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CLINICAL RESEARCH STUDY

Chronic Kidney Disease in Patients with Non-ST-Segment Elevation Acute Coronary Syndromes

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ABSTRACT

PURPOSE: Chronic kidney disease has been linked to high mortality rates in patients with ST-segment elevation myocardial infarction but has not been well described for patients with non-ST-segment elevation acute coronary syndromes. We examined the treatment and outcomes of patients with both non-ST-segment elevation acute coronary syndromes and moderate to severe chronic kidney disease.

SUBJECTS AND METHODS: We evaluated 45 343 patients with non-ST-segment elevation acute coronary syndromes enrolled in the CRUSADE Quality Improvement Initiative and compared treatments and outcomes in patients with and without moderate to severe chronic kidney disease.

RESULTS: Patients presenting with moderate to severe chronic kidney disease (n = 6560) were older, more often diabetic, and more likely to present with signs of congestive heart failure. Adherence to Class IA/IB guidelines recommendations was lower in patients with moderate to severe chronic kidney disease, who were significantly less likely to be treated with medications, undergo invasive cardiac procedures, and be given discharge counseling. Moderate to severe chronic kidney disease was associated with a 50% increased risk of mortality and a 70% increased likelihood of transfusion. Despite having a higher risk of adverse outcomes, patients with moderate to severe chronic kidney disease were treated less aggressively than patients with normal renal function.

CONCLUSIONS: These findings suggest that, in patients with moderate to severe chronic kidney disease, safety concerns about adverse outcomes and the absence of trial data for this population may limit the use of guidelines-recommended therapies and interventions for non-ST-segment elevation acute coronary syndromes. The decreased use of discharge counseling in patients with moderate to severe chronic kidney disease and non-ST-segment elevation acute coronary syndromes may represent therapeutic nihilism. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Chronic kidney disease; Acute coronary syndromes; Quality improvement; Guidelines

Substantial evidence demonstrates the lethal consequences of acute myocardial infarction in patients with chronic kidney disease. Mortality rates are reportedly as high as 73%

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after acute myocardial infarction in patients with end-stage renal disease.¹ However, patients with chronic kidney disease are less likely to receive lifesaving treatments such as antithrombotic therapies, antiplatelet agents, and revascularization procedures.^{2,3} Much of these data have been obtained from large multicenter registries that have predominantly studied patients with acute ST-segment elevation myocardial infarction or have treated acute myocardial infarction as a single disease entity.¹⁻⁸

Because of the heterogeneous nature of acute coronary syndromes, the knowledge gained from these studies may not

be applicable to the large population of patients with non-ST-segment elevation acute coronary syndromes. ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndromes are distinct diseases with different treatments. In patients with chronic kidney disease, non-ST-segment elevation acute coronary syndromes are more common than ST-segment-elevation acute myocardial infarction,⁹ yet the relationship between non-ST-segment elevation acute coronary syndromes and renal dysfunction is not well characterized. We sought to compare treatment patterns and outcomes for patients with non-ST-segment elevation acute coronary syndromes, with and without moderate to severe chronic kidney disease, and to determine adherence rates for Class IA/IB recommendations from American College of Cardiology/American Heart Association guidelines for the treatment of patients with non-ST-segment elevation acute coronary syndromes.¹⁰

METHODS

Overall Population

From January 1, 2001, to December 31, 2003, a total of 88 097 patients with non-ST-segment elevation acute coronary syndromes were enrolled in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse outcomes with Early Implementation of the American College of Cardiology/American Heart Association guidelines) Quality Improvement Initiative. During the study period, 465 US hospitals located in 45 states participated in CRUSADE. The inclusion and exclusion criteria for patients enrolled in CRUSADE are illustrated in Figure 1. Patients transferred from other institutions into CRUSADE hospitals were included in our analysis if they were transferred within 24 hours of their index clinical symptoms. Patients who were transferred in from a non-CRUSADE hospital or were first evaluated in an inpatient setting were excluded. Because of privacy regulations, we did not collect outcome data on patients transferred out of participating hospitals, and therefore these patients were also excluded from the analysis. To minimize the number of patients transferred in or out, only patients who were treated at “full-service” hospitals (defined as facilities capable of cardiac catheterization, percutaneous coronary intervention, and coronary artery bypass grafting) were included. The resulting population consisted of 45 343 patients from 312 hospitals. Moderate to severe chronic kidney disease was a dichotomous variable defined as either serum creatinine

greater than 2.0 mg/dL or the need for dialysis.¹¹ The data-collection form did not specify which criterion was met for chronic kidney disease; thus, exact data on serum creatinine and dialysis status were not available.

