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EDITORIAL COMMENT

$P2Y_{12}$ Inhibitors in Patients With Chronic Kidney Disease

The Known Unknown*

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Chronic kidney disease (CKD) is widely prevalent in the United States, is increasing in incidence, and is strongly associated with increased cardiovascular mortality and morbidity (1,2). Among registry-based studies, the prevalence of CKD among patients with acute coronary syndromes (ACS) has ranged from 30% to 40%, a proportion that is remarkably higher than that seen in clinical trials (3,4). The exclusion or underrepresentation of patients with CKD in clinical trials results in a relative evidence vacuum and these patients are often treated based on data extrapolated from patients without CKD (5).

Patients with CKD have more extensive coronary artery disease, are less likely to undergo revascularization, and have a worse short- and long-term outcome after undergoing coronary revascularization (3,4,6,7). Although intuitively one would expect more aggressive medical therapy to have a greater impact in these patients, this is particularly challenging with respect to antiplatelet therapy because the presence of CKD is associated with an increase in the risk of both bleeding and thrombotic events. This double jeopardy comes into play when considering the specific choice of $P2Y_{12}$ inhibitor in patients undergoing percutaneous coronary intervention (PCI) for ACS because the more potent agents, ticagrelor and prasugrel, are associated with a reduction in thrombotic events and an increase in bleeding events compared with clopidogrel in the broader population (8,9). It remains unclear whether the presence of CKD impacts the relative risk and benefit of using specific $P2Y_{12}$ inhibitors.

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In this issue of *JACC: Cardiovascular Interventions*, Baber et al. (10) present the results of an observational study comparing the outcomes of patients who underwent PCI for ACS and were discharged on clopidogrel or prasugrel. In this study of 19,832 patients, approximately 28% had CKD defined as glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 using the CKD Epidemiology Collaboration definition and were less likely to receive prasugrel compared with those without CKD (11% vs. 24%). As expected, bleeding and thrombotic events on follow-up were significantly higher in patients with CKD. Use of prasugrel was associated with a lower unadjusted incidence of both thrombotic and bleeding events and these differences were attenuated after propensity-stratified analysis.

The low use of prasugrel among patients with CKD in this study is notable and mirrors prior reports (11). The study also attempts to explore the comparative efficacy and safety of prasugrel and clopidogrel in patients with CKD, but it may be premature to use the results of this study to guide clinical care.

When evaluating a clinical study using propensity score analysis, it is important to assess the methodological approach to ensure that all necessary steps have been taken to minimize bias (12–14). Although the goal of the propensity score is to predict treatment assignment, the overarching objective is to minimize bias so that treatment effects can be estimated with greater precision. First, the

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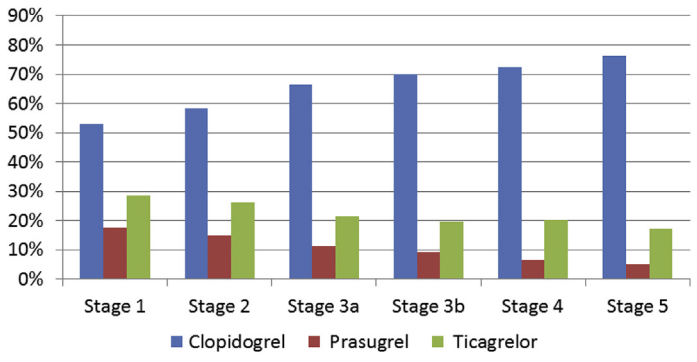
population must be carefully selected: patients who are ineligible for receiving either of the study (exposures) treatments for clinical reasons should be excluded. Failure to follow this elementary step introduces confounding that cannot be adjusted away statistically. Second, the propensity score model should only include variables that are measured before the exposure. The estimated propensity scores are then used to create an observational study and this can be accomplished by a variety of matching techniques (e.g., greedy matching, optimal matching, exact matching). Stratification is a coarsened matching technique that is associated with greater bias but is favored by some because it permits use of almost all available data. The next step involves testing for covariate balance between the 2 treatment groups. Subsequent analysis should account for the matching structure and should be followed by sensitivity testing to assess for unmeasured confounding. The failure to pay attention to these key steps has resulted in a number of studies producing results that violate biological plausibility (e.g., studies demonstrating better survival but no difference in revascularization when comparing drug-eluting with bare-metal stents).

