Association of Decreased Glomerular Filtration Rate with Racial Differences in Survival after Acute Myocardial Infarction

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Summary

Background and objectives African-American race and decreased kidney function have been associated with higher mortality after acute myocardial infarction (AMI). However, whether there are racial differences in the prevalence or prognostic importance of renal insufficiency in AMI is unknown.

Design, setting, participants & measurements Among 1847 AMI patients enrolled in the multicenter Prospective Registry Evaluating Myocardial Infarction Event and Recovery (PREMIER) study, estimated glomerular filtration rate (eGFR) was used to stratify prognosis and to examine potential interactions among eGFR, race, and mortality. Multivariable proportional hazards regression was used to examine the effect of race and eGFR on 3.5-year all-cause mortality.

Results Race and eGFR were significantly associated with mortality. After adjustment for eGFR alone, differences in mortality by race were substantially attenuated (unadjusted hazard ratio [HR] for African Americans = 1.56 [95% confidence interval {CI}= 1.2 to 2.1]; eGFR-adjusted HR = 1.32 [95% CI = 0.99 to 1.75]). A similar magnitude of attenuation in racial differences in survival was observed after adjustment for all covariates except eGFR (HR = 1.29 [95% CI = 0.96 to 1.72]). A final model adjusting for all covariates only slightly attenuated the association further. No interaction between race and eGFR was detected.

Conclusions Renal insufficiency, which may represent chronic kidney disease, is a prognostically important comorbidity in African Americans after AMI. However, the effect of decreased eGFR on mortality is comparable between races, suggesting that preventing renal insufficiency in African Americans could be an important target to reduce racial disparities in post-AMI survival.

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Introduction

Understanding and eliminating racial disparities in the prevalence, treatment, and outcomes of cardiovascular disease is a national priority (1–3). Studies have suggested that African Americans, as compared with Caucasians, have significantly higher mortality after acute myocardial infarction (AMI) (4–9). However, such differences may be eliminated after adjusting for sociodemographic differences and comorbidities, as evidenced by a recent demonstration that the differences in a range of post-AMI outcomes were virtually eliminated after adjusting for patient characteristics present at the time of hospital presentation (10).

In seeking to understand and eliminate racial disparities in post-AMI outcomes, defining racial differences in the prevalence and prognostic importance of renal insufficiency, in the form of decreased estimated glomerular filtration rate (eGFR), is critically important. Renal insufficiency and chronic kidney disease (CKD) are known to be independent risk factors for mortality after AMI (11–14). Although prevalence of CKD itself does not appear to differ by race (15,16) in the general population, African Americans are believed to progress more rapidly to ESRD (15,17,18). Whether the greater prevalence of advanced renal insufficiency (*e.g.*, an eGFR < 30 ml/min per 1.73 m^2) in African Americans accounts for much of the racial differences in survival, or whether the survival of African Americans with advanced renal insufficiency is worse than that of Caucasians with comparable levels of renal insufficiency, is unknown. This distinction is important because if there is a similar prognosis across races with advanced renal insufficiency, then a key opportunity to eliminate racial disparities in post-AMI prognosis might be the prevention of the racial differences in the occurrence and progression of renal insufficiency in African Americans. In distinction, if African Americans with advanced renal insufficiency have a worse prognosis than Caucasians with similar degrees of renal dysfunction, then it would be important to better understand the biologic and treatment mechanisms underlying this phenomenon so as to learn how

best to minimize racial disparities among AMI patients with renal insufficiency and CKD.

To address this gap in knowledge, we analyzed a multicenter, prospective registry of AMI patients to examine the extent to which renal insufficiency at the time of AMI mediates long-term, all-cause mortality in AMI survivors. We specifically sought to investigate whether there is a significant interaction by race on the association of renal insufficiency and mortality and, if not, the degree to which the prevalence of renal insufficiency in African-American AMI patients explains their poorer long-term survival. Addressing these issues has the potential to inform future study designs investigating the causes of racial disparities in post-AMI outcomes and can guide the development of strategies to minimize such disparities.

