Myocardial Injury in Patients With Sepsis and Its Association With Long-Term Outcome

BACKGROUND: Sepsis is frequently complicated by the release of cardiac troponin, but the clinical significance of this myocardial injury remains unclear. We studied the associations between troponin release during sepsis and 1-year outcomes.

METHODS AND RESULTS: We enrolled consecutive patients with sepsis in 2 Dutch intensive care units between 2011 and 2013. Subjects with a clinically apparent cause of troponin release were excluded. High-sensitivity cardiac troponin I (hs-cTnI) concentration in plasma was measured daily during the first 4 intensive care unit days, and multivariable Cox regression analysis was used to model its association with 1-year mortality while adjusting for confounding. In addition, we studied cardiovascular morbidity occurring during the first year after hospital discharge. Among 1258 patients presenting with sepsis, 1124 (89%) were eligible for study inclusion. Hs-cTnI concentrations were elevated in 673 (60%) subjects on day 1, and 755 (67%) ever had elevated levels in the first 4 days. Cox regression analysis revealed that high hs-cTnI concentrations were associated with increased death rates during the first 14 days (adjusted hazard ratio, 1.72; 95% confidence interval, 1.14–2.59 and hazard ratio, 1.70; 95% confidence interval, 1.10–2.62 for hs-cTnI concentrations of 100–500 and >500 ng/L, respectively) but not thereafter. Furthermore, elevated hs-cTnI levels were associated with the development of cardiovascular disease among 200 hospital survivors who were analyzed for this end point (adjusted subdistribution hazard ratio, 1.25; 95% confidence interval, 1.04–1.50).

CONCLUSIONS: Myocardial injury occurs in the majority of patients with sepsis and is independently associated with early—but not late—mortality, as well as postdischarge cardiovascular morbidity.

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WHAT IS KNOWN

- Sepsis is frequently complicated by the release of cardiac troponin (indicating myocardial injury).
- Troponin release is associated with increased case fatality during sepsis, but its impact on long-term mortality and cardiovascular morbidity remains unclear.

WHAT THE STUDY ADDS

- Systematic cardiac troponin measurements reveal that troponin release during sepsis is independently associated with increased short-term, but not long-term, death rates.
- High troponin concentrations (>100 ng/L) do not convey additional mortality risk compared with moderately elevated levels (>26 ng/L).
- Patients exhibiting troponin release during sepsis are at increased risk of acquiring new cardiovascular medication prescriptions during the first year after hospital discharge

Myocardial dysfunction affects approximately half of patients with sepsis admitted to intensive care units (ICUs).[1] Cardiac abnormalities can involve both the left and right ventricles and may include both systolic and diastolic dysfunctions.[2] Studies have shown that plasma concentrations of troponin, as biomarker of myocardial injury, correlate well with functional abnormalities seen on echocardiography.[3] Importantly, troponin levels were independently associated with mortality after sepsis in 2 recent meta-analyses.[4,5] Both studies, however, noted significant limitations of the existing literature. For example, many previous studies were hampered by small sample sizes,[3,6–16] nonsystematic blood sampling for troponin measurement,[12,17,18] and a general lack of adequate adjustment for potential confounders.[6–9,13,15] In addition, most reports focused exclusively on short-term mortality, with possible associations between troponin release and long-term mortality and cardiovascular morbidity remaining largely unstudied.[4] As a result, it is currently uncertain whether troponin release has significant impact on morbidity and mortality after sepsis.

To address these uncertainties, we performed daily measurements of high-sensitivity cardiac troponin I (hs-cTnI) plasma concentrations in a large cohort of patients presenting to the ICU with sepsis and determined their association with mortality and cardiovascular morbidity during the first year after hospital discharge.

METHODS

Study Population

The current analysis was embedded within the MARS (Molecular Diagnosis and Risk Stratification of Sepsis) initiative, a prospective cohort study in the mixed ICUs of 2 tertiary care hospitals in The Netherlands.[19] We included consecutive patients presenting to the ICU with sepsis between 2011 and 2013. Sepsis was prospectively defined according to the 1991 American College of Chest Physicians/Society of Critical Care Medicine consensus definitions.[20] The post hoc likelihood of infection had to be rated at least probable, using criteria as described in detail previously.[21] In addition, the clinical onset of infection had to occur in a time period ranging from 2 days before until 1 day after ICU admission. We excluded patients with inflammatory processes primarily involving the heart (ie, myocarditis, pericarditis, and endocarditis), patients after recent cardiac surgery, and those after cardiopulmonary resuscitation (because these conditions are all known to potentially result in significant troponin release unrelated to sepsis). An opt-out consent procedure was in place, as approved by the medical ethical committee of the University Medical Center Utrecht under protocol number 10-056C/15–232. The data that support the findings of this study are available from the corresponding author on reasonable request.

Data Collection

Trained observers prospectively collected detailed information on patient characteristics, comorbidities, and disease severity (including daily sequential organ failure assessment [SOFA] scores). In addition, heparin plasma was obtained from all patients on a daily basis and stored for analysis at –80°C within 4 hours of sampling. Subsequently, we measured troponin concentrations in plasma during the first 4 days in ICU, using a high-sensitivity troponin I assay (Abbott ARCHITECT STAT, Abbott Laboratories, Abbott park, IL). The upper reference limit for this test is 26 ng/L based on the 99th percentile of measurements reported in healthy men and women, and the coefficient of variation is 10% at the 3 ng/L level according to the manufacturer's specification.[22] Troponin measurements performed as part of this study were not made available to the treating clinicians.

Outcomes

The primary study outcome was all-cause mortality within the first year after ICU admission, for which vital status was retrieved through the Dutch municipal registry. As a secondary outcome, we assessed the occurrence of cardiovascular disease during the first year after hospital discharge. To this end, we combined clinical information as collected in the MARS cohort with reimbursement data as provided by a large Dutch health insurance company (Achmea, Zeist, The Netherlands). To ensure the privacy of patients, records were pseudonymized via a trusted third party (ZorgTTP, Houten, The Netherlands) before data were merged. The Achmea Health Database is representative of the urbanized Dutch population and contains all drug prescriptions delivered by pharmacists both before and after hospitalization for the sepsis episode.[23] Anatomical Therapeutic Chemical (ATC) codes were used to determine whether patients received drugs from any of the following 6 major categories of cardiovascular medication:(1) β-blockers (ATC-code C07), (2) lipid-lowering drugs (ATC-code C10), (3) drugs acting on the renin–angiotensin system

