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Prognosis for Adverse Events in Suspected ACS Without MI, and Subgroups With or Without History of Incident and Previous MACE Using the Atellica IM High-Sensitivity Troponin I Assay

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Background

Cardiac troponin (cTn) is well established as the preferred biomarker to aid in the diagnosis of myocardial infarction (MI).[1] In addition, elevated cTnI levels provide useful prognostic information relative to short- and long-term risk of all-cause mortality (ACM) and major adverse cardiac events (MACE) in patients presenting with signs and symptoms of acute coronary syndrome (ACS).[1-4] The high-sensitivity assay on the Atellica IM Analyzer, previously cleared as an aid in diagnosis of MI, is now also cleared for use in the United States as an aid in prognosis for 30-, 90-, 182-, and 365-day ACM and MACE in patients presenting with signs and symptoms suggestive of ACS.[5]

Objective

This study evaluated the association between hs-cTnI concentrations at initial presentation and ACM or MACE among emergency department patients presenting with signs and symptoms suspicious of ACS. MACE is defined as MI, cardiac death, heart failure hospitalization, or urgent revascularization. Patients that were adjudicated with MI were excluded from the analysis.

Materials and Methods

Study Population

- Adult patients suspected of ACS (n=2374) at 29 U.S. sites between 2014 and 2016 were prospectively followed for up to one year. Patients diagnosed with MI (type 1 and type 2) at presentation (n=310; 13%) were excluded. Analyses were performed on the remaining population (n=2064). Two subgroup analyses were also performed — one for a subcohort without known prior cardiovascular events (hereafter designated as no incident/prior MACE), and the other for a subcohort with incident or prior MACE. This gave a subcohort of 1190 patients with no incident/prior MACE and a subcohort of 874 patients with incident or prior MACE. Enrollment criteria comprised adults at least 22 years old with signs and symptoms suggestive of ACS prompting a hs-cTnI test and patient consent. Only patients who declined to participate were excluded.
- hs-cTnI concentrations were measured at presentation—baseline (time zero) in lithium heparin plasma samples using the Atellica IM High-Sensitivity (hs) Troponin I (TnIH) assay. The median time of the baseline blood draw was 93 minutes after ED presentation. The baseline blood draw was 45 minutes (median) after the ED blood draw.

Atellica IM High-Sensitivity Troponin I (TnIH) Assay

- The Atellica IM TnIH assay is a 3-site sandwich immunoassay that uses direct chemiluminescent technology, with a measuring range of 2.50 to 25,000.00 ng/L, limit of detection of 1.60 ng/L, and limit of quantitation of 2.50 ng/L. In apparently healthy individuals, the overall (female and male) 99th percentile upper reference limit (URL) value was 45.20 ng/L (lithium heparin).[5]

Analysis

- Pre- and post-test risks, adjusted hazard ratios (aHRs) and unadjusted hazard ratios (HRs), along with their corresponding 95% confidence intervals (CIs), were computed to compare the probability of events between subjects with baseline hs-cTnI levels above the 99th percentile URL and subjects at or below it. Cox proportional hazards regression analysis was conducted to estimate HRs and aHRs. The adjusted model included covariates such as eGFR, hypertension, prior history of revascularization, prior heart failure, and sex. Plots of cumulative incidence (absolute risk) of ACM versus time were based on the complement of the Kaplan-Meier survival curve.

Results

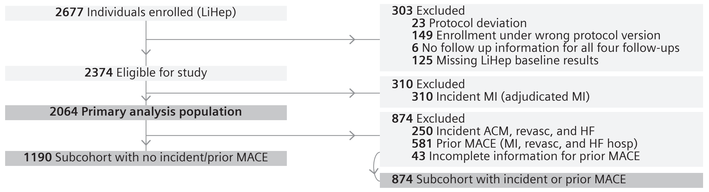


Figure 1. CONSORT diagram of enrolled patients for lithium heparin plasma (LiHep) samples.

Table 1: Demographics of the primary analysis population, excluding patients with adjudicated MI.