Materials and Methods

Overall Design and Characteristics of the Study

Patients in the present investigation were drawn from those enrolled in the Prospective Registry Evaluating Myocardial Infarction: Event and Recovery (PREMIER) study. PREMIER was a prospective cohort study of the care and outcomes of patients after AMI enrolled from 19 U.S. centers between January 2003 and June 2004 (19). The study was designed to quantify a broad range of potential mediators of outcome, including patients' demographic, health, economic, and psychosocial status as well as their medical comorbidities, disease severity, site of care, treatment, discharge medications, and discharge instructions.

Participants

All patients at each PREMIER center with a positive serum troponin test or elevated serum creatinine kinase-MB level were screened for possible inclusion. Eligibility criteria required an age ≥18 years; elevated troponin (I or T) or creatinine phosphokinase-MB; additional supporting evidence of an AMI (*e.g.*, prolonged ischemic symptoms or electrocardiographic ST-wave changes); and either initial presentation at, or transfer to, the enrolling institution within the first 24 hours of presentation. Patients with elevated cardiac enzymes as a complication of elective coronary revascularization were not eligible. For the purpose of this study, only patients who identified themselves as Caucasian or African American were included in the analyses. Figure 1 demonstrates the derivation of the study sample used for analysis. Of the 2498 participants enrolled in PREMIER, 651 were excluded, leaving a final study sample of 1847 individuals.

Careful consideration was given to the issue of site exclusion because insufficient racial variability at a care site substantially diminishes, or even eliminates, its contribution to a race-based analysis. For this reason, sites that treated small numbers of African Americans were excluded from analysis.

The study protocol was approved by the institutional review boards at each institution, and all patients provided informed consent to participate.

Data Collection and Variables

Comprehensive medical chart abstractions were performed by trained data collectors, and a detailed patient interview was performed during the index AMI admission. During this interview, the patient's self-identified racial category, the primary independent variable in this study, was recorded. Where possible, data collection elements conformed to the American College of Cardiology Clinical Data Standards for Acute Coronary Syndromes (19,20). Of note, any hematologic or solid organ tumor (primary or metastatic), excluding nonmelanoma skin cancers, was categorized as "cancer."

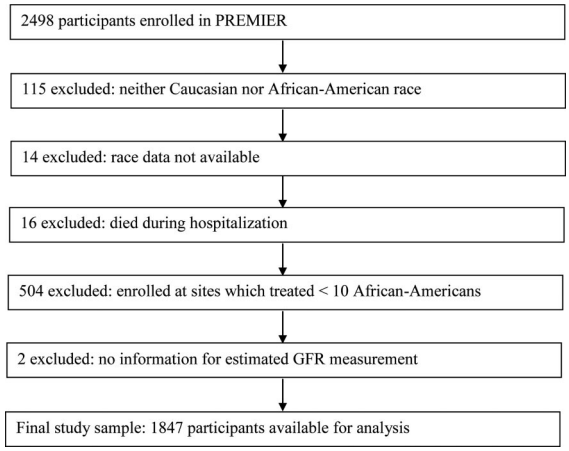


Figure 1. | Analytic sample derived from the PREMIER participants.

Assessment of Renal Function

The standard four-variable Modification of Diet in Renal Disease equation was used to estimate GFR and subjects were stratified by renal function (21).

Creatinine values at discharge were used for this study. Creatinine was measured at each care site during the course of clinical care, and various assays, reflecting the practices used by the respective sites, were used.

An eGFR >90 ml/min per 1.73 m^2 was considered "normal," 60 to 90 ml/min per 1.73 m^2 was classified as "mild renal dysfunction," 30 to 59.9 ml/min per 1.73 m^2 was classified as "moderate dysfunction," and <30 ml/min per 1.73 m^2 indicated "severe dysfunction."

