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# Serum Blood Urea Nitrogen as an Independent Marker of Subsequent Mortality Among Patients With Acute Coronary Syndromes and Normal to Mildly Reduced Glomerular Filtration Rates

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**OBJECTIVES** We hypothesized that elevated blood urea nitrogen (BUN) would be associated with adverse outcomes independent of serum creatinine (sCr)-based estimates of kidney function in patients with acute coronary syndromes (ACS).

**BACKGROUND** Although lower glomerular filtration rates (GFR) have prognostic significance among patients with ACS, estimates of GFR based on sCr may perform less accurately among patients with milder kidney dysfunction. In this population in particular, BUN, which can reflect increased proximal tubular reabsorption in addition to decreased GFR, may have independent prognostic value.

**METHODS** Data were drawn from 9,420 patients with unstable coronary syndromes from Orbofiban in Patients With Unstable Coronary Syndromes-Thrombolysis In Myocardial Infarction (OPUS-TIMI)-16, a trial that excluded patients with sCr >1.6 mg/dl or estimated creatinine clearance <40 ml/min.

**RESULTS** Patients with elevated BUN were older, had a higher prevalence of comorbidities, and had higher heart rates, lower systolic blood pressures, and an abnormal Killip class more often on admission. In univariate analyses, as well as in stratified and multivariable analyses including sCr-based estimates of GFR as a covariate, a stepwise increase in mortality occurred with increasing BUN (multivariable hazard ratio with BUN 20 to 25 mg/dl 1.9, 95% confidence interval 1.3 to 2.6; with BUN ≥25 mg/dl 3.2 [95% confidence interval 2.2 to 4.7]) compared with BUN ≤20 mg/dl. A higher BUN was also associated with increased mortality among strata of troponin-I, B-type natriuretic peptide, and C-reactive protein concentrations.

**CONCLUSIONS** Among patients with unstable coronary syndromes and predominantly normal or mildly reduced GFR, an elevated BUN is associated with increased mortality, independent of sCr-based estimates of GFR and other biomarkers. (J Am Coll Cardiol 2005;45:1781–6)
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The relationship between chronic kidney disease (CKD) and adverse cardiovascular outcomes is well established in patients with acute coronary syndromes (ACS) (1–3). Most prior studies have utilized serum creatinine (sCr), estimated creatinine clearance (eCrCl), or sCr-based estimates of glomerular filtration rate (eGFR) (4) to assess kidney function. However, estimates of kidney function based primarily upon sCr are imperfect and may not adequately assess acute changes in actual glomerular filtration rate (GFR) or other aspects of kidney function, particularly when the GFR is only mildly reduced (5,6).

The blood urea nitrogen (BUN) concentration has been considered a less specific marker of kidney function than sCr, eCrCl, or eGFR. However, in addition to reflecting GFR, BUN may rise independent of changes in GFR or sCr owing to enhanced proximal tubular reabsorption under the activation of the sympathetic nervous and renin-angiotensin-aldosterone systems (7). Although BUN has been associated with adverse outcomes and has been previously incorporated into myocardial infarction risk prediction models (8,9), BUN has not been investigated in ACS patients without myocardial infarction or in conjunction with other measures of kidney function. Thus, whether BUN provides marginal predictive power after accounting for an sCr-based estimate of kidney function is unclear. In this study, we aimed to determine whether there was an independent increase in risk observed with higher BUN across strata of sCr, eCrCl, and

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**Abbreviations and Acronyms**

| | |
|---|---|
| ACS | = acute coronary syndromes |
| BNP | = B-type natriuretic peptide |
| BUN | = blood urea nitrogen |
| CKD | = chronic kidney disease |
| CRP | = C-reactive protein |
| eCrCl | = estimated creatinine clearance |
| eGFR | = estimated glomerular filtration rate |
| GFR | = glomerular filtration rate |
| OPUS-TIMI-16 | = Orbofiban in Patients With Unstable Coronary Syndromes-Thrombolysis In Myocardial Infarction-16 trial |
| sCr | = serum creatinine |

eGFR and hypothesized that an elevated BUN would be associated with adverse outcomes independent of other clinical and laboratory characteristics, including biomarker levels.

