Clin Chem. Author manuscript; available in PMC 2013 February 11.

Published in final edited form as:

Clin Chem. 2009 October ; 55(10): 1809–1815. doi:10.1373/clinchem.2009.127241.

Short- and Long-Term Risk Stratification Using a Next-Generation, High-Sensitivity Research Cardiac Troponin I (hs-cTnI) Assay in an Emergency Department Chest Pain Population

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Abstract

BACKGROUND—The next-generation, high-sensitivity cardiac troponin assays can measure quantifiable concentrations of cTn in a majority of individuals, but there are few studies assessing these assays for risk stratification. The present study was undertaken to determine if a research hs-cTnI assay can be useful for predicting death/myocardial infarction (MI), both short- and long-term, in an emergency department acute coronary syndrome (ACS) population.

METHODS—In a cohort of 383 subjects, originally recruited in 1996, presenting to the emergency department with symptoms suggestive of ACS, the heparin plasma obtained at initial presentation was thawed and measured in 2007 with a research hs-cTnI assay. AccuTnI (Beckman Coulter) measurements were made on these same samples in 2003. The population was divided into 4 groups by hs-cTnI: <5.00, 5.00 –9.99, 10.00 – 40.00, and >40.00 ng/L. Kaplan–Meier, Cox proportional hazards, ROC curves, and logistic regression analyses were used to identify which hs-cTnI concentrations were predictive of death/MI within 10 years after presentation.

RESULTS—There were significant differences between the hs-cTnI groups for the probability of death/MI up to 10 years after presentation ($P < 0.05$). At 6 months, patients with hs-cTnI ≥10.00

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Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article

Authors' Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.

Consultant or Advisory Role: A.R. MacRae, Beckman Coulter; A.S. Jaffe, Siemens, Beckman Coulter, Ortho Diagnostics, Singulex, Nanosphere, Inverness, Critical Diagnostics, GlaxoSmithKline, and Novartis.

Stock Ownership: None declared.

Honoraria: P.A. Kavsak, Beckman Coulter.

Expert Testimony: None declared.

ng/L were at higher risk for death/MI (hazard ratio >3.7; $P < 0.05$) compared with those having hs-cTnI <5.00 ng/L. ROC curve analysis for death/MI at 30 days with the hs-cTnI assay had an area under the curve of 0.74 (95% CI 0.65–0.82), with logistic models yielding an optimal assay threshold of 12.68 ng/L.

CONCLUSIONS—This research hs-cTnI assay appears useful for risk stratification for death/MI in an ACS population.

In recent years, there has been enthusiasm for the development of more sensitive cardiac troponin (cTn)[5] assays (1–3). The reports about these efforts to date have indicated that cTn is measurable in a majority of individuals and that the 99th percentile concentration is lower than previously thought (approximately 10 ng/L), and the increased sensitivity of these new assays may allow changing patterns to be more easily recognized (4 –9). The next step in the validation process is determining whether measurement with these hs-cTn assays can identify individuals at risk for an adverse outcome. In the present study, we measured hs-cTnI with a preproduction research assay in patients presenting with symptoms suggestive of acute coronary syndrome (ACS) and assessed if concentrations measured by this high-sensitivity assay were prognostic for short- and/or long-term risk of death and/or myocardial infarction (MI).

Materials and Methods

After ethics approval, in 1996, patients presenting with symptoms suggestive of ACS were enrolled in a cardiac biomarkers study (n = 448). Based on time from onset of pain, blood specimens were collected from the study population in heparin tubes and plasma was separated by centrifugation and frozen until 2003, when cTnI was measured in the specimens using the AccuTnI™ assay (Beckman Coulter) (10, 11). Specimens with sufficient volume were thawed from storage at −70 °C for a second time in 2007 and measured with a research hs-cTnI assay (Beckman Coulter) (9). For this analysis, we selected as the study cohort the 383 subjects whose earliest presentation specimens had both AccuTnI and hs-cTnI concentrations.