	Primary analysis population (all patients excluding adjudicated MI) n=2064	≤ Overall 99th Percentile n=1874	> Overall 99th Percentile n= 190
Age, years (median, IQR)	56 (47-64)	55 (47-64)	59 (50-68)
Male	54.8% (1131/2064)	53.7% (1007/1874)	65.3% (124/190)
Race			
White	56.0% (1155/2064)	57.8% (1083/1874)	37.9% (72/190)
Black or African American	40.2% (829/2064)	38.3% (718/1874)	58.4% (111/190)
Asian	0.9% (19/2064)	0.9% (17/1874)	1.1% (2/190)
Native Hawaiian or Other Pacific Islander	0.1% (3/2064)	0.1% (2/1874)	0.5% (1/190)
American Indian or Alaskan Native	0.5% (11/2064)	0.5% (10/1874)	0.5% (1/190)
Other or more than one race	2.3% (47/2064)	2.4% (44/1874)	1.6% (3/190)
Ethnicity			
Hispanic or Latino	8.4% (171/2046)	8.6% (159/1857)	6.3% (12/189)
Not Hispanic or Latino	91.6% (1875/2046)	91.4% (1698/1857)	93.7% (177/189)
Body Mass Index (kg/m^2)			
< 30	51.4% (1013/1969)	51.6% (920/1782)	49.7% (93/187)
≥ 30	48.6% (956/1969)	48.4% (862/1782)	50.3% (94/187)
Risk Factors			
Hypertension	68.1% (1403/2060)	66.4% (1243/1871)	84.7% (160/189)
Dyslipidemia	39.4% (782/1985)	38.9% (701/1801)	44.0% (81/184)
Diabetes	28.3% (581/2055)	27.1% (506/1865)	39.5% (75/190)
Current Smoker	25.8% (533/2064)	25.7% (482/1874)	26.8% (51/190)
LVEF<40%*	7.3% (135/1854)	5.7% (97/1694)	23.8% (38/160)
History			
Previous Revascularization	26.4% (532/2013)	25.7% (470/1832)	34.3% (62/181)
Previous MI	19.3% (383/1980)	18.3% (330/1806)	30.5% (53/174)
Heart Failure	19.5% (396/2034)	16.5% (306/1850)	48.9% (90/184)
CKD-EPI eGFR Intervals (mL/min/1.73m^2)			
< 60	17.4% (356/2043)	14.7% (273/1853)	43.7% (83/190)
≥ 60	82.6% (1687/2043)	85.3% (1580/1853)	56.3% (107/190)
Chronic Medication			
Statins	42.3% (866/2046)	40.7% (755/1857)	58.7% (111/189)

Numerical data (Age) is presented as median (interquartile range) and categorical data is presented as percent (frequency).
*LVEF, known depressed left ventricular ejection fraction (LVEF<40%).

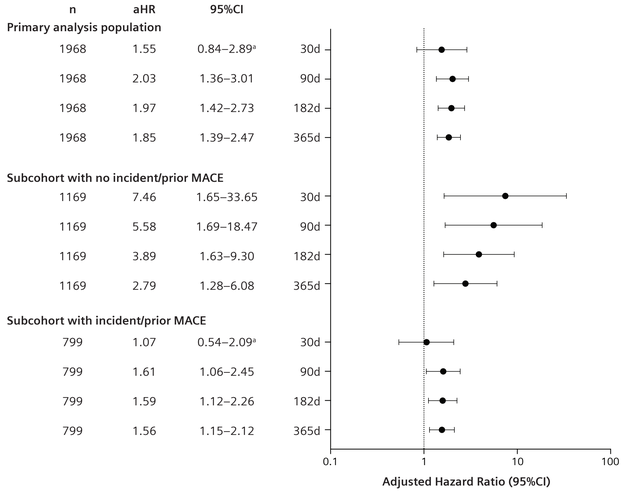
Patients in the primary analysis population and both subcohorts with presentation baseline cTnI above the 99th percentile URL had greater rates of ACM/MACE at one year (Table 2).