## METHODS

Clinical and laboratory data were drawn from 9,420 patients with ACS and available BUN data enrolled in the Orbofiban in Patients With Unstable Coronary Syndromes-Thrombolysis In Myocardial Infarction (OPUS-TIMI)-16 trial of the oral glycoprotein IIb/IIIa inhibitor orbofiban. Patients were eligible for enrollment if they presented within 72 h of the onset of ischemic symptoms with high-risk features (10); patients with admission sCr >1.6 mg/dl or eCrCl <40 ml/min were excluded owing to concerns regarding renal clearance of orbofiban. Patients with significant systemic bleeding were also excluded. Patients were randomly assigned to one of the following three treatment arms: 50 mg orbofiban twice daily, 50 mg orbofiban twice daily for one month followed by 30 mg orbofiban twice daily, or placebo. Subject follow-up was obtained at a minimum of six months.

**Table 1.** Baseline Characteristics

| | BUN <20 mg/dl (n = 7,796) | BUN 20–25 mg/dl (n = 1,029) | BUN ≥25 mg/dl (n = 595) | p for Trend |
|---|---|---|---|---|
| Demographics | | | | |
| Age (yrs) | 59 (51, 68) | 67 (59, 74) | 70 (63, 76) | <0.001 |
| Weight (kg) | 80 (70, 90) | 78 (68, 88) | 75 (68, 87) | <0.001 |
| Male gender | 72.6% | 72.3% | 66.9% | 0.01 |
| Current smoker | 39.2% | 23.7% | 21.5% | <0.001 |
| History of congestive heart failure | 3.6% | 11.3% | 13.3% | <0.001 |
| History of hypertension | 40.5% | 52.7% | 56.8% | <0.001 |
| History of diabetes mellitus | 19.3% | 27.5% | 34.8% | <0.001 |
| Hypercholesterolemia | 28.4% | 29.2% | 25.7% | 0.38 |
| Comorbidities | | | | |
| Prior myocardial infarction | 26.7% | 32.1% | 32.5% | <0.001 |
| History of CKD | 3.6% | 3.7% | 3.5% | 0.96 |
| History of vascular disease | 6.3% | 11.1% | 9.9% | <0.001 |
| Medications on admission | | | | |
| Aspirin | 38.0% | 46.7% | 45.2% | <0.001 |
| Beta-blocker | 27.2% | 30.7% | 31.8% | 0.001 |
| Calcium channel blocker | 23.6% | 30.3% | 28.7% | <0.001 |
| Diuretic | 11.1% | 23.0% | 32.2% | <0.001 |
| ACE inhibitor | 18.4% | 29.2% | 35.0% | <0.001 |
| Cholesterol-lowering agents | 20.2% | 21.9% | 20.2% | 0.54 |
| Clinical data | | | | |
| Hours from index to randomization | 40 (25, 56) | 42 (26, 59) | 43 (26, 59) | 0.03 |
| Systolic blood pressure (mm Hg) | 128 (113, 140) | 130 (115, 145) | 130 (110, 140) | 0.20 |
| Heart rate (beats/min) | 70 (62, 80) | 72 (64, 80) | 72 (64, 83) | <0.001 |
| Killip class II–IV | 6.6% | 15.2% | 24.5% | <0.001 |
| ST-segment deviation | 70.5% | 74.9% | 77.1% | <0.001 |
| STEMI | 32.8% | 30.6% | 31.0% | 0.15 |
| UA/non–STEMI | 67.2% | 69.4% | 69.0% | |
| Elevated cardiac markers (local) | 70.6% | 68.9% | 71.1% | 0.72 |
| Serum creatinine | 0.8 (0.7, 0.9) | 1.0 (0.9, 1.2) | 1.2 (1.0, 1.4) | <0.001 |
| Creatinine clearance | 106.7 (83.7, 133.3) | 77.7 (60.3, 96.7) | 61.6 (48.7, 78.8) | <0.001 |
| Estimated GFR (MDRD) | 95.7 (82.3, 112.5) | 74.5 (62.4, 89.1) | 60.5 (48.9, 74.1) | <0.001 |
| CK-MB (× upper limit of normal) | 3.3 (1.0, 10.4) | 2.3 (0.9, 9.9) | 3.5 (1.0, 10.1) | 0.46 |
| White blood cell count | 7.9 (6.5, 9.7) | 8.2 (6.7, 10.2) | 9.0 (7.1, 11.6) | <0.001 |
| Hemoglobin | 13.7 (12.8, 14.7) | 13.6 (12.6, 14.5) | 13.1 (12.0, 14.3) | <0.001 |
| CRP (mg/l, n = 3,143) | 10 (4, 33) | 10 (3, 34) | 18 (6, 68) | <0.001 |
| BNP (pg/ml, n = 2,445) | 74.8 (42.0, 128.2) | 101.2 (57.9, 188.2) | 129.6 (72.3, 233.1) | <0.001 |

