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Connecting the Cs Coronaries, Creatinine, Compliance, CRUSADE

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Chronic kidney disease (CKD) is highly prevalent in the United States, affecting one in six individuals over the age of 20.¹ Left untreated, CKD can result in end stage renal disease (ESRD) necessitating either hemodialysis or renal transplantation. The National Kidney Foundation, along with the American College of Cardiology (ACC) and the American Heart Association (AHA) recognize CKD as a coronary heart disease (CHD) risk equivalent.^{2, 3} Many of the risk factors for CKD – diabetes, hypertension, and obesity – also underlie coronary artery disease (CAD). Therefore, it should not be surprising that CAD is highly prevalent among CKD patients and accounts for significant morbidity and mortality.⁴⁻⁷ Furthermore, the risk of cardiovascular events, including mortality, correlate with the severity of the CKD.^{4, 8} These findings underlie the importance of aggressively diagnosing and treating CAD in patients with CKD.

The ACC/AHA guidelines for management of patients with acute coronary syndromes (ACS) – both unstable angina / non ST elevation myocardial infarction (MI) and ST elevation MI – are similar for patients with and without CKD, with the exception of the need to adjust the dosing of drugs that are renally excreted.^{3, 9} These guidelines provide the scientific evidence underlying the use of specific pharmacologic and procedural therapies among patients with ACS. Standard pharmacologic therapies include the prescription of aspirin, a thienopyridine (clopidogrel, ticlopidine), anticoagulation (unfractionated heparin, low molecular weight heparin), beta blockers, ACE inhibitors or angiotensin receptor blockers, and lipid lowering agents.¹⁰ The administration and timing of reperfusion therapy (thrombolytic therapy or primary coronary intervention) is an additional measure among patients with an ST elevation myocardial infarction. There is increasing evidence that physicians are less likely to adhere, or comply with these quality indicators in patients with CKD.¹¹⁻¹⁵

In this issue of the *American Journal of Kidney Disease*, Patel et al. examines the interaction between CKD and hospital quality indicator performance on the utilization of evidence-based acute myocardial infarction (AMI) therapies. The source of the data is the CRUSADE registry, an observational cohort of 81,374 patients with non-ST elevation acute coronary syndromes treated at 327 hospitals between 2003 and 2006. Hospitals were ranked into 4 groups (“leading” group had top performance and “lagging” group had worst performance) based on the proportion of patients without contraindications were provided standard pharmacologic therapies. Both in-hospital prescriptions (aspirin, beta blockers, clopidogrel, heparin, and glycoprotein 2b3a inhibitors) and discharge prescriptions (aspirin, clopidogrel, ACE-I, and lipid-lowering therapies) were examined. Patients from hospitals within the same rank were then divided into deciles based on the estimated glomerular filtration rate (GFR) and the proportion of patients who received standard pharmacologic therapies was calculated. The

authors assessed the role of estimated GFR, hospital rank, and the interaction between these variables on medication adherence (leading vs. lagging hospitals). Better performing hospitals had lower prescribing rates for several therapies with increased severity of renal dysfunction. In contrast, lower performing hospitals had similar prescribing rates across severity of renal dysfunction.

The most noteworthy finding of this observational study was the underutilization of standard AMI therapies among patients with CKD. Both in-hospital prescriptions (aspirin, clopidogrel, heparin, and GP2b3a inhibitors) and discharge prescriptions (aspirin, clopidogrel, lipid-lowering agents, and ACE inhibitors) decreased with progressive decline in glomerular filtration rate. These findings are consistent with prior observational studies of ACS patients.¹¹⁻¹⁶ In one of the earliest investigations, McCullough et al. reported the combined use of aspirin and beta blocker in ST elevation MI patients decreased from 64% in patients with preserved renal function to 35% in patients with a GFR < 46 ml/min. Shiplak et al. analyzed data from the Cooperative Cardiovascular Project (CCP), a retrospective study of AMI patients age 65 and older, and observed a decrease in use of both pharmacotherapies and cardiovascular procedure with progressive decline in renal function. In another analysis of AMI patients from the CCP, Berger et al. observed a marked reduction in the use of aspirin, beta blockers, and ACE inhibitors in ESRD patients compared to non-ESRD patients.¹³ Wright et al, in a single center analysis, found the use of standard AMI therapies steadily decreased with worsening category of renal function, reaching a nadir in the small proportion of patients on hemodialysis.¹⁴ These findings were most recently confirmed by Santopinto et al. in an analysis of the GRACE registry, a prospective observational study of ACS patients.¹⁵