Patients with CKD who were treated with prasugrel in this study were more likely to be younger and less likely to have high-risk features such as anemia, known cerebrovascular disease, prior coronary artery bypass grafting, or history of congestive heart failure. It is not surprising that these patients had better unadjusted survival and lower unadjusted bleeding compared with those patients treated with clopidogrel. However, given the lack of details of the analytical plan, it is uncertain if the lack of difference in any outcome between CKD patients treated with prasugrel or clopidogrel observed in the propensity-adjusted analysis is extant or simply reflects unmeasured confounding.

The results of this study therefore must be viewed in context of prior randomized data. In the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) study, 1,490 (11%) patients had a creatinine clearance of ≤60 ml/min and randomization to prasugrel compared with clopidogrel was associated with a 14% relative risk reduction in the primary endpoint of cardiovascular death, myocardial infarction, and urgent target vessel revascularization (15.1% vs. 17.5%) in this subgroup (8). The data from the PLATO (Platelet Inhibition and Patient Outcomes) trial are more intriguing with a much greater benefit of ticagrelor compared with clopidogrel among patients with CKD defined as a GFR ≤60 ml/min as estimated by the Modification of Diet in Renal Disease equation (an absolute risk reduction [ARR] in the primary endpoint of vascular death, myocardial infarction, and stroke of 6%; relative risk reduction [RRR] 29%) in patients with CKD compared with an ARR of 1.1% (RRR 10%) in those with normal renal function (15). The observed differences were even more striking for total mortality (ARR 5.3%, RRR 36%) in those with CKD compared with an ARR 0.5% (RRR 9%) for those with normal renal function. There were numerically a greater number of major bleeding events with ticagrelor in all patients but the relative safety of the 2 agents was not impacted by renal function.

FIGURE 1 Contemporary $P2Y_{12}$ Inhibitor Choice in CKD Patients Undergoing PCI



The choice of $P2Y_{12}$ inhibitor agent at discharge in patients with different degrees of renal function and undergoing stent-based percutaneous coronary intervention for acute coronary syndromes in 2015 in Michigan (data from Blue Cross Blue Shield of Michigan Cardiovascular Consortium). Stage 1, estimated glomerular filtration rate (eGFR) ≥90 ml/min/1.73 m^2; Stage 2, eGFR 60 to 89 ml/min/1.73 m^2; Stage 3a, eGFR 45 to 59 ml/min/1.73 m^2; Stage 3b, eGFR 30 to 44 ml/min/1.73 m^2; Stage 4, eGFR 15 to 29 ml/min/1.73 m^2; Stage 5, eGFR <15 ml/min/1.73 m^2 or on dialysis.

Results of subgroup analysis should always be considered with healthy skepticism but the strong survival advantage of ticagrelor in this study cannot be completely ignored. In the absence of the data to the contrary, and given the magnitude of the observed differences, it may be prudent to consider ticagrelor as the preferred $P2Y_{12}$ inhibitor in patients with CKD who undergo PCI for ACS while recognizing the limited body of data to support such decision making.

Figure 1 provides a snapshot of the discharge $P2Y_{12}$ inhibitor among patients undergoing stent-based PCI for ACS in Michigan in 2015 (Mr. Milan Seth, personal communication, BMC2, May 26, 2017). Clopidogrel was the predominant $P2Y_{12}$ inhibitor to be prescribed to this cohort, with ticagrelor a distant second, and the use of potent $P2Y_{12}$ inhibitors

declined with increasing severity of renal dysfunction. This would suggest that the subgroup analysis of the PLATO trial has not swayed the clinical community far enough, and in our collective practice the ideal $P2Y_{12}$ inhibitor in patients with CKD remains a known unknown.

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