(ACT-code C09), (4) antithrombotic drugs (ATC-code B01A), (5) nitrates (ATC-code C01DA), and (6) diuretics (ATC-code C03).[24] The secondary outcome new or worsened cardiovascular disease was subsequently defined as a ≥2 increase in the number of concurrent categories of cardiovascular medication (as listed above) used by the patient in the first year after hospital discharge as compared with preadmission chronic use. Medication use was based on whether a patient had filled at least 1 prescription for the drug at his/her pharmacy. As a sensitivity analysis, we required at least 2 prescriptions to fulfill the definition of medication use. New drug prescriptions have been used in the literature before as proxies for various cardiovascular events, including atrial fibrillation,[25] ischemic heart disease,[26] and congestive heart failure.[27] A recent study assessing the accuracy of newly prescribed nitrates and antithrombotic drugs as a proxy for incident hospitalizations with major cardiovascular disease found a sensitivity of 71% and specificity of 94%.[28]

Statistical Analysis

Multivariable Cox regression analysis was used to study the relationship between troponin release during sepsis and mortality up to 1 year after ICU admission. We adjusted for potential confounders that were selected a priori based on their reported associations with both myocardial injury and death in the literature.[3,18,29,30] These included age, sex, smoking status, admission type (surgical versus medical), site of infection (pulmonary, abdominal, and other), and a history of chronic renal insufficiency, diabetes mellitus, hypertension, peripheral vascular disease, myocardial infarction, chronic obstructive pulmonary disease, and congestive heart failure (for full definitions of chronic comorbidities, see Table I in the Data Supplement). In addition, we adjusted for acute disease severity at ICU admission by adding the Acute Physiology and Chronic Health Evaluation IV score and vasopressor use as confounders. We deliberately did not adjust for other factors that occur during ICU stay, such as acute kidney injury, because this may be an intermediate on the causal pathway from myocardial injury to death. For the secondary outcome, we used multivariable Cox regression analysis with competing risks (new or worsened cardiovascular disease and death). Cause-specific hazard ratios (HRs) were first estimated for both (competing) end points. A Fine and Gray model was then used to estimate a subdistribution HR reflecting the association between troponin release and new or worsened cardiovascular disease during the first year after sepsis while accounting for competing events. Potential confounders for this analysis included all demographic and chronic comorbidities as listed above, as well as the number of cardiovascular drug categories prescribed before ICU admission, and whether a troponin measurement ordered by the treating clinicians during ICU stay was elevated. The latter element was included to minimize bias because of misclassification of the outcome (ie, spuriously attributing drug treatment to new or worsened cardiovascular disease when in fact it was started in response to clinically recognized troponin release).

For the primary analysis, we used the hs-cTnI concentration measured at ICU admission as the determinant of interest. For our secondary outcome, follow-up time started at the moment of hospital discharge, and for this reason, we used the peak hs-cTnI concentration measured during the first 4 days in ICU as determinant. All hs-cTnI levels were transformed using a natural logarithm before model fitting. We subsequently assessed linearity of the relationship between predictor and outcome for all continuous variables using restricted cubic splines. If a spline fit significantly improved the model (using a likelihood ratio test), then a nonlinear relationship was assumed to be present. In addition, the proportional hazards assumption was tested by visual inspection of scaled Schoenfeld residuals and by testing for statistically significant interactions of covariates with time. In case the proportional hazards assumption appeared to be violated, we divided follow-up time into discrete segments and subsequently obtained separate HR for each time period. It is important to note that period-specific HRs have the limitation that they only represent the effect of exposure for patients who have at least survived until that time point.[31] In addition, HRs provide a measure of relative effect and thus no information about absolute survival probabilities. Therefore, we also constructed adjusted survival curves, using inverse probability weighting to adjust for confounding.[32] Details on this methodology can be found in the Data Supplement.

We performed multiple imputation for missing data under the assumption of data being missing at random (see Data Supplement). All analyses were performed using SAS version 9.4 (SAS institute, Cary, NC) or R version 3.2.2 (R foundation for Statistical Computing, 2015).

RESULTS

During the study period, a total of 1256 patients were admitted to the participating ICU's for presumed sepsis with a post hoc infection likelihood rated at least probable, of whom 1124 (89%) were eligible for study inclusion (Figure 1). Among these, 673 (60%) subjects had a troponin level above the upper reference limit of the test (26 ng/L) on day 1, and an additional 82 (7%) developed raised concentrations within the first 4 days in the ICU. In this group of 755 (67%) patients (ever) having troponin release, median hs-cTnI plasma concentrations on days 1 through 4 were 109 (interquartile range [IQR], 39–394), 103 (IQR, 38–449), 79 (IQR, 31–281), and 82 (IQR, 32–253) ng/L, respectively. Of note, 568 (84%) of the 673 patients who had raised troponin on day 1 also had elevated levels on all subsequent days. Patients with elevated troponin concentrations were older, more severely ill, and had more comorbidities than patients with normal troponin levels (Table 1).

Association With Mortality

Crude mortality rates in the ICU, in hospital, and after 1 year were higher in patients having elevated compared with normal hs-cTnI plasma concentrations at admission (Table 1). Initial multivariable Cox regression revealed that the proportional hazards assumption

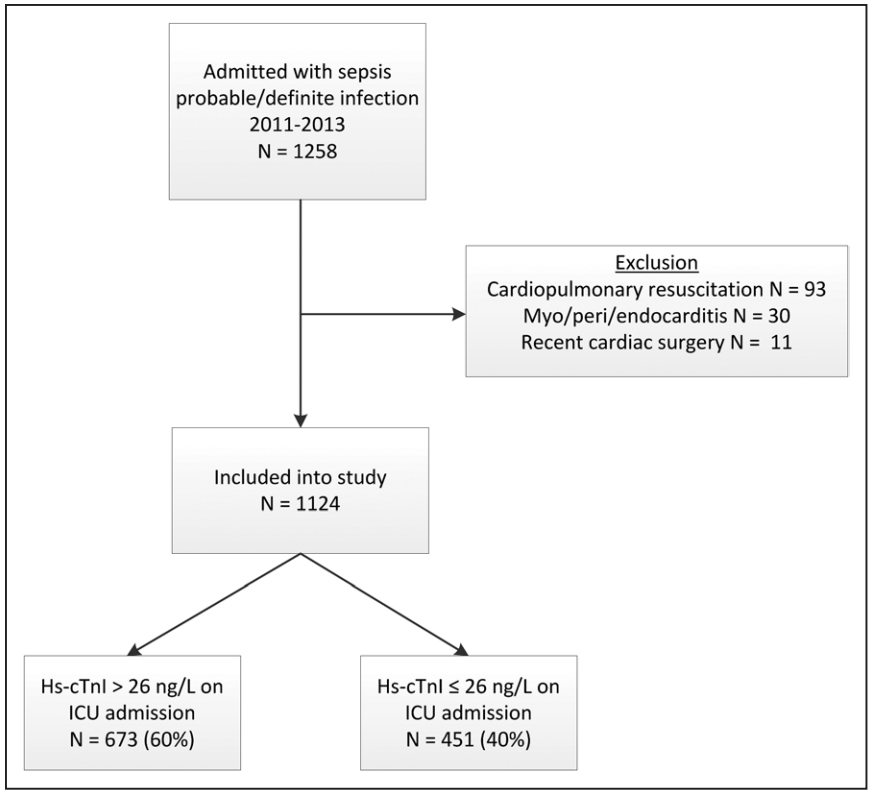

Figure 1. Patient inclusion flow chart.
hs-cTnI indicates high-sensitivity cardiac troponin I; and ICU, intensive care unit.