Follow-Up and Outcome Measure

The outcome of this study was 3.5-year all-cause mortality. Survival status was confirmed through information obtained from family members of patients during follow-up telephone interview efforts and by matching patients' names, dates of birth, and social security numbers to the Social Security Death Master File, which was last accessed on June 30, 2008.

Statistical Methods

Fifty-nine baseline demographic, comorbidity, psychosocial, socioeconomic, and treatment factors were compared between races using the χ^2 test for categorical variables and independent *t* tests for continuous variables. Unadjusted data are presented as frequency and rates or means ± SD. Skewed distributions were compared using the Wilcoxon rank-sum test and are presented as medians and interquartile ranges.

The primary analysis used multivariable proportional hazards regression to examine the effect of race and eGFR on 3.5-year all-cause mortality. To determine the independent associations of eGFR with mortality, four models were sequentially constructed: (*1*) a model adjusted only for site of admission; (*2*) a model adjusted for site and all other covariates except eGFR category; (*3*) a model adjusted for site and eGFR category alone; and (*4*) a final model adjusted for site, all covariates, and eGFR. Model covariates were chosen based on their presumed clinical relevance and demonstrated importance in previous reports (22). Covariates included demographic (age, sex), socioeconomic factor (education), risk behavior (smoking status), comorbidity (prior coronary artery disease, prior cerebrovascular accident, congestive heart failure, hypertension, hypercholesterolemia, diabetes mellitus, chronic lung disease, cancer, and body mass index), AMI type (ST-elevation AMI *versus* not), acute noncardiac condition warranting admission (23), left ventricular systolic function (<40% *versus* not), acute heart rate, and laboratory variables (initial hematocrit and glucose). Potential interaction between eGFR and race was specifically assessed during modeling using a first-order interaction term.

To help facilitate the clinical interpretation of the relative importance of the attenuation of racial differences in post-AMI survival due to renal insufficiency, we informally quantified the proportion of excess relative risk in African Americans accounted for by eGFR using the formula $(HR_{\text{adj-GFR}} - HR_{\text{adj+GFR}})/(HR_{\text{adj-GFR}} - 1.0)$, where $HR_{\text{adj-GFR}}$ denotes the hazard ratio (HR) adjusted for site and patient factors but excluding eGFR category and $HR_{\text{adj+GFR}}$ denotes the corresponding HR including eGFR. This ratio thus expresses the excess mortality risk in African Americans after including eGFR as compared with the excess risk adjusting for all factors except eGFR (24,25).

To establish the robustness of the findings, we performed two separate sensitivity analyses. The first included all individuals treated at any site at which at least one African American was enrolled. The second used propensity adjustment for race (26) to adjust for the substantial differences in covariates that varied by race. Propensity scores were computed using logistic regression analyses to predict the probability of being African American, and these propensity scores were included in the mortality models, along with race, to balance the covariates that varied by race. The balance of propensity scores was assessed by graphically viewing propensity score distributions within each race and comparing standardized differences in covariates across deciles of propensity score (27,28).

Missing model covariate data were minimal and were absent for only 5% of one covariate, and under 2% for six other covariates. However, because approximately 10% of the patients had a missing covariate for at least one data field, we performed multiple imputation using IVEWARE software (29).

Restricted cubic spline terms were included for all continuous covariates to adjust for possible nonlinearity (30), and proportional hazards assumptions were tested using Schoenfeld residuals and verified for all proportional hazards models. All tests for statistical significance were two-tailed with an α level of 0.05. All analyses were conducted using SAS software, release 9.1.3 (SAS Institute, Cary, NC) and R version 2.6.0.