CLINICAL SIGNIFICANCE

- Patients with moderate to severe chronic kidney disease and non-ST-elevation acute coronary syndromes are at high risk for in-hospital adverse events including mortality.
- Despite their high risk characteristics, these patients are less likely to receive antiplatelets, antithrombotics, early invasive procedures, and discharge counseling.
- These disparities probably reflect therapeutic nihilism, concern of complications, and the absence of randomized controlled trials for this patient population.

Data Analysis

For the descriptive analysis, mean values were used to describe continuous variables, and percentages were reported for categorical variables. Baseline demographics, clinical characteristics, care patterns, and in-hospital outcomes were compared between patients with and without moderate to severe chronic kidney disease. The Wilcoxon and chi-square tests were used to test for differences between continuous and categorical variables, respectively.

The association between moderate to severe chronic kidney disease and acute medication use, procedure use, and in-hospital outcomes was assessed using the generalized estimating equation approach to logistic regression.¹² The generalized estimating equation is used to adjust for the correlation in outcomes of

patients within the same hospital. The correlation occurs because of factors such as hospital peculiarities or patient characteristics that may be unique to a specific hospital. The technique renders unbiased and efficient estimates of the parameters associated with the variable of interest and its covariates. The models were adjusted for baseline patient characteristics including age, sex, body mass index, race, family history of coronary artery disease, hypertension, diabetes, smoking status, hypercholesterolemia, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior congestive heart failure, prior stroke, ST-segment depression, transient ST-segment elevation, positive cardiac markers, signs of congestive heart failure, heart rate, systolic blood pressure, and insurance status, as well as for provider and hospital characteristics (eg, physician specialty, total number of hospital beds, region of the country, and academic or nonacademic hospital status). A *P* value of less than .05 was established as the level of statistical significance for all tests. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS

Clinical Characteristics of the Study Population

Of the 45 343 patients meeting inclusion criteria, 6560 patients (14.5%) were classified as having moderate to severe

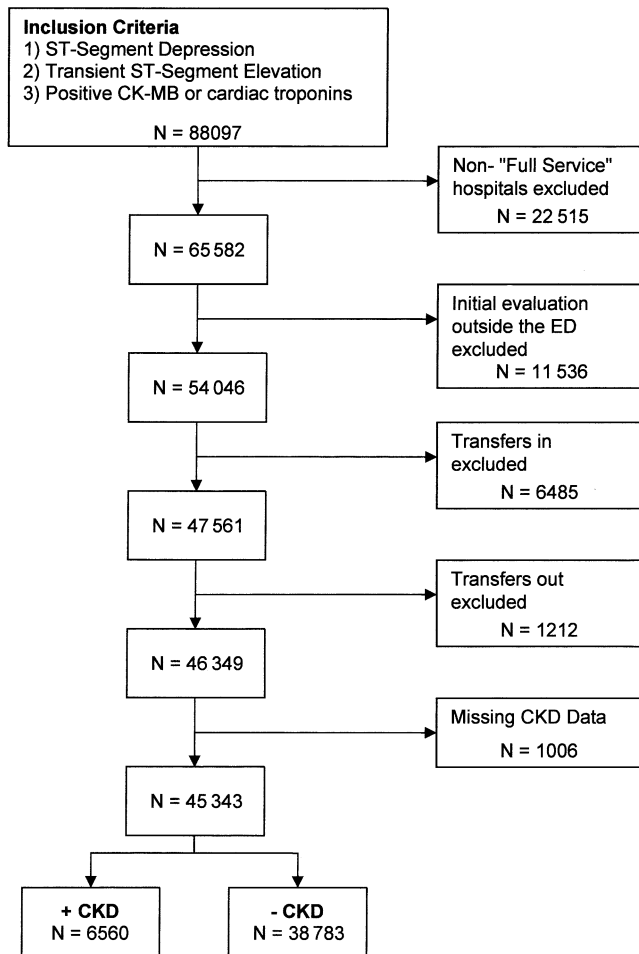


Figure 1 Exclusion and inclusion criteria. Transient was defined as less than 30 minutes. A positive serum marker assay (creatinine kinase-MB or cardiac troponin) was based on the local institution's diagnostic cut-off. Full-service hospitals were defined as hospitals with facilities for cardiac catheterization, percutaneous coronary intervention, and coronary artery bypass grafting. CK-MB = creatine kinase-MB; ED = emergency department; CKD = moderate to severe chronic kidney disease.