for this analysis was violated (see Figure I in the Data Supplement). In addition, the use of restricted cubic splines for hs-cTnI significantly improved model fit (*P* value for likelihood ratio test, 0.04). For these reasons, we performed cox regression analyses while splitting follow-up time into distinct periods to accommodate nonproportionality and incorporating spline functions for hs-cTnI to accommodate the nonlinear association.

Figure 2 shows the relationship between hs-cTnI plasma concentrations and mortality rate for 2 distinct time periods after sepsis onset (ie, days 0–14 and 14–365). There was a steady increase in the hazard of dying during the first 2 weeks for rising troponin concentrations up to ≈100 ng/L, yet further troponin release did not lead to a higher mortality rate during this time period (Figure 2A). These findings were confirmed in a multivariable Cox regression analysis using categorization (rather than spline transformation) of troponin values, revealing that both moderate (100–500 ng/L) and high (>500 ng/L) hs-cTnI levels were associated with significantly increased—but very similar—death rates (adjusted HR, 1.72; 95% confidence interval [CI], 1.14–2.59 and adjusted HR, 1.70; 95% CI, 1.10–2.62; Table II in the Data Supplement). In contrast, neither mild, moderate, nor high levels of troponin were associated with increased death rates during the time period ranging from day 14 to 365 (Figure 2B; Table II in the Data Supplement).

To gain a deeper understanding of the relationship between troponin release and early sepsis mortality, we analyzed SOFA scores at the time of death in patient who died within the ICU in the first 14 days (n=160). Patients having elevated hs-cTnI at admission (129 of 160; 81%) more often died with renal failure than subjects having normal hs-cTnI concentrations (renal SOFA score 4 [IQR, 2–4] versus 0 [IQR, 0–2]; *P*<0.001) while no differences in other organ systems or total SOFA score were observed (data not shown).

Figure 3 shows the adjusted survival curves for patients with normal hs-cTnI, as well as mild, moderate, and high levels of hs-cTnI release at ICU admission. After 1 year, there was no statistically significant difference in estimated survival between normal (59%; 95% CI, 54%–65%) and mild (51%; 95% CI, 45%–58%; *P* value, 0.07), moderate (55%; 95% CI, 48%–63%; *P* value, 0.40), or high hs-cTnI concentrations (53%; 95% CI, 44%–64%; *P* value, 0.29).

Association With Cardiovascular Morbidity

Among the 1124 study participants, 787 survived until hospital discharge. A subgroup of 226 (29%) of these were matched to the Achmea Health Database; 23 patients were excluded because they already used medication comprising ≥5 cardiovascular drug categories before the onset of sepsis (and were thus not at risk of developing the outcome), and 3 additional patients were excluded because of missing prescription data, leaving 200 patients for this secondary analysis. Patients carrying health insurance by Achmea had similar char-

Table 1. Characteristics of Patients Admitted to the Intensive Care Unit With Sepsis (n=1124)

	Normal hs-cTnI on Admission (n=451)*	Elevated hs-cTnI on Admission (n=673)*	*P* Value
Demographics			
Age, y	60 (49–68)	65 (53–73)	<0.01
Male gender	287 (64%)	397 (59%)	0.12
BMI	25 (22–28)	25 (23–29)	0.12
Medical history			
Diabetes mellitus	66 (15%)	137 (20%)	0.01
Hypertension	95 (21%)	234 (35%)	<0.01
Chronic renal insufficiency	27 (6%)	122 (18%)	<0.01
COPD	55 (12%)	94 (14%)	0.39
Congestive heart failure	5 (1%)	41 (6%)	<0.01
Prior myocardial infarction	17 (4%)	63 (9%)	<0.01
Peripheral vascular disease	39 (9%)	94 (14%)	<0.01
Site of infection			
Pulmonary	189 (42%)	296 (44%)	0.41
Abdominal	119 (26%)	223 (33%)	
Other	143 (32%)	154 (23%)	
ICU admission characteristics			
Surgical admission	137 (30%)	149 (22%)	<0.01
APACHE IV score	69 (52–86)	83 (66–104)	<0.001
Mechanical ventilation†	334 (74%)	506 (75%)	0.67
Vasopressor use†	252 (56%)	471 (70%)	<0.001
Troponin measurement‡	52 (12%)	178 (26%)	<0.001
Severe sepsis	213 (47%)	456 (68%)	<0.001
Septic shock	74 (16%)	234 (35%)	<0.001
Length of stay, d	4 (2–9)	4 (2–10)	0.47
Outcome			
ICU mortality	54 (12%)	153 (23%)	<0.01
Hospital mortality	99 (22%)	238 (35%)	<0.01
1-year mortality	167 (37%)	342 (51%)	<0.01

Data are presented as medians (Q1–Q3) or absolute numbers (percentage). APACHE indicates Acute Physiology and Chronic Health Evaluation; BMI, body mass index, COPD, chronic obstructive pulmonary disease; hs-cTnI, high-sensitivity cardiac troponin I; and ICU, intensive care unit.

*An hs-cTnI level ≤26 ng/L was considered normal and hs-cTnI >26 ng/L was considered elevated.

†In the first 24 hours of ICU admission.

‡Number of patients in whom troponin measurement was ordered on clinical indication within the first ICU day.