Values in parentheses indicate 25th and 75th percentiles.

ACE = angiotensin-converting enzyme; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CK = creatinine kinase; CKD = chronic kidney disease; CRP = C-reactive protein; GFR = glomerular filtration rate; STEMI = ST-elevation myocardial infarction; UA = unstable angina.

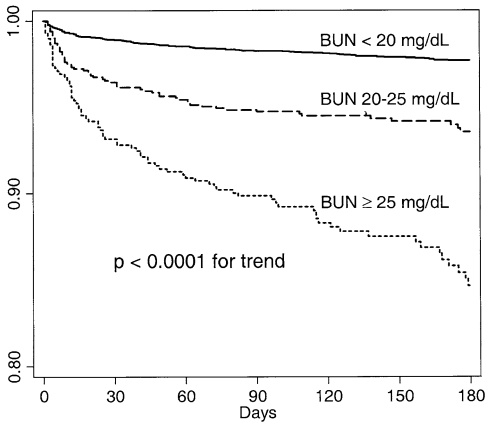


**Figure 1.** Kaplan-Meier survival estimates by blood urea nitrogen (BUN) level.

Laboratory data, including BUN, were obtained at the time of enrollment and were assayed at a central core laboratory. The eCrCl was calculated by the Cockcroft-Gault equation. The eGFR was calculated using the abbreviated Modification of Diet in Renal Disease formula (4). Levels of C-reactive protein (CRP) were measured in 3,143 patients as part of a nested case-control study within the OPUS-TIMI-16 trial; B-type natriuretic peptide (BNP) was measured in 2,445 patients in the orbofiban 50/50 treatment group; troponin-I was measured in 2,514 patients in the placebo group. The core laboratory upper limit of normal for BUN was 25 mg/dl. Patients were divided into three groups: those with BUN <20 mg/dl, BUN 20 to 25 mg/dl, and BUN ≥25 mg/dl.

**Statistical analysis.** Continuous variables are reported as the median (25%, 75% interquartile range). Linear regression and the chi-square test and test for trend were used to compare variables across ordered categories. Kaplan-Meier survival curves and six-month event rates were estimated, and the log-rank test and test of trend were used for comparisons among groups. Stratified analyses were performed to assess for potential confounding by significant covariates. Cox proportional hazards regression was used in multivariable analyses with mortality at the outcome variable, including as candidate covariates other known correlates of mortality and baseline characteristics associated with higher BUN ($p < 0.05$) in univariate analyses. The proportional hazards assumption for the model was confirmed. As biomarker data were not available for all patients, these were not included as covariates in the initial multivariable model, but were included in stratified analyses and in further multivariable models. Analyses were performed using Stata 8.2 (Stata Corp., College Station, Texas).

