Association between Natriuretic Peptides and Mortality among Patients Admitted with Myocardial Infarction: A Report from the ACTION Registry®–GWTG™

Benjamin M. Scirica,1* Mitul B. Kadakia,2 James A. de Lemos,3 Matthew T. Roe,4 David A. Morrow,1 Shuang Li,4 Stephen D. Wiviott,1 and Michael C. Kontos,5 on behalf of the National Cardiovascular Data Registry

BACKGROUND: Patients with increased blood concentrations of natriuretic peptides (NPs) have poor cardiovascular outcomes after myocardial infarction (MI). The objectives of this analysis were to evaluate the utilization and the prognostic value of NP in a large, real-world MI cohort.

METHODS: Data from 41,683 patients with non–ST-segment elevation MI (NSTEMI) and 27,860 patients with ST-segment elevation MI (STEMI) at 309 US hospitals were collected as part of the ACTION Registry®–GWTG™ (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get with the Guidelines) (AR-G) between July 2008 and September 2009.

RESULTS: B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) was measured in 19,528 (47%) of NSTEMI and 9,220 (33%) of STEMI patients. Patients in whom NPs were measured were older and had more comorbidities, including prior heart failure or MI. There was a stepwise increase in the risk of in-hospital mortality with increasing BNP quartiles for both NSTEMI (1.3% vs 3.2% vs 5.8% vs 11.1%) and STEMI (1.9% vs 3.9% vs 8.2% vs 17.9%). The addition of BNP to the AR-G clinical model improved the C statistic from 0.796 to 0.807 (P < 0.001) for NSTEMI and from 0.848 to 0.855 (P < 0.003) for STEMI. The relationship between NPs and mortality was similar in patients without a history of heart failure or cardiogenic shock on presentation and in patients with preserved left ventricular function.

CONCLUSIONS: NPs are measured in almost 50% of patients in the US admitted with MI and appear to be used in patients with more comorbidities. Higher NP concentrations were strongly and independently associated with in-hospital mortality in the almost 30,000 patients in whom NPs were assessed, including patients without heart failure.

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Lipids, Lipoproteins, and Cardiovascular Risk Factors

1 TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; 2 Cardiovascular Division, Hospital of the University of Pennsylvania, Philadelphia, PA; 3 Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX; 4 Duke Clinical Research Institute and Division of Cardiology, Duke University Medical Center, Durham, NC; 5 Division of Cardiology, Pauley Heart Center, Virginia Commonwealth University, Richmond, VA.

* Address correspondence to this author at: TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital, 75 Francis St., Boston, MA 02115. Fax 617-734-7329; e-mail bscirica@partners.org.

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Nonstandard abbreviations: NP, natriuretic peptides; BNP, B-type NP; NT-proBNP, N-terminal pro-BNP; ACS, acute coronary syndrome; NSTEMI, non–ST-segment elevation myocardial infarction; NCDR (National Cardiovascular Data Registry); AR-G, ACTION Registry®–GWTG™ (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get with the Guidelines); IQR, interquartile range; LVEF, left ventricular ejection fraction; GEE, generalized estimating equation; OR, odds ratio; NRI, net reclassification improvement; IDI, integrated discrimination improvement; ORadj, adjusted OR.
Little is known about how these published data and guideline recommendations have influenced practice patterns regarding utilization of NPs in patients with ACS. Moreover, the performance of NP for improving risk stratification has yet to be evaluated in a large unselected population-based cohort of patients with acute MI, especially when measured in the context of modern comprehensive risk assessment models and standard cardiac biomarkers such as cardiac troponin. The objectives of these analyses therefore were to evaluate the utilization of NPs and to determine whether NPs offer incremental prognostic information in addition to standard risk tools in real-life clinical practice utilizing the National Cardiovascular Data Registry (NCDR)® ACTION Registry®–GWTG™. (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get with the Guidelines) (AR-G).