Table 2. Pre- and post-test risks and unadjusted hazard ratios using the overall 99th percentile value (lithium heparin plasma).

Follow-up time points	Prevalence of ACM/MACE			Baseline cTnI levels ≤99th percentile			Baseline cTnI levels >99th percentile			Unadjusted hazard ratio (95% CI)[a]
	Total No. of patients	No. of ACM/ MACE events	Pre-test risk of ACM/ MACE (%)	Total No. of patients	No. of ACM/ MACE events	Post-test risk of ACM/MACE (%, 95% CI)	Total No. of patients	No. of ACM/ MACE events	Post-test risk of ACM/MACE (%, 95% CI[b])	
Primary Analysis Population Excluding Adjudicated MI										
30 Days	2064	67	3.2	1874	51	2.7 (2.4–3.1)	190	16	8.4 (5.5–12.6)	3.21 (1.83–5.64)
90 Days	2064	146	7.1	1874	106	5.7 (5.1–6.2)	190	40	21.1 (16.4–26.6)	4.03 (2.80–5.80)
182 Days	2064	227	11.0	1874	171	9.1 (8.5–9.8)	190	56	29.5 (24.0–35.6)	3.66 (2.71–4.95)
365 Days	2064	317	15.4	1874	242	12.9 (12.2–13.6)	190	75	39.5 (33.3–46.0)	3.64 (2.81–4.72)
Subcohort With No History of Incident/Prior MACE										
30 Days	1190	9	0.8	1137	6	0.5 (0.3–0.8)	53	3	5.7 (2.2–13.6)	10.89 (2.72–43.53)
90 Days	1190	17	1.4	1137	13	1.1 (0.9–1.5)	53	4	7.5 (3.2–16.7)	6.84 (2.23–20.98)
182 Days	1190	37	3.1	1137	30	2.6 (2.3–3.1)	53	7	13.2 (6.9–23.9)	5.28 (2.32–12.02)
365 Days	1190	58	4.9	1137	50	4.4 (4.0–4.9)	53	8	15.1 (8.1–26.4)	3.69 (1.75–7.79)
Subcohort With History of Incident or Prior MACE										
30 Days	874	58	6.6	737	45	6.1[d] (5.3–7.0)	137	13	9.5[d] (5.9–14.8)	1.61 (0.87–2.98)[c]
90 Days	874	129	14.8	737	93	12.6 (11.4–13.9)	137	36	26.3 (20.4–33.2)	2.24 (1.52–3.29)
182 Days	874	190	21.7	737	141	19.1 (17.8–20.5)	137	49	35.8 (29.0–43.2)	2.09 (1.51–2.90)
365 Days	874	259	29.6	737	192	26.1 (24.6–27.6)	137	67	48.9 (41.4–56.4)	2.21 (1.67–2.92)

[a]Univariate Cox PH regression analysis; [b]CI = Confidence Interval; [c]Not Statistically Significant (based on 95% CI); [d]Difference in post-test risks not statistically significant.

The adjusted hazard ratio results at the 30-day, 90-day, 182-day, and 365-day follow-up times are presented in Figure 2.



[a]Not statistically significant (based on 95% CI)

Figure 2. Adjusted hazard ratios for ED patients–prognosis for ACM/MACE compared for patients with hs-cTnI values above and at/below the overall 99th percentile.

The primary analysis population and the subcohort with incident or prior MACE were adjusted for prior revascularization, prior heart failure, estimated glomerular filtration rate (eGFR), hypertension, and sex. The subcohort with no incident/prior MACE was adjusted for eGFR, hypertension, and sex. For each cohort data set, smoking, diabetes, BMI, race, and age were also evaluated and were not significantly associated with cumulative ACM/MACE statistically. Prior MI, statins, and LVEF were evaluated and removed from the model due to observed multicollinearity. n: number of patient samples tested. aHR: adjusted hazard ratio, obtained using Cox PH multivariable regression analysis. 95%CI: 95% confidence interval. Results are for lithium heparin samples.