Results

Participant baseline characteristics are shown in Table 1. As expected, statistically significant differences between races were noted for many characteristics. African-American participants were younger, more likely to be female, more likely to have diabetes and hypertension, and were less likely to have hypercholesterolemia. African Americans also had a higher frequency of previous manifestations of vascular disease, including prior myocardial infarction, congestive heart failure, cerebrovascular accidents, and peripheral vascular disease. The index AMI was more likely to be a non-ST elevation AMI in African Americans than in Caucasians. Finally, renal disease was substantially more common in African Americans, who had lower mean eGFR and a greater prevalence of advanced renal insufficiency (eGFR <30 ml/min).

Unadjusted Kaplan–Meier survival plots are shown in Figure 2. Overall 42-month mortality of the cohort was 17.1%, with 316 participant deaths. Figure 2a demonstrates significantly better unadjusted survival for Caucasians relative to African Americans. Figure 2b shows survival across the study sample by strata of eGFR, illustrating progressively worse survival for patients with worse eGFR categories.

Figure 3 summarizes the primary analysis of all-cause mortality by race. The first (parent) model, which is site stratified but otherwise unadjusted for covariates and category of eGFR, illustrates an HR for African Americans of 1.56 (95% confidence interval [CI] 1.18 to 2.06). After adjusting for all covariates except eGFR, the HR decreased to 1.29 (95% CI 0.96 to 1.72). In the third model, which adjusts only for eGFR category, the HR for African Americans was 1.32 (95% CI 0.99 to 1.75), a difference similar in magnitude to the previous model that adjusted for all other racial differences in baseline and treatment characteristics except eGFR. The final fully adjusted model, including eGFR and all other covariates, resulted in a modest, further attenuation of the HR for mortality for African Americans as compared with Caucasians (HR 1.20, 95% CI 0.90 to 1.62). The final model is shown in detail in Supplementary Table 1.

We performed several sensitivity analyses to test the robustness of our findings. First, we performed a reanalysis incorporating all sites that treated at least one African American. The analytic sample increased from 1847 to 2116 (one large site treated 230 individuals, but because all were Caucasian, it was not included). There was virtually no change in our findings: the site-stratified, but otherwise unadjusted, HR became 1.54 (95% CI 1.17 to 2.02); the HR adjusting for all covariates except eGFR became 1.26 95% CI (0.95 to 1.68); the HR adjusting only for eGFR category became 1.31 (95% CI 0.99 to 1.73); and the HR for the final fully adjusted model became 1.19 (95% CI 0.89 to 1.59). A second sensitivity analysis using propensity methods to adjust for sociodemographic and clinical differences between racial groups revealed comparable findings (data not shown).

Table 1. Participant baseline characteristics.

Variable	Caucasian	African American	*P*
Total, *n*	1333	514	
Age, years[a]	61.7 ± 12.9	57.3 ± 13.2	<0.001
Male, *n* (%)	940 (70.5)	283 (55.1)	<0.001
Current smoker, *n* (%)	431 (32.6)	208 (41.1)	<0.001
High school education, *n* (%)	677 (51.8)	130 (26.0)	<0.001
Body mass index, kg/m^2[a]	29.2 ± 6.4	29.1 ± 7.1	0.859
Prior myocardial infarction, *n* (%)	269 (20.2)	133 (25.9)	0.008
Prior coronary artery disease, *n* (%)	440 (33.0)	188 (36.6)	0.147
Prior congestive heart failure, *n* (%)	109 (8.2)	135 (26.3)	<0.001
Prior cerebrovascular event, *n* (%)	73 (5.5)	57 (11.1)	<0.001
Prior peripheral vascular disease, *n* (%)	128 (9.6)	31 (6.0)	0.014
Hypertension, *n* (%)	799 (59.9)	406 (79.0)	<0.001
Diabetes, *n* (%)	335 (25.1)	207 (40.3)	<0.001
Hypercholesterolemia, *n* (%)	681 (51.1)	212 (41.2)	<0.001
Chronic lung disease, *n* (%)	188 (14.1)	79 (15.4)	0.488
Cancer, *n* (%)	114 (8.6)	29 (5.6%)	0.036
Final MI study diagnosis			<0.001
STEMI, *n* (%)	651 (48.8)	124 (24.1)	
NSTEMI, *n* (%)	682 (51.2)	390 (75.9)	
Ejection fraction <40%, *n* (%)	324 (24.3)	155 (30.3)	0.009
Initial acute heart rate, beats/min[a]	79.1 ± 20.2	85.9 ± 22.3	<0.001
Serum creatinine, mg/dl, median (IQR)	1.0 (0.9 to 1.2)	1.2 (0.9 to 2.0)	<0.001
Hematocrit, g/dl[a]	40.5 ± 5.8	38.4 ± 6.6	<0.001
eGFR category, ml/min per 1.73 m^2			<0.001
0.0 to 29.9	67 (5.0)	112 (21.8)	
30.0 to 59.9	285 (21.4)	92 (17.9)	
60.0 to 89.9	650 (48.8)	139 (27.0)	
≥90.0	331 (24.8)	171 (33.3)	