Materials and Methods

Between July 2008 and September 2009, data for 41 683 patients with NSTEMI and 27 860 patients with STEMI were captured at 309 US hospitals participating in the AR-G, a quality improvement registry of patients in the US with MI. Participating sites enrolled consecutive patients to ensure an unselected population. MI as defined for registry inclusion requires (a) ischemic symptoms at rest, lasting ≥10 min, occurring within 24 h of admission for NSTEMI and 72 h for STEMI and (b) electrocardiogram changes associated with STEMI (new left bundle-branch block or persistent ST-segment elevation ≥1 mm in 2 or more contiguous electrocardiographic leads) or (c) positive cardiac markers associated with NSTEMI (creatinine kinase MB or troponin I/T greater than the local laboratory upper limit of the reference interval) within 24 h after initial presentation. Patients were ineligible if they developed ischemic symptoms that meet the diagnostic criteria for STEMI and NSTEMI during hospitalization or were originally admitted for clinical conditions unrelated to STEMI and NSTEMI diagnosis (6).

Hospitals in this registry are diverse in size, teaching status, capacity, and region. Participating hospitals collect data through retrospective chart review using standardized data collection tools which do not require direct contact with individual patients. Data collected include patient demographics, presenting features, prehospital therapy, in-hospital therapy, hospital discharge therapy, timing of care delivery, laboratory tests, procedure use, and in-hospital patient outcomes. This registry was either approved by an institutional review board or the data were considered quality assurance data and not subject to institutional review board approval on the basis of individual site determinations (6).

Data definitions for the elements, including the definitions for the clinical endpoints of in-hospital mortality, NSTEMI, STEMI, heart failure, and cardiogenic shock, are available online (http://www.ncdr.com/WebNCDR/NCDRDocuments/ACTION_v2_CodersDataDictionary_2.1.1.pdf). NCDR has validated the data through a Data Quality Program to ensure accuracy and data completeness (7). Heart failure is defined as any of the following clinical symptoms of heart failure, described as unusual dyspnea on light exertion, recurrent dyspnea occurring in the supine position, fluid retention, or the description of rales, jugular venous distension, pulmonary edema on physical exam, or pulmonary edema on chest x-ray presumed to be cardiac dysfunction. A low ejection fraction without clinical evidence of heart failure does not qualify as heart failure. Cardiogenic shock is defined as a sustained (>30 min) episode of systolic blood pressure <90 mmHg, and/or cardiac index <2.2 L·min⁻¹·m⁻² determined to be secondary to cardiac dysfunction, and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support to maintain blood pressure and cardiac index above those specified levels. Transient episodes of hypotension reversed with intravenous fluid or atropine do not constitute cardiogenic shock. The first locally measured concentration of NT-ProBNP or BNP within 48 h of presentation was reported. Concentrations of NPs are reported as nanograms per liter and presented as medians with interquartile ranges (IQRs). The NP assay name was not collected. For statistical analyses, NPs were categorized in quartiles and further categorized using an accepted BNP cutpoint of 80 ng/L (8, 9). Normal left ventricular ejection fraction (LVEF) was defined as ≥50%.

Statistical Analyses

For summary statistics, the median was used for continuous variables and percentage was used for categorical variables. The multivariable associations between in-hospital mortality and NP values were assessed using a generalized estimating equations (GEEs) logistic regression model to account for clustering within the same hospital. Compound symmetric working correlation matrix and empirical (sandwich) SE estimates were used in the GEE method. The main interest variable NPs were categorized in quartiles in the multivariable model. The variables in the validated AR-G clinical in-hospital mortality model (10) were used for risk adjustment, including age, baseline serum creatinine, systolic blood pressure, heart failure and/or cardiogenic shock at presentation, ST-segment changes, heart rate, ratio of peak troponin to the upper limit of the reference interval, and prior peripheral arterial disease. Odds ratios (ORs) and 95% CIs were presented.
The clinical value of adding BNP to risk prediction models was further examined by comparing the C statistic (also known as the area under the ROC curve) calculated from the AR-G clinical in-hospital mortality model with the C statistic after adding BNP values to the AR-G clinical in-hospital mortality model. The difference of 2 C statistics was tested with the method of DeLong et al. (11). The net reclassification improvement (NRI) metric described by Pencina and colleagues (12) was also used to examine the clinical value of adding BNP to risk prediction models. Additionally, integrated discrimination improvement (IDI) was assessed as a method to quantify the differences in the probabilities for events and nonevents based on the addition of the new biomarkers to the model (12).

