Cardiac Troponin Measurement in the Critically Ill: Potential for Guiding Clinical Management

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Background: Elevated cardiac troponin (cTn) in the absence of acute coronary syndromes (ACS) is associated with increased mortality in critically ill patients. There are no evidence-based interventions that reduce mortality in this group.

Objectives: We performed a retrospective investigation of the Veterans Administration Inpatient Evaluation Center database to determine whether drugs used in ACS (β-blockers, aspirin, and statins) are associated with reduced mortality in critically ill patients.

Methods: Thirty-day mortality was determined for non-ACS patients admitted to any Veterans Administration Intensive Care Unit between October 1, 2007, and September 30, 2008, adjusted for severity of illness. Troponin assay values were normalized across institutions.

Results: Multivariate analyses for 30-day mortality showed an odds ratio (OR) of 1.82 for patients with high cTn (P < 0.0001, cTn > 10% coefficient of variation) and 1.18 for intermediate cTn (P = 0.0021, cTn between lowest limit detectable and 10% coefficient of variation) compared with patients with no elevation, adjusting for severity of illness (n = 19,979). Logistic regression models showed that patients with no or intermediate elevations of cTn taking statins within 24 hours of cTn measurement had a lower mortality than patients not taking statins (OR, 0.66; 95% confidence interval [95% CI], 0.53–0.82; P = 0.0003), whereas patients with high cTn had a lower mortality if they were taking β-blockers or aspirin within 24 hours of cTn measurement compared to patients not taking β-blockers or aspirin (β-blockers: OR, 0.80; 95% CI, 0.68–0.94; P = 0.0077; aspirin: OR, 0.81; 95% CI, 0.69–0.96; P = 0.0134).

Conclusions: This retrospective study confirms an association between elevated troponin and outcomes in critically ill patients without ACS and identifies statins, β-blockers, and aspirin as potential outcome modifiers in a cTn-dependent manner.

Key Words: cardiac troponin, critically ill, β-blocker, aspirin, statin

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by this method. The backward elimination logistic regression model was used to statistically adjust for drug interactions among these 3 classes of medication.

Troponin Measurements
Both cTnT (cTnT) and cTnI (cTnI), components of a protein complex required for myocardial contraction, are well documented indicators of myocardial damage.\textsuperscript{11} The cTnT assays are standardized across institutions, however, cTnI assays are not. We therefore normalized values for cTnI using the appropriate manufacturer assay information. Appendix 2 provides a detailed list of the assays used and their reference ranges (μg/L). The peak cTnI or cTnT measured within 24 hours from admission to discharge from the ICU was extracted. Facilities were sent a survey asking them to identify which troponin assay they were using. Standard ranges for each assay were used across all facilities. If this information was not available, these patients were excluded from the mortality analysis (n = 3207). The cTnI below the lowest limit detectable was classified as no elevation, levels between the lowest limit detectable and the 10% coefficient of variation (CV) were classified as intermediate elevation, and levels greater than the 10% CV were classified as high elevation. This classification was used to normalize cTn values across a range of values familiar to practitioners, not to classify patients according to the presence or absence of myocardial infarction. The 10% CV for cTnI was the lowest concentration of cTnI in which the assay has a CV of 10% or less. The CV is a measure of variability that adjusts for the magnitude of the mean between assays, as compared to the standard deviation. The 10% CV is determined by assay manufacturers using samples of cTnI of known concentrations and is a measure of precision of the assay. For assays contemporary with this investigation, cTnI concentrations at the 99th percentile (accepted definition of myocardial infarction)\textsuperscript{11} were within the “intermediate range” (see Appendix 2), and the cTnI concentration for the 10% CV was greater than the 99th percentile cTnI concentration.

A large group of patients (30,943) did not have cTn measured and were not included in the mortality analysis; ramifications of this are discussed in the Limitations section. Appendices 3 and 4 present baseline characteristics between those with nondefinable troponin (n = 34,150) and those with definable troponin (n = 27,713).

Study Outcomes
The primary outcome was 30-day mortality with respect to aspirin, β-blocker, or statin use in each group: patients with negative cTn, intermediate cTn, or high cTn.

Severity of Illness Model
The IPEC uses a statistical model to predict the probability of mortality. This ICU risk-adjusted model was modeled after APACHE III and has been validated against and used with VA data since 1995.\textsuperscript{12–15} This model includes laboratory values primarily, but also the primary diagnosis/procedure on admission to the ICU, comorbid diagnoses, use of immunosuppressant drugs,
TABLE 1. Variables Used to Determine the Severity of Illness in the IPEC Model

| Variable                                    | Description                                                                 |
|----------------------------------------------|-----------------------------------------------------------------------------|
| Serum albumin, g/L                           |                                                                             |
| Serum bilirubin, mg/dL                       |                                                                             |
| Blood-urea-nitrogen, mg/dL                   |                                                                             |
| Hematocrit, %                                |                                                                             |
| Blood glucose, mg/dL                         |                                                                             |
| Serum sodium, mEq/L                          |                                                                             |
| White blood cell count ($\times 10^3$ mm$^3$) |                                                                             |
| Partial pressure of arterial oxygen (PaO$_2$)|                                                                             |
| Partial pressure of arterial carbon dioxide (PaCO$_2$) |                     |
| pH                                           |                                                                             |
| Glomerular filtration rate (age, sex, and race adjusted) |               |
| Primary diagnosis/procedure on admission to the ICU |                     |
| Age                                          |                                                                             |
| Comorbid diagnoses                           |                                                                             |
| Use of immunosuppressant drugs               |                                                                             |
| Source of admission into the ICU             |                                                                             |
| Length of stay before the ICU stay           |                                                                             |

source of admission into the ICU, and length of stay before the ICU stay (Table 1). For each laboratory value, the most abnormal value within 48 hours of admission (24 hours before or after) was used. If there was no laboratory value within this time frame, the mean of the normal range for that value was substituted.\textsuperscript{13}

