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Associations Between Chronic Kidney Disease and Outcomes With Use of Prasugrel Versus Clopidogrel in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

A Report From the PROMETHEUS Study

Usman Baber, MD, MS,[a] Jaya Chandrasekhar, MBBS, MS,[a] Samantha Sartori, PhD,[a] Melissa Aquino, MS,[a] Annapoorna S. Kini, MBBS,[b] Samir Kapadia, MD,[c] William Weintraub, MD,[d] Joseph B. Muhlestein, MD,[e] Birgit Vogel, MD,[a] Michela Faggioni, MD,[a] Serdar Farhan, MD,[a] Sandra Weiss, MD,[d] Craig Strauss, MD,[f] Catalin Toma, MD,[g] Anthony DeFranco, MD,[h] Brian A. Baker, PharmD,[i] Stuart Keller, BS Pharm,[j] Mark B. Effron, MD,[j,k] Timothy D. Henry, MD,[l] Sunil Rao, MD,[m] Stuart Pocock, PhD,[n] George Dangas, MD, PhD,[b] Roxana Mehran, MD[a]

ABSTRACT

OBJECTIVES This study sought to compare clinical outcomes in a contemporary acute coronary syndrome (ACS) percutaneous coronary intervention (PCI) cohort stratified by chronic kidney disease (CKD) status.

BACKGROUND Patients with CKD exhibit high risks for both thrombotic and bleeding events, thus complicating decision making regarding antiplatelet therapy in the setting of ACS.

METHODS The PROMETHEUS study was a multicenter observational study comparing outcomes with prasugrel versus clopidogrel in ACS PCI patients. Major adverse cardiac events (MACE) at 90 days and at 1 year were defined as a composite of death, myocardial infarction, stroke, or unplanned revascularization. Clinically significant bleeding was defined as bleeding requiring transfusion or hospitalization. Cox regression multivariable analysis was performed for adjusted associations between CKD status and clinical outcomes. Hazard ratios for prasugrel versus clopidogrel treatment were generated using propensity score stratification.

RESULTS The total cohort included 19,832 patients, 28.3% with and 71.7% without CKD. CKD patients were older with greater comorbidities including diabetes and multivessel disease. Prasugrel was less often prescribed to CKD versus non-CKD patients (11.0% vs. 24.0%, respectively; $p < 0.001$). At 1 year, CKD was associated with higher adjusted risk of MACE (1.27; 95% confidence interval: 1.18 to 1.37) and bleeding (1.46; 95% confidence interval: 1.24 to 1.73). Although unadjusted rates of 1-year MACE were lower with prasugrel versus clopidogrel in both CKD (18.3% vs. 26.5%; $p < 0.001$) and non-CKD (10.9% vs. 17.9%; $p < 0.001$) patients, associations were attenuated after propensity stratification. Similarly, unadjusted differences in 1-year bleeding with prasugrel versus clopidogrel (6.0% vs. 7.4%; $p = 0.18$ in CKD patients; 2.6% vs. 3.5%; $p = 0.008$ in non-CKD patients) were not significant after propensity score adjustment.

CONCLUSIONS Although risks for 1-year MACE were significantly higher in ACS PCI patients with versus without CKD, prasugrel use was 50% lower in patients with renal impairment. Irrespective of CKD status, outcomes associated with prasugrel use were not significant after propensity adjustment. These data highlight the need for randomized studies evaluating the optimal antiplatelet therapy in CKD patients with ACS. (J Am Coll Cardiol Intv 2017;10:2017–25)

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CKD = chronic kidney disease

DES = drug-eluting stent(s)

GPI = glycoprotein 2b3a inhibitor

HPR = high platelet reactivity

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

ST = stent thrombosis

Patients with chronic kidney disease (CKD) exhibit high risk for both thrombotic and bleeding events following percutaneous coronary intervention (PCI), particularly in the setting of acute coronary syndrome (ACS) (1–4). CKD is associated with high platelet reactivity (HPR) in vivo (5,6), greater systemic comorbidities, and extensive angiographic disease (5,7). In this context, potent $P2Y_{12}$ inhibitor therapies may be especially beneficial in this high-risk patient population for early and medium-term reductions in thrombotic events.

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Concomitantly with ischemic risk, CKD patients also have heightened risk for bleeding (8), associated with greater morbidity and mortality (9–11). Thus, decision making for potent antithrombotic therapies is challenging in these patients and the best strategy is currently unclear. Although guidelines recommend use of bare-metal stents and minimum 1 month of dual antiplatelet therapy in patients at prohibitive risk for bleeding, specific recommendations for antiplatelet therapy in CKD patients undergoing PCI are currently lacking (12). We therefore examined the patient characteristics, treatment differences, and outcomes in patients with and without CKD undergoing contemporary ACS PCI from the PROMETHEUS study, an observational study of ACS patients undergoing PCI (13).