Sensitivity analyses were performed to evaluate the relationship between NP and outcomes in 2 subpopulations: patients with no history of heart failure and no heart failure or cardiogenic shock on admission (9620 NSTEMI patients and 6109 STEMI patients) and patients with LVEF within reference intervals (7640 NSTEMI patients and 3282 STEMI patients). A P value of <0.05 was considered statistically significant. All analyses were performed using SAS software (version 9.2, SAS Institute).

Results

Utilization of NPs

BNP or NT-proBNP was measured in 19,528 (47%) of 41,683 patients who presented with NSTEMI and in 9,220 (33%) of 27,860 patients who presented with STEMI. The distribution of hospitals according to the proportion of patients who had an NP measured is presented in Fig. 1. NPs were more likely to be measured in patients who were older or female; had a history of hypertension, diabetes, lung disease, MI, and heart failure; or presented with signs of heart failure or cardiogenic shock. Patients who had an NP measured were more likely to have extensive coronary artery disease but less likely to have a revascularization procedure. Over 90% of patients with and without NPs measured had LVEF assessed. An LVEF of ≥50% was less common among patients with NPs measured (47% vs 64% in NSTEMI and 41% vs 53% in STEMI). NPs were more likely to be measured in academic centers compared to nonacademic hospitals (50% vs 46% for NSTEMI and 35% vs 32% for STEMI). Patients in whom NPs were measured had higher rates of in-hospital mortality (5.4% vs 2.5%, P < 0.001) and cardiogenic shock (4.0% vs 1.7%, P < 0.001) compared to those patients in whom NPs were not measured (see Tables 1 and 2 in the Data Supplement that accompanies the online version of this report at http://www.clinchem.org/content/vol59/issue8).

Clinical Characteristics and NPs

Among patients with an NP measured (n = 28,597), BNP was measured more commonly than NT-proBNP (91% vs 9%). In NSTEMI, the median BNP was 316 ng/L (IQR 95, 855 ng/L) and NT-proBNP was 1910 ng/L (IQR 545, 6694 ng/L). In STEMI, the median BNP

Fig. 1. Utilization of NP measurements as assessed by the proportion of patients in whom NPs were measured per individual hospital.

Fewer than 25% of hospitals measured NPs in more than 75% of patients admitted with MI.
was 132 ng/L (IQR 35, 435 ng/L) and NT-proBNP was 831 ng/L (IQR 154, 3271 ng/L). A BNP \( \geq 80 \text{ ng/L} \) was identified in 13 171 (78%) of patients with NSTEMI and in 4882 (60%) of patients with STEMI.

As expected, NSTEMI and STEMI patients with greater comorbidities, delayed presentation, heart failure, and shock on admission had higher concentrations of BNP. Heart failure on admission was present in 69% of NSTEMI patients and 43% of STEMI patients in the highest BNP quartiles compared with 5% in the lowest BNP quartiles. A total of 53% of patients in the highest quartile of NP in NSTEMI and 44% in the highest quartile of STEMI had 3-vessel coronary disease, although rates of revascularization in NSTEMI and reperfusion therapy in STEMI were lower in the higher quartiles of BNP (see online Supplemental Tables 3 and 4).

### BNP AND OUTCOMES

There was a stepwise increase in the rates of in-hospital death with each quartile of BNP in NSTEMI and STEMI, with a similar and consistent pattern for death within 48 h of admission, heart failure, or cardiogenic shock (Table 1). After adjustment for variables included in the mortality model, a significant graded association remained between BNP and in-hospital mortality, with a >3-fold increased risk observed in the highest quartile compared to the lowest quartile (Fig. 2).

Similar patterns were observed for NT-proBNP and outcomes (data not shown).