## RESULTS

The median BUN was 15.1 mg/dl (12.0, 18.4). There was a stepwise increase in the degree of baseline comorbidity as well as in adverse presenting characteristics among patients with increasing BUN (Table 1). The frequency of a reported history of CKD before the index admission was similar among groups. Consistent with the exclusion criteria of the OPUS-TIMI-16 trial, the median sCr was 0.8 mg/dl (0.7, 1.0), with a median eCrCl of 100.0 ml/min (77.1, 127.7) and a median eGFR of 91.9 ml/min/1.73 $m^2$ (76.8, 108.8).

**BUN and cardiovascular outcomes.** Higher concentrations of BUN were associated with a stepwise increase in mortality at 30 days and throughout the follow-up period (Fig. 1). Patients with higher BUN were more likely to have recurrent myocardial infarction and congestive heart failure by 30 days (Fig. 2), were less likely to undergo revascularization, were more likely to experience a stroke, and also had more frequent adjudicated bleeding events.

**Stratified analyses.** The association between BUN and mortality remained significant in analyses stratified by age, normal or abnormal eGFR (Fig. 3A), sCr <1.2 or >1.2 (Fig. 3B), and eCrCl (Fig. 3C). Blood urea nitrogen was associated with stepwise increases in mortality in all three study treatment groups (to placebo or one of two doses of

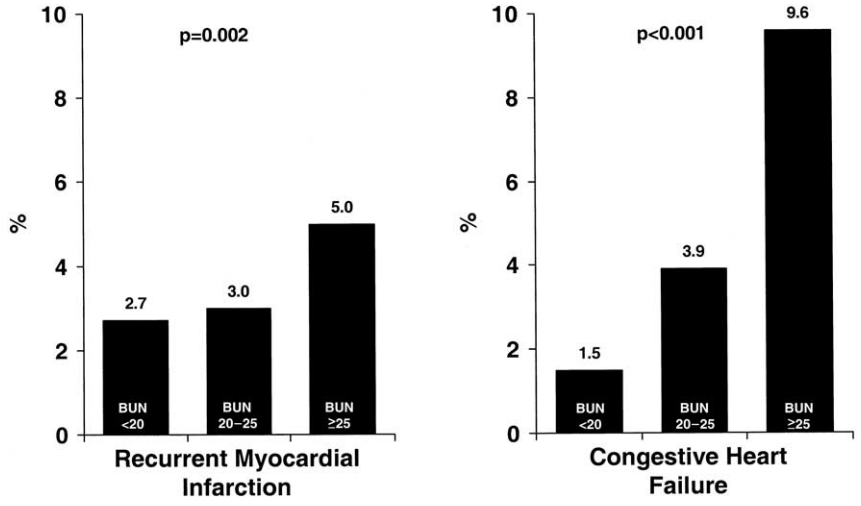


**Figure 2.** Association of blood urea nitrogen with 30-day recurrent myocardial infarction and congestive heart failure.