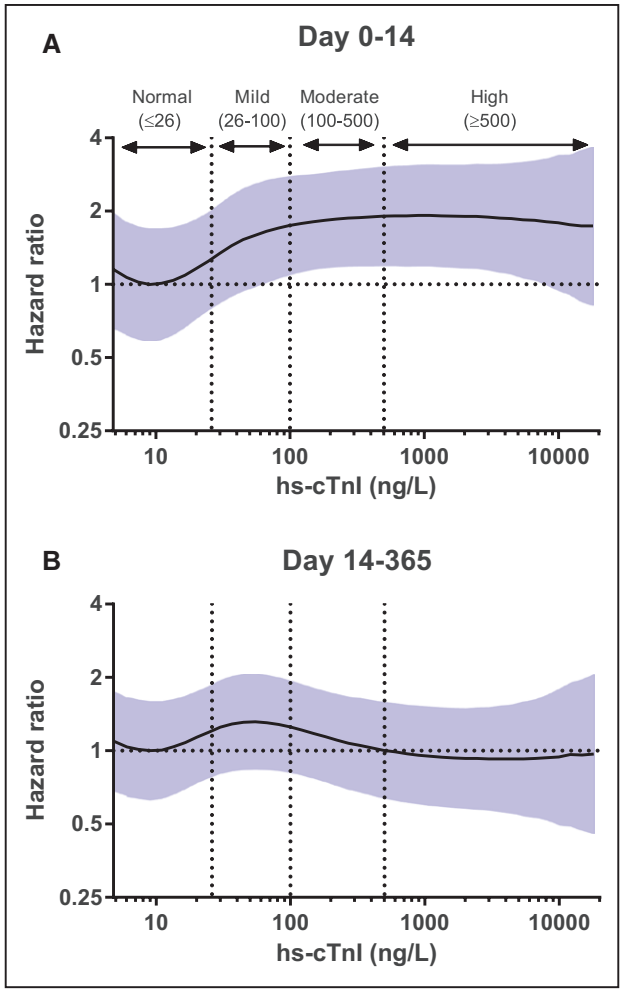

Figure 2. Adjusted hazard ratio plots for the effect of troponin on mortality across different time periods (n=1124).

A and **B**, The blue bands represent 95% confidence intervals. Hazard ratio for high-sensitivity cardiac troponin I (hs-cTnI) is adjusted for age, sex, chronic renal insufficiency, peripheral vascular disease, diabetes mellitus, hypertension, prior myocardial infarction, chronic obstructive pulmonary disease, active smoker, congestive heart failure, site of infection, Acute Physiology and Chronic Health Evaluation IV score, and vasopressor requirement.

acteristics compared with those who were insured by other companies (Table III in the Data Supplement). The 122 patients of this subgroup who had troponin release during sepsis received more cardiovascular drugs in the first year after hospital discharge than before the sepsis episode while the 78 patients having normal hs-cTnI plasma concentrations during their first 4 days in the ICU did not (Table 2; Figure II in the Data Supplement).

As a result, 20 (16%) subjects with troponin release met predefined criteria for new or worsened cardiovascular disease, compared with only 4 (5%) patients with hs-cTnI ≤26 ng/L (*P* value, 0.02). This association remained after multivariable adjustment for confounders (adjusted cause-specific HRs, 1.25; 95% CI, 1.00–1.55; *P* value, 0.045). A Fine-Gray model, accounting for the competing end point of death, showed a similar relationship (adjusted subdistribution HR, 1.25; 95% CI, 1.05–1.50; *P* value, 0.015). A sensitivity analysis requiring at least 2 prescriptions filled at the pharmacy to establish cardiovascular medication use yielded similar results (data not shown).

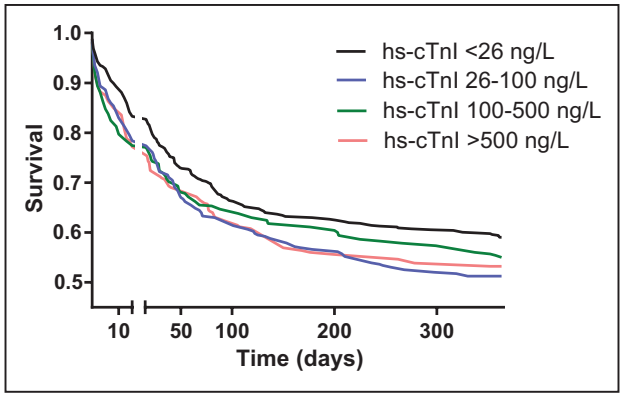

Figure 3. Adjusted survival curves for different categories of troponin release on intensive care unit admission (n=1124).
hs-cTnI indicates high-sensitivity cardiac troponin I.

DISCUSSION

We performed a detailed analysis of the relationship between myocardial injury and mortality in a large cohort of patients with sepsis and found that troponin release at ICU admission was associated with early, but not late, mortality. This association was nonlinear, indicating that progressive troponin release beyond hs-cTnI plasma concentrations of ≈100 ng/L does not convey an additional mortality risk. Furthermore, raised hs-cTnI levels during the first 4 days in the ICU were associated with increased use of new cardiovascular medication after hospital discharge.

Although an association between troponin release and short-term mortality after sepsis has been reported before, no studies evaluated the possibility of a nonlinear relationship.[4,5] Prior studies either categorized troponin concentrations or simply assumed a linear outcome relation, and these approaches may lead to loss of information or even erroneous conclusions.[33–35] We observed a clear nonlinear relationship with mortality, yet it remains uncertain whether this represents causality. However, there are several pathophysiological mechanisms that could explain a possible pathogenic link. For example, troponin release is known to be a marker of poor left and right ventricular functions during sepsis,[2,3] and reduced cardiac output may impair tissue perfusion and increase the risk of death.[36] Analysis of SOFA scores at the time of death revealed that patients with hs-cTnI release on admission were more likely to subsequently develop renal failure, which fits the theory that myocardial injury might lead to reduced cardiac output, thereby increasing the risk of renal injury. However, it should be noted that both the incidence of chronic kidney injury was already dissimilar at baseline. In our study, extreme troponin peaks were not associated with additional deaths relative to milder troponin levels. Perhaps, high hs-cTnI concentrations no longer accurately reflect deterioration of cardiac function, or perhaps active medical treatment blunts the effects of underlying myocardial dysfunction. Nonetheless, increased short-term mortality has now repeatedly been reported across various clinical settings, and it is thus essential that future studies attempt to uncover the underlying pathogenesis of myocardial injury during sepsis. This may lead to therapies (such as heart rate control or antiplatelet therapy) aimed at improving (short-term) survival.