chronic kidney disease. Patients with moderate to severe chronic kidney disease were older and more likely to have diabetes mellitus, congestive heart failure, and previous coronary artery disease (Table 1). In addition, patients with moderate to severe chronic kidney disease were more likely to present with signs of congestive heart failure and hemodynamic instability.

Early Management and In-Hospital Outcomes

After adjustment for covariates and confounders, the odds of receiving antiplatelets, antithrombotics, or early invasive procedures were lower for patients with moderate to severe chronic kidney disease than for those without (Table 2). No difference in beta-blocker administration was observed. Overall, patients with moderate to severe chronic kidney disease had worse in-hospital outcomes (Table 3). Death, reinfarction, and red blood cell transfusions were more

likely in patients with moderate to severe chronic kidney disease than in patients with normal renal function. We found that patients with moderate to severe chronic kidney disease also were more likely to develop congestive heart failure and cardiogenic shock.

Discharge Medications and Therapy

Table 4 shows comparisons of discharge medications and counseling interventions for patients with and without moderate to severe chronic kidney disease. On discharge, patients with moderate to severe chronic kidney disease were less likely to be prescribed aspirin and clopidogrel. However, there was little difference between the 2 groups in the discharge prescription of beta-blockers, angiotensin-converting enzyme inhibitors, and lipid-lowering prescriptions. Interventions such as smoking cessation counseling, dietary modification, and cardiac rehabilitation occurred less often in the moderate to severe chronic kidney disease group.

DISCUSSION

Our analysis of the CRUSADE Quality Improvement Initiative database shows that patients with moderate to severe chronic kidney disease and non-ST-segment elevation acute coronary syndromes are more likely to have in-hospital complications and less likely to receive American College of Cardiology/American Heart Association guidelines-recommended therapies in the acute setting.

The relationship between impaired creatinine clearance and an increase in post-acute myocardial infarction mortality has been well documented.^{1,3,6-8} The findings from our analysis suggest that this association can be applied to the population with non-ST-segment elevation acute coronary syndromes as well. Our analysis also reveals that patients with moderate to severe chronic kidney disease have a higher rate of nonfatal in-hospital complications such as reinfarction and cardiogenic shock. The reasons for this high rate of fatal and nonfatal in-hospital complications are likely multifactorial. Patients with moderate to severe chronic kidney disease are a high-risk group predisposed to accelerated atherosclerosis.¹³ In addition, they have increased inflammation,^{14,15} higher sympathetic tone,¹⁶ and an increased activation of the renin-angiotensin-aldosterone system. When presenting to the emergency department, they are also more likely to have high-risk characteristics such as older age, diabetes mellitus, previous coronary artery disease, left ventricular hypertrophy, and congestive heart failure.² The observed association between impaired creatinine clearance and in-hospital complications remains even after adjustment for these comorbidities.

Our study shows that moderate to severe chronic kidney disease is independently associated with a decreased use of antithrombotic and antiplatelet medications. This connection has been described as therapeutic nihilism.¹⁷ However, the reluctance to use these medications in patients with moderate to severe chronic kidney disease most likely reflects the prevalence of high-risk clinical characteristics in

Table 1 Baseline Patient Demographics and Clinical Characteristics

Patient Characteristics	CKD (n = 6560)	Non-CKD (n = 38 783)	P Value
Age, y*	74.0 (63, 82)	67.0 (56, 78)	<.0001
Male sex	58.8	59.1	.6233
Diabetes mellitus			
Insulin dependent	27.2	9.2	<.0001
Non-insulin dependent	26.4	20.0	
Hypertension	84.7	67.7	<.0001
Dyslipidemia	50.1	47.1	<.0001
Current or recent smoker	16.4	28.2	<.0001
Prior CHF	45.2	14.9	<.0001
Prior MI	44.2	29.4	<.0001
Prior PCI	25.6	22.7	<.0001
Prior CABG	31.0	19.7	<.0001
Prior stroke	20.4	9.4	<.0001
ECG characteristics			
ST-segment depression	38.9	38.2	<.0001
Transient ST-segment elevation	5.0	7.4	
Both	1.1	2.2	
Positive markers	91.5	88.0	<.0001
Signs of CHF	43.7	19.8	<.0001
Hypotension†	4.8	2.7	<.0001
Tachycardia‡	28.9	21.8	<.0001
Inpatient service			
Cardiologist	43.5	58.0	<.0001
Noncardiologist	55.4	41.1	