[a]Continuous data shown as mean ± 1 SD.
MI, myocardial infarction; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation infarction; IQR, interquartile range.

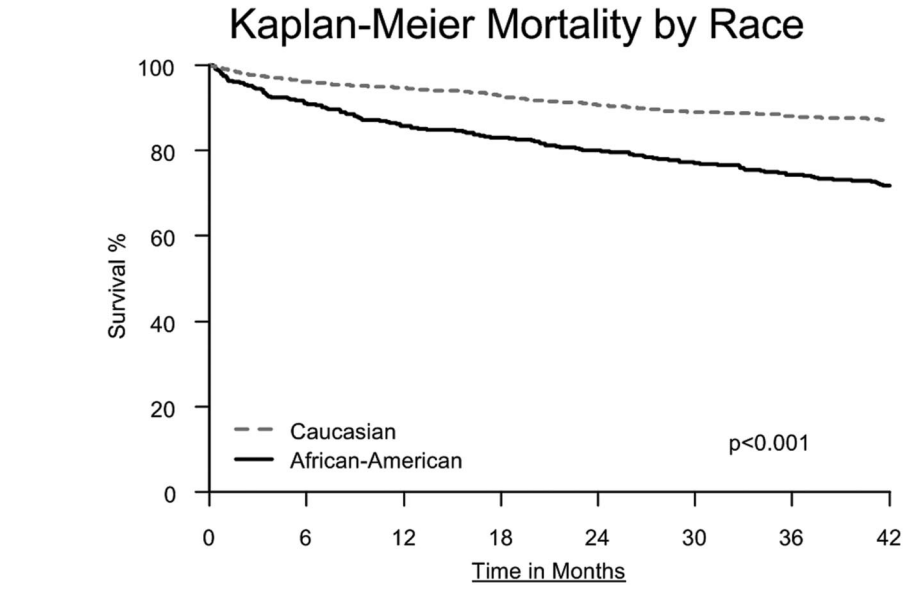
Although not the primary aim of our analysis, we sought to contextualize the relative magnitude of the excess risks attributable to renal insufficiency alone, relative to all other factors combined (except renal insufficiency), in African Americans compared with Caucasians. We characterized the excess risk in African Americans, relative to Caucasians, of renal insufficiency alone to be 31.0% (calculated as [(1.29 − 1.20)/(1.29 − 1.00)]). Analogously, the excess risk to African Americans due to all other factors except renal insufficiency was 37.5% [(1.32 − 1.20)/(1.32 − 1.00)], indicating that these risks were broadly comparable in magnitude.

To examine whether the adverse prognostic association of CKD with outcome was different in African Americans as compared with Caucasians, a formal statistical test of interaction between race and eGFR on mortality was performed, which was NS (P = 0.52). This is demonstrated graphically in Figure 4. For each of the four categories of eGFR, the HR of mortality for African Americans was not significantly worse than that of Caucasians, although a NS trend for worse survival among African-Americans with the most advanced renal insufficiency was suggested (HR = 1.77; 95% CI = 0.94 to 3.34).