The hs-cTnI assay is reported to have a limit of the blank concentration of 1.03 ng/L, with a limit of detection of 2.06 ng/L, and attains 20% CV and 10% CV at concentrations of 2.95 ng/L and 8.66 ng/L, respectively (9). The hs-cTnI assay uses the same antibodies as the current AccuTnI assay, which has been demonstrated to provide consistent (stable) measurements after multiple freeze/thaws and over 10 years of storage (9, 12, 13). The increased sensitivity with this research hs-cTnI assay was obtained by increases in the incubation time and the sample volume and by changes to the microparticle capture bead (9). The hs-cTnI and AccuTnI assays were correlated ($r = 0.87$); however, the estimated 99th percentiles for cTn in heparin plasma appeared to be different between the assays (9.20 ng/L for hs-cTnI vs 0.04 μg/L for AccuTnI) (9, 14). The preliminary estimate of the 99th percentile for the hs-cTnI assay was derived from a small group (n = 125) of younger individuals (age ≤55 years). Because our study cohort was older (median age 64 years; Table

[5]Nonstandard abbreviations: cTn, cardiac troponin; ACS, acute coronary syndrome; MI, myocardial infarction; HR, hazard ratio.

1), we opted to subgroup our population into categories that divided the population nearly evenly based on AccuTnI concentrations that have been shown previously to have prognostic value (11, 13, 15). For the AccuTnI assay, we classified subjects into 3 groups: ≤0.01 μg/L (n = 227); 0.02–0.04 μg/L (n = 78); and >0.04 μg/L (n = 78). Owing to the increased analytical sensitivity of the hs-cTnI assay, we subdivided subjects into 4 groups based on hs-cTnI results: <5.00 ng/L (n = 92); 5.00 –9.99 ng/L (n = 93); 10.00 – 40.00 ng/L (n = 93); and >40.00 ng/L (n = 105). To clearly distinguish which cTn concentrations were derived from the hs-cTnI assay, the reported units are in ng/L compared to the AccuTnI assay with reported units in μg/L.

We obtained health outcomes in the study cohort via linkage to the Registered Persons Data Base for mortality outcomes and the Canadian Institute for Health Information Discharge Abstract Database for Ontario hospital discharges associated with MI, which has been shown to be accurate and is consistent in our previous analyses (11, 16). Based on the earliest subsequent readmission for MI and/or date of death, we created indicators to reflect whether an event (readmission or death) occurred within 30 days, 6 months, 1, 2, 5, and 10 years postpresentation. If a patient died without previous MI, follow-up was censored at the date of death. The outcomes were captured as events postpresentation (i.e., either during index hospitalization or afterward). We assessed the time to an adverse event by Kaplan–Meier survival curves with differences between groups determined by the log rank test. We used the Cox proportional hazard model to compare time to an event while adjusting for age and sex. Hazard ratios (HRs) were generated for each cTn group relative to the lowest concentration group (≤0.01 μg/L for AccuTnI and <5.00 ng/L for hs-cTnI) and were derived by partial likelihood estimation. Significance of the association was based on the Wald χ^2 statistic. Between-group comparisons of central tendency (means, medians) were based on ANOVA and the Kruskal–Wallis test. We used the Pearson χ^2 test statistic to compare proportions. ROC curve analyses were performed for end point death/MI at 30 days and 1 and 10 years, with logistic regression modeling used to find the optimal concentration cutoffs. Briefly, we derived the optimal cutoff concentrations for cTnI and hs-cTnI by first building logistic models with the cTnI or hs-cTnI variable as the covariate, for each value observed to obtain a *c*-statistic, with the maximum *c*-statistic from all models used to identify the optimal cutoff. As the distributions of hs-cTnI and the AccuTnI concentrations were heavily skewed, we used log transformation first, then performed univariate analysis in the logistic regression model for log(hs-cTnI) or log(AccuTnI) using death or MI as the outcome. For the final models, we calculated *c*-statistics with 95% CIs for each model and compared *c*-statistics among the different models using a nonparametric approach.

All statistical analyses were performed using SAS and Graphpad prism software. We considered *P* values <0.05 statistically significant.

Results

The median time from onset of pain to the first specimen was 3 h (interquartile range 2– 6) (Table 1). Kaplan–Meier survival curves for death alone, MI alone, and the combined end point death/MI indicated differences in event-free survival between the 4 hs-cTnI groups up to 10 years after presentation (Fig. 1). Cox proportional hazards analyses indicated that those