CKD = moderate to severe chronic kidney disease; CHF = congestive heart failure; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; ECG = electrocardiograph.

*All data presented as percentages except age, presented as median (25th, 75th percentile).

†Hypotension defined as systolic blood pressure less than <100 mm Hg.

‡Tachycardia defined as heart rate >100 beats/min.

this population and an awareness of the increased risk for bleeding complications associated with the use of these drugs. The risk of major bleeding is increased in patients with moderate to severe chronic kidney disease⁹ and may be attributed to platelet dysfunction caused by uremia.¹⁸ In addition, many of these medications are eliminated by the kidneys, thus requiring renal dosing (Table 5).

To date, studies of the benefits of antiplatelet and antithrombotic treatments in this high-risk patient population have been

limited to subanalyses of larger randomized controlled trials. Aspirin use in patients with chronic kidney disease has been found to be beneficial.^{19,20} Although clopidogrel is hepatically eliminated, its efficacy and safety in patients with chronic kidney disease and non-ST-segment elevation acute coronary syndromes have yet to be established. In several subanalyses, enoxaparin and glycoprotein IIb/IIIa inhibitors have been shown to improve mortality and cardiovascular outcomes, with no significant increase in major bleeding, in patients with

Table 2 Acute Medications and Interventions by Renal Status*

Acute Medications	CKD % (n = 6560)	Non-CKD % (n = 38 783)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Aspirin	89.4	92.6	0.66 (0.60-0.73)	0.86 (0.78-0.95)
Beta-blocker	77.8	78.5	0.90 (0.84-0.96)	1.00 (0.93-1.07)
GP IIb/IIIa	19.6	37.4	0.43 (0.39-0.47)	0.67 (0.62-0.74)
Clopidogrel	33.8	42.8	0.69 (0.65-0.74)	0.86 (0.78-0.95)
Heparin, any	76.7	83.8	0.62 (0.57-0.67)	0.78 (0.72-0.84)
Invasive Procedures				
Catheter	47.6	73.8	0.33 (0.31-0.36)	0.52 (0.34-0.80)
Catheter <48 h	23.4	52.3	0.30 (0.27-0.32)	0.52 (0.48-0.57)
PCI	22.4	42.1	0.42 (0.39-0.45)	0.67 (0.62-0.71)
PCI <48 h	10.8	30.1	0.31 (0.28-0.34)	0.55 (0.50-0.60)
CABG	6.9	12.8	0.51 (0.46-0.56)	0.64 (0.57-0.71)

CKD = moderate to severe chronic kidney disease; GP IIb/IIIa = glycoprotein IIb/IIIa inhibitors; Cath = cardiac catheterization; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft.

*Patients with contraindications to antiplatelet or antithrombotic medications were excluded from this portion of the analysis.

Table 3 In-Hospital Outcomes by Renal Status

Outcomes	CKD% (n = 6560)	Non-CKD% (n = 38 783)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Death	9.0	3.6	2.62 (2.32-2.97)	1.54 (1.35-1.75)
Reinfarction	3.7	2.7	1.34 (1.17-1.53)	1.25 (1.10-1.43)
Death or reinfarction	11.6	5.8	2.08 (1.86-2.32)	1.45 (1.30-1.61)
Cardiogenic shock	4.5	2.3	1.93 (1.68-2.23)	1.37 (1.16-1.61)
Congestive heart failure	16.5	8.1	2.16 (1.97-2.36)	1.18 (1.09-1.29)
Transfusions	24.7	12.9	2.16 (2.02-2.31)	1.76 (1.65-1.88)

CKD = moderate to severe chronic renal insufficiency; OR = odds ratio; CI = confidence interval.

chronic kidney disease and non-ST-segment elevation acute coronary syndromes.²¹⁻²³ However, patients with moderate to severe chronic kidney disease were excluded from these trials. Until randomized controlled trials include patients with severe renal impairment, the true risks and benefits of antithrombotic and antiplatelet medical therapies in this population will not be fully known.