METHODS

STUDY SAMPLE. The PROMETHEUS study was a multicenter observational study conducted between January 1, 2010, and June 30, 2013, in 8 U.S. centers that maintained a prospective PCI database with 1-year follow-up (13). The study was approved by the ethics committees of all centers. The data points for extraction were jointly agreed on by the study investigators and followed standardized definitions of the National Cardiovascular Data Registry Catheterization PCI database. Data management, quality checks, statistical analyses, and results reporting were the responsibility of the data coordinating center at the Icahn School of Medicine at Mount Sinai (New York, New York). The sponsors did not have access to data.

The study sample comprised all ACS patients undergoing PCI and treated with dual antiplatelet therapy using aspirin and either prasugrel or clopidogrel. Of the total study population (n = 19,914), glomerular filtration rate values were available in 19,832 patients included in this analysis. The analysis was stratified for the presence of CKD, defined as glomerular filtration rate <60 ml/min/1.73 m^2 using the CKD-Epidemiology collaboration definition (14). The PCI procedure and related management was per standard of care and at the discretion of the treating physicians. Similarly, selection of patients for prasugrel or clopidogrel was directed by the treating physician.

ENDPOINTS AND DEFINITIONS. The primary endpoint of the main study was 90-day major adverse cardiac events (MACE), a composite of death, myocardial infarction (MI), stroke, or unplanned revascularization. Secondary endpoints included the individual components of the primary endpoint, stent thrombosis (ST), and clinically significant bleeding, which was defined as bleeding needing hospitalization or transfusion. Study endpoints were site reported in each center's database and were not adjudicated.

From the [a]Division of Cardiology, Icahn School of Medicine at Mount Sinai, New York, New York; [b]Division of Cardiology, Mount Sinai Hospital, New York, New York; [c]Division of Cardiology, Cleveland Clinic, Cleveland, Ohio; [d]Division of Cardiology, Christiana Care Health System, Newark, Delaware; [e]Division of Cardiology, Intermountain Heart Institute, Salt Lake City, Utah; [f]Division of Cardiology, Minneapolis Heart Institute, Minneapolis, Minnesota; [g]Division of Cardiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [h]Division of Cardiology, Aurora Cardiovascular Services, Milwaukee, Wisconsin; [i]Daiichi Sankyo, Parsippany, New Jersey; [j]Eli Lilly and Company, Indianapolis, Indiana; [k]Division of Cardiology, John Ochsner Heart and Vascular Center, Ochsner Medical Center, New Orleans, Louisiana; [l]Division of Cardiology, Cedars-Sinai Heart Institute, Los Angeles, California; [m]Division of Cardiology, Duke University, Durham, North Carolina; and the [n]London School of Hygiene and Tropical Medicine, London, United Kingdom. The PROMETHEUS study was sponsored and funded by Daiichi Sankyo and Eli Lilly and Company. Dr. Kini has served on the Speakers Bureau of the American College of Cardiology; and has received consulting fees from WebMD. Mr. Keller is a salaried employee of and owns stock in Eli Lilly and Company. Dr. Effron is a former employee of and currently owns stock in Eli Lilly and Company. Mr. Baker is an employee of Daiichi Sankyo. Dr. Henry has received research grant support from Eli Lilly and Daiichi Sankyo. Dr. Mehran has received institutional grant support from The Medicines Company, Bristol-Myers Squibb/Sanofi, and Eli Lilly and Company/Daiichi Sankyo; and has served as a consultant to Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, Janssen Pharmaceuticals, Regado Biosciences, Maya Medical, Merck & Co., and The Medicines Company. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Baber and Chandrasekhar contributed equally to this work.