Clearly, the underutilization of pharmacologic therapies in ACS patients with CKD is now well established. The unanswered question is: What factors explain this phenomenon? First and foremost, AMI therapies have not been well studied in patients with CKD and are not accepted as “standard of care” by many physicians. Patients with CKD were either excluded or under-represented from early randomized clinical trials of ACS.¹⁷ Few registries prospectively sought to assess cardiovascular complications among patients with CKD, or, renal complications among patients with cardiovascular disease. Hematologic, metabolic, and endocrinologic abnormalities in CKD patients may increase the incidence or severity of side effects of standard AMI therapies, thereby limiting their utilization.¹⁸ A classic example is the concern regarding antiplatelet therapy – aspirin and thienopyridines – in CKD patients who tend to manifest anemia and platelet dysfunction. Second, heterogeneity regarding the definition of CKD has led to inconsistency in the literature. Remote studies utilized serum BUN or creatinine to assess the severity of disease. More recent studies have adopted creatinine clearance rate (estimated by the Cockcroft-Gault formula) or glomerular filtration rate (estimated by the Modification of Diet in Renal Disease formula), to assess the severity of renal insufficiency. Some studies included patients with ESRD whereas other studies specifically excluded these patients. In fact, it was not until 2002 that the K/DOQI clinical practice guidelines standardized the categorization of CKD.¹⁹ Finally, a pragmatic issue results from the fact that patients with CAD and CKD are often co-managed by cardiologists and nephrologists with different practice styles and different guidelines. Consequently, the utilization of specific medical therapies might vary by physician specialty and inpatient therapies may not be transitioned to post-discharge therapies.

Patel et al. stratify their analysis by hospital performance on cardiovascular quality indicators. This methodology of identifying discrepancies in quality of care has fundamental merit because it shifts the paradigm from the physician to the health care system. Identifying top performing hospitals can be accomplished by either examining processes (performance on quality indicators) or health care outcomes (mortality, rehospitalization).^{10, 20, 21} Bradley et al. assessed hospital performance in the CMS/JCAHO AMI core process measures using

2002-2003 data from 962 hospitals participating in the National Registry of Myocardial Infarction and correlated these measures with hospital-level, risk-standardized, 30-day mortality rates derived from Medicare claims data.²¹ Although several of the process measures were significantly correlated with risk-standardized, 30-day mortality rates, together they explained only 6.0% of hospital-level variation in the mortality. Thus, quality indicators alone cannot suffice as a surrogate of mortality. Wang et al. examined the ranking of hospitals for “heart and heart surgery” in the *US News & World Report* and found the 30-day risk-standardized mortality rates for AMI were lower for ranked than nonranked hospitals.²¹ An observational analysis of the CRUSADE registry found the composite adherence rate was significantly associated with in-hospital mortality, with observed mortality decreasing from 6.3% for the lowest adherence quartile to 4.2% for the highest quartile.²² After risk adjustment, every 10% increase in composite adherence at a hospital was associated with an analogous 10% decrease in its patients' likelihood of in-hospital mortality.

Applying the aforementioned methodology, top performing (“leading”) hospitals would be expected to deliver key therapies independent of renal function while hospitals with poor performance (“lagging”) would be less likely to provide individual therapies to patients with worse renal function. Unfortunately, the patterns between hospital performance and severity of renal dysfunction identified by Patel et al. were inconsistent. In fact, the hypothesis that higher performing hospitals would have higher rates of prescribing at all levels of eGFR was only established for ACE inhibitors. For many of the medications, stochastic significance is demonstrated but the small magnitude of difference in the odds ratio leads one to question the clinical significance of the findings. In examining the interaction between renal dysfunction and hospital performance on the utilization of various therapies, one would expect to see a “dose effect” across levels of hospital performance. Unfortunately, this does not appear to be the case for the various medications, and in fact, the statistical analysis excludes the interquartile groups and compares only the “leading” and “lagging” hospitals.

A major limitation of the analysis by Patel et al. was the exclusion of patients with ESRD. Although no specific mention is made regarding this high-risk population, the eGFR range had a lower limit of 20 mL/min and therefore presumably excluded dialysis patients. The incidence of AMI in patients with prevalent CKD and prevalent ESRD are 4.2% and 7.7%, respectively.²³ Following an AMI, the one-year mortality in dialysis patients is 59%.²⁴ There is a paucity of data regarding therapy among these patients, in particular, because they were historically excluded from randomized clinical trials.¹³ It would have been interesting to have known how leading and lagging hospitals had performed on the various quality indicators.