In this analysis, we found that patients with moderate to severe chronic kidney disease are less likely to receive cardiac catheterizations or revascularization procedures. These patients are more likely to have had previous coronary artery bypass grafting or percutaneous coronary intervention, multivessel disease, or complex plaque morphology when compared with patients with normal renal function, which may contribute to this treatment disparity.²⁴ In addition, the fear of contrast-induced nephropathy likely contributes to a reluctance to perform cardiac catheterizations in patients with renal dysfunction. Patients with a creatinine clearance less than 60 mL/min are at high risk for developing contrast-induced nephropathy, which is associated with a 15-fold increased risk of adverse cardiac events.²⁵ Patients with chronic kidney disease undergoing primary percutaneous coronary intervention also have lower success rates and higher rates of restenosis compared with patients without chronic kidney disease.²⁶

The effectiveness of revascularization procedures in improving clinical outcomes among patients with chronic kidney

disease is not clearly known because most studies have been observational or retrospective in nature. When compared with either medical therapy alone or coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty has been shown to improve,²⁷ worsen,²⁸⁻³⁰ or have no effect on survival³¹ in patients with chronic kidney disease. The choice of the optimal revascularization therapy may be based on the severity of renal impairment.³¹ Improved techniques and the development of coronary artery stents have improved procedural success rates and made percutaneous coronary intervention a more viable option in patients with chronic kidney disease.²⁶ In addition, a subanalysis of the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTIC)-Thrombolysis In Myocardial Infarction (TIMI) 18 study showed that aggressive early invasive management decreases the risk of death, nonfatal acute myocardial infarction, and acute coronary syndromes rehospitalizations at 30 days and 6 months in patients with mild to moderate chronic kidney disease.³² With the development of new revascularization technologies and preventive measures for contrast-induced nephropathy,^{33,34} the benefits of invasive strategies most likely outweigh the risks of contrast-induced nephropathy in patients with chronic kidney disease and non-ST-segment elevation acute coronary syndromes. However, the practice patterns observed in our analysis do not reflect these recent findings.

Table 4 Discharge Medications and Recommendations

Discharge Treatment	CKD % (n = 6560)	Non-CKD % (n = 38 783)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Aspirin	86.9	90.7	0.66 (0.61-0.73)	0.82 (0.75-0.89)
Beta-blocker	84.7	83.8	1.00 (0.92-1.09)	1.01 (0.93-1.10)
Clopidogrel*	46.5	56.9	0.68 (0.64-0.72)	0.87 (0.82-0.93)
ACE inhibitor†	59.8	61.1	0.92 (0.84-1.00)	0.76 (0.69-0.83)
Lipid-lowering agent, any‡	79.1	80.6	0.87 (0.79-0.96)	0.93 (0.84-1.04)
Smoking cessation counseling§	48.4	66.6	0.53 (0.45-0.61)	0.70 (0.60-0.81)
Dietary modifications	69.8	73.5	0.83 (0.77-0.88)	0.94 (0.88-1.00)
Cardiac rehabilitation referral	31.6	42.7	0.65 (0.60-0.70)	0.84 (0.78-0.90)

CKD = moderate to severe chronic renal insufficiency; OR = odds ratio; CI = confidence interval; ACE = angiotensin-converting enzyme.

*Among patients without interventional procedures.

†For patients with congestive heart failure, ejection fraction <40%, diabetes mellitus, or hypertension.

‡For patients with history of hyperlipidemia or measured low-density-lipoprotein cholesterol >100 mg/dL.

§For patients with history of current smoking only.

||For patients with non-ST elevation myocardial infarction only.

