (%)	1041 (33.5)	1746 (31.5)	683 (30.0)	387 (35.5)	324 (28.9)	.001
Coronary angiography, No. (%)	2071 (66.6)	2980 (53.7)	1472 (64.7)	769 (70.6)	859 (76.6)	<.001
30-d mortality, No. (%)	124 (4.0)	169 (3.0)	80 (3.5)	42 (3.9)	36 (3.2)	.04
In-hospital event, No. (%)[a]	644 (20.7)	884 (15.9)	261 (11.5)	91 (8.4)	96 (8.6)	<.001

Abbreviations: ACSIS, Acute Coronary Syndrome Israeli Survey; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; EHS-ACS, European Heart Survey on Acute Coronary Syndrome; KD, kidney disease; MASCARA, Manejo del Síndrome Coronario Agudo Registro Actualizado.
[a] Defined as death, reinfarction, or recurrent angina during hospitalization.

according to the data. The risks of in-hospital events and 30-day mortality were assessed using multivariate logistic regression models. Prespecified covariates in the multivariate models included age, sex, the presence of diabetes mellitus, a history of treated hypertension, current smoking, previous coronary artery disease, Killip class higher than II (corresponding to pulmonary edema [Killip III] or cardiogenic shock [Killip IV] during hospitalization for the index event), the presence of KD, and the performance of coronary angiography during hospitalization. To account for center-level variation, generalized mixed models were performed including center as a random-effects variable. The association between coronary angiography and outcomes in the KD subgroups was assessed by including a coronary angiography–kidney function interaction term in the multivariate models. In a secondary analysis, we also evaluated the outcome by the type of coronary revascularization procedure the patient had undergone (ie, percutaneous coronary intervention or coronary artery bypass graft surgery vs no intervention). The statistical software used for the analyses was R version 2.7.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The baseline characteristics of the 13 141 study patients in the 5 surveys included in the analysis are given in **Table 2**. The median eGFR in the total study population was 70.9 mL/min/1.73 m^2, and 31.8% of the study population (n=4181) had KD, as defined by an eGFR less than 60 mL/min/1.73m^2. In the subgroup of patients with KD, the median eGFR was 47 mL/min/1.73 m^2. Thus, 82.3% (n=3439) of patients with KD had moderate renal dysfunction (as defined by an eGFR of 30-59 mL/min/1.73 m^2) and 17.7% (n=742) had severe renal dysfunction (as defined by an eGFR <30 mL/min/1.73 m^2).

Patients with KD exhibited a significantly higher frequency of baseline clinical risk factors, including older age, diabetes mellitus, treated hypertension, and history of coronary artery disease (**Table 3**). Similarly, during hospitalization, patients with KD had a higher Killip class, lower hemoglobin and cholesterol values, and higher glucose levels and were treated at a significantly lower frequency with intravenous and oral medications compared with patients without KD (Table 3).

CLINICAL COURSE BY THE PRESENCE OF KD

During hospitalization for the index event, the rates of major ischemic coronary events, including recurrent infarction and angina after infarction, were significantly higher in patients with KD (7.9% and 12.7%, respectively) compared with patients without KD (3.3% [*P*<.001] and 11.1% [*P*=.006], respectively). Furthermore, bleeding rates were more than 3-fold higher (Table 3) and in-hospital and 30-day mortality rates were more than 4-fold higher in patients with KD compared with patients without KD (**Figure 1**). Consistently, in multivariate analysis, the presence of KD was shown to be associated with a significant 2-fold-higher risk of in-hospital and 30-day mortality (*P*<.001 for both) after adjustment for baseline clinical characteristics and Killip class (**Table 4**).

The higher mortality risk associated with KD was observed in patients with moderate (eGFR, 30-59 mL/min/1.73 m^2) and more severe (eGFR, <30 mL/min/1.73 m^2) renal dysfunction (Table 4). Thus, patients with moderate renal dysfunction had significantly higher risk of in-hospital (71%, *P*=.005) and 30-day (46%, *P*=.01) case fatality compared with patients without KD, and patients with severe KD had a more than 4-fold higher risk of case fatality (*P*<.001 for both).

CORONARY ANGIOGRAPHY AND OUTCOME IN PATIENTS WITH AND WITHOUT KD

Coronary angiography during the index hospitalization was performed in more than half of the study population, with the highest frequency in patients enrolled in the ACSISs (Table 2). Patients with and without KD who did not undergo coronary angiography exhibited a higher frequency of baseline risk factors, including a lower eGFR, previous coronary artery disease, and older age (data not shown).