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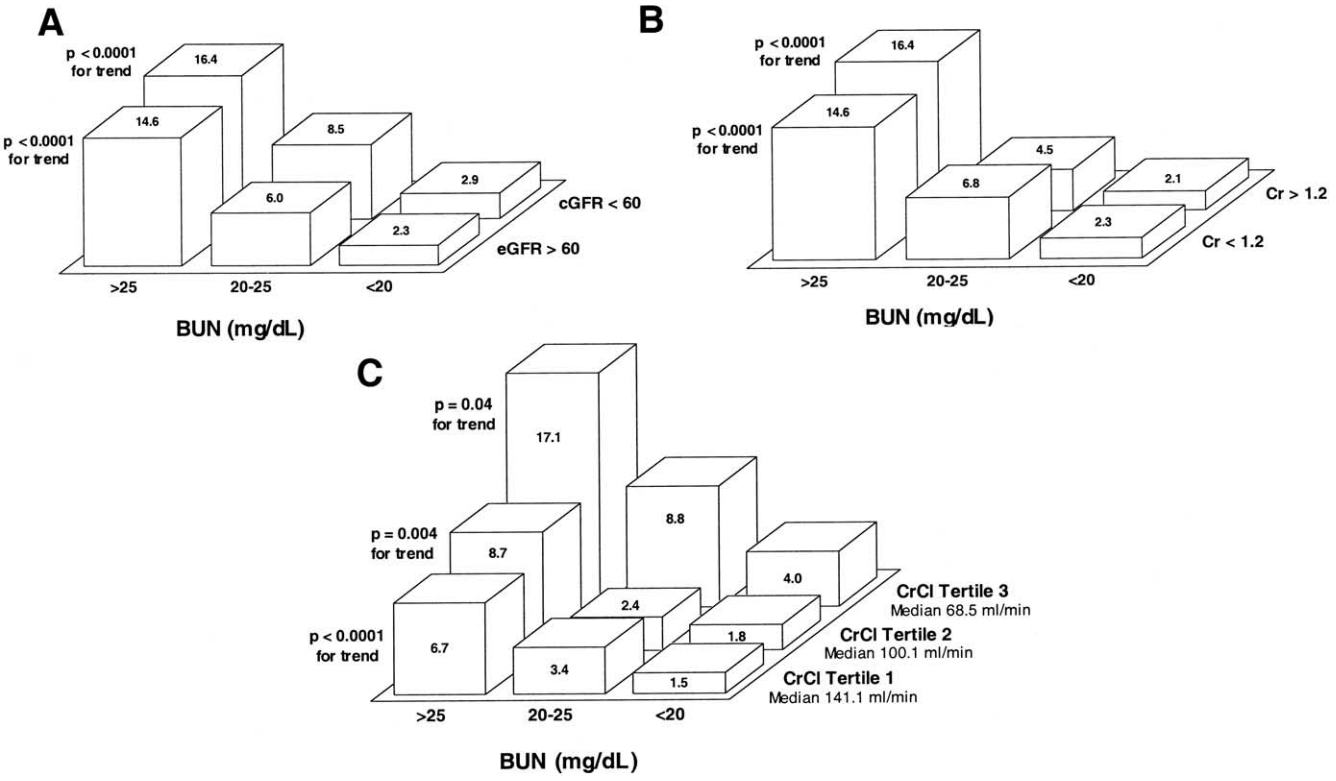


**Figure 3.** **(A)** Relation of blood urea nitrogen (BUN) and mortality estimates at six months stratified by estimated glomerular filtration rate (eGFR). **(B)** Relation of BUN and mortality estimates at six months stratified by serum creatinine. **(C)** Relation of BUN and mortality estimates at six months stratified by estimated creatinine clearance (CrCl).

orbofiban) and irrespective of the type of ACS: ST-segment elevation myocardial infarction (STEMI) (1.8% vs. 7.2% vs. 15.5%, $p < 0.001$), non-STEMI (2.9% vs. 7.9% vs. 17.7%, $p < 0.001$), and unstable angina (2.3% vs. 5.3% vs. 13.8%, $p < 0.001$). Stepwise increases in mortality with higher BUN were also observed when the data were stratified by the presence of ST-segment deviation; cardiac marker elevation, including baseline troponin-I status; and baseline hemoglobin.

Blood urea nitrogen was associated with increased mortality when stratified by Killip class (Fig. 4A) and BNP level ($n = 2,445$) (Fig. 4B). Among the 3,143 patients with available CRP data, BUN was associated with increased mortality when stratified by CRP using a cutpoint of 15 mg/l, a value previously shown to offer discriminatory capacity in the dataset.