### DISCRIMINATION AND RECLASSIFICATION

The addition of BNP to the mortality model significantly improved the discrimination as assessed by the C statistic (from 0.796 to 0.807, \( P < 0.001 \), for NSTEMI and from 0.848 to 0.855, \( P = 0.003 \), for STEMI) and IDI, and reclassification as determined by NRI (Table 2).

### PATIENTS WITHOUT A HISTORY OF HEART FAILURE OR SHOCK, OR WITH PRESERVED LVEF

Among patients with no history of heart failure and no heart failure or shock on admission, the median concentration of BNP was 136 ng/L (IQR 45, 364 ng/L) for NSTEMI \( (n = 9620) \) and 81 ng/L (IQR 25, 264 ng/L) for STEMI \( (n = 6109) \). The relationship between NP and death was similar in this lower risk population, with a stepwise increase in the risk of death observed with increasing quartiles of BNP (Fig. 3A), and in patients with a BNP \( >80 \text{ ng/L} \) [adjusted OR (ORadj) 2.02; 95%, CI 1.44–2.83; \( P < 0.001 \) in STEMI and ORadj 2.77; 95%, CI 1.71–4.49; \( P < 0.001 \) in NSTEMI]. The addition of BNP to the clinical model improved met-

### Table 1. In-hospital outcomes according to NP quartiles.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>BNP Q1</th>
<th>BNP Q2</th>
<th>BNP Q3</th>
<th>BNP Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSTEMI</strong> ( (n = 17803) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5.3%</td>
<td>1.3%</td>
<td>3.2%</td>
<td>5.8%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Death within 48 h of admission</td>
<td>1.6%</td>
<td>0.4%</td>
<td>0.7%</td>
<td>1.7%</td>
<td>3.5%</td>
</tr>
<tr>
<td>MI</td>
<td>1.2%</td>
<td>1.0%</td>
<td>1.0%</td>
<td>1.1%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>12.3%</td>
<td>2.7%</td>
<td>6.9%</td>
<td>17.1%</td>
<td>22.8%</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>4.0%</td>
<td>1.8%</td>
<td>2.5%</td>
<td>5.2%</td>
<td>6.8%</td>
</tr>
<tr>
<td><strong>STEMI</strong> ( (n = 8478) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>7.9%</td>
<td>1.9%</td>
<td>3.9%</td>
<td>8.2%</td>
<td>17.9%</td>
</tr>
<tr>
<td>Death within 48 h of admission</td>
<td>3.1%</td>
<td>0.8%</td>
<td>1.2%</td>
<td>3.2%</td>
<td>7.2%</td>
</tr>
<tr>
<td>MI</td>
<td>1.7%</td>
<td>1.0%</td>
<td>1.1%</td>
<td>2.0%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>13.6%</td>
<td>3.1%</td>
<td>6.9%</td>
<td>14.6%</td>
<td>30.3%</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>9.7%</td>
<td>4.0%</td>
<td>6.4%</td>
<td>10.0%</td>
<td>18.5%</td>
</tr>
</tbody>
</table>
rics of discrimination and reclassification (Table 2). In patients with LVEF within reference intervals, the median concentration of BNP was 157 ng/L (IQR 50, 447 ng/L) for NSTEMI (n = 7640) and 65 ng/L (IQR 21, 200 ng/L) for STEMI (n = 3238). A similar stepwise increase in the risk of death was observed with increasing quartiles in all subgroups (Fig. 3B) and in patients with a BNP ≥ 80 ng/L (ORadj 2.57; 95%, CI 1.32–4.97; \( P < 0.001 \)) in STEMI and ORadj 2.59; 95%, CI 1.39–4.82; \( P = 0.003 \) in NSTEMI). The addition of BNP to the clinical model improved the metrics of discrimination but not reclassification (Table 2).

Discussion

In this cohort of almost 70,000 patients admitted to US hospitals with an acute MI, NPs were measured in almost 50% of patients admitted with NSTEMI and one-third of patients with STEMI. Utilization of NP measurements was higher among patients who had more comorbidities and those presenting with signs of heart failure or cardiogenic shock. Among the almost 30,000 patients who had an NP measured, higher concentrations of NPs were strongly and independently associated with in-hospital mortality in patients with STEMI and NSTEMI, even after extensive adjustments for baseline characteristics and severity of presentation, and after excluding patients with a history of heart failure or heart failure/cardiac shock on presentation, as well as those with impaired left ventricular systolic function. Moreover, the addition of BNP to a validated clinical risk model significantly improved model discrimination and risk classification for inpatient mortality.