Discussion

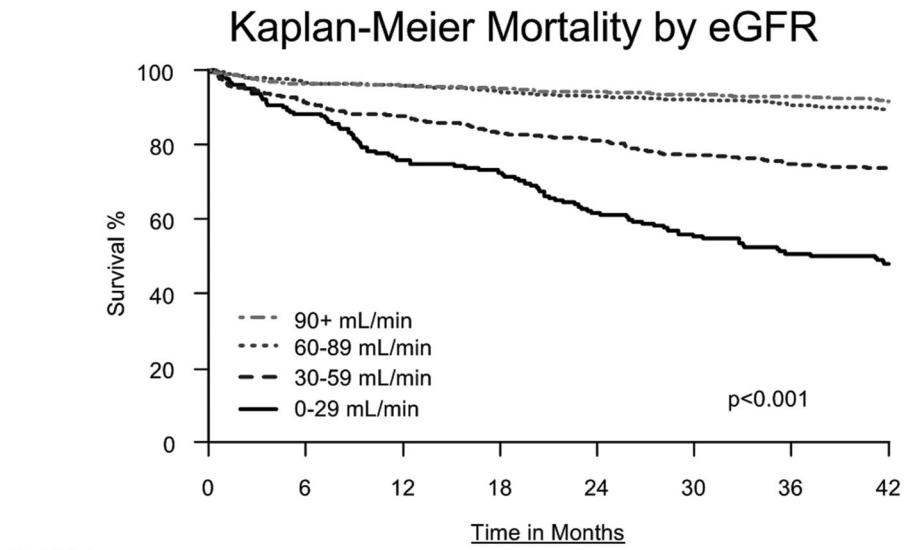
Using a large, well characterized multicenter cohort of AMI patients (19), we examined the extent to which renal insufficiency was associated with post-AMI survival in African Americans and Caucasians and whether this association differed by race. Congruent with prior reports about the prognostic importance of renal insufficiency and CKD itself (11–14,31–33), we found that decreased eGFR is independently associated with greater long-term post-AMI mortality; indeed, the 3.5-year unadjusted survival of individuals in the lowest strata of eGFR was half that of those with preserved kidney function. Additionally, we replicated and extended the findings of other investigators by demonstrating that the effect of renal insufficiency was similar between African Americans and Caucasians, and that the greater prevalence of advanced renal insufficiency in African Americans (approximately 50% higher than in Caucasians) accounted for a substantial proportion of the unadjusted excess mortality in that population.

Given the importance of understanding and eradicating racial disparities in health outcomes (1–3), the issue of whether and how renal insufficiency and CKD are associated with racial differences in mortality and processes of care is an area of considerable debate (31,34–40). Accordingly, we sought to use the rich array of clinical information collected in PREMIER participants to perform a detailed investigation into whether and how decreased eGFR influences post-AMI survival by race. To contextualize our findings, we estimated the relative magnitude of the effects of eGFR and found that 31.0% of the



N at Risk

Caucasian	1333	1282	1253	1226	1199	1178	1163	1149
African-American	514	466	431	416	401	386	372	359



N at Risk

90+ mL/min	502	483	472	469	464	460	458	452
60-89 mL/min	789	762	750	736	725	719	709	698
30-59 mL/min	377	345	329	311	304	289	280	275
0-29 mL/min	179	158	133	126	107	96	88	83

Figure 2. | Unadjusted Kaplan–Meier survival curve showing all-cause 3.5-year mortality (a) by race and (b) by strata of eGFR.

excess hazard in African Americans was accounted for after adjusting for eGFR alone, whereas 37.5% of the excess hazard could be attributed to all other covariates combined. This serves to provide a broad framework that underscores the importance of renal insufficiency on post-AMI mortality outcomes. Given the similar associations between diminished eGFR and mortality in African Americans and Caucasians, as suggested by a NS interaction among race, eGFR, and outcome, our results suggest that a primary goal should be the prevention of renal insufficiency and, potentially, the progression of CKD among African Americans. This would likely be a more productive direction than a search for pathophysiological differences among kidney disease patients of different races (37).