Table 5 Elimination of Antiplatelet and Antithrombotic Medications

Medication	Dose Adjustment Required?	Comments
Aspirin	*	Precaution in patients with severe chronic kidney disease
Clopidogrel	No	No difference in bleeding times between healthy patients and patients with chronic kidney disease
Enoxaparin	Yes	Dose adjustment needed in patients with CrCl <30 mL/min
Eptifibatid	Yes	For serum creatinine between 2 and 4 mg/dL, bolus should be decreased to 135 μ g/kg, and infusion rate should be decreased to 0.5 \cdot μ g \cdot kg min. No data exist for serum creatinines >4 mg/dL.
Tirofiban	Yes	For CrCl <30 mL/min, infusion rate should be halved.
Abciximab	No	

Recommendations on dose adjustments on antiplatelet and antithrombotic medications based on Fernandez et al.³⁷

CrCl = creatinine clearance.

*No recommendations found. Fernandez et al 2003³⁷ and the *Physicians' Desk Reference*.³⁸

The decreased use of smoking cessation counseling, dietary modification, and cardiac rehabilitation referral in patients with moderate to severe chronic kidney disease is an intriguing finding. These recommendations pose little risk and cost to the patient, but have potential health benefits. The reason for this observation is unclear, but provides additional evidence that therapeutic nihilism does occur in this high-risk patient group.

LIMITATIONS

Moderate to severe chronic kidney disease was treated as a dichotomous variable; actual serum creatinine values or proteinuria were not recorded, making it impossible to assess the impact of the varying degrees of chronic kidney disease on treatment and outcomes. Similarly, dialysis status was not recorded. Previous studies have reported that only 5.0% to 13.1% of patients with moderate chronic kidney disease to kidney failure are on dialysis.^{2,3} As a result, the presence of patients on dialysis in our study has the potential to have a significant effect on our findings because postmyocardial infarction mortality rates worsen with decreasing kidney function.^{3,8} However, Beattie and colleagues² found that patients on dialysis who had myocardial infarction were less likely to die in the hospital (adjusted relative risk 5.4) when compared with patients without dialysis with a corrected creatinine clearance of less than 46.2 mL/min/72 kg (adjusted relative risk 8.8). As a result, the true effect of patients on dialysis on our findings is unclear. Selection bias may have been introduced by the exclusion of patients from hospitals without full-service revascularization capabilities and of patients who were transferred to other hospitals. These exclusions also may limit our ability to generalize our findings to smaller or nontertiary care hospitals. Misclassification bias may also have occurred, because the diagnosis of non-ST-segment elevation acute coronary syndromes is difficult in this patient population. Elevated cardiac biomarkers have been reported in asymptomatic patients on dialysis,^{35,36} especially cardiac troponin T.³⁷ However, more than 80% of the hospitals predominantly tested for cardiac troponin I. We did not record bleeding events because no standardized bleeding definition has been validated in ob-

servational studies, and bleeding events are often poorly documented in medical records. We did not record hematocrit, so we could not characterize the severity of blood loss; instead we defined bleeding events by the need for transfusion. Because patients with moderate to severe chronic kidney disease are more likely to have baseline anemia and are routinely transfused, this analysis may have been confounded by the use of transfusions to characterize bleeding complications. We also did not record whether patients were taking an aldosterone receptor blocker, and this may explain why angiotensin-converting enzyme inhibitors were less commonly used in patients with moderate to severe chronic kidney disease. In addition, we did not consider functional limitations for determining the proportion of patients receiving cardiac rehabilitation.

CONCLUSIONS

Patients with moderate to severe chronic kidney disease and non-ST-segment elevation acute coronary syndromes are at higher risk for death, blood transfusions not related to coronary artery bypass grafting, and cardiogenic shock. Despite these high-risk characteristics, patients with moderate to severe chronic kidney disease are less likely to be treated with antithrombotics, antiplatelets, and invasive procedures. Lack of adherence to the American College of Cardiology/American Heart Association guidelines for non-ST-segment elevation acute coronary syndromes is likely because of the fear of an increased bleeding risk and contrast-induced nephropathy in patients with moderate to severe chronic kidney disease. Recent evidence suggests that low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, and early invasive strategies are beneficial in patients with moderate to severe chronic kidney disease and non-ST-segment elevation acute coronary syndromes, but our current observations do not reflect universal acceptance of these findings. Additional randomized controlled trials specifically evaluating patients with moderate to severe chronic kidney disease are needed to delineate the optimal therapeutic approach for these high-risk patients. Low-risk discharge interventions such as smoking cessation counseling, dietary modification, and cardiac rehabilitation occurred

less often in patients with moderate to severe chronic kidney disease, most likely representing therapeutic nihilism.

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