Statistical Methods

Severity of Illness

A logistic regression model, similar to the IPEC model described above, was run on the cohort to obtain the predicted mortality for each patient at 30 days. This model was run because it was important to get an estimate of the severity of illness in a population without ACS. The logistic regression model assigns the probability of mortality to each patient (between 0 and 1). The linear predictor from this 30-day mortality was used as a covariate in subsequent troponin analyses to adjust for severity of illness. Laboratory values were modeled using restricted cubic splines, with the exception of PaCO$_2$ and pH which were combined and included as a categorical variable. Age was calculated at the time of hospital admission and modeled using a restricted cubic spline. Admission source was modeled as a categorical variable and included the following sources: outpatient clinic, emergency department, nursing home, operating room, other hospital ward, acute care ward, and other. Immunosuppressant drug use was modeled as a dichotomous variable (1, on immunosuppressants; 0, not on immunosuppressants) using a list of immunosuppressant drugs in the pharmacy package. The length of stay before ICU was calculated as the amount of time between hospital admission and ICU admission and was modeled using restricted cubic splines. A dichotomous variable was created to indicate whether or not the patient had an International Classification of Diseases-9 procedure code within the 24 hours surrounding ICU admission.

Descriptive statistics (frequencies and means) were generated for each variable included in the risk adjustment model. Appendices 3 and 4 contain the categorical and continuous variables used to perform the risk adjustments, respectively. The average probability of mortality, referred to as severity of illness in these analyses, was calculated among troponin elevation categories and by medication use.

Troponin Levels and Mortality

Univariate analyses examining the relationship between 30-day mortality and troponin elevation were conducted using $\chi^2$ tests. To determine if troponin is associated with mortality at 30 days after adjusting for severity of illness, a logistic regression model was run. This model included the linear predictor for each patient from the initial severity of illness calculation and troponin. Odds ratios (OR) and 95% confidence interval (95% CI) were calculated to compare mortality in patients with no troponin elevation to patients with high troponin or intermediate troponin elevation.

Medication Use and Outcome

Univariate analyses examining the relationship between mortality and medication use among each troponin elevation category were conducted using $\chi^2$ tests. Initial multivariate analyses suggested a significant interaction between cTn level and medication use (likelihood ratio test based on $\chi^2$ statistic of 9.837 with 3 degrees of freedom; $P = 0.0200$). Therefore, to determine if the use of $\beta$-blockers and/or statins and/or aspirin is associated with mortality reduction after adjusting for severity of illness, stratified logistic regression models were run. These models included the linear predictor for each patient from the initial severity of illness calculation, indicators for $\beta$-blockers, statins, and aspirin, and the interaction between $\beta$-blockers, statins, and/or aspirin. Stratified analyses were conducted among (1) those with no troponin elevation, (2) those with intermediate troponin elevation, and (3) those with high troponin elevation.
TABLE 2. Descriptive Statistics Age and Severity of Illness Increase With cTn, Whereas GFR Decreases With cTn

|               | cTn Negative (n = 7681) | cTn Intermediate (n = 8527) | cTn High (n = 3771) |
|---------------|--------------------------|----------------------------|---------------------|
| Age (SD), y   | 63.7 (12.5)              | 66.8 (12.4)                | 69.0 (12.2)         |
| Severity of illness (SD) | 0.09 (0.15)              | 0.14 (0.18)                | 0.22 (0.24)         |
| GFR (SD)      | 73.9 (42.5)              | 64.8 (39.6)                | 53.5 (43.8)         |

with high troponin elevation. All 3 logistic regression models were run for 30-day mortality. Both main effects and backward elimination models were conducted. The backward elimination model differs from the main effects model in that it includes not only the main effects of β-blockers, statins, and aspirin but also the interactions among these medications. In addition, terms are forced out one by one because they no longer achieve statistical significance at the 0.05 level. The inclusion significance level for the final backward elimination models was 0.05. Odds ratios and 95% CI were calculated for all covariates remaining in the backward elimination model. The final significance level used for all inferences was adjusted to account for the multiple tests as a result of stratification. Analyses were adjusted for severity of illness. SAS Version 9.3 was used for all analyses.

RESULTS

Characteristics of Patients

The cohort was predominantly men (96.6%) and white (68.7%). The majority of the patients were admitted for a respiratory diagnosis (18.7%), followed by infection (16.6%), gastrointestinal (15.5%), and cancer (12%) (Fig. 2). Patients who were cTn-negative were younger and had better renal function (Table 2), factors that were adjusted for in the mortality analysis.