Our findings are concordant with most studies in other clinical settings that have suggested the absence of important interactions between race and renal insufficiency on cardiovascular outcomes. For example, in a single-center study of patients undergoing percutaneous coronary inter-

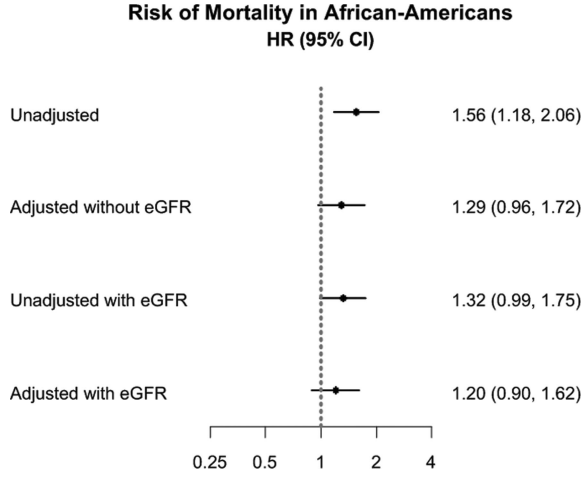


Figure 3. | Forest plot showing the risk of mortality at 3.5 years in African Americans compared with Caucasians, by model.

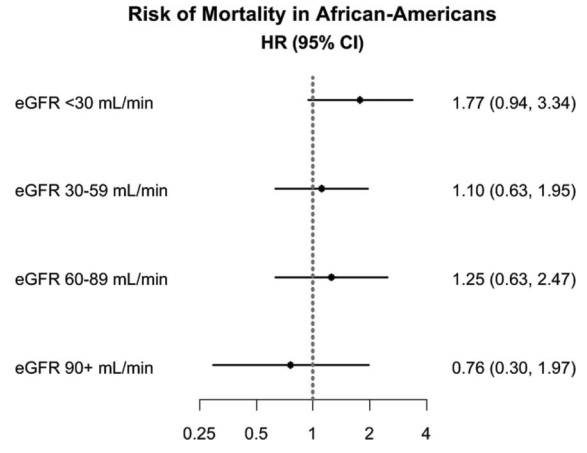


Figure 4. | Forest plot showing the interactive effect between race and CKD (shown as different strata of eGFR) on 3.5-year all-cause mortality.

vention, Cardarelli and colleagues did not find a CKD-race interaction influencing 1-year mortality (33). Similarly, Manjunath *et al.* found only a NS and clinically modest trend for an interaction between race and eGFR on incident atherosclerotic cardiovascular disease outcomes during a mean follow-up of 6.2 years in the Atherosclerosis Risk in Communities study (32). In the only other similar study in post-AMI patients, Newsome *et al.* (31) found a statistically significant interaction between race and eGFR, but in this large study the significance of the interaction and the clinical magnitude of the effect were quite modest. Our study differs from others because we capitalized on the uniquely rich source of information provided by PREMIER on the characteristics of the patients themselves and the details of their AMI severity and management and because our analysis specifically examined the magnitude of risk conferred by renal insufficiency in comparison with the risk conferred by other traditional risk factors.

The findings presented here underscore the need to determine why African Americans more commonly have advanced renal insufficiency and how this can be better prevented. Although there is a greater prevalence of risk factors for kidney disease in African Americans, including the potentially preventable comorbidities of hypertension and diabetes, these risk factors appear inadequate to explain the greater prevalence of advanced renal insufficiency and ESRD (15,36). Whether African Americans advance more rapidly through the earlier stages of CKD (15) and/or dwell longer at very late stages of disease (31,37) is unknown, but this may explain the hypothesized greater prevalence of advanced renal insufficiency in African Americans.