Most investigations thus far have only reported on short-term mortality after troponin release, leaving long-term outcomes largely unstudied. However, a cohort study in patients with end-stage renal disease suggested that troponin elevation was associated with mortality up to 4 years after sepsis onset.[14] In contrast, we did not observe an association with death rates beyond day 14, perhaps because our cohort included patients having a greater burden of acute disease sever-

Table 2. Cardiovascular Drug Use Before and After Admission in Hospital Survivors of Sepsis (n=200)

	ICU hs-cTnI ≤26 ng/L (n=78)			ICU hs-cTnI >26 ng/L (n=122)		
	Before Admission	After Admission	*P* Value	Before Admission	After Admission	*P* Value
No. of cardiovascular drug categories	1 (0–2)	1 (0–2)	0.41	1 (0–3)	2 (0–3)	0.002
Selected drug categories						
β-Blockers	15 (19%)	16 (21%)	0.76	34 (28%)	46 (38%)	0.02
ACE inhibitors/AR blockers	17 (22%)	17 (22%)	1.00	30 (25%)	36 (30%)	0.36
Lipid-lowering drugs	21 (27%)	20 (26%)	0.65	44 (36%)	42 (34%)	0.69
Antithrombotic drug	22 (28%)	31 (40%)	0.03	51 (42%)	66 (54%)	0.007
Nitrates	4 (5%)	1 (1%)	0.08	3 (2%)	8 (7%)	0.03
Diuretics	14 (18%)	15 (19%)	0.74	28 (23%)	40 (33%)	0.01

Data are presented as median (Q1–Q3) or absolute number (percentage). McNemar test or Wilcoxon signed-rank test were used as appropriate. ACE indicates angiotensin-converting enzyme; AR, angiotensin receptor; hs-cTnI, high-sensitivity cardiac troponin I; and ICU, intensive care unit.

ity, yet who (mostly) did not have chronic renal disease. This notion is supported by another study that also did not observe a relationship between cardiac troponin T concentrations and late mortality in a cohort of sepsis patients admitted to ICU who survived the first 30 days after disease onset.[18] Although we found no association with late mortality, we did observe an association between hs-cTnI concentrations and the increased use of new cardiovascular medications after hospital discharge. Sepsis survivors are known to be at increased risk for cardiovascular events after hospital discharge compared with matched population controls,[37,38] and we found that troponin release during ICU stay might identify patients especially prone to this complication. Our findings are corroborated by a recent study in patients who were admitted to the hospital with community-acquired pneumonia, which also showed that high troponin levels on admission were associated with the development of cardiovascular events during follow-up.[39] Regardless of whether this association is causal or merely prognostic, troponin release during sepsis could act as an important alarm signal for physicians, identifying patients at high risk of cardiovascular complications, and future studies should evaluate whether they may benefit from preventative strategies.

Our study has several limitations. First, we chose to accommodate nonproportional hazards during follow-up by splitting time into 2 distinct periods. Because the cutoff point for defining these time periods was selected based on a plot of the Schoenfeld residuals, the resulting Cox model should be viewed as a post hoc analysis. We opted to categorize follow-up time in favor of other methods of dealing with nonproportional hazards, such as Gray's survival model,[40] because it allowed us to better depict the nonlinear associations (Figure 2). Despite the post hoc nature of these decisions, the large study cohort (including >1000 patients with sepsis) provided ample statistical power to explore nonlinear and time-dependent relationships. Second, our definition of new or worsened cardiovascular disease was based on newly prescribed cardiovascular medications. Use of a proxy, rather than direct observation of the outcome of interest, may lead to misclassification. Furthermore, some of the new cardiovascular drug prescriptions filled at the pharmacy shortly after discharge might in fact already have been initiated during hospital stay. Thus, these prescriptions may not reflect true new morbidity but rather be related to secondary cardiovascular prophylaxis after clinically recognized troponin release in the ICU. However, we included clinically recognized troponin events as a confounder in our analysis to limit potential bias by such misclassification. Nonetheless, because the number of patients included in our analysis of the secondary end point was low relative to the many potential confounders in the model, we regard this analysis as exploratory.

CONCLUSIONS

Myocardial injury occurs in a majority of patients with sepsis and is independently associated with early—but not late—mortality. Furthermore, patients sustaining myocardial injury during their ICU stay are at increased risk of developing new or worsened cardiovascular disease during the first year after hospital discharge.

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DISCLOSURES

None.

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FOOTNOTES

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Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org.