Troponin and Mortality

Figure 3 shows the univariate analysis illustrating troponin level and 30-day mortality, Table 3 shows the tabulated results from each group. About 10.7% of the patients died at 30 days if they had no cTn elevation, whereas 16.6% of patients died if they had intermediate cTn, and 31.7% died at 30 days if they had high cTn (P < 0.0001). After adjusting for severity of illness, mortality among critically ill patients was proportional to cTn levels and statistically significant. Multivariate analysis showed that the odds of death were 1.82 times greater for patients with high cTn compared with no cTn elevation, and 1.18 times greater for patients with intermediate cTn compared with no cTn elevation (P < 0.0001), after adjusting for severity of illness. The differences between the intermediate and high cTn groups were also statistically significant. Patients who did not have a cTn level measured had a lower severity of illness than those patients who had the blood test: cTn not measured, mean severity of illness, 0.07 (SD 0.14, n = 34,150), cTn measured, mean severity of illness 0.13 (SD 0.19, n = 27,713).

Medication Use and Outcome

Univariate analyses showed an increase in mortality proportional to cTn level within each medication class. Thirty-day mortality in those with no cTn elevation, intermediate cTn, and high cTn was 31.3%, 38.5%, and 40.6%, respectively, for patients on β-blockers (P < 0.0001); 14.9%, 19.0%, and 22.7%, respectively, for patients on statins (P < 0.0001); and 15.9%, 21.4%, and 31.2%, respectively, for patients on aspirin (P < 0.0009). The results from the main effects model indicate that among those with no cTn elevation, statins were associated with lower mortality at 30 days (Table 4; OR, 0.68; 95% CI, 0.54–0.86). In those with an intermediate cTn elevation, statins were again associated with lower mortality at 30 days (OR, 0.69; 95% CI, 0.59–0.81). No relationships between mortality and β-blockers or aspirin were statistically significant for patients with negative or intermediate cTn. In contrast, among those with a high cTn elevation, statins were no longer statistically significant at 30 days, however, β-blockers (OR, 0.81; 95% CI, 0.68–0.95) and aspirin (OR, 0.81; 95% CI, 0.69–0.96) were associated with lower mortality. All analyses were adjusted for severity of illness. Inferences from the stratified models held up to multiple testing criteria.

The results from the backward elimination model were similar to the results from the main effects model (Table 5). In patients with no cTn or intermediate cTn elevation, statins alone were associated with lower mortality at 30 days (negative cTn: OR, 0.66; 95% CI, 0.53–0.82; intermediate cTn: OR, 0.69; 95% CI, 0.58–0.80). No relationships between mortality and β-blockers or aspirin were statistically significant for these groups. Patients with high cTn elevation, however, demonstrated an associated reduction in mortality with β-blockers (OR, 0.80; 95% CI, 0.68–0.94) and

FIGURE 3. Relationship between 30-day mortality and troponin level: no cTn elevation, 10.7% 30-day mortality; intermediate cTn, 16.6% 30-day mortality; high cTn, 31.7% 30-day mortality.
The relationship between cTn and mortality in critically ill patients is not new,1,3,4,8,16 but the actual 99th percentile of cTnI or T to consider a sample suggestive of myocardial infarction has been set by consensus,11 but the actual value of cTnI can vary based on the assay used. Cardiac troponin T values, however, are uniform because the assay is produced by a single manufacturer. One strength of this analysis is that cTnI values were normalized based on established cutoffs determined by the assay used, and this provided a large sample of patients within each cTnI range. This work and the majority of published studies support the finding that cTn elevation in critically ill patients is associated with increased mortality. Increasing mortality risk from no cTn elevation to intermediate to high cTn elevation also suggests that cTn may be a continuous marker of mortality risk, as it is in patients with an ACS.21 The timing of cTn assessment may impact the observed result. This analysis used the highest cTn level that occurred on admission to the ICU. In a recent prospective observational study of septic patients, cTnI was highest on the first day of admission and decreased thereafter.22 It is likely that our analysis included the earliest, therefore highest, cTn measurement.

The role of high sensitivity cTnT testing (hs-cTnT) in identifying ICU patients at increased mortality risk is not clear. The high sensitivity assays can detect as little as 10 ng/L of troponin in the serum as opposed to a lower limit of detection of 32 ng/L in contemporary cTnT testing.23 It is expected that high sensitivity testing would identify a larger group of at-risk patients who may benefit from the addition of aspirin, β-blocker, and statin. In a recent prospective observational study, hs-cTnT was measured in 144 consecutive ICU patients.24 Sixty-two patients (43%) had evidence of hs-cTnT elevation without findings of an ACS, a larger group than was found in a previous study using the contemporary assays (19%).16 The non-ACS patients identified with hs-cTnT testing had a higher mortality risk, as it is in patients with an ACS.21 Also, it suggests that cTn may be a continuous marker of mortality risk from no cTn elevation to intermediate to high cTn elevation.

### DISCUSSION

The purpose of this investigation was to determine whether treatments administered to patients with cTn elevation in the setting of critical illness are associated with improved short-term mortality. This large retrospective study demonstrated 2 major findings: first, that cTn is associated with 30-day mortality in critically ill patients in the absence of ACS, and second, that statins, aspirin, and β-blockers were associated with decreased mortality in a cTn-dependent manner.