In the total study population, in-hospital and 30-day case-fatality rates were significantly lower in patients who underwent coronary angiography during hospitalization (1.4% and 2.2%, respectively) than in those who did not (4.2% and 6.1%, respectively; *P*<.001 for both). Con-

Table 3. Characteristics by the Presence of Kidney Disease as Defined by the eGFR

Characteristic	No Kidney Disease: eGFR, ≥60 mL/min/1.73 m² (n = 8960)	Kidney Disease: eGFR, <60 mL/min/1.73 m² (n = 4181)	*P* Value
History			
Women, No. (%)	2244 (25.0)	1954 (46.7)	<.001
Age, mean (SD), y	63.1 (11.9)	73.1 (9.99)	<.001
Diabetes mellitus, No. (%)	2273 (25.4)	1514 (36.2)	<.001
Hypertension, No. (%)	5263 (58.7)	3156 (75.5)	<.001
Current smokers, No. (%)	5145 (57.4)	1665 (39.8)	<.001
History of CAD, No. (%)	5997 (66.9)	3212 (76.8)	<.001
In-hospital characteristics and events			
Killip class >II, No. (%)[a]	193 (2.2)	329 (7.9)	<.001
eGFR, median (first-third quartiles)	80.0 (70.3-92.8)	47.3 (35.6-54.7)	<.001
Hemoglobin, mean (SD), g/dL	14.0 (1.74)	12.7 (2.00)	<.001
Glucose, mean (range), mg/dL	117 (99-157)	139 (108-203)	<.001
Total cholesterol, mean (SD), mg/dL	198 (46.1)	193 (48.8)	<.001
Angiography, No. (%)	6065 (67.7)	2086 (49.9)	<.001
PCI, No. (%)	3463 (38.6)	1089 (26.0)	<.001
CABG surgery, No. (%)	662 (7.4)	243 (5.8)	.001
Heparin (any type), No. (%)[b]	1703 (82.4)	828 (79.5)	.05
GP IIb/IIIa inhibitors, No. (%)[b]	496 (24.0)	207 (19.9)	.01
Reinfarction, No. (%)	214 (2.4)	131 (3.1)	.01
Recurrent angina, No. (%)	991 (11.1)	532 (12.7)	.006
Bleeding, No. (%)[b]	26 (1.3)	43 (4.1)	<.001
Case fatality, No. (%)	94 (1.0)	224 (5.4)	<.001
Postdischarge medications and events, No. (%)			
Aspirin[b]	1767 (85.4)	817 (78.4)	<.001
Clopidogrel[b]	1246 (60.3)	536 (51.4)	<.001
β-Blockers	6889 (76.9)	2809 (67.2)	<.001
ACE inhibitors/ARBs	5212 (58.2)	2476 (59.2)	.003
Statins	6351 (70.9)	2485 (59.4)	<.001
30-d case fatality, No. (%)	151 (1.7)	300 (7.2)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CABG, coronary artery bypass graft; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; GP, glycoprotein; PCI, percutaneous coronary intervention.

SI conversion factors: To convert total cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimeters per liter, multiply by 0.0555; and hemoglobin to grams per liter, multiply by 10.

[a] Corresponding to pulmonary edema (Killip III) or cardiogenic shock (Killip IV) during hospitalization for the index event.

[b] Data were available only in a subset of 3110 patients enrolled in the Manejo del Síndrome Coronario Agudo Registro Actualizado study (GFR, ≥60 mL/min/1.73 m² [n = 2068]; GFR < 60 mL/min/1.73 m² [n = 1042]).

sistently, coronary angiography was associated with a significantly lower risk of death in the total study population (**Table 5**; model 1).

A significantly lower proportion of patients with KD (49.9%) underwent coronary angiography compared with patients without KD (67.8%; $P<.001$). The lower event rates associated with coronary angiography in the total study population were consistent in patients with and without KD (**Figure 2**). Thus, in multivariate analysis, patients with KD who underwent coronary angiography experienced a 36% ($P=.05$) and a 40% ($P<.001$) lower risk of in-hospital and 30-day mortality, respectively, compared with patients with KD who did not undergo coronary angiography (Table 5; model 2). The association between coronary angiography and lower in-hospital and 30-day mortality risk was not significantly different between patients with and without KD (*P* value for KD–coronary angiography interactions: $P=.31$ and .83, respectively [Table 5; model 2]) but was nonsignificantly attenuated in patients with severe KD (Table 5; model 3).