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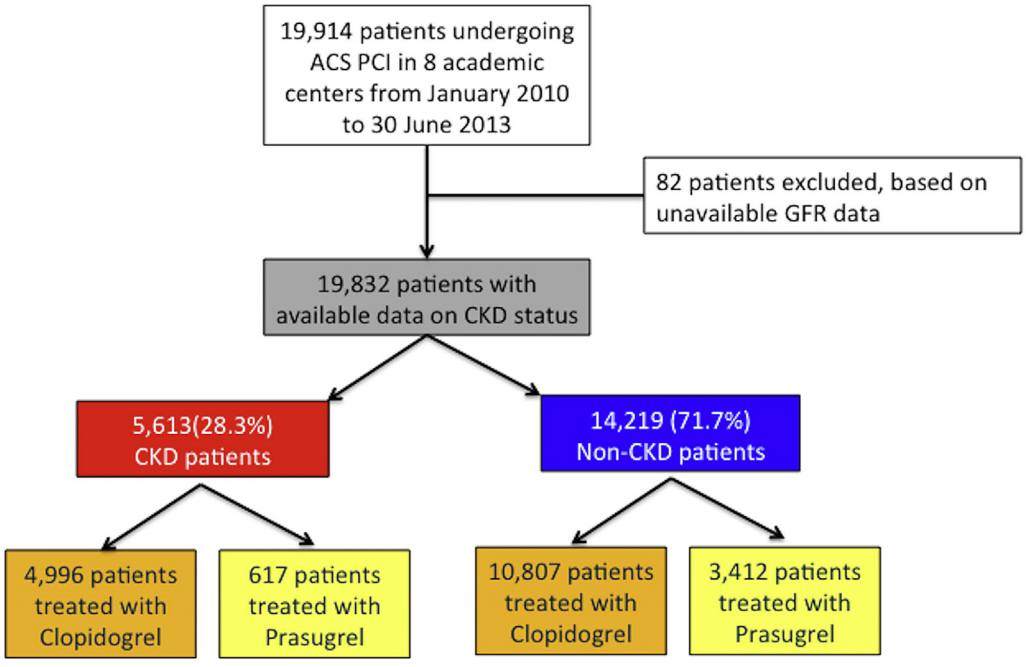
FIGURE 1 Study Flow



ACS = acute coronary syndrome(s); CKD = chronic kidney disease; GFR = glomerular filtration rate; PCI = percutaneous coronary intervention.

For this analysis we evaluated the clinical endpoints at 90 days and at 1 year.

STATISTICAL ANALYSIS. Groups for comparison were patients with and without CKD. Categorical data are presented as numbers and percentages and compared using the chi-square test. Continuous data are presented as mean ± SD and compared using the parametric Student *t* test. We also examined the use of prasugrel by CKD status in select high thrombotic risk indications including ST-segment elevation MI, diabetes, patients receiving stent diameter <3.0 mm, and patients with ≥2 vessels treated (15,16). Event rates are presented using the Kaplan Meier method and compared using the log-rank test. Hazard ratios and confidence intervals were generated for adjusted risks of 90-day and 1-year outcomes in CKD patients versus non-CKD patients (reference: non-CKD patients) with multivariable Cox regression models using the following variables: age, African American or other race, body mass index, diabetes, hypertension, hemoglobin, previous PCI, coronary artery disease presentation, multivessel disease, stent type, stent length, prasugrel use, bivalirudin use, and center. To account for the hierarchical nature of our data (i.e., patients within centers), we repeated our primary analyses by including center as a random effect, yielding very similar results to our main findings (data not shown). Hazard ratios and confidence intervals were generated for adjusted risks of 90-day and 1-year outcomes associated with prasugrel use (reference: clopidogrel) using propensity score stratification adjustment methods for the propensity to receive prasugrel. All data were analyzed using Stata version 14.0 (StataCorp, College Station, Texas) or SAS version 9.4 (SAS Institute, Cary, North Carolina); p values <0.05 were considered significant.

RESULTS

The study sample comprised 19,832 patients, 28.3% (n = 5,613) with CKD and 71.7% (n = 14,219) without CKD (Figure 1). Tables 1 and 2 show the baseline characteristics of the groups. CKD patients were more often women with significantly higher prevalence of several baseline comorbidities including older age, diabetes, anemia, and prior revascularization compared with non-CKD patients. Procedurally, CKD patients were more likely to have multivessel disease and receive bare-metal stents and bivalirudin, but less likely to be treated with glycoprotein 2b3a inhibitors (GPIs) than were