### Troponin as an Independent Marker of Mortality

The relationship between cTn and mortality in critically ill patients is not new,1,3,4,8,16 but not all published work is in agreement.20 A limitation of studies using cTnI as a marker is that there are many cTnI assay manufacturers. The decision to use the 99th percentile of cTnI or T to consider a sample suggestive of myocardial infarction has been set by consensus,11 but the actual value of cTnI can vary based on the assay used. Cardiac troponin T values, however, are uniform because the assay is produced by a single manufacturer. One strength of this analysis is that cTnI values were normalized based on established cutoffs determined by the assay used, and this provided a large sample of patients within each cTnI range. This work and the majority of published studies support the finding that cTn elevation in critically ill patients is associated with increased mortality. Increasing mortality risk from no cTn elevation to intermediate to high cTn elevation also suggests that cTn may be a continuous marker of mortality risk, as it is in patients with an ACS.21 The timing of cTn assessment may impact the observed result. This analysis used the highest cTn level that occurred on admission to the ICU. In a recent prospective observational study of septic patients, cTnI was highest on the first day of admission and decreased thereafter.22 It is likely that our analysis included the earliest, therefore highest, cTn measurement.

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### TABLE 3: Effect of Troponin Level on Mortality: cTn Cohorts With Other Cardiac Diagnoses (27,713) and Without Other Cardiac Diagnoses (19,979)

| Mortality, d | Effect | cTn Cohort With Other Cardiac Diagnoses (n=27,713) | cTn cohort Without Other Cardiac Diagnoses (n = 19,979) |
|-------------|--------|-----------------------------------------------|-----------------------------------------------------|
| 30          | Troponin—intermediate vs none | Odds Ratio (CI) | P          | Odds Ratio (CI) | P          |
|             | 1.18 (1.07–1.30) | 0.0012 | 1.18 (1.06–1.31) | 0.0021 |
|             | Troponin—high vs none   | 1.79 (1.61–2.00) | <0.0001 | 1.82 (1.62–2.04) | <0.0001 |
|             | Troponin—high vs intermediate | 1.53 (1.39–1.68) | <0.0001 | 1.54 (1.39–1.71) | <0.0001 |

Odds ratios adjusted for severity of illness. Severity of illness was statistically significant in all models (P < 0.0001).

### TABLE 4: Effect of Medication Use on Mortality According to cTn Level—Main Effects Model

| Troponin Elevation | Mortality, d | Effect | cTn Cohort With Other Cardiac Diagnoses (n = 27,713) | cTn Cohort Without Other Cardiac Diagnoses (n = 19,979) |
|-------------------|-------------|--------|-----------------------------------------------|-----------------------------------------------------|
| None              | 30          | On β-blocker | Odds Ratio (95% CI) | P          | Odds Ratio (95% CI) | P          |
|                   |             | 0.89 (0.75–1.06) | 0.1899 | 0.93 (0.77–1.12) | 0.4310 |
|                   |             | On statin    | 0.66 (0.53–0.82) | 0.0001 | 0.68 (0.54–0.86) | 0.0011 |
|                   |             | On aspirin   | 0.87 (0.71–1.07) | 0.1999 | 0.91 (0.72–1.15) | 0.4287 |
| Intermediate      | 30          | On β-blocker | 0.94 (0.83–1.06) | 0.2994 | 0.98 (0.85–1.12) | 0.7440 |
|                   |             | On statin    | 0.70 (0.61–0.81) | <0.0001 | 0.69 (0.59–0.81) | <0.0001 |
|                   |             | On aspirin   | 0.92 (0.80–1.06) | 0.2480 | 0.99 (0.84–1.16) | 0.8507 |
| High              | 30          | On β-blocker | 0.82 (0.70–0.94) | 0.0063 | 0.81 (0.68–0.95) | 0.0090 |
|                   |             | On statin    | 0.99 (0.84–1.17) | 0.9095 | 0.99 (0.82–1.19) | 0.9105 |
|                   |             | On aspirin   | 0.77 (0.66–0.90) | 0.0007 | 0.81 (0.69–0.96) | 0.0165 |

cTn cohorts with other cardiac diagnoses (27,713) and cTn cohort without other cardiac diagnoses (19,979). Odds ratio adjusted for severity of illness. Severity of illness was statistically significant in all models (P < 0.0001).
Although cTn levels were not measured in these subjects, it is likely that the majority would have fallen into the high cTn group.

A meta-analysis of randomized controlled clinical trials of statins in septic patients, and a systematic review that included observational studies, provide conflicting results. Observational studies suggest a benefit from statin use, whereas randomized controlled clinical trials show no benefit in severe sepsis. It is possible that patients should be assessed for cTn, as our data suggests. In a randomized, double blind, placebo controlled study of statin use in septic patients on the ward, 40 mg of atorvastatin prevented conversion of sepsis to severe sepsis (4% vs 24%, P = 0.007). The mean APACHE II score for this group correlated to an anticipated mortality rate of 15%. This was similar to the cTn none and cTn intermediate groups in our investigation (mortality rates 10.7% and 16.6%, respectively). Statins may therefore benefit a lower-risk group.

That statins may benefit patients who are less severely ill, whereas β-blockers and aspirin may benefit patients who are more severely ill, suggesting different mechanisms of disease process intervention in each group. Unpublished studies from this group suggest microvascular obstruction as a cause for end-organ damage in extremely ill patients. Thus, benefit from aspirin would make sense in that the antiplatelet effect may mitigate microvascular obstruction. The benefits from β-blockers may be largely cardioprotective by reducing cardiac work and myocardial oxygen demand, as is observed in patients presenting with a myocardial infarction. Significant cTn release indicates myocardial damage has occurred.