In summary, patients with elevated creatinine (CKD and ESRD) are at high risk of developing coronary artery disease as well as other manifestations of atherosclerosis. The CRUSADE registry reinforces the perception of compliance failure; showing standard AMI therapies remain underutilized in patients with CKD. Unfortunately, the relationship between worsening renal function and lack of adherence to guidelines cannot be adequately explained by individual hospital performance. Only when physicians “Connect the Cs” – recognizing the risk of premature CAD in patients in CKD and Crusading for Compliance with the ACS guidelines – will patient outcomes be improved.

References

1. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* Jan;2003 41(1):1–12. [PubMed: 12500213]
2. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in

- Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* Oct 28;2003 108(17):2154–2169. [PubMed: 14581387]
3. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation* Aug 3;2004 110(5):588–636. [PubMed: 15289388]
 4. Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J. The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. *Ann Intern Med* Jan 6;2004 140(1):9–17. [PubMed: 14706967]
 5. Drey N, Roderick P, Mullee M, Rogerson M. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *Am J Kidney Dis* Oct;2003 42(4):677–684. [PubMed: 14520617]
 6. Foley RN, Murray AM, Li S, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* Feb;2005 16(2):489–495. [PubMed: 15590763]
 7. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* Mar 22;2004 164(6):659–663. [PubMed: 15037495]
 8. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* Sep 23;2004 351(13):1296–1305. [PubMed: 15385656]
 9. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation* Aug 14;2007 116(7):e148–304. [PubMed: 17679616]
 10. Weston CF. Performance indicators in acute myocardial infarction: a proposal for the future assessment of good quality care. *Heart* Nov;2008 94(11):1397–1401. [PubMed: 18931156]
 11. McCullough PA, Sandberg KR, Borzak S, Hudson MP, Garg M, Manley HJ. Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. *Am Heart J* Aug; 2002 144(2):226–232. [PubMed: 12177638]
 12. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* Oct 1;2002 137(7):555–562. [PubMed: 12353942]
 13. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. *J Am Coll Cardiol* Jul 16;2003 42(2):201–208. [PubMed: 12875751]
 14. Wright RS, Reeder GS, Herzog CA, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med* Oct 1;2002 137(7):563–570. [PubMed: 12353943]
 15. Santopinto JJ, Fox KA, Goldberg RJ, et al. Creatinine clearance and adverse hospital outcomes in patients with acute coronary syndromes: findings from the global registry of acute coronary events (GRACE). *Heart* Sep;2003 89(9):1003–1008. [PubMed: 12923009]
 16. Beattie JN, Soman SS, Sandberg KR, et al. Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction. *Am J Kidney Dis* Jun;2001 37(6):1191–1200. [PubMed: 11382688]
 17. Novak JE, Szczech LA. Feast and famine: epidemiology and clinical trials in chronic kidney disease. *J Am Soc Nephrol* Jan;2008 19(1):2–4. [PubMed: 18003784]
 18. Han JH, Chandra A, Mulgund J, et al. Chronic kidney disease in patients with non-ST-segment elevation acute coronary syndromes. *Am J Med* Mar;2006 119(3):248–254. [PubMed: 16490471]

19. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* Feb;2002 39(2 Suppl 1):S1–266. [PubMed: 11904577]
20. Bradley EH, Herrin J, Elbel B, et al. Hospital quality for acute myocardial infarction: correlation among process measures and relationship with short-term mortality. *Jama* Jul 5;2006 296(1):72–78. [PubMed: 16820549]
21. Wang OJ, Wang Y, Lichtman JH, Bradley EH, Normand SL, Krumholz HM. “America’s Best Hospitals” in the treatment of acute myocardial infarction. *Arch Intern Med* Jul 9;2007 167(13): 1345–1351. [PubMed: 17620526]
22. Peterson ED, Roe MT, Mulgund J, et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. *Jama* Apr 26;2006 295(16):1912–1920. [PubMed: 16639050]
23. U.S. Renal Data System. *USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda: National Institute of Diabetes and Digestive and Kidney Diseases; 2006. Cardiovascular Special Studies; p. 178-179.
24. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* Sep 17;1998 339(12):799–805. [PubMed: 9738087]