participants with cTn >40.00 ng/L or 0.04 μg/L were at higher risk for the combined end point death/MI at 30 days compared with the referent groups ($P < 0.01$; Table 2). Analysis for either MI or death alone indicated that only those subjects with cTn >40.00 ng/L or 0.04 μg/L were at higher risk for MI within 30 days (HR 13.2, 95% CI 1.73–99.9, $P = 0.01$ for hs-cTnI; HR 26.1, 95% CI 5.91–115, $P < 0.01$ for AccuTnI) but not death ($P > 0.10$). At 6 months and 1 year, in addition to the >40.00 ng/L groups, only the 10.00 –40.00 ng/L group was at higher risk for the combined end point (death/MI) at these time points. Further analysis at 1 and 2 years indicated that participants with hs-cTnI concentrations in the 10.00 – 40.00 ng/L group were at higher risk for death alone (HR 3.64, 95% CI 1.04 –12.7, $P = 0.04$ at 1 year; HR 4.06, 95% CI 1.54 –10.7, $P < 0.01$ at 2 years); however, participants in the group with AccuTnI concentrations of 0.02– 0.04 μg/L were not found to be at increased risk (HR 1.56, 95% CI 0.69 –3.54, $P = 0.29$ at 1 year; HR 1.64, 95% CI 0.86 –3.11, $P = 0.13$ at 2 years). Using the combined end point (death/MI) at 2, 5, and 10 years, participants presenting with AccuTnI ≥0.02 μg/L or hs-cTnI ≥10.00 ng/L were at higher risk compared with the referent groups ($P < 0.05$; Table 2). ROC curve analysis for death/MI at 30 days had an area under the curve of 0.74 (95% CI 0.66 – 0.82) for the hs-cTnI assay compared with 0.81 (95% CI 0.73– 0.90) for the AccuTnI assay ($P = 0.05$). The derived optimal cutoff concentrations of hs-cTnI and AccuTnI at 30 days were 12.68 ng/L (sensitivity 0.83; specificity 0.57) and 0.03 μg/L (sensitivity 0.80; specificity 0.77), respectively (Fig. 2). At 1 and 10 years, using the same approach, the optimal cutoff hs-cTnI concentrations were 12.68 ng/L and 9.30 ng/L, respectively, and for the AccuTnI these concentrations were 0.02 μg/L and 0.01 μg/L.

Discussion

These data add to our understanding of novel high-sensitivity troponin assays. The increased analytical sensitivity of the hs-cTnI assay allowed us to identify that individuals who presented with hs-cTnI concentrations ≥10.00 ng/L were at higher risk of death/MI within 1 year after their presentation. For short-term risk (i.e., within 30 days), only those individuals with increased cTn (>40 ng/L or >0.04 μg/L) were at higher risk compared to those with low cTnI concentrations. This inconsistency in the relationship of concentrations of cTn to short- and long-term risks could reflect the fact that a relative paucity of short-term events may have led to an underpowered analysis; however, despite this inconsistency, the concentration cutoff at the 99th percentile derived for the AccuTnI assay (i.e., 0.04 μg/L) seems suitable for short-term risk stratification. This finding is supported by logistic regression modeling for AccuTnI, where the optimal cutoff was 0.03 μg/L for death/MI within 30 days; for the hs-cTnI assay, however, this concentration cutoff was 12.68 ng/L. A larger study is necessary to confirm the optimal cutoff for short-term risk stratification using this hs-cTnI assay. Beyond 30 days, the hs-cTnI assay provided additional information regarding risk in the early time frame (i.e., ≤1 year), whereas detectable concentrations at presentation by the AccuTnI assay (e.g., 0.02– 0.04 μg/L) were not able to provide such discriminatory utility in this early time frame. Consistent with other findings (13, 17), these detectable concentrations with the AccuTnI assay were prognostic at 2, 5, and 10 years. As noted by Morrow and Antman (18), the increased sensitivity of these newer assays requires that we

refine what we consider “normal.” Alternatively, one could start using risk prediction in place of cut values (19).

The data we present are preliminary, and additional studies will be required to confirm these findings and assess the relationship between these lower concentrations and available therapies. Specific limitations include our inability to separate noncardiovascular death from cardiovascular death in our population. Moreover, limited sample volumes in the stored samples precluded our ability to retest those samples with divergent cTn concentrations (i.e., specimens with AccuTnI concentrations ≤0.01 μg/L that had corresponding hs-cTnI concentrations >40.00 ng/L); such divergence in results between the assays might have negatively affected the specificity of the research hs-cTnI assay. Also, the fact that only the admission samples were used in this analysis is another limitation, because serial changes as well as peak concentrations may be more clinically relevant for an ACS population (20). Additional work using this research hs-cTnI assay in a larger ACS population with multiple specimens to assess both change and peak concentrations over the first 24 h after pain onset would provide a richer dataset to truly assess both the diagnostic and prognostic power of this hs-cTnI assay. Despite these limitations, the findings of our current study extend our understanding and offer promise that novel high-sensitivity cardiac troponin assays will improve our ability to triage and treat patients with possible cardiac injury.