Lastly, our investigation indicates that medications should be considered in all studies of mortality in critically ill patients,
as our data clearly show that medications are associated with outcome modification.

CONCLUSIONS

This large retrospective observational cohort study suggests that elevated cTn in critically ill patients without an ACS is an independent risk factor of 30-day mortality. Using 2 statistical models, our data further show lower 30-day mortality in both cTn-positive or -negative groups, depending on pharmacologic treatment. Patients with no or intermediate cTn elevation had a significantly lower associated risk of death if treated with statins, whereas cTn positive patients had a significantly lower associated risk of death if treated with aspirin and/or β-blockers. The presence of cTn in the blood of critically ill patients may identify populations of patients who benefit from different treatments, and in addition suggests a different pathophysiological mechanism of increased mortality in each group. This work supports the need for prospective translational studies that investigate the mechanisms of improved mortality in each group.

LIMITATIONS

There are several important limitations to this investigation. This is a retrospective investigation of all patients who happened to get a cTn level drawn during admission. It is possible that some of the patients who had the test drawn may have had some cardiovascular complaint or sign reflecting a higher degree of illness. This is supported by our data. Patients who did not have cTn measured were less severely ill than patients who had cTn measured. Addition of patients with a lower severity of illness might impact our finding that statins improved the outcome in patients with no cTn; however, this remains to be shown in a prospective clinical trial. We were only able to assay medication use during the hospital stay. We do not know whether the medications were being taken before admission, or for how long the medications were administered after the cTn assay. We cannot conclude from our work that cTn is a continuous variable. A large prospective clinical trial could clarify this and may also provide cutoff values. Lastly, high sensitivity assays were not available for wide use during the period of data collection. As discussed, hs-cTnT assays may improve the resolution at the lower cTn levels, but this remains to be investigated.

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REFERENCES

1. Ammann P, Maggiorini M, Bertel O, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. J Am Coll Cardiol. 2003;41:2004–2009.
2. John J, Woodward DB, Wang Y, et al. Troponin-I as a prognosticator of mortality in severe sepsis patients. J Crit Care. 2010;25:270–275.
3. Reynolds T, Cecconi M, Collinson P, et al. Raised serum cardiac troponin I concentrations predict hospital mortality in intensive care unit patients. Br J Anaesth. 2012;109:219–224.
4. Stein R, Gupta B, Agarwal S, et al. Prognostic implications of normal (<0.10 ng/ml) and borderline (0.10 to 1.49 ng/ml) troponin elevation levels in critically ill patients without acute coronary syndrome. Am J Cardiol. 2008;102:509–512.
5. Vasile VC, Chai HS, Abdeldayem D, et al. Elevated cardiac troponin T levels in critically ill patients with sepsis. Am J Med. 2013;126:1114–1121.
6. Ammann P, Fehr T, Minder EI, et al. Elevation of troponin I in sepsis and septic shock. Intensive Care Med. 2001;27:965–969.
7. Martin M, Mullenix P, Rhee P, et al. Troponin increases in the critically injured patient: mechanical trauma or physiologic stress? J Trauma. 2005;59:1086–1091.
8. Hassan B, Morsy S, Siam A, et al. Myocardial injury in critically ill children: a case control study. ISRN Cardiol. 2014;2014:919150.
9. Hamilton MA, Toner A, Cecconi M. Troponin in critically ill patients. Minerva Anestesiol. 2012;78:1039–1045.
10. Alpert JS, Thyesken KA, White HD, et al. Diagnostic and therapeutic implications of type 2 myocardial infarction: review and commentary. Am J Med. 2014;127:105–108.
11. Thyesken K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012;60:1581–1598.
12. Render ML, Welsh DE, Kollet M, et al. Automated computerized intensive care unit severity of illness measure in the Department of Veterans Affairs: preliminary results. SISVistA Investigators. Scrutiny of ICU Severity Veterans Health Systems Technology Architecture. Crit Care Med. 2000;28:3540–3546.
13. Render ML, Kim HM, Welsh DE, et al.; VA ICU Project (VIP) Investigators. Automated intensive care unit risk adjustment: results from a National Veterans Affairs study. Crit Care Med. 2003;31:1638–1646.
14. Render ML, Kim HM, Deddens J, et al. Variation in outcomes in Veterans Affairs intensive care units with a computerized severity measure. Crit Care Med. 2005;33:930–939.
15. Render ML, Deddens J, Freeberg R, et al. Veterans Affairs intensive care unit risk adjustment model: validation, updating, recalibration. Crit Care Med. 2008;36:1031–1042.
16. Lim W, Cook DJ, Griffith LE, et al. Elevated cardiac troponin levels in critically ill patients: prevalence, incidence, and outcomes. Am J Crit Care. 2006;15:280–288.
17. Babuin L, Vasile VC, Rio Perez JA, et al. Elevated cardiac troponin I is an independent risk factor for short- and long-term mortality in medical intensive care unit patients. Crit Care Med. 2008;36:759–765.
18. Salim A, Hadjizacharia P, Brown C, et al. Significance of troponin elevation after severe traumatic brain injury. J Trauma. 2008;64:46–52.
19. Vasile VC, Chai HS, Kamhautta S, et al. Significance of elevated cardiac troponin T levels in critically ill patients with acute respiratory disease. Am J Med. 2010;123:1049–1058.
20. Tiruvoipati R, Sultana N, Lewis D. Cardiac troponin I does not independently predict mortality in critically ill patients with severe sepsis. Emerg Med Australas. 2012;24:151–158.
21. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med. 1996;335:1342–1349.
22. Kloche K, Jonquet O, Cristol JP. The diagnostic challenge of myocardial infarction in critically ill patients: do high-sensitivity troponin measurements add more clarity or more confusion? Crit Care. 2014;18:148.
23. de Lemos JA. Increasingly sensitive assays for cardiac troponins: a review. JAMA. 2013;309:2262–2269.
24. Ostermann M, Forni LG. Measuring biomarkers of acute kidney injury during renal replacement therapy: wisdom or folly? Crit Care. 2014;18:155.
25. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA. 2013;310:1683–1691.
26. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA. 1993;270:2957–2963.
27. Otto GP, Sossdorf M, Boetel J, et al. Effects of low-dose acetylsalicylic acid and atherosclerotic vascular diseases on the outcome in patients with severe sepsis or septic shock. Platelets. 2013;24:480–485.