Regardless of the mechanism, the opportunity to ameliorate the progression of renal insufficiency and treat factors associated with renal insufficiency and progression of CKD is likely to be present via conscientious application of the clinical performance measures advocated by the National Kidney Foundation (21) and the Renal Physicians Association (http://www.qualitymeasures.ahrq.gov/summary/summary.aspx?doc_id = 539). The appropriate application of such performance measures to help determine how and why patient treatments, such as timing of referral to a nephrologist (41) or attainment of LDL targets (42), vary by race seems warranted. In particular, measuring adherence with clinical performance measures, particularly in African Americans, may be an effective, systematic way to minimize the progression of renal disease in this population. An overarching approach to minimize the effect of renal insufficiency and CKD, taking into account community- and individual-level vulnerabilities in biologic and environmental arenas (39), is likely to require a multipronged effort that includes education and health promotion, access to care for risk factor detection and treatment, and increased cultural sensitivity to overcome known barriers to performance measure adherence.

Our study should be interpreted in the context of the following potential limitations. Our study is retrospective in nature and, as a result, it is not possible to make inferences about causality. It is also important to appreciate that our estimation of the attenuation of excess risk in African Americans due to eGFR (alone) and to all other factors (combined) has not been precisely estimated with a formal consideration of CIs; this calculation was merely designed to place the effects respective factors within a rough qualitative framework of attributable risk. Additionally, our definition of renal insufficiency was based on a single assessment of serum creatinine at discharge. That creatinine was measured in the peri-AMI period means that eGFR may have been influenced by patients' acute presentation, introducing a potential source of bias. However, several important factors mitigate against this. First, in our anecdotal experience, it is relatively uncommon that AMI is associated with significant acute renal failure that persists until discharge. Second, we undertook an analysis of the TRIUMPH study (a study of AMI very comparable to PREMIER), as yet unpublished, which demonstrated that, at 6 months of follow-up, approximately 94% of patients with AMI had eGFR values within ± 20 ml/min of their presenting eGFR at the time of AMI, a finding that varied

little by race. Although we believe that reduced eGFR values broadly reflect CKD, we cannot rule out the distinct possibility that reduced eGFR may in fact represent the effects of acute kidney injury, and, as such, may be a marker of a more severe AMI.

Another limitation is that creatinine determinations differed by assay used. Because creatinines were measured at each treating site during the course of clinical care (as opposed to at a central laboratory site), and because various assay techniques were used across the sites, no attempt was made to standardize to isotope dilution–mass spectroscopy creatinine values. Although this undoubtedly introduced some variability into the determination of eGFR, it is unlikely that this variability was differentially distributed between races. The study was designed to draw broad conclusions using many patients, so minor differences in "true" eGFR values, especially if these did not differ by race, are unlikely to substantially alter our results. Additionally, we were unable to adjust for post-AMI therapies (including hypertension and diabetes control) that could affect long-term survival, and we cannot discount the possibility of residual confounding in the analysis, despite the broad number of factors that were included in this study.

In summary, we found that African-American patients with renal insufficiency experienced post-AMI survival comparable to Caucasians after adjustment for a wide variety of covariates. Importantly, adjustment of eGFR level alone appeared to reduce the observed disparity in unadjusted survival nearly as much as all other adjusted factors combined, supporting the concept that an effective way to minimize the unadjusted racial differences in outcomes may be to prevent the development of renal insufficiency and, perhaps, the progression of CKD in African Americans. Further investigation into the reasons why kidney disease burden is higher in African Americans who have AMIs than in Caucasians and into what interventions might minimize this phenomenon are urgently needed to optimize post-AMI outcomes in cardiovascular disease patients.

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Disclosures

None.

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