TABLE 1 Baseline Characteristics

	CKD (n = 5,613)	Non-CKD (n = 14,219)	p Value
Age, yrs	71.97 ± 10.84	61.41 ± 11.49	<0.0001
Female	2,390 (42.6)	3883 (27.3)	<0.0001
African American	598 (10.7)	1527 (10.7)	0.8611
BMI, kg/m^2	29.52 ± 6.17	30.08 ± 6.17	<0.0001
Diabetes	2,757 (49.1)	4783 (33.6)	<0.0001
Diabetes on insulin	1,182 (21.1)	1335 (9.4)	<0.0001
Hypertension	5,136 (91.5)	11181 (78.6)	<0.0001
Dyslipidemia	4,900 (87.3)	11719 (82.4)	<0.0001
Smoking	788 (14.0)	4197 (29.5)	<0.0001
Prior MI	2,060 (36.7)	3872 (27.2)	<0.0001
Prior PCI	1,562 (27.8)	3446 (24.2)	<0.0001
Prior CABG	1,359 (24.2)	2052 (14.4)	<0.0001
Prior cerebrovascular disease	1,079 (19.2)	1293 (9.1)	<0.0001
Prior CHF	1,864 (33.2)	2374 (16.7)	<0.0001
Left ventricular ejection fraction, %	48.99 ± 14.96	52.69 ± 12.46	<0.0001
Prior PAD	1,109 (19.8)	1307 (9.2)	<0.0001
Anemia	1,591 (28.3)	1286 (9.0)	<0.0001
CAD presentation			<0.0001
Unstable angina	3,156 (56.2)	8016 (56.4)	
STEMI	1,655 (29.5)	3739 (26.3)	
NSTEMI	802 (14.3)	2463 (17.3)	

Values are mean ± SD or n (%).

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Procedural Characteristics

	CKD (n = 5,613)	Non-CKD (n = 14,219)	p Value
Multivessel disease	2,751 (49.0)	5,633 (39.6)	<0.0001
PCI vessel			
Left main	280 (5.0)	386 (2.7)	<0.0001
Left anterior descending	2,457 (43.8)	6,407 (45.1)	0.1012
Circumflex	1,739 (31.0)	4,128 (29.0)	0.0067
Right coronary artery	1,894 (33.7)	4,869 (34.2)	0.5047
At least 1 B2/C type lesion	3,798 (67.7)	9,747 (68.5)	0.7939
At least 1 lesion with moderate/severe calcification	1,005 (17.9)	1,752 (12.3)	<0.0001
At least 1 bifurcation lesion	607 (10.8)	1,504 (10.6)	0.4064
Total stent length, mm	30.53 ± 21.27	30.73 ± 20.59	0.5519
Minimum stent diameter, mm	2.95 ± 0.50	2.97 ± 0.50	0.0025
Stent type			
At least 1 first-generation DES	710 (12.6)	2,042 (14.4)	0.0017
At least 1 second-generation DES	3,676 (65.5)	9,858 (69.3)	<0.0001
At least 1 BMS	1,505 (26.8)	2,973 (20.9)	<0.0001
Procedural anticoagulation			
Bivalirudin	4,143 (73.8)	10,258 (72.1)	0.0180
GPI	1,044 (18.6)	3,503 (24.6)	<0.0001
LMWH	60 (1.1)	147 (1.0)	0.9404

Values are n (%) or mean ± SD.

BMS = bare-metal stent(s); DES = drug-eluting stent(s); GPI = glycoprotein 2b3a inhibitor; LMWH = low molecular weight heparin; other abbreviations as in Table 1.

non-CKD patients. There were no differences in PCI indication and over half of both groups presented with unstable angina.

Approximately 11% of CKD patients and 24.0% of non-CKD patients received prasugrel following PCI. When frequency of prasugrel use was evaluated by CKD status in special patient populations with diabetes, ST-segment elevation MI presentation, stent diameter <3.0 mm, and ≥2 vessels treated, we observed that regardless of these high thrombotic risk indications, prasugrel use was uniformly lower in CKD compared with non-CKD patients (**Figure 2**).

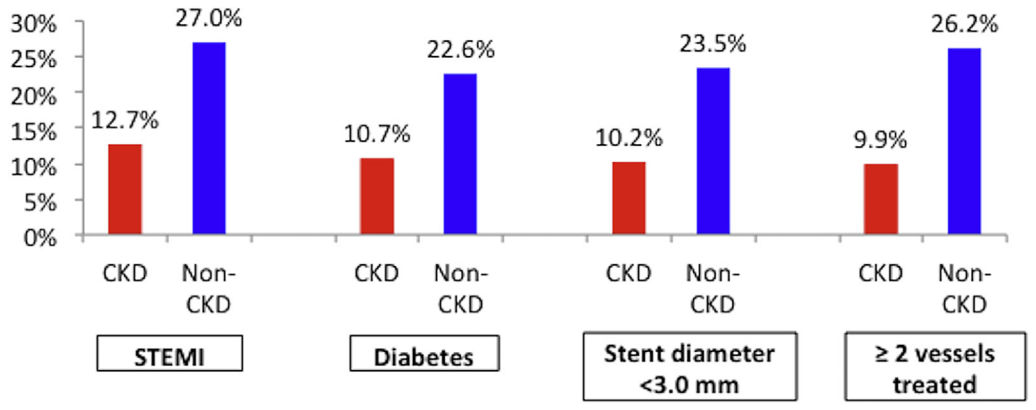
At both 90 days and 1 year CKD patients had a significantly greater incidence of ischemic and bleeding outcomes (**Table 3**). After multivariable adjustment for potential confounders, the presence of CKD was associated with greater risk for MACE, death, MI, and bleeding at both 90 days and at 1 year. There were no differences in the incidence of revascularization and ST between the groups. To understand the thrombotic risk associated with MI (NSTEMI and STEMI) versus unstable angina presentation, we examined for differences in 1-year MI outcomes separately in CKD and non-CKD groups. Unadjusted rates of 1-year MI were significantly greater in patients with MI versus unstable angina presentation, regardless of CKD status. No interaction was observed for risk of 1-year MI by CKD status and PCI presentation (Online Figure 1).