Over the past decade, multiple studies have consistently demonstrated a consistent, graded relationship between higher concentrations of NPs and the risk of death and heart failure following ACS (8, 9, 13–16). The majority of studies, though, were performed within clinical trial populations, which by design generally exclude patients with greater comorbidities, in particular heart failure or shock on presentation. Moreover, clinical trials tend to underenroll elderly individuals and women (17). One prior large registry that included NP results was limited to patients with NSTEMACS (non–ST-segment elevation acute coronary syndrome) (5). Thus generalization of the prognostic value of NPs to a broad population of patients with MI has lacked confirmation in large, community-based populations such as were included in our study, which included patients admitted to over 300 US hospitals.
Table 2. Improvement in discrimination and reclassification for in-hospital mortality after addition of BNP.

<table>
<thead>
<tr>
<th></th>
<th>NSTEMI</th>
<th>STEMI</th>
<th></th>
<th>C statistic</th>
<th>NRI P value</th>
<th>IDI P value</th>
<th></th>
<th>C statistic</th>
<th>NRI P value</th>
<th>IDI P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P compared to clinical model</td>
<td>NRI P value</td>
<td>IDI P value</td>
<td>P compared to clinical model</td>
<td>NRI P value</td>
<td>IDI P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td>0.796</td>
<td>—</td>
<td>—</td>
<td></td>
<td>0.848</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AR-G clinical model</td>
<td>0.807 (P &lt; 0.001)</td>
<td>0.0326 (P = 0.0469)</td>
<td>0.00408 (P = 0.0008)</td>
<td></td>
<td>0.855 (P = 0.003)</td>
<td>0.0669 (P = 0.0003)</td>
<td>0.00851 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ BNP</td>
<td></td>
<td></td>
<td></td>
<td>0.764</td>
<td>—</td>
<td>—</td>
<td></td>
<td>0.804</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Patients without prior heart failure or heart failure/cardiogenic shock on presentation</td>
<td></td>
<td></td>
<td></td>
<td>0.799 (P &lt; 0.001)</td>
<td>0.0702 (P = 0.0759)</td>
<td>0.0116 (P = 0.0006)</td>
<td></td>
<td>0.820 (P = 0.00979)</td>
<td>0.0874 (P = 0.0376)</td>
<td>0.0152 (P = 0.0003)</td>
</tr>
<tr>
<td>AR-G clinical model</td>
<td>0.798</td>
<td>—</td>
<td></td>
<td>0.867</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>+ BNP</td>
<td>0.822 (P = 0.00226)</td>
<td>0.0159 (P = 0.684)</td>
<td>0.00550 (P = 0.110)</td>
<td></td>
<td>0.876 (P = 0.159)</td>
<td>0.0727 (P = 0.224)</td>
<td>0.0133 (P = 0.0172)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig. 3. In-hospital mortality according to the quartile of BNP in patients with NSTEMI and STEMI limited to (A) patients with no history of heart failure and no heart failure (HF) or cardiogenic shock on presentation and (B) patients with preserved left ventricular function (LVEF ≥50%).

sCr, serum creatinine; SBP, systolic blood pressure; cTn:ULN, cardiac troponin: upper limits of normal; PAD, peripheral artery disease.
The evaluation and eventual incorporation of new prognostic tests requires that a new test offers significant and incremental improvement above other currently employed techniques (18). In this analysis, NPs significantly improved the ability to identify patients at highest risk of inpatient mortality. When added to a validated clinical model that incorporates baseline characteristics and details of clinical presentation (10), NPs provided incremental prognostic information as assessed by improvement in the C statistic, NRI, and IDI. This is noteworthy given how well the NCDR AR-G mortality model performed without NP (C statistic = 0.798 for NSTEMI and 0.848 for STEMI) and also because it uses a single, short-term endpoint, inhospital mortality. Therefore, in this registry population and among subpopulations without a history or clinical signs of heart failure or who had LVEF within reference intervals, NPs fulfill this standard of proof. This is in contrast to several smaller studies that did not find any improvement of the C statistic for in-hospital mortality with the addition of NPs to other clinical risk scores (19, 20).