Acknowledgments

Research Funding: Canadian Institutes of Health Research. P.A. Kavsak, Beckman Coulter. A.S. Jaffe, Siemens and Beckman Coulter. Reagents were provided as an unrestricted grant by Beckman Coulter.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

Special thanks to the Clinical Research and Clinical Trials Laboratory, Hamilton, for performing the laboratory measurements.

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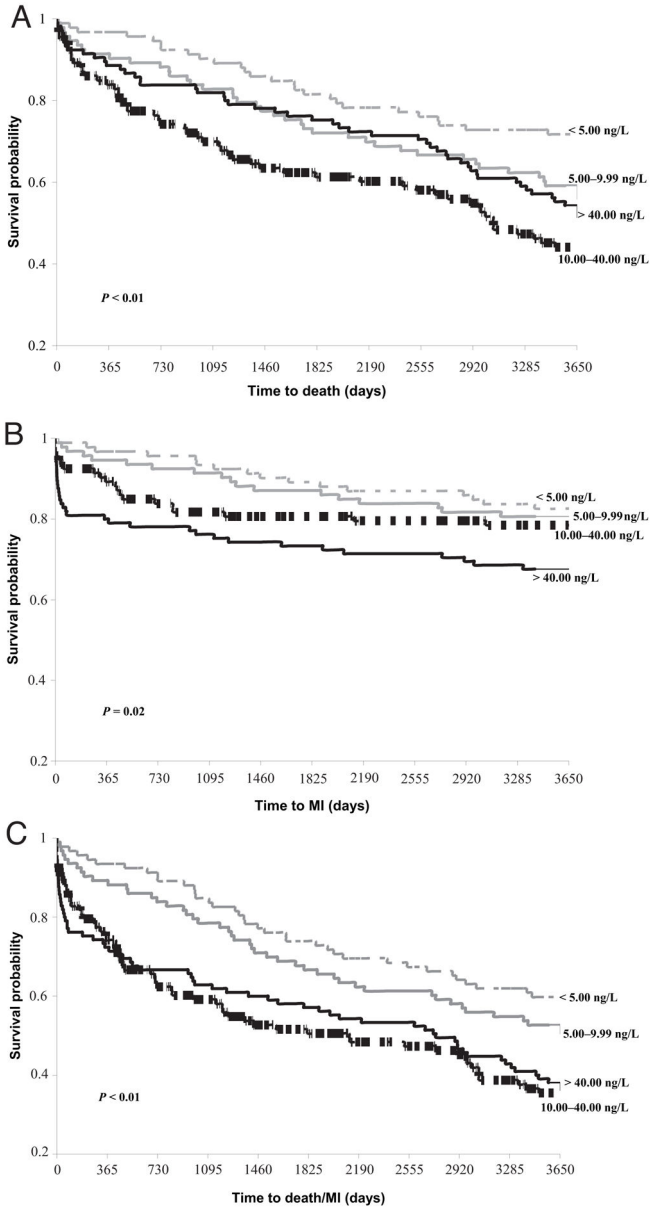
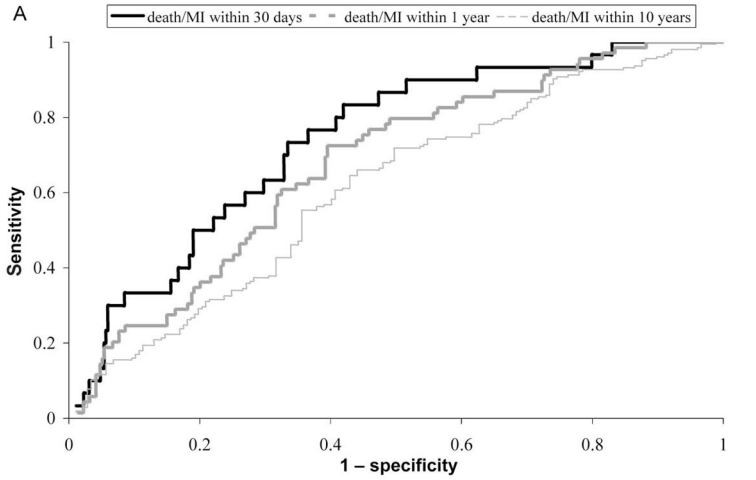
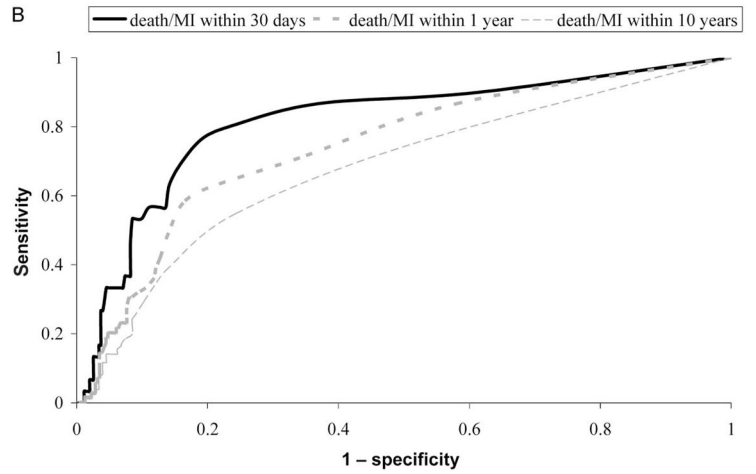