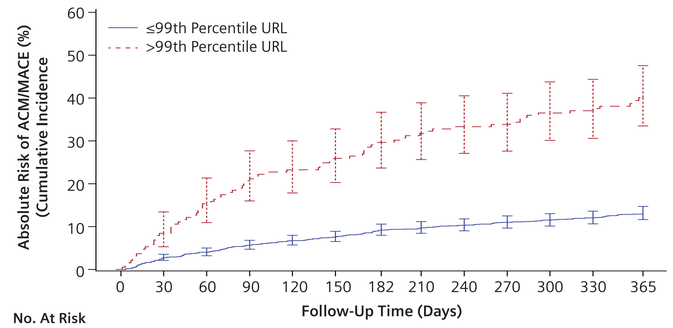
The type of events and the breakdown of ACM/MACE outcomes for patients with cTnI concentrations above and at/below the 99th percentile are presented in Table 3.

Table 3. Event type summary for the three populations using the overall 99th percentile value (lithium heparin plasma).

Lithium Heparin Plasma	Primary Analysis Population Excluding for Adjudicated AMI			Subcohort with No Incident/Prior MACE			Subcohort with Incident or Prior MACE		
Type of Event	Total	≤99th Percentile	>99th Percentile	Total	≤99th Percentile	>99th Percentile	Total	≤99th Percentile	>99th Percentile
Total	**2064**	**1874**	**190**	**1190**	**1137**	**53**	**874**	**737**	**137**
Survived to day 365 with no ACM/MACE	1724	1610	114	1118	1073	45	606	537	69
Censor (Loss to follow-up)	23	22	1	14	14	0	9	8	1
ACM/MACE	317	242	75	58	50	8	259	192	67
Breakdown of ACM/MACE outcomes, n (%)									
Cardiac Death	12 (3.79)	11 (4.55)	1 (1.33)	2 (3.45)	2 (4.00)	0 (0.00)	10 (3.86)	9 (4.69)	1 (1.49)
HF Hospitalization	192 (60.57)	136 (56.20)	56 (74.67)	29 (50.00)	23 (46.00)	6 (75.00)	163 (62.93)	113 (58.85)	50 (74.63)
Incident Death	8 (2.52)	5 (2.07)	3 (4.00)	NA	NA	NA	8 (3.09)	5 (2.60)	3 (4.48)
AMI	21 (6.62)	16 (6.61)	5 (6.67)	4 (6.90)	3 (6.00)	1 (12.50)	17 (6.56)	13 (6.77)	4 (5.97)
AMI, HF Hospitalization	2 (0.63)	1 (0.41)	1 (1.33)	NA	NA	NA	2 (0.77)	1 (0.52)	1 (1.49)
AMI, Urgent Revas	7 (2.21)	7 (2.89)	0 (0.00)	NA	NA	NA	7 (2.70)	7 (3.65)	0 (0.00)
AMI, Urgent Revas, Cardiac Death	1 (0.32)	0 (0.00)	1 (1.33)	1 (1.72)	0 (0.00)	1 (12.50)	NA	NA	NA
AMI, Urgent Revas, HF Hospitalization	1 (0.32)	1 (0.41)	0 (0.00)	NA	NA	NA	1 (0.39)	1 (0.52)	0 (0.00)
Other Death[a]	40 (12.62)	33 (13.64)	7 (9.33)	14 (24.14)	14 (28.00)	0 (0.00)	26 (10.04)	19 (9.90)	7 (10.45)
Urgent Revas	32 (10.09)	31 (12.81)	1 (1.33)	8 (13.79)	8 (16.00)	0 (0.00)	24 (9.27)	23 (11.98)	1 (1.49)
Urgent Revas, HF Hospitalization	1 (0.32)	1 (0.41)	0 (0.00)	NA	NA	NA	1 (0.39)	1 (0.52)	0 (0.00)