When examined by GFR category, a stepwise increase in risk gradient was noted for adjusted risk of 1-year MACE, MI, and death with GFR 30 to 59 ml/min/1.73 m^2 and GFR <30 ml/min/1.73 m^2, compared to GFR ≥60 ml/min/1.73 m^2 (Online Figure 2).

Online Tables 1 and 2 show the baseline characteristics by CKD status and thienopyridine type. Prasugrel-treated CKD patients were more often younger, men, and non-African American with lower prevalence of prior revascularization. In both CKD and non-CKD groups, prasugrel patients were more likely to receive GPIs and drug-eluting stents (DES). At 90 days and at 1-year, regardless of CKD status, prasugrel use was associated with lower incidence of ischemic events compared with clopidogrel use without greater bleeding (**Tables 4 and 5**).

On propensity score-stratified analysis, prasugrel versus clopidogrel use was associated with a trend toward lower MACE at 90 days and significantly lower MACE at 1-year in non-CKD patients but not in CKD patients, without evidence of interaction (**Figure 3**). A borderline interaction was observed for 1-year MI—prasugrel was associated with lower MI in non-CKD patients but not in CKD patients

FIGURE 2 Frequency of Prasugrel Use in High-Risk Patient Subgroups



Frequency of prasugrel use among chronic kidney disease (CKD) and non-CKD patients in the following patient groups: ST-segment elevation myocardial infarction (STEMI), diabetes, stent diameter <3.0 mm, ≥ 2 vessels treated.

(p for interaction = 0.05). There were no adjusted differences in bleeding by drug regardless of CKD status.

DISCUSSION

The main findings of the present report are as follows: 1) CKD patients undergoing ACS PCI have greater baseline comorbidities and significantly higher adjusted risks for 90-day and 1-year MACE, MI, and bleeding but not revascularization or ST compared with those without renal impairment; 2) despite the higher baseline ischemic risk, the frequency of prasugrel use was 50% lower in CKD patients versus non-CKD patients, suggesting that clinical decision making with respect to the potency of antiplatelet pharmacotherapy is influenced to a larger extent by the potential for bleeding harm versus therapeutic efficacy; and 3) the adjusted treatment effect of prasugrel versus clopidogrel on both ischemic and bleeding events at 90 days and 1 year was uniform irrespective of CKD status.

RISK ASSESSMENT AND PRASUGREL PRESCRIPTION. Aligned with prior reports, this analysis shows that CKD patients undergoing PCI are more often women and have greater comorbidities including older age, lower body mass index, diabetes, anemia, prior revascularization, and other vasculopathy (3,17,18). Others studies have shown CKD to be a marker (5) or even an independent predictor (6) of HPR, linked with an increase in thrombotic outcomes (19). In the ADAPT DES (Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents) study, patients with creatinine clearance <30 ml/min had ~20% higher prevalence of HPR compared with non-CKD patients (5). Angiographically, CKD patients in our cohort had more extensive, complex, or calcified disease including higher prevalence of obstructive left main stem disease.