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28. Sossdorf M, Otto GR, Boettel J, et al. Benefit of low-dose aspirin and non-steroidal anti-inflammatory drugs in septic patients. *Crit Care*. 2013;17:402.

29. Thomas G, Hraiech S, Loundou A, et al. Statin therapy in critically-ill patients with severe sepsis: a review and meta-analysis of randomized clinical trials. *Minerva Anestesiol*. 2015;81:921–930.

30. Tralhão AF, Cés de Souza-Dantas V, Salluh JI, Póvoa PM. Impact of statins in outcomes of septic patients: a systematic review. *Postgrad Med*. 2014;126:45–58.

31. Patel JM, Snaith C, Thickett DR, et al. Randomized double-blind placebo-controlled trial of 40 mg/day of atorvastatin in reducing the severity of sepsis in ward patients (ASEPSIS Trial). *Crit Care*. 2012;16:R231.

32. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:e78–e140.

33. 2012 Writing Committee Members, Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction: updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2012;126:875–910.
### Appendix 1: Medications

| Medication Type | Medication Class | Medication Name          |
|----------------|------------------|--------------------------|
| β-Blockers     | CV100            | Atenolol                 |
|                |                  | Bisoprolol Fumarate      |
|                |                  | C-Metoprolol             |
|                |                  | Carvedilol               |
|                |                  | Esmolol                  |
|                |                  | Laβlol                   |
|                |                  | Metoprolol               |
|                |                  | Nadolol                  |
|                |                  | Pindolol                 |
|                |                  | Propranolol              |
|                |                  | Sotalol                  |
| Statins        | CV350            | Atorvastatin             |
|                |                  | Ezetimibe                |
|                |                  | Fluvastatin              |
|                |                  | Lovastatin               |
|                |                  | Pravastatin              |
|                |                  | Rosuvastatin             |
|                |                  | Simvastatin              |
| Aspirin        | CN103            | ASA/Butalbital/Caffeine   |
|                |                  | Aspirin                  |
|                |                  | Choline/Trisalicylate     |

### Appendix 2: Troponin Assays

| Manufacturer  | Assay          | LLD (µg/L) | LLD-10%CV (µg/L) | 10% CV (µg/L) | 99% Cutoff/10% CV (µg/L)* |
|---------------|----------------|------------|------------------|---------------|----------------------------|
| Abbott        | AxSYM          | <0.14      | 0.14–1.3         | >1.3          | 0.3/1.22                    |
| Abbott        | Architect      | 0.009      | 0.009–0.212      | 0.212         | —                           |
| Bayer         | ACS:180        | <0.03      | 0.03–0.45        | >0.45         | 0.1/0.37                    |
| Bayer         | ACS Centaur    | <0.02      | 0.02–0.45        | >0.45         | 0.1/0.33                    |
| Beckman Coulter| Access/Access 2| <0.01      | 0.01–0.1         | >0.1          | 0.04/0.09                   |
| Biosite       | Triage         | <0.19      | 0.19–0.69        | >0.69         | —                           |
| Dade Behring  | Dimension RxL  | <0.04      | 0.04–0.21        | >0.21         | 0.07/0.26                   |
| Dade Behring  | Stratus CS     | <0.03      | 0.03–0.13        | >0.13         | —                           |
| DPC           | Immulite       | <0.2       | 0.2–0.8          | >0.8          | 0.2/0.32                    |
| Ortho         | Vitros         | <0.038     | 0.038–0.2        | >0.2          | 0.1/0.44                    |
| Roche         | Elecsys        | <0.01      | 0.01–0.04        | >0.04         | 0.01/0.04                   |
| Abbott        | ISTAT          | <0.02      | 0.02–0.10        | >0.10         | —                           |

*From Wu, Alan H. B. Chapter 2, Contemporary Cardiology: Cardiovascular Biomarkers: Pathophysiology and Disease Management. Ed. Morrow, D. A. 2006.