APPENDIX: MARS CONSORTIUM

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REFERENCES

1. Zaky A, Deem S, Bendjelid K, Treggiari MM. Characterization of cardiac dysfunction in sepsis: an ongoing challenge. *Shock*. 2014;41:12–24. doi: 10.1097/SHK.0000000000000065.
2. Pulido JN, Afessa B, Masaki M, Yuasa T, Gillespie S, Herasevich V, Brown DR, Oh JK. Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. *Mayo Clin Proc*. 2012;87:620–628. doi:10.1016/j.mayocp.2012.01.018
3. Landesberg G, Jaffe AS, Gilon D, Levin PD, Goodman S, Abu-Baih A, Beeri R, Weissman C, Sprung CL, Landesberg A. Troponin elevation in severe sepsis and septic shock: the role of left ventricular diastolic dysfunction and right ventricular dilatation*. *Crit Care Med*. 2014;42:790–800. doi:10.1097/CCM.0000000000000107
4. Sheyin O, Davies O, Duan W, Perez X. The prognostic significance of troponin elevation in patients with sepsis: a meta-analysis. *Heart Lung*. 2015;44:75–81. doi: 10.1016/j.hrtlng.2014.10.002.
5. Bessière F, Khenifer S, Dubourg J, Durieu I, Lega JC. Prognostic value of troponins in sepsis: a meta-analysis. *Intensive Care Med*. 2013;39:1181–1189. doi: 10.1007/s00134-013-2902-3.
6. Spies C, Haude V, Fitzner R, Schröder K, Overbeck M, Runkel N, Schaffartzik W. Serum cardiac troponin T as a prognostic marker in early sepsis. *Chest*. 1998;113:1055–1063.
7. Turner A, Tsamitros M, Bellomo R. Myocardial cell injury in septic shock. *Crit Care Med*. 1999;27:1775–1780.
8. ver Elst KM, Spapen HD, Nguyen DN, Garbar C, Huyghens LP, Gorus FK. Cardiac troponins I and T are biological markers of left ventricular dysfunction in septic shock. *Clin Chem*. 2000;46:650–657.
9. Ammann P, Maggiorini M, Bertel O, Haenseler E, Joller-Jemelka HI, Oechslin E, Minder EI, Rickli H, Fehr T. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. *J Am Coll Cardiol*. 2003;41:2004–2009.
10. Mehta NJ, Khan IA, Gupta V, Jani K, Gowda RM, Smith PR. Cardiac troponin I predicts myocardial dysfunction and adverse outcome in septic shock. *Int J Cardiol*. 2004;95:13–17. doi: 10.1016/j.ijcard.2003.02.005.
11. Brivet FG, Jacobs FM, Colin P, Prat D, Grigoriu B. Cardiac troponin level is not an independent predictor of mortality in septic patients requiring medical intensive care unit admission. *Crit Care*. 2006;10:404. doi: 10.1186/cc3990.
12. John J, Awab A, Norman D, Dernaika T, Kinasewitz GT. Activated protein C improves survival in severe sepsis patients with elevated troponin. *Intensive Care Med*. 2007;33:2122–2128. doi: 10.1007/s00134-007-0816-7.
13. Yucel T, Memiş D, Karamanlioglu B, Süt N, Yuksel M. The prognostic value of atrial and brain natriuretic peptides, troponin I and C-reactive protein in patients with sepsis. *Exp Clin Cardiol*. 2008;13:183–188.
14. Kang EW, Na HJ, Hong SM, Shin SK, Kang SW, Choi KH, Lee HY, Han DS, Han SH. Prognostic value of elevated cardiac troponin I in ESRD patients with sepsis. *Nephrol Dial Transplant*. 2009;24:1568–1573. doi: 10.1093/ndt/gfn730.
15. Scott EC, Ho HC, Yu M, Chapital AD, Koss W, Takanishi DM Jr. Pre-existing cardiac disease, troponin I elevation and mortality in patients with severe sepsis and septic shock. *Anaesth Intensive Care*. 2008;36:51–59.
16. Mehta S, Granton J, Gordon AC, Cook DJ, Lapinsky S, Newton G, Bandayrel K, Little A, Siau C, Ayers D, Singer J, Lee TC, Walley KR, Storms M, Cooper DJ, Holmes CL, Hebert P, Presneill J, Russell JA; Vasopressin and Septic Shock Trial (VASST) Investigators. Cardiac ischemia in patients with septic shock randomized to vasopressin or norepinephrine. *Crit Care*. 2013;17:R117. doi: 10.1186/cc12789.
17. 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. doi: 10.1111/j.1742-6723.2011.01530.x.
18. Vasile VC, Chai HS, Abdeldayem D, Afessa B, Jaffe AS. Elevated cardiac troponin T levels in critically ill patients with sepsis. *Am J Med*. 2013;126:1114–1121. doi: 10.1016/j.amjmed.2013.06.029.
19. Klein Klouwenberg PM, Cremer OL, van Vught LA, Ong DS, Frencken JF, Schultz MJ, Bonten MJ, van der Poll T. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. *Crit Care*. 2015;19:319. doi: 10.1186/s13054-015-1035-1.
20. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101:1644–1655.
21. Klein Klouwenberg PM, Ong DS, Bos LD, de Beer FM, van Hooijdonk RT, Huson MA, Straat M, van Vught LA, Wieske L, Horn J, Schultz MJ, van der Poll T, Bonten MJ, Cremer OL. Interobserver agreement of Centers for Disease Control and Prevention criteria for classifying infections in critically ill patients. *Crit Care Med*. 2013;41:2373–2378. doi: 10.1097/CCM.0b013e3182923712.
22. Bohula May EA, Bonaca MP, Jarolim P, Antman EM, Braunwald E, Giugliano RP, Newby LK, Sabatine MS, Morrow DA. Prognostic performance of a high-sensitivity cardiac troponin I assay in patients with non-ST-elevation acute coronary syndrome. *Clin Chem*. 2014;60:158–164. doi: 10.1373/clinchem.2013.206441.
23. Smeets HM, de Wit NJ, Hoes AW. Routine health insurance data for scientific research: potential and limitations of the Agis Health Database. *J Clin Epidemiol*. 2011;64:424–430. doi: 10.1016/j.jclinepi.2010.04.023.
24. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC Classification and DDD Assignment 2015*. Oslo, Norway:WHO; 2015. http:// www.whocc.no. Accessed October 17, 2016.
25. Christiansen CF, Christensen S, Mehnert F, Cummings SR, Chapurlat RD, Sørensen HT. Glucocorticoid use and risk of atrial fibrillation or flutter: a population-based, case-control study. *Arch Intern Med*. 2009;169:1677–1683. doi: 10.1001/archinternmed.2009.297.
26. Williams D, Bennett K, Feely J. Evidence for an age and gender bias in the secondary prevention of ischaemic heart disease in primary care. *Br J Clin Pharmacol*. 2003;55:604–608.
27. Rasmussen JN, Gislason GH, Abildstrom SZ, Rasmussen S, Gustafsson I, Buch P, Friberg J, Køber L, Torp-Pedersen C, Madsen M, Stender S. Statin use after acute myocardial infarction: a nationwide study in Denmark. *Br J Clin Pharmacol*. 2005;60:150–158. doi: 10.1111/j.1365-2125.2005.02408.x.
28. Pouwels KB, Voorham J, Hak E, Denig P. Identification of major cardiovascular events in patients with diabetes using primary care data. *BMC Health Serv Res*. 2016;16:110. doi: 10.1186/s12913-016-1361-2.
29. Markou N, Gregorakos L, Myrianthefs P. Increased blood troponin levels in ICU patients. *Curr Opin Crit Care*. 2011;17:454–463. doi: 10.1097/MCC.0b013e3283491f0d.
30. Røsjø H, Varpula M, Hagve TA, Karlsson S, Ruokonen E, Pettilä V, Omland T; FINNSEPSIS Study Group. Circulating high sensitivity troponin T in severe sepsis and septic shock: distribution, associated factors, and relation to outcome. *Intensive Care Med*. 2011;37:77–85. doi: 10.1007/s00134-010-2051-x.
31. Hernán MA. The hazards of hazard ratios. *Epidemiology*. 2010;21:13–15. doi: 10.1097/EDE.0b013e3181c1ea43.
32. Cole SR, Hernán MA. Adjusted survival curves with inverse probability weights. *Comput Methods Programs Biomed*. 2004;75:45–49. doi: 10.1016/j.cmpb.2003.10.004.
33. Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression and Survival Analysis. 2nd ed. Springer International Publishing Switzerland. 2015. 2015:18–21.