We performed a secondary analysis that evaluated the outcome of patients with KD by the type of coronary intervention that was performed. This analysis showed similar trends for the association between percutaneous coronary intervention and a lower risk of in-hospital and 30-day mortality in patients with KD (odds ratio [OR], 0.61; 95% confidence interval [CI], 0.34-1.09; and 0.34; 0.19-0.60, respectively), whereas the association between coronary artery bypass graft surgery and outcomes in the KD population was less pronounced (0.66; 0.28-1.58; and 0.85; 0.49-1.80, respectively), possibly owing to sample size limitations.

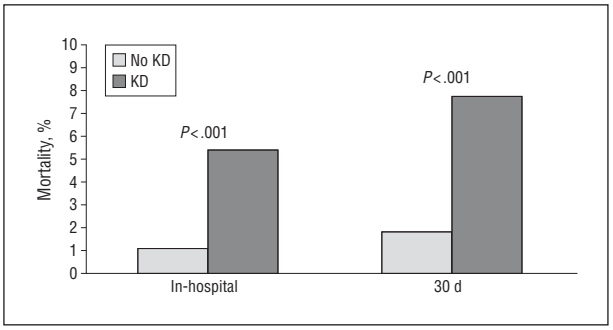

Figure 1. In-hospital and 30-day mortality rates in patients with and without kidney disease (K D).

Table 4. Multivariate Analysis: Adjusted ORs for In-hospital and 30-Day Case Fatality[a]

	In-hospital Case Fatality (n = 9214)		30-d Case Fatality (n = 8528)	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
KD (eGFR, <60 mL/min/1.73 m^2) vs no KD (eGFR, ≥60 mL/min/1.73 m^2)	2.11 (1.48-3.00)	<.001	1.95 (1.46-2.61)	<.001
Moderate KD (eGFR, 30-59 mL/min/1.73 m^2) vs no KD[b]	1.71 (1.17-2.49)	.005	1.46 (1.07-2.00)	.01
Severe KD (eGFR, <30 mL/min/1.73 m^2) vs no KD[b]	4.11 (2.53-6.68)	<.001	4.84 (3.27-7.16)	<.001
Age	1.05 (1.04-1.07)	<.001	1.06 (1.05-1.08)	<.001
Female sex	0.70 (0.47-1.04)	.08	0.83 (0.60-1.14)	.25
Hypertension	0.78 (0.55-1.13)	.19	0.80 (0.59-1.07)	.13
Diabetes mellitus	1.20 (0.86-1.69)	.28	1.25 (0.95-1.66)	.11
History of CAD	0.90 (0.59-1.37)	.61	0.98 (0.69-1.38)	.90
Current smoking	1.01 (0.69-1.49)	.95	1.10 (0.80-1.50)	.57
Killip class >II[c]	42.2 (30.15-59.09)	<.001	17.99 (13.51-23.96)	<.001

Abbreviations: CAD, coronary artery disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; KD, kidney disease; OR, odd ratio.
[a] Multivariate models are further adjusted by including the enrolling center as a random-effects variable.
[b] Adjusted ORs for the effect of the degree of KD were obtained from a separate model in which the estimates for the additional covariates were almost identical to those obtained in the main model that adjusted for the overall effect of KD.
[c] Corresponding to pulmonary edema (Killip III) or cardiogenic shock (Killip IV) during hospitalization for the index event.

Table 5. Multivariate Analysis: Adjusted ORs of In-hospital and 30-Day Case Fatality for Coronary Angiography by the Presence and Severity of Kidney Disease[a]