**Multivariable analyses.** A stepwise increase in mortality was observed with increasing levels of BUN (HR 1.9 [1.3 to 2.6] with BUN 20 to 25 mg/dl; HR 3.2 [2.2 to 4.7] with BUN ≥25 mg/dl) in a multivariable model adjusting for baseline covariates (Table 2). This association was unchanged when either eCrCl or sCr was substituted in the model in place of eGFR and when the model was limited to patients without adjudicated bleeding complications during the follow-up period. The independent and graded association between BUN and mortality persisted after further adjustment for troponin-I, CRP, or BNP in patients in whom these data were available.

## DISCUSSION

Whereas prior studies have demonstrated an association between CKD and adverse outcomes in patients with ACS, the majority of these studies have employed creatinine-based metrics (sCr, eCrCl, or eGFR) to estimate kidney

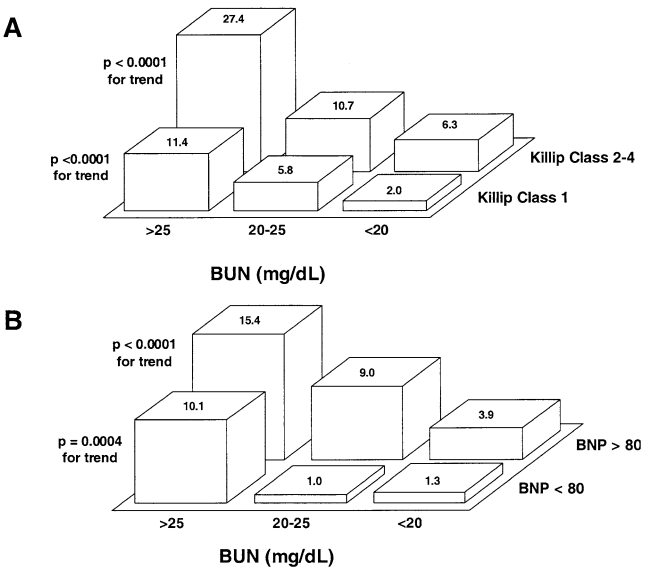


**Figure 4.** **(A)** Relation of blood urea nitrogen (BUN) and mortality estimates at six months stratified by Killip class. **(B)** Relation of BUN and mortality estimates at six months stratified by B-type natriuretic peptide (BNP).

**Table 2.** Multivariable Model of Mortality by Six Months

| Variable | Hazard Ratio | 95% CI | p Value |
|---|---|---|---|
| BUN <20 mg/dl | Reference | — | — |
| BUN 20–25 mg/dl | 1.86 | 1.30–2.65 | 0.001 |
| BUN ≥25 mg/dl | 3.22 | 2.23–4.67 | <0.001 |
| Age (per yr) | 1.05 | 1.03–1.06 | <0.001 |
| Abnormal Killip class | 1.79 | 1.32–2.45 | <0.001 |
| Diuretic use before to admission | 1.75 | 1.29–2.37 | <0.001 |
| Baseline hemoglobin (per g/dl) | 0.86 | 0.79–0.94 | 0.001 |
| Admission systolic blood pressure (per mm Hg) | 0.99 | 0.98–1.00 | 0.002 |
| History of peripheral vascular disease | 1.58 | 1.14–2.18 | 0.006 |
| History of diabetes mellitus | 1.41 | 1.07–1.86 | 0.015 |
| Weight (per kg) | 0.99 | 0.98–1.00 | 0.021 |
| Elevated cardiac markers | 1.42 | 1.05–1.91 | 0.021 |
| Orbofiban 50 mg/30 mg study group | 1.43 | 1.05–1.95 | 0.022 |
| Admission heart rate (beat/min) | 1.01 | 1.00–1.02 | 0.029 |
| eGFR (ml/min/1.73 $m^2$) | 1.00 | 1.00–1.01 | 0.071 |
| Hours from index event to randomization | 1.00 | 0.99–1.00 | 0.197 |
| ST-segment deviation | 1.21 | 0.89–1.65 | 0.217 |
| Orbofiban 50 mg/50 mg study group | 1.22 | 0.88–1.68 | 0.226 |
| ACE inhibitor use before admission | 1.19 | 0.88–1.62 | 0.264 |
| Male gender | 1.11 | 0.82–1.50 | 0.491 |
| History of congestive heart failure | 1.12 | 0.76–1.65 | 0.573 |
| History of hypertension | 0.99 | 0.75–1.32 | 0.953 |