34. Sauerbrei W, Royston P, Binder H. Selection of important variables and determination of functional form for continuous predictors in multivariable model building. *Stat Med*. 2007;26:5512–5528. doi: 10.1002/sim.3148.
35. Royston P, Sauerbrei W. *Multivariable Model-Building. A Pragmatic Approach Based on Fractional Polynomials for Modelling Continuous Variables*. Chichester, United Kingdom: John Wiley and Sons; 2008:58–67.
36. Bloch A, Berger D, Takala J. Understanding circulatory failure in sepsis. *Intensive Care Med*. 2016;42:2077–2079. doi: 10.1007/s00134-016-4514-1.
37. Ou SM, Chu H, Chao PW, Lee YJ, Kuo SC, Chen TJ, Tseng CM, Shih CJ, Chen YT. Long-term mortality and major adverse cardiovascular events in sepsis survivors. A nationwide population-based study. *Am J Respir Crit Care Med*. 2016;194:209–217. doi: 10.1164/rccm.201510-2023OC.
38. Yende S, Linde-Zwirble W, Mayr F, Weissfeld LA, Reis S, Angus DC. Risk of cardiovascular events in survivors of severe sepsis. *Am J Respir Crit Care Med*. 2014;189:1065–1074. doi: 10.1164/rccm.201307-1321OC.
39. Cangemi R, Calvieri C, Falcone M, Bucci T, Bertazzoni G, Scarpellini MG, Barillà F, Taliani G, Violi F; SIXTUS Study Group. Relation of cardiac complications in the early phase of community-acquired pneumonia to long-term mortality and cardiovascular events. *Am J Cardiol*. 2015;116:647–651. doi: 10.1016/j.amjcard.2015.05.028.
40. Kasal J, Jovanovic Z, Clermont G, Weissfeld LA, Kaplan V, Watson RS, Angus DC. Comparison of Cox and Gray's survival models in severe sepsis. *Crit Care Med*. 2004;32:700–707.

Myocardial Injury in Patients With Sepsis and Its Association With Long-Term Outcome

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SUPPLEMENTAL MATERIAL

Myocardial injury in patients with sepsis and its association with long-term outcome

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Supplemental methods

Multiple imputation

Multiple imputation was performed using the "Amelia II" package in R [1]. This uses a bootstrap based expectation maximization algorithm to impute missing values and assumes that data are at least 'missing at random'. Among a total of 3219 observable days in ICU until day 4, plasma samples were missing on 304 (9%) occasions. The proportion of cases with one or more missing values was 16% and the number of imputed datasets was set at 15 [2]. All variables used in the main analysis model were also included in the imputation model. In addition several 'auxilliary' variables were included: intensive care unit (ICU) length of stay, maximum lactate level in the first 24 hours, sequential organ failure assessment (SOFA) scores of the first 4 days, and the high sensitivity cardiac troponin I (hs-cTnI) values of the first four days. If a hs-cTnI value is missing on day 2 for example, then the surrounding measurements (day 1 & day 3) will contain important information which should be included in the imputation model. To this effect we used the 'lag' and 'lead' function within the 'Amelia II' package. Results from analyses with imputed data were combined using Rubin's rules. Basic descriptives were based on imputed values. As an example: table 1 of the main manuscript divides patients into those with a hs-cTnI above and below 26ng/L. For patients with missing hs-cTnI on day 1 the categorization was based on the mean hs-cTnI across all imputed datasets. Analysis of our secondary endpoint (cardiovascular disease) was based on a complete case analysis as only 3% (6/200) of patients had missing data in this sub cohort.

Inverse probability weighting

Inverse probability weighting (IPW) aims to control for confounding by creating a pseudo population where there is no longer an association between confounder and exposure. This pseudo population is obtained by weighting each individual patient according to the inverse of their probability of exposure. We used IPW to construct adjusted survival curves [3]. The exposure was categorical

(normal/low/moderate/high hs-cTnI), therefore we performed a multinomial logistic regression to calculate the IPW using the 'IPW' package version 1.0-11 in R. All confounders for the main analysis were included as covariates for this regression model. Subsequently a weighted Kaplan-Meier curve was constructed using the IPW and robust standard errors were obtained using the 'svykm' function from the 'survey' package version 3.31-5 in R. This approach has the advantage that the resulting survival curves are adjusted for confounding while simultaneously allowing hs-cTnI to have non-proportional hazards. Inverse probability weights were truncated at the first and 99th percentile.

Supplementary table 1. Definitions of chronic comorbidities

Comorbidity	**Definition**
Diabetes mellitus	History of diabetes mellitus requiring treatment with medication
Hypertension	Chronic hypertension requiring treatment with medication
Chronic renal insufficiency	Chronic renal insufficiency (creatinine >177 µmol/L) or chronic dialysis
COPD	Obstructive pulmonary disease requiring medical treatment
Congestive heart failure	NYHA class 2-4, documented reduced left ventricular ejection fraction (<45%) or orthopnea requiring medical treatment
Prior myocardial infarction	History of myocardial infarction
Peripheral vascular disease	Intermittent claudication, percutaneous transluminal angioplasty, or bypass for arterial insufficiency

COPD chronic obstructive pulmonary disease, *NYHA* New York Heart Association.

Supplementary table 2. Cox regression analyses relating troponin plasma concentrations on ICU day 1 to mortality within specific follow-up periods (n= 1124)

Time period	**Troponin category**	**Crude**		**Adjusted***	
		HR (95% CI)	*p-value*	*HR (95% CI)*	*p-value*
Day 0-14	Normal (<26 ng/L)	Ref.		Ref.	
	Mild (26-100 ng/L)	1.75 (1.15-2.68)	0.01	1.39 (0.90-2.16)	0.13
	Moderate (100-500 ng/L)	2.55 (1.70-3.84)	<0.001	1.72 (1.14-2.59)	0.01
	High (>500 ng/L)	3.01 (2.00-4.53)	<0.001	1.70 (1.10-2.62)	0.02
Day 14-365	Normal (<26 ng/L)	Ref.		Ref.	
	Mild (26-100 ng/L)	1.35 (1.01-1.82)	0.04	1.22 (0.91-1.67)	0.19
	Moderate (100-500 ng/L)	1.11 (0.79-1.55)	0.56	0.92 (0.65-1.30)	0.62
	High (>500 ng/L)	1.18 (0.82-1.69)	0.39	0.90 (0.61-1.33)	0.60

* Adjusted for: age, sex, chronic renal insufficiency, peripheral vascular disease, diabetes mellitus, hypertension, myocardial infarction, COPD, smoking, congestive heart failure, site of infection, APACHE IV score, and vasopressor requirement.

ICU intensive care unit, *HR* hazard ratio, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *APACHE* acute physiology and chronic health evaluation.