Fig. 1.

Kaplan–Meier curves for the probability of death (A), MI (B), and the combined end point death/MI (C) based on the hs-cTnI groups up to 10 years after presentation.



Outcome (death/MI)	AUC	Lower 95% CI of AUC	Upper 95% CI of AUC	Optimal hs-cTnI (ng/L)	Sensitivity	Specificity
within 30 days	0.74	0.66	0.82	12.68	0.83	0.57
within 1 year	0.68	0.61	0.74	12.68	0.72	0.60
within 10 years	0.61	0.55	0.67	9.30	0.65	0.57



Outcome (death/MI)	AUC	Lower 95% CI of AUC	Upper 95% CI of AUC	Optimal AccuTnI (μg/L)	Sensitivity	Specificity
within 30 days	0.81	0.73	0.90	0.03	0.80	0.77
within 1 year	0.74	0.68	0.81	0.02	0.71	0.66
within 10 years	0.68	0.62	0.73	0.01	0.75	0.49

Fig. 2. ROC curve analysis for death/MI at 30 days, 1 year, and 10 years for hs-cTnI (A) and AccuTnI (B)

AUC, area under the curve.

Table 1

Study cohort characteristics based on hs-cTnI concentration groupings.[a]

	hs-cTnI, ng/L					
Variable	**<5.00**	**5.00–9.99**	**10.00–40.00**	**>40.00**	**All**	***P* value**
n	92	93	93	105	383	
Demographics						
Age at presentation						
Mean (SD)	60.3 (14.0)	62.6 (14.7)	65.7 (13.4)	62.6 (13.7)	62.8 (14.0)	0.070
Median (IQR)[b]	60 (49–71)	63 (52–74)	68 (56–76)	65 (51–74)	64 (51–74)	0.064
Sex, n (%)						
Female	40 (43.5)	40 (43.0)	32 (34.4)	41 (39.0)	153 (39.9)	0.559
Male	52 (56.5)	53 (57.0)	61 (65.6)	64 (61.0)	230 (60.1)	
Previous MI, n (%)	20 (21.7)	22 (23.7)	24 (25.8)	35 (33.3)	101 (26.4)	0.261
1996 MI diagnosis, n (%)	<6	<6	15 (16.1)	38 (36.2)	57 (14.9)	<0.001
Median cTn concentration						
hs-cTnI, ng/L (IQR)	3.95 (3.11–4.44)	6.82 (5.59–8.02)	17.74 (12.80–25.89)	112.9 (69.77–270.2)	10.67 (5.18–50.73)	<0.001
AccuTnI, μg/L (IQR)	0.00 (0.00–0.01)	0.01 (0.00–0.02)	0.02 (0.01–0.04)	0.08 (0.01–0.32)	0.01 (0.00–0.03)	<0.001
Median time from onset until measurement, h (IQR)	4 (2–5)	3 (2–9)	3 (2–5)	4 (2–12)	3 (2–6)	0.069
Outcome, n (%)						
MI						
Within 30 days	<6	<6	<6	15 (14.3)	22 (5.7)	<0.001
Within 6 months	<6 (1.1)	<6 (3.2)	7 (7.5)	20 (19.0)	31 (8.1)	<0.001
Within 1 year	<6	<6	10 (10.8)	21 (20.0)	30 (10.2)	<0.001
Within 2 years	<6	7 (7.5)	15 (16.1)	23 (21.9)	49 (12.8)	<0.001
Within 5 years	10 (10.9)	12 (12.9)	18 (19.4)	28 (26.7)	68 (17.8)	0.016
Within 10 years	16 (17.4)	18 (19.4)	20 (21.5)	34 (32.4)	88 (23.0)	0.053
Death						
Within 30 days	<6	<6	<6	<6	8 +(2.1)	0.367
Within 6 months	<6	7 (7.5)	12 (12.9)	8 (7.6)	30 (7.8)	0.112