Despite these higher-risk features, prasugrel use was 50% lower in CKD compared with non-CKD patients in this study, a practice pattern that may be attributable to several factors. First, concerns for

TABLE 3 Clinical Outcomes at 90 Days and at 1 Year in CKD and Non-CKD Patients

	CKD (n = 5,613)	Non-CKD (n = 14,219)	p Value	Adjusted Hazard Ratio (95% CI)*	p Value
90 days					
MACE	633 (12.0)	991 (7.5)	<0.001	1.25 (1.11–1.40)	<0.001
Death	252 (4.9)	176 (1.4)	<0.001	1.59 (1.28–1.99)	<0.001
Myocardial infarction	236 (4.5)	397 (3.0)	<0.001	1.25 (1.03–1.52)	0.021
Unplanned revascularization	211 (4.2)	511 (4.0)	0.618	1.08 (0.90–1.31)	0.403
Bleeding	242 (4.6)	270 (2.0)	<0.001	1.51 (1.23–1.85)	<0.001
Definite/probable ST	15 (0.3)	45 (0.3)	0.555	0.84 (0.44–1.62)	0.603
1 yr					
MACE	1,284 (25.6)	1,999 (16.2)	<0.001	1.27 (1.18–1.37)	<0.001
Death	560 (11.4)	399 (3.3)	<0.001	1.59 (1.37–1.85)	<0.001
Myocardial infarction	387 (7.9)	584 (4.6)	<0.001	1.36 (1.17–1.58)	<0.001
Unplanned revascularization	539 (11.7)	1,257 (10.5)	0.044	1.07 (0.95–1.20)	0.286
Bleeding	359 (7.3)	410 (3.3)	<0.001	1.46 (1.24–1.73)	<0.001
Definite/probable ST	24 (0.5)	64 (0.5)	0.846	1.00 (0.59–1.70)	0.994

Values are n (%). Events rates are calculated as Kaplan-Meier estimates. *Adjusted for the following covariates: age, race, BMI, diabetes, hypertension, hemoglobin, previous PCI, CAD presentation, multivessel disease, bivalirudin use, stent type, stent length, center, and prasugrel use. Reference group: non-CKD patients.

CI = confidence interval; MACE = major adverse cardiovascular event(s); ST = stent thrombosis; other abbreviations as in Table 1.

TABLE 4 90-Day Clinical Outcomes Stratified by CKD Status and Thienopyridine Type

	CKD			Non-CKD			
	Prasugrel (n = 617)	Clopidogrel (n = 4,996)	Propensity-Stratified Hazard Ratio (95% CI)	Prasugrel (n = 3,412)	Clopidogrel (n = 10,807)	Propensity-Stratified Hazard Ratio (95% CI)	p Value for Interaction
MACE	47 (8.2)	586 (12.5)	1.07 (0.78–1.47)	168 (5.3)	823 (8.3)	0.87 (0.72–1.03)	0.973
Death	11 (2.0)	241 (5.2)	0.93 (0.50–1.73)	11 (0.4)	165 (1.7)	0.49 (0.26–0.92)	0.158
Myocardial infarction	17 (2.9)	219 (4.7)	1.10 (0.66–1.87)	56 (1.7)	341 (3.4)	0.80 (0.59–1.09)	0.483
Unplanned revascularization	22 (4.0)	189 (4.2)	1.17 (0.72–1.89)	116 (3.7)	395 (4.1)	1.04 (0.83–1.31)	0.890
Bleeding	21 (3.6)	221 (4.7)	1.06 (0.66–1.72)	53 (1.7)	217 (2.2)	1.02 (0.73–1.42)	0.901
Definite/probable ST	1 (0.2)	14 (0.3)	0.50 (0.06–4.29)	14 (0.4)	31 (0.3)	0.98 (0.49–1.98)	0.460

Values are n (%) unless otherwise indicated.
Abbreviations as in Tables 1 and 3.

therapeutic risk may be larger than the potential for therapeutic benefit in certain high-risk populations, including those with renal impairment. Similar findings, for example, have been reported for women and elderly patients after PCI (20,21). Second, clinical reluctance may be influenced by the dearth of randomized data showing the magnitude of benefit and harm with use of potent antiplatelet therapy in CKD patients. Subgroup analyses from randomized trials have produced conflicting and inconsistent results, further complicating decision making in this regard (22–24). Third, traditional approaches toward lowering thrombotic risk, such as lipid lowering with statins, may yield less benefit in the unique atherosclerotic phenotype present in patients with moderate to advanced CKD (25).

CLINICAL OUTCOMES WITH CKD. Our findings of greater adjusted risks for MACE and MI in CKD patients are consistent with previous observations (3,26). Pathophysiologically, accelerated atherosclerosis and thrombotic events in CKD are the culmination of several factors such as heightened inflammatory state, oxidative stress, endothelial dysfunction, and HPR, including non-$P2Y_{12}$ pathway-mediated platelet activation (27–29). Interestingly, there were no differences by CKD status in the rates of revascularization or ST in our study, where more than 70% of patients received second-generation DES. This is in line with other data with the use of new generation stents (26). Our observations also consolidate existing published data on higher bleeding risk in CKD patients. This may be the result of ineffective platelets, anemia, and thrombocytopenia in this mostly elderly and female patient population (8,30,31). Interestingly, assessment of platelet reactivity may allow balanced selection of CKD patients at greater ischemic risk who may benefit from potent therapies such as prasugrel without the tradeoff of greater bleeding (5).