LLD indicates lowest limit detectable.
### Appendix 3: Categorical Variables Used in Risk Adjustment

| Characteristic                          | cTn Cohort With Other Cardiac Diagnoses (n = 27,713) | cTn Not Measured + No cTn Assay Information (n = 30,943 + 3207 = 34,150) | cTn Cohort Without Other Cardiac Disease (n = 19,979) |
|----------------------------------------|-----------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------|
|                                        | N         | % of Study Cohort | N         | % of Study Cohort | N         | % of Study Cohort |
| Male*                                  | 26,677   | 96.3             | 34,150   | 94.8             | 19,304   | 96.6             |
| Race*                                  |          |                  |          |                  |          |                  |
| African American                       | 5641     | 20.4             | 6436     | 18.9             | 3932     | 19.7             |
| American Indian/Alaskan native         | 139      | 0.5              | 151      | 0.4              | 101      | 0.5              |
| Asian/native Hawaiian/other            | 240      | 0.9              | 339      | 0.9              | 157      | 0.8              |
| Pacific                                |          |                  |          |                  |          |                  |
| White                                  | 18,836   | 68.0             | 23,089   | 68               | 13,723   | 68.7             |
| Unknown                                | 2857     | 10.3             | 4134     | 12.1             | 2066     | 10.3             |
| Source of Admission into ICU           |          |                  |          |                  |          |                  |
| Ward                                   | 6769     | 24.4             | 5478     | 16.0             | 5274     | 26.4             |
| Operating room                         | 4793     | 17.3             | 16,087   | 47.1             | 3875     | 19.4             |
| Other hospital                         | 488      | 1.8              | 511      | 1.5              | 311      | 1.6              |
| Clinic                                 | 6490     | 23.4             | 4409     | 12.9             | 4293     | 21.5             |
| Nursing home                           | 698      | 2.5              | 551      | 1.6              | 547      | 2.7              |
| Psychiatric ward                       | 190      | 0.7              | 161      | 0.5              | 156      | 0.8              |
| Rehabilitation                         | 94       | 0.3              | 104      | 0.3              | 76       | 0.4              |
| Emergency department                   | 8185     | 29.5             | 6837     | 20.0             | 5442     | 27.2             |
| Unknown                                | 6        | 0.0              | 12       | 0.0              | 5        | 0.0              |
| On immunosuppressant                   | 3916     | 14.1             | 3036     | 8.9              | 3139     | 15.7             |
| Procedure within 24 h of ICU admission | 5268     | 19.01            | 16,828   | 49.3             | 4285     | 21.5             |
| Diagnosis                              |          |                  |          |                  |          |                  |
| Behavioral, mental, and psychiatric disorders | 175  | 0.6                 | 236      | 0.7              | 175      | 0.9              |
| Cancers                                | 2402     | 8.7              | 7079     | 20.7             | 2402     | 12.0             |
| Cardiac/circulation                    | 7734     | 27.9             | 4790     | 14.0             | N/A      | N/A              |
| Complications                          | 808      | 2.9              | 1468     | 4.3              | 808      | 4.0              |
| Endocrine/nutritional diseases         | 1036     | 3.7              | 1182     | 3.46             | 1036     | 5.2              |
| Gastrointestinal diseases              | 3086     | 11.1             | 4,437    | 13               | 3086     | 15.5             |
| Genitourinary disease                  | 212      | 0.8              | 691      | 2.0              | 212      | 1.1              |
| Hematologic                            | 282      | 1.0              | 294      | 0.9              | 282      | 1.4              |
| Infectious                             | 3310     | 11.9             | 2642     | 7.7              | 3310     | 16.6             |
| Neurological                           | 1441     | 5.2              | 2798     | 8.2              | 1441     | 7.2              |
| Orthopedic and trauma                  | 1029     | 3.7              | 2760     | 8.1              | 1029     | 5.2              |
| Renal                                  | 1084     | 3.9              | 896      | 2.6              | 1084     | 5.4              |
| Respiratory diseases                   | 3742     | 13.5             | 2630     | 7.7              | 3742     | 18.7             |
| Rheumatologic/connective              | 121      | 0.4              | 130      | 0.4              | 121      | 0.6              |
| Tissue                                 |          |                  |          |                  |          |                  |
| Substance abuse/toxicity               | 983      | 3.6              | 1426     | 4.2              | 983      | 4.9              |
| Other                                  | 268      | 1.1              | 691      | 2.0              | 268      | 1.3              |
| Comorbidities                          |          |                  |          |                  |          |                  |
| CHF                                    | 3527     | 12.7             | 1769     | 5.2              | 2515     | 12.6             |
| Valvular disease                       | 1277     | 4.6              | 725      | 2.1              | 648      | 3.2              |
| Pulmonary circulation disorders        | 1022     | 3.7              | 479      | 1.4              | 659      | 3.3              |
| Peripheral vascular disorders          | 1347     | 4.9              | 1504     | 4.4              | 953      | 4.8              |
| Hypertension                           | 14,565   | 52.6             | 16,246   | 47.6             | 10,219   | 51.2             |
| Paralysis                              | 931      | 3.4              | 937      | 2.7              | 788      | 3.9              |
| Other neurological disorders           | 1691     | 6.1              | 1533     | 4.5              | 1410     | 7.1              |
| Chronic pulmonary disease              | 5873     | 21.2             | 5501     | 16.1             | 4209     | 21.1             |
| Diabetes, uncomplicated                | 6183     | 22.3             | 6280     | 18.4             | 4200     | 21.0             |
| Diabetes, complicated                  | 1437     | 5.2              | 1102     | 3.2              | 987      | 4.9              |