CI = confidence interval; eGFR = estimated glomerular filtration rate; other abbreviations as in Table 1.

function. The present study adds to these observations by demonstrating that BUN is associated with increased mortality in a heterogeneous group of ACS patients with normal to mildly reduced GFR, independent of baseline clinical characteristics, sCr-based estimates of kidney function, and other biomarkers. These findings particularly highlight the importance and complexity of assessing kidney function among patients with ACS.

Both BUN and sCr are imperfect measures of kidney function and are influenced by factors other than GFR (11). In particular, the BUN concentration is determined by the balance of urea generation and excretion by the kidneys, the latter being dependent on the extent of urea reabsorption. Urea is reabsorbed with sodium and water in the proximal tubule in a passive process, whereas in the more distal nephron, urea reabsorption is closely linked to water reabsorption under the influence of antidiuretic hormone (12), which in turn is affected by angiotensin-II (7). Thus, in addition to reflecting GFR, an elevated BUN can further reflect a state of renal hypoperfusion from hypovolemia, renovascular disease, or reduced cardiac output (13,14). In these states, BUN may rise independent of a change in GFR or sCr due to enhanced urea reabsorption under the activation of the sympathetic nervous and renin-angiotensin-aldosterone systems (7), known correlates of cardiovascular risk. This may be of particular relevance in patients with milder reductions in GFR, such as those patients included in the present analysis.

The majority of studies in patients with ACS have focused on sCr, eCrCl, and eGFR as the metrics of kidney function associated with adverse outcomes. The current study demonstrates that the prognostic value of elevated BUN is independent of elevated sCr, eCrCl, and eGFR, and parallels observations among patients with congestive heart failure (14,15). Although sCr-based estimates of kidney function did not appear to provide additional prognostic value in the multivariable analysis after accounting for BUN, only 7.7% of patients in this study had moderate-severe impairment of eGFR owing to the exclusion criteria of the OPUS-TIMI-16 trial. This may have limited the power to detect differences in outcomes when combining BUN and sCr-based estimates of kidney function together. Alternatively, BUN may add prognostic value to sCr-based estimates of kidney function primarily among patients with milder degrees of impairment in GFR, who constitute the majority of patients with ACS.

Notably, the association between BUN and cardiovascular outcomes remained significant across strata of other biomarkers associated with increased cardiovascular risk, namely troponin-I, BNP, and CRP. In addition, the association between BUN levels and mortality was evident at values of 20 to 25 mg/dl, suggesting that even minimal elevations in BUN may be a marker of adverse outcomes.

**Study limitations.** This analysis is a nonrandomized retrospective analysis, and as such it is possible that both identified and unidentified confounders may have influenced the outcomes despite attempts to control for these factors through stratified and multivariable analyses. For example, the more prevalent use of diuretics at baseline among patients with elevated BUN may have been a surrogate of greater risk conveyed through occult congestive heart failure, other edematous states, or more profound hypertension. More specific information regarding types of medications (e.g., loop diuretics vs. thiazide diuretics, use of angiotensin receptor blockers) was not available. Furthermore, clinicians were not blinded to patient laboratory data, and, as such, there may have been unmeasured treatment differences among BUN groups that could have influenced outcomes. Our observation of an independent association between BUN concentration and mortality in patients with ACS may also be explained by factors that increase urea generation as well as urea reabsorption, including increased tissue catabolism or high dietary protein intake.

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