Variable	hs-cTnI, ng/L				All	*P* value
	<5.00	5.00–9.99	10.00–40.00	>40.00		
Within 1 year	<6	8 (8.6)	15 (16.1)	12 (11.4)	38 (9.9)	0.029
Within 2 years	<6	11 (11.8)	24 (25.8)	17 (16.2)	57 (14.9)	0.001
Within 5 years	17 (18.5)	26 (28.0)	36 (38.7)	26 (24.8)	105 (27.4)	0.018
Within 10 years	26 (28.3)	38 (40.9)	52 (55.9)	48 (45.7)	164 (42.8)	0.002
MI/death						
Within 30 days	<6	<6	9 (9.7)	17 (16.2)	30 (7.8)	<0.001
Within 6 months	<6	8 (8.6)	18 (19.4)	25 (23.8)	55 (14.4)	<0.001
Within 1 year	6 (6.5)	10 (10.8)	24 (25.8)	29 (27.6)	69 (18.0)	<0.001
Within 2 years	8 (8.7)	15 (16.1)	35 (37.6)	35 (33.3)	93 (24.3)	<0.001
Within 5 years	24 (26.1)	31 (33.3)	46 (49.5)	45 (42.9)	146 (38.1)	0.006
Within 10 years	37 (40.2)	44 (47.3)	60 (64.5)	65 (61.9)	206 (53.8)	0.001

[a] Privacy constraints prohibit the display of cells from groups of <6 individual patients.

[b] IQR, interquartile range.

Table 2

Cox proportional hazard model of time to death/MI using presentation specimen (after adjusting for age and sex).

Time since presentation	AccuTnI concentration, μg/L	HR relative to AccuTnI ≤	95% CI	*P* value	hs-cTnI concentration, ng/L	HR relative to hs-cTnI <5.00	95% CI	*P* value
30 days	>0.04	14.68	4.96–43.48	<0.01	>40.00	7.20	1.66–31.21	0.01
	0.02–0.04	3.37	0.89–12.75	0.07	10.00–40.00	3.60	0.76–16.94	0.11
					5.00–9.99	0.91	0.13–6.50	0.93
6 months	>0.04	7.78	4.03–15.04	<0.01	>40.00	5.82	2.02–16.75	<0.01
	0.02–0.04	2.03	0.88–4.68	0.10	10.00–40.00	3.77	1.26–11.27	0.02
					5.00–9.99	1.83	0.55–6.08	0.33
1 year	>0.04	5.42	3.09–9.53	<0.01	>40.00	4.58	1.90–11.04	<0.01
	0.02–0.04	1.91	0.97–3.77	0.06	10.00–40.00	3.38	1.37–8.33	0.01
					5.00–9.99	1.50	0.55–4.14	0.43
2 years	>0.04	4.37	2.69–7.10	<0.01	>40.00	4.32	2.00–9.32	<0.01
	0.02–0.04	2.09	1.22–3.60	0.01	10.00–40.00	4.01	1.85–8.70	<0.01
					5.00–9.99	1.70	0.72–4.02	0.23
5 years	>0.04	2.73	1.85–4.03	<0.01	>40.00	1.94	1.18–3.18	0.01
	0.02–0.04	1.78	1.18–2.67	0.01	10.00–40.00	1.89	1.15–3.11	0.01
					5.00–9.99	1.19	0.70–2.03	0.53
10 years	>0.04	2.34	1.68–3.26	<0.01	>40.00	1.85	1.23–2.77	<0.01
	0.02–0.04	1.70	1.21–2.39	<0.01	10.00–40.00	1.66	1.10–2.52	0.02
					5.00–9.99	1.15	0.74–1.79	0.53