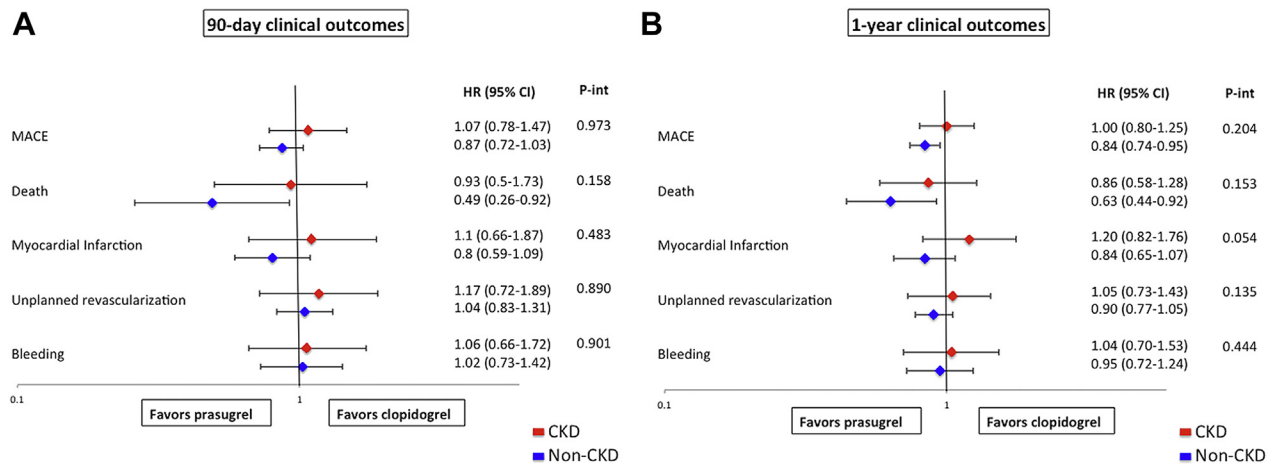
The excess and comparable risks for both thrombotic and bleeding outcomes associated with CKD are also consistent with emerging prediction algorithms for provision of prolonged or more potent antiplatelet therapy after PCI. Yeh et al. (16) for example found that hazards for both ischemic and hemorrhagic events associated with renal impairment were almost identical in a randomized trial cohort. Similar findings were reported from an observational registry (3). In aggregate, these results, in concert with our findings, highlight the

TABLE 5 1-Year Clinical Outcomes Stratified by CKD Status and Thienopyridine Type

	CKD			Non-CKD			
	Prasugrel (n = 617)	Clopidogrel (n = 4,996)	Propensity-Stratified Hazard Ratio (95% CI)	Prasugrel (n = 3,412)	Clopidogrel (n = 10,807)	Propensity-Stratified Hazard Ratio (95% CI)	p Value for Interaction
MACE	100 (18.3)	1,184 (26.5)	1.00 (0.80–1.25)	330 (10.9)	1,669 (17.9)	0.84 (0.74–0.95)	0.204
Death	28 (5.3)	532 (12.1)	0.86 (0.58–1.28)	33 (1.1)	366 (4.0)	0.63 (0.44–0.92)	0.153
Myocardial infarction	34 (6.3)	353 (8.1)	1.20 (0.82–1.76)	86 (2.8)	498 (5.2)	0.84 (0.65–1.07)	0.054
Unplanned revascularization	55 (10.5)	484 (11.8)	1.05 (0.78–1.43)	243 (8.1)	1,014 (11.3)	0.90 (0.77–1.05)	0.135
Bleeding	33 (6.0)	326 (7.4)	1.04 (0.70–1.53)	78 (2.6)	332 (3.5)	0.95 (0.72–1.24)	0.444
Definite/probable ST	2 (0.4)	22 (0.5)	0.52 (0.11–2.45)	21 (0.7)	43 (0.5)	1.07 (0.60–1.91)	0.295

Values are n (%) unless otherwise indicated. Events rates are calculated as Kaplan-Meier estimates. Reference = clopidogrel.
Abbreviations as in Tables 1 and 3.