	In-hospital Mortality		30-d Mortality	
Model	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Model 1: effect in the total population				
Angiography (yes/no)	0.53 (0.37-0.75)	<.001	0.53 (0.40-0.72)	<.001
Model 2: effect by the presence of kidney disease				
Angiography in those with eGFR ≥60 mL/min/1.73 m^2	0.45 (0.26-0.78)	.005	0.52 (0.34-0.79)	.001
Angiography in those with eGFR <60 mL/min/1.73 m^2	0.64 (0.41-1.00)	.05	0.60 (0.41-0.87)	<.001
Interaction eGFR <60 mL/min/1.73 m^2: angiography (yes/no)		.31		.83
Model 3: effect in kidney disease subgroups				
Angiography in those with eGFR ≥60 mL/min/1.73 m^2	0.46 (0.26-0.79)	.005	0.53 (0.34-0.81)	.001
Angiography in those with eGFR of 30-59 mL/min/1.73 m^2	0.52 (0.30-0.88)	.01	0.54 (0.34-0.85)	<.001
Angiography in those with eGFR <30 mL/min/1.73 m^2	1.31 (0.58-2.94)	.51	0.80 (0.41-1.54)	.17
Interaction eGFR in 3 categories: angiography (yes/no)		.09		.62

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.
[a] All the models are further adjusted by age, sex, hypertension, diabetes mellitus, history of coronary artery disease, current smoking, and Killip class higher than II (corresponding to pulmonary edema [Killip III] or cardiogenic shock [Killip IV] during hospitalization for the index event) and by including the enrolling center as a random-effects variable.

Despite the significantly lower mortality risk associated with coronary angiography, patients with KD who underwent coronary angiography still exhibited higher residual rates of in-hospital (3.3%) and 30-day (4.6%) mortality than did patients without KD who underwent coronary angiography (0.7% and 1.3%, respectively) (Figure 2). Accordingly, in multivariate analysis, the presence of KD remained an independent risk factor for in-hospital (odds ratio, 2.10; 95% confidence interval, 1.23-3.59) and 30-day (1.70; 1.07-2.68) mortality even in patients who underwent coronary angiography during hospitalization.

COMMENT

These results, derived from large-scale multinational ACS registries, provide several important clinical implications regarding the clinical course of patients with NSTE-ACS and KD: (1) in a real-world setting, patients with KD compose approximately one-third of the NSTE-ACS population, with most having moderate renal dysfunction; (2) the presence of KD is an independent and powerful predictor of in-hospital and 30-day mortality in patients with NSTE-ACS and is associated with approximately a 2-fold higher risk of death; (3) a management strategy that includes coronary angiography during the index hospitalization is independently associated with a significantly lower mortality risk in patients with NSTE-ACS and KD. However, KD remains an independent risk factor for death even after coronary intervention.

Clinical trials have provided limited information on the risks associated with varying degrees of renal dysfunction in patients with NSTE-ACS, possibly because most of this population is excluded from these studies.[6]

Furthermore, most ACS trials rely on serum creatinine concentration for inclusion criteria and outcome analyses, despite the fact that it is an insensitive indicator of renal function. Thus, the present data regarding the outcome of patients with ACS and renal insufficiency are derived mostly from cohort studies. An analysis of patients with ACS enrolled in GRACE (Global Registry of Acute Coronary Events) demonstrated that creatinine clearance is an important independent predictor of hospital death and major bleeding.[21] Similarly, a large cohort study comprising 130 099 patients showed that renal insufficiency is associated with a significantly higher mortality rate in elderly patients with acute myocardial infarction.[5] These studies, however, included patients with STE- and NSTE-ACS, in whom outcomes and management strategies, including coronary intervention, are different. In contrast, the present study was performed in a real-world setting and included solely patients with NSTE-ACS. Thus, the present results extend previous data regarding the effect of KD in the overall ACS population and demonstrate that in patients with NSTE-ACS, moderate and severe renal dysfunction are associated with a significantly higher risk of death, independent of baseline clinical risk factors or disease severity on presentation.

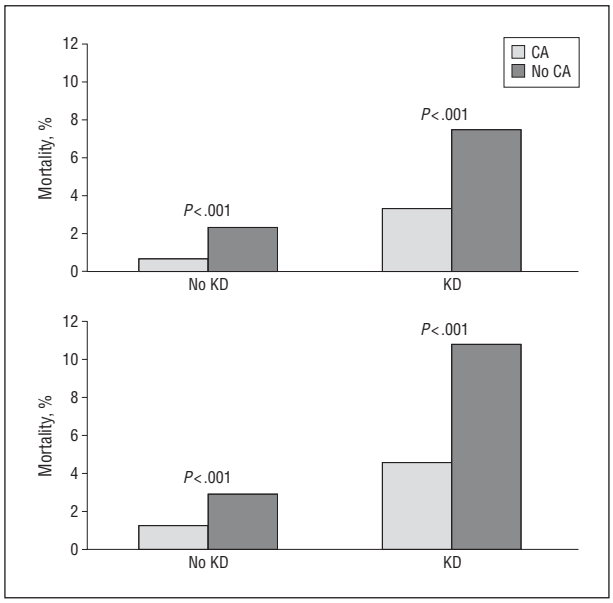

Figure 2. In-hospital (A) and 30-day (B) mortality rates in patients who did and did not undergo coronary angiography (CA) by the presence of kidney disease (KD).