(Continued on next page)
Appendix 3: (Continued)

| Characteristic                                    | cTn Cohort With Other Cardiac Diagnoses (n = 27,713) | cTn Not Measured + No cTn Assay Information (n = 30,943 + 3207 = 34,150) | cTn Cohort Without Other Cardiac Disease (n = 19,979) |
|--------------------------------------------------|-----------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------|
|                                                  | N         | % of Study Cohort | N         | % of Study Cohort | N         | % of Study Cohort |
| Hypothyroidism                                   | 1437      | 5.2               | 1387      | 4.1               | 990       | 5.0               |
| Renal failure                                    | 3202      | 11.6              | 2201      | 6.5               | 2287      | 11.5              |
| Liver disease                                    | 1651      | 6.0               | 2177      | 6.4               | 1384      | 6.9               |
| Peptic ulcer disease excluding bleeding          | 32        | 0.1               | 32        | 0.1               | 27        | 0.1               |
| AIDS                                             | 164       | 0.6               | 252       | 0.7               | 134       | 0.7               |
| Lymphoma                                         | 278       | 1.0               | 227       | 0.7               | 218       | 1.1               |
| Metastatic cancer                                | 1060      | 3.8               | 1454      | 4.3               | 943       | 4.7               |
| Solid tumor without metastasis                   | 1772      | 6.4               | 1857      | 5.4               | 1404      | 7.0               |
| Rheumatoid arthritis/collvascular diseases       | 304       | 1.1               | 288       | 0.8               | 220       | 1.1               |
| Coagulopathy                                     | 1377      | 5.0               | 1222      | 3.6               | 1145      | 5.7               |
| Obesity                                          | 1296      | 4.7               | 1288      | 3.8               | 826       | 4.1               |
| Weight loss                                      | 1044      | 3.8               | 926       | 2.7               | 892       | 4.5               |
| Fluid and electrolyte disorders                  | 6128      | 22.1              | 4540      | 13.3              | 5004      | 25.1              |
| Blood loss anemia                                | 289       | 1.0               | 346       | 1.0               | 256       | 1.3               |
| Deficiency anemias                               | 4154      | 15.0              | 3696      | 10.8              | 3228      | 16.2              |
| Alcohol abuse                                    | 1980      | 7.1               | 2151      | 6.3               | 1541      | 7.7               |
| Drug abuse                                       | 986       | 3.6               | 902       | 2.6               | 699       | 3.5               |
| Psychoses                                        | 1617      | 5.8               | 1748      | 5.1               | 1229      | 6.2               |
| Depression                                       | 1705      | 6.2               | 1924      | 5.6               | 1244      | 6.2               |

*Not used in risk adjustment.

Appendix 4: Continuous Variables Used in Risk Adjustment

| Characteristics                          | Mean (SD) cTn Cohort With Other Cardiac Diagnoses (n = 27,713) | Mean (SD) cTn Not Measured + No cTn Assay Information (n = 30,943 + 3207 = 34,150) | Mean (SD) cTn Cohort Without Other Cardiac Disease (n = 19,979) |
|------------------------------------------|---------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------|
| Age, y                                   | 66.0 (12.7)                                                   | 62.7 (12.5)                                                                      | 66.1 (12.6)                                                  |
| Length of stay, d*                       | 3.6 (5.8)                                                     | 2.7 (4.0)                                                                         | 4.0 (6.4)                                                    |
| Length of stay before ICU, d             | 1.1 (2.7)                                                     | 1.0 (2.4)                                                                         | 1.3 (2.9)                                                    |
| White blood cell count, $\times 10^3$ mm$^3$ | 11.3 (11.3)                                                  | 10.5 (8.3)                                                                        | 12.1 (12.7)                                                  |
| Serum albumin, g/L                       | 3.5 (0.9)                                                     | 3.7 (0.8)                                                                         | 3.4 (0.9)                                                    |
| Serum bilirubin, mg/dL                   | 1.1 (1.9)                                                     | 1.1 (2.2)                                                                         | 1.2 (2.2)                                                    |
| Blood urea nitrogen, mg/dL               | 29.2 (24.8)                                                   | 22.4 (20)                                                                         | 30.4 (26.3)                                                  |
| Serum creatinine, mg/dL                  | 1.8 (1.8)                                                     | 1.4 (1.6)                                                                         | 1.8 (1.9)                                                    |
| Blood glucose, mg/dL                     | 163.8 (129.2)                                                 | 147.2 (103.5)                                                                     | 171.8 (142.9)                                                |
| Hematocrit, %                            | 36.6 (7.1)                                                    | 36.6 (6.7)                                                                        | 35.9 (7.3)                                                   |
| Serum sodium, mEq/L                      | 136.7 (5.8)                                                   | 137 (5.2)                                                                         | 136.4 (6.3)                                                  |
| Glomerular filtration rate               | 65.5 (39.4)                                                   | 77.6 (38)                                                                         | 66.2 (42.2)                                                  |
| PaO$_2$                                  | 93.5 (53.5)                                                   | 103.7 (62.3)                                                                      | 93.4 (57.1)                                                  |
| PaCO$_2$                                 | 41.4 (13.5)                                                   | 40.1 (9.0)                                                                        | 42.0 (15.1)                                                  |
| pH                                       | 7.4 (0.1)                                                     | 7.4 (0.1)                                                                         | 7.4 (0.1)                                                    |

*Not used in risk adjustment.