FIGURE 3 Adjusted Hazard for 90-Day and 1-Year Clinical Events With Prasugrel Compared to Clopidogrel Stratified by Chronic Kidney Disease



(A) 90-day propensity adjusted outcomes by chronic kidney disease (CKD) status and thienopyridine type. **(B)** 1-year propensity adjusted outcomes by CKD status and thienopyridine type. CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event(s); P-int = p for interaction.

relevance of bleeding concerns as a major determinant of clinical decision making toward provision of prasugrel in CKD patients, even in the setting of ACS.

EFFECT OF ANTIPLATELET THERAPY IN CKD PATIENTS. Pharmacodynamic studies suggest that CKD patients have profound suppression of platelet reactivity and reduction in HPR status with prasugrel compared with clopidogrel (23,32,33). However, clinical findings have been conflicting. The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) study showed similar relative risk reductions in the primary MACE endpoint with prasugrel versus clopidogrel in patients with and without CKD (22). On the other hand, the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial did not show superior outcomes with prasugrel compared with clopidogrel in medically managed ACS patients irrespective of CKD status, despite significant reductions in platelet reactivity with prasugrel in all stages of CKD (23,34). Nevertheless, the findings of the TRILOGY ACS trial may not be applicable to ACS patients undergoing PCI.

Furthermore, our study postdates these trials by a few years and comparatively our patients had greater use of second-generation DES and bivalirudin along with lower use of GPIs, which might have contributed to the different outcomes. Nevertheless, we did not find differences by CKD status in the treatment effect of prasugrel versus clopidogrel. First, this may be due to lower rate of prasugrel use in CKD patients, thereby limiting the sample size to detect an interaction by thienopyridine type. Second, CKD patients selected for prasugrel were healthier and may have lower platelet reactivity than clopidogrel-treated patients, thereby not being positioned to derive benefit from potent inhibition, after adjustment for potential confounders. Third, CKD patients have non-$P2Y_{12}$ pathway-mediated HPR, endothelial dysfunction, and a proinflammatory milieu in ACS, which remains unchallenged despite potent $P2Y_{12}$ inhibition (5,8,35). Finally, we did not record episodes of antiplatelet cessation or switching events beyond discharge, which might have differently impacted outcomes.

STUDY STRENGTHS AND LIMITATIONS. This analysis is the largest report of CKD patients treated with prasugrel or clopidogrel in contemporary ACS PCI–including a high volume of DES use, bivalirudin for anticoagulation, and lower GPI use. Importantly, however, these findings are drawn from observational registry data, which were not centrally adjudicated. Bleeding was defined using the study definition for clinically significant bleeding rather than with validated bleeding scales, and may be subject to under-reporting. Similarly, the effect of cessation and switching of therapies is relevant but was not collected, and therefore could not be used to support our results.

CONCLUSIONS

CKD patients undergoing contemporary PCI for ACS have significantly greater adjusted risks for 90-day and 1-year MACE and bleeding compared with non-CKD patients. Nevertheless, use of prasugrel was significantly lower in CKD patients, suggesting a greater emphasis on bleeding harm as compared with therapeutic efficacy with respect to provision of prasugrel versus clopidogrel. After adjustment, there were no differences in the associations between prasugrel and outcomes compared with clopidogrel. These data suggest the need for randomized trial evidence to guide therapy in CKD patients with ACS undergoing PCI.

ADDRESS FOR CORRESPONDENCE: Dr. Roxana Mehran, The Zena and Michael A. Wiener Cardiovascular Institute, The Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, New York 10029-6574. E-mail: roxana.mehran@mountsinai.org.

PERSPECTIVES

WHAT IS KNOWN? Patients with CKD exhibit high risks for both thrombotic and bleeding events, complicating decision making regarding antiplatelet therapy.

WHAT IS NEW? In the PROMETHEUS multicenter observational study of patients undergoing coronary stenting for ACS (n = 19,832), 28.3% patients had CKD. Prasugrel use was 50.0% lower in CKD versus non-CKD patients (11.0% vs. 24.0%; $p < 0.001$). At 1 year, CKD was associated with greater risk of MACE (composite of death, MI, stroke, or unplanned revascularization) (1.27; 95% confidence interval: 1.18 to 1.37) and clinically significant bleeding (1.46; 95% confidence interval: 1.24 to 1.73). Irrespective of CKD status, outcomes with prasugrel use were not significant after propensity adjustment (p for interaction = 0.20).

WHAT IS NEXT? These data indicate the need for randomized data on optimal antiplatelet therapy in CKD patients with ACS.

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APPENDIX For supplemental tables and figures, please see the online version of this article.