The presence of KD has been demonstrated to complicate the treatment of patients with NSTE-ACS. Specifically, baseline renal dysfunction can increase the risk of acute kidney injury after coronary angiography,[22] complicate percutaneous coronary interventions,[8-11] and increase the bleeding risk of anticoagulant and antithrombotic drugs,[23] necessitating appropriate dose titration. Accordingly, data do indicate that renal dysfunction is a strong predictor of adverse outcomes during and after coronary intervention procedures,[7-12] whereas information regarding the benefit of coronary intervention in patients with KD after hospitalization for NSTE-ACS is limited to subanalyses of clinical trials that included few patients with renal dysfunction.[13,14] The present data show that in patients with NSTE-ACS and KD, a management strategy that included coronary angiography during hospitalization was independently associated with a significant 40% lower risk of 30-day mortality. Furthermore, the reduction in mortality risk associated with coronary angiography was not significantly different between patients who did and did not exhibit KD. Despite this, however, coronary angiography was performed in a significantly lower proportion of patients with KD. These findings are consistent with recent data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation) Quality Improvement Initiative registry[24] regarding lower rates of coronary intervention in patients with NSTE-ACS and renal dysfunction and with information about the underuse of evidence-based medical treatments for NSTE-ACS, including aspirin, β-blockers, and glycoprotein IIb/IIIa antagonists, in the KD population.[25-27]

Patients with KD who were referred for coronary angiography during hospitalization still experienced a relatively high residual mortality rate and were further shown to exhibit a significantly higher risk of death compared with patients without KD who underwent coronary angiography. The higher residual event rate in patients with KD occurred despite the fact that the present study population derived from recent ACS surveys in which contemporary methods of coronary revascularization were used. These findings further stress the independent effect of KD, regardless of management strategies, in the NSTE-ACS population. Also note that the association between coronary angiography and lower mortality risk was nonsignificantly attenuated in patients with severe KD, suggesting that more caution should be exercised before revascularization procedures in patients with NSTE-ACS and advanced renal dysfunction.

The present study comprises clinical information from observational multinational ACS surveys and, therefore, provides real-world data regarding the clinical course and outcome of nonrandomized and unselected patients with NSTE-ACS. Thus, patients with KD and those undergoing coronary angiography in the present study harbored a significantly greater frequency of baseline clinical risk factors, and a possible selection bias may exist regarding the outcome after coronary angiography in the KD population. In addition, ejection fraction was not consistently recorded in the EUPHORIC Project database, and, therefore, this important factor was not included in the multivariate models. The present findings, however, persisted after adjustment for baseline clinical factors and for the severity of disease during hospitalization, further supporting the consistency of the present results.

Although the Modification of Diet in Renal Disease equation has been shown to be a reliable means of estimating the GFR,[20] it is an indirect measure of renal function and is limited by the fact that it uses serum creatinine concentration, which may be affected by nonrenal factors. Due to inconsistent data collection regarding di-

alysis therapy in study patients, we did not evaluate the effect of treatment with dialysis on the outcome of patients with KD and end-stage renal disease.

In conclusion, the present study demonstrates that KD is common in hospitalized patients with NSTE-ACS and that renal dysfunction, at all levels, is a powerful predictor of subsequent mortality in this population. We showed that patients with KD referred for coronary angiography during hospitalization experience significantly lower mortality risk despite relatively high residual event rates. These findings suggest that (1) eGFR should be routinely calculated in hospitalized patients with NSTE-ACS because current reliance on serum creatinine concentration may fail to identify an important proportion of this high-risk population; (2) coronary angiography should be strongly considered in NSTE-ACS with KD without contraindication; and (3) additional prevention and therapeutic measures are required in patients with NSTE-ACS and KD, even after coronary intervention, due to a relatively high residual mortality rate in this high-risk population. These measures may include possible early stabilization before coronary intervention, measures for the prevention of contrast-induced acute kidney injury, and careful follow-up of renal function after coronary intervention procedures.

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