Several studies have demonstrated that NPs also offer incremental prognostic information when used together with cardiac troponin (16, 21). In our study, after adjustment for the degree of troponin elevation above the upper limit of the reference interval, an indirect estimate of infarct size, NPs remained significantly associated with an increased risk of in-hospital mortality.

Measurement of NPs appears to improve risk stratification of patients with MI beyond baseline clinical variables and quantitative results of cardiac troponin. Consistent data on how an increased NP result should guide specific therapy or treatment in ACS are lacking, (2) although some (21) but not all studies (22) suggest that revascularization may improve outcomes in patients with increased NPs. Studies specifically designed to evaluate whether specific treatment strategies targeted at patients with increased NPs can modify the associated risk or are useful to follow therapy are needed to better define the utility of routine measurement of NPs in ACS (2, 23).

An important distinction between this registry and prior studies is that NPs were measured at the treating physician’s discretion, which resulted in inherently different utilization patterns. Based on the clinical characteristics and the overall higher concentrations of NPs observed in our study compared to most previously reported investigations, it appears that physicians measured NPs more frequently in patients who were sicker and more likely to have a prior heart failure or signs of heart failure on admission. For example, the median concentration of BNP was 316 ng/L in NSTEMI patients and 132 ng/L in STEMI; in contrast, in a lower-risk clinical trial population in which NPs were assessed in all patients, the median BNP was 81 ng/L (8). Another difference from clinical trial populations was the higher concentration of NPs among patients with NSTEMI compared to those with STEMI. This was likely due to the codiagnosis of heart failure in patients with MI, in particular in patients with NSTEMI, who tend to have more comorbidities compared to patients presenting with STEMI. Additionally, the lower median concentration of NPs in patients with STEMI may reflect testing that occurred at the time of admission, rather than several hours after presentation, when values are typically higher.

As in any observational study, there is always concern over residual confounding. In addition to robust multivariable modeling, we attempted to minimize confounding by performing sensitivity analyses that excluded patients with a history or evidence of heart failure or impaired ventricular systolic function. The consistency of the relationship between NPs and outcomes in patients with heart failure and preserved ventricular function further supports the hypothesis that NPs improve risk stratification, even among a population without any clinically overt heart failure. Another consideration when comparing data from different hospitals is that NPs were assessed with commercially available assays that vary in terms of sensitivity and precision on the basis of the specific antibody used to detect NP. Introduction of newer assays since these data were collected further limits generalizability to the most current generation of NP assays (24, 25). We did not collect data regarding which assay was used at each hospital and therefore can neither compare assay performance nor comment about specific cutpoints for each individual assay. Moreover, over the past several years, the introductions of more sensitive troponin assays have improved diagnosis and prognosis in MI Because none of the high-sensitive troponin assays are approved for use in the US, we are unable to evaluate NPs in the context of a more sensitive assays of necrosis.

Utilization of NPs in patients presenting with MI in the US varies widely between hospitals, and overall, NPs are measured in almost 50% of patients. Clinicians appear to measure NPs in patients with greater comorbidities who would otherwise be considered at highest risk. In over 30,000 patients with MI, we found that NPs significantly improved the risk discrimination for in-hospital mortality beyond a validated clinical risk score; however, the incremental improvement in risk stratification was found even among patients who would typically be considered lower risk based on the absence of a history of heart failure or presenting signs of cardiogenic shock or heart failure, and those with preserved LVEF. Therefore it is in this population, who

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otherwise would be considered at low risk, that NPs may add the greatest incremental benefit for risk stratification. Specific treatment strategies targeted toward patients with increased concentrations of NPs should be a focus of future prospective studies.

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References