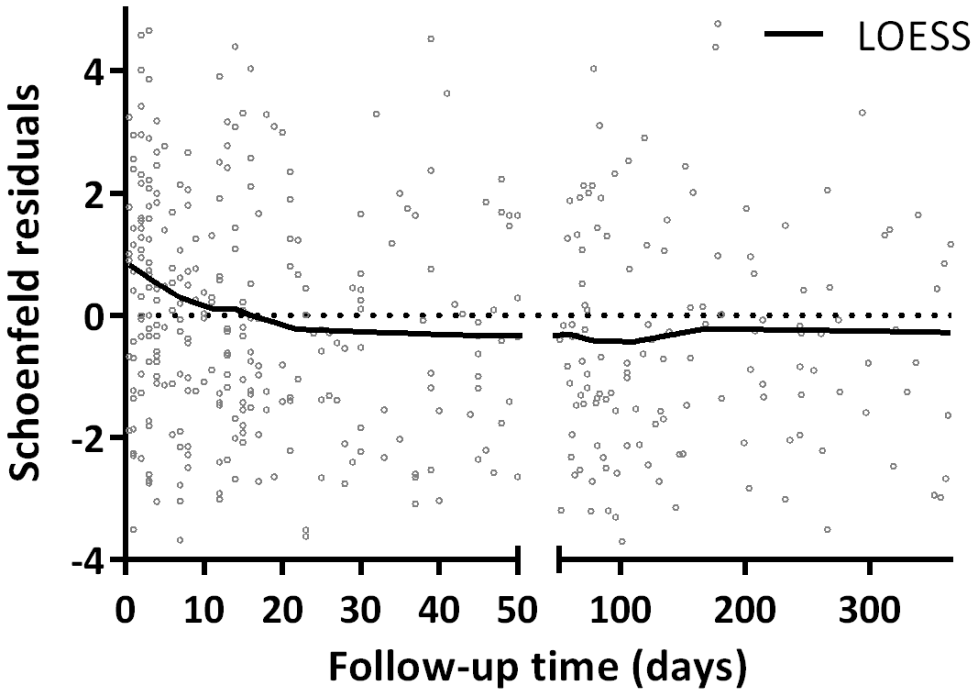
Supplementary table 3. Patient characteristics of hospital survivors by insurance provider (n=787)

	Insured by other company (n=561)	**Insured by Achmea (n=226)**	**p-value**
Age	62 (49-70)	62 (49-70)	0.97
Male	349 (62%)	129 (57%)	0.18
BMI	25 (22-28)	25 (22-28)	0.62
Medical history			
Diabetes mellitus	109 (19%)	39 (17%)	0.48
Hypertension	170 (30%)	55 (24%)	0.09
Chronic renal insufficiency	55 (10%)	33 (15%)	0.05
COPD	71 (13%)	40 (18%)	0.07
Congestive heart failure	27 (5%)	7 (3%)	0.28
Myocardial infarction	45 (8%)	11 (5%)	0.12
Peripheral vascular disease	50 (9%)	30 (13%)	0.07
Site of infection - Pulmonary - Abdominal - Other	 243 (43%) 131 (23%) 187 (33%)	 102 (45%) 46 (20%) 78 (35%)	0.66
Admission characteristics			
Surgery directly before ICU admission	151 (27%)	61 (27%)	0.98
APACHE IV score	71 (57-89)	70 (55-89)	0.42
Vasopressor use within 24 hours	333 (59%)	125 (55%)	0.30
Length of ICU stay (days)	4 (2-8)	4 (2-8)	0.81
Length of hospital stay (days)	25 (13-45)	23 (13-45)	0.88

Data are presented as median (Q1-Q3) or absolute number (percentage).

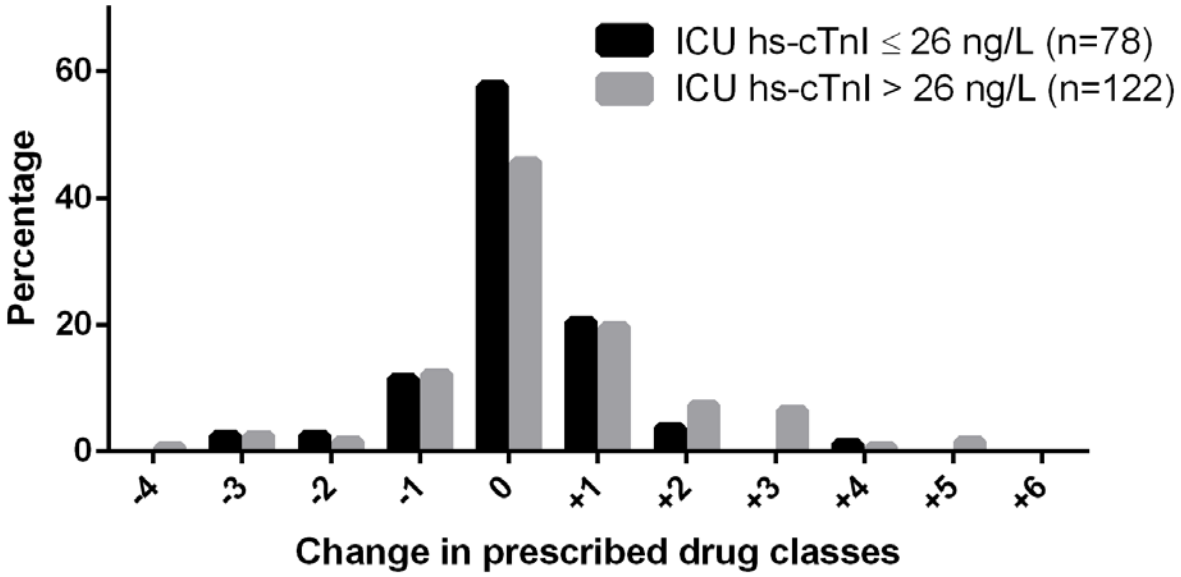
COPD chronic obstructive pulmonary disease, *ICU* intensive care unit, *APACHE* acute physiology and chronic health evaluation.

Supplementary figure 1. Plot of Schoenfeld residuals of day 1 hs-cTnI against follow-up time



Hs-cTnI high-sensitivity cardiac troponin I, *LOESS* Locally estimated scatterplot smoothing.

Supplementary figure 2. Histogram of the difference between the number of cardiovascular drugs prescribed before and after hospital admission split by troponin elevation (n= 200)



The figure displays the change in prescribed classes of cardiovascular drugs (number of drug class prescriptions after hospital discharge - number drug class prescriptions before hospital discharge). If a patient who receives medication from 4 different drug classes before hospitalization, for example, dies quickly after hospital discharge they may not have filled any prescriptions at the pharmacy yet , leading to a large negative score (0-4 = -4).

Hs-cTnI high-sensitivity cardiac troponin I, *ICU* intensive care unit.

Supplemental references

1. Honaker J, King G, Blackwell M. Amelia ii: A program for missing data. *Journal of Statistical Software*. 2011;45:1-47.
2. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in medicine*. 2011;30:377-399. doi:10.1002/sim.4067
3. Cole SR, Hernan MA. Adjusted survival curves with inverse probability weights. *Computer methods and programs in biomedicine*. 2004;75:45-49. doi:10.1016/j.cmpb.2003.10.004