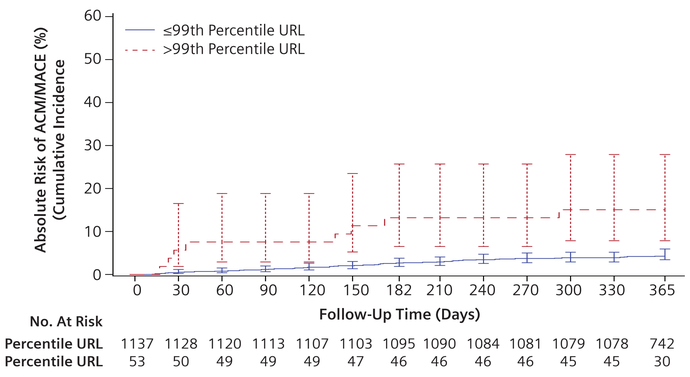
[a]Other death, known (n=19 patients): Subcohort with no history of incident/prior MACE (n=8)—acute respiratory failure (1); cancer, bladder (1); cancer, lung (3); cancer, undefined (1); chronic kidney disease (1); septic shock (1). Subcohort with history of incident or prior MACE (n=11)—acute respiratory failure (1); aspiration (1); cancer, pancreatic (1); cancer, undefined (1); cardiac arrest, cause unspecified (1); chronic kidney disease (1); heart failure, coronary artery disease (1); hemorrhage, intracranial (1); hypertensive crisis (1); pulmonary embolism, bilateral (1); stroke (1). Other death, unknown (n=21 patients): Subcohort with no history of incident or prior MACE (n=6). Subcohort with history of incident or prior MACE (n=15).

Kaplan Meier plots of cumulative incidence of ACM/MACE events over a one-year period are presented in Figure 3.



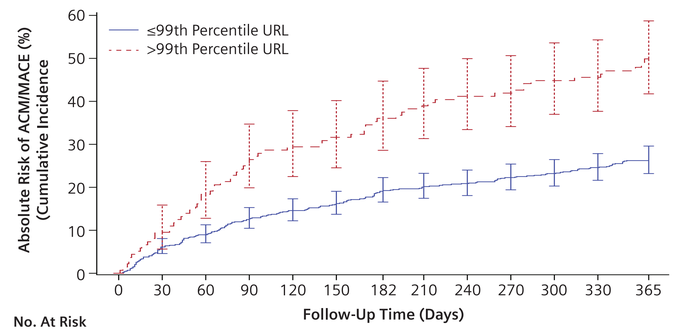
No. At Risk													
≤99th Percentile URL	1874	1818	1788	1754	1732	1717	1685	1672	1660	1647	1638	1626	1107
>99th Percentile URL	190	173	160	150	145	140	133	129	126	125	120	119	74

A. Primary analysis population.



No. At Risk													
≤99th Percentile URL	1137	1128	1120	1113	1107	1103	1095	1090	1084	1081	1079	1078	742
>99th Percentile URL	53	50	49	49	49	47	46	46	46	46	45	45	30

B. Subcohort with no incident/prior MACE.



No. At Risk													
≤99th Percentile URL	737	690	668	641	625	614	590	582	576	566	559	548	365
>99th Percentile URL	137	123	111	101	96	93	87	83	80	79	75	74	44

C. Subcohort with incident or prior MACE.

Figure 3. Kaplan-Meier plots presenting cumulative incidence over one year for ACM and MACE for patients with hs-cTnI concentrations above and at/below the overall 99th percentile URL (sexes combined). A. Primary analysis population. B. Subcohort with no incident/prior MACE. C. Subcohort with incident or prior MACE. Patients with adjudicated MI diagnosis during initial presentation were excluded. Results are for lithium heparin samples.

Conclusion

The results of this study show that patients with hs-cTnI concentrations above the overall 99th percentile URL and no adjudicated MI diagnosis were at increased risk of ACM and MACE over a one-year period compared to patients with hs-cTnI concentrations at/below the overall 99th percentile URL. At one year, the risk difference for the primary analysis population was 26.6%, and the risk difference for the subcohort with no incident/prior MACE was 10.7%.

In patients presenting to the emergency department with signs and symptoms suggestive of ACS, the Atellica IM TnIH assay can aid in prognosis for 30-, 90-, 182-, and 365-day ACM and MACE.

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