Analytical Performance of the Siemens Healthineers ADVIA Centaur High-Sensitivity Troponin I Assay

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Background

The ADVIA Centaur® High-Sensitivity Troponin I (TNIH) Assay is for in vitro diagnostic use in the quantitative measurement of cardiac troponin I in human serum or plasma using the ADVIA Centaur® XP and ADVIA Centaur® XPT Immunoassay Systems.[1] In 2015, the European Society of Cardiology published guidelines that proposed algorithms for faster rule-in or rule-out of acute myocardial infarction (AMI) in patients admitted in the acute-care setting and for the management of non-ST-elevation myocardial infarction (NSTEMI) patients.[2] Serial measurements with high-sensitivity troponin I (cTnI) assays will more accurately and precisely measure changes in cTnI concentrations, enabling the discrimination of acute from chronic cTnI elevations and affording acceptable rule-in and rule-out claims within 1 to 3 hours.[2]

The goal of these studies was to verify the analytical performance of the ADVIA Centaur TNIH Assay as described in the Instructions for Use[1] using data obtained at four sites in Europe (Table 1). Because clinical assessments were not known by the laboratory, values were normalized to the respective 99th percentiles of a healthy population. Then the performance of the ADVIA Centaur TNIH Assay and a second assay found at each site were compared.

Methods

Principles of the procedure

The ADVIA Centaur TNIH Assay is a three-site sandwich immunoassay using direct chemiluminometric technology. The solid phase reagent is magnetic latex particles conjugated with streptavidin, with two bound biotinylated capture monoclonal antibodies each recognizing a unique cTnI epitope. The Lite reagent comprises a conjugate whose architecture consists of a proprietary acridinium ester (tri-sulfo propyl acridinium ester [TSPAE]) that enhances chemiluminescent detection and a recombinant anti-human cTnI sheep FAb covalently attached to bovine serum albumin (BSA) for chemiluminescent detection. The use of the FAb reduces the potential interference with heterophilic antibodies and rheumatoid factor. TSPAE is a new generation of high-yield acridinium esters developed by Siemens Healthineers for enhanced chemiluminescent detection. Simultaneous addition of solid phase reagent and detection reagent to the sample forms a classic sandwich immune complex that is subsequently washed. Chemiluminescence is initiated and measured. The accumulated light signal is directly related to the sample cTnI concentration. The time to first result is 18 minutes.[1]

Precision

Repeatability (within-run) and within-lab (total) precision were tested according to the governing standard CLSI EP05-A3: Evaluation of Precision Performance of Quantitative Measurement Methods.[7] Precision studies were performed at four sites with the ADVIA Centaur TNIH Assay using four samples comprising controls (serum) and a serum pool. The studies were performed at each site using one reagent lot and one instrument. For each sample, n = 5/day for each of five days, which totals 25 replicates/sample over five days and 100 replicates/sample over five days for the four sites combined. TNIH precision serum pools were aliquoted and frozen prior to the start of the study. Each testing day, a new set of aliquots was thawed. Data analysis was completed using a nested, two-factor (days and runs nested within days) ANOVA model. Repeatability and within-lab precision estimates were calculated using the Precision Summary by GDMS version 3.8, EP05-2A validation evaluation tool version 1.3.

Assay precision requirements as stated in the Instructions for Use are presented in Table 2.[1]

Limitations of the study include the fact that adjudication of patients was not available; however, preliminary observations were made, including comparisons of patient statistics using values normalized to the 99th percentile of a healthy population, and comparing the number of patients with undetectable cardiac troponin.

Comparison of number of subjects with undetectable troponin (<LoD), and values <99th percentile

A different set of leftover laboratory samples was examined at each site. Because clinical data was not available, the number of subjects with values below the LoD and below the 99th percentile as reported in the respective IFU was compared.

Normalized data comparison

Comparison of the ADVIA Centaur TNIH Assay and one other assay at each site—Dimension Vista®, ADVIA Centaur TnI-Ultra™, Roche TnT hs, or Abbott ARCHITECT hs TnI—was performed by normalizing values to the respective 99th percentile claimed by the manufacturer (i.e., normalized value = value/99th percentile) (Table 7).

Kinetics of cardiac troponin I

For a limited number of subjects, values were obtained at presentation and different times after presentation. The values normalized to the respective 99th percentile for the ARCHITECT High Sensitivity Troponin I (hs TnI) and the ADVIA Centaur TNIH assays were compared.

Table 1. European sites and investigator information.

Site	Principal Investigator	Site Address	Instruments	Assay
1	Dr. Guillaume Lefèvre Head of Biochemistry & Hormonology Lab	Department of Biochemistry et Hormonology, Tenon Hospital – APHP – HUEP Paris 75020 -France	ADVIA Centaur XP	ADVIA Centaur High-sensitivity Troponin I (TNIH)[1]
			Abbott ARCHITECT	STAT High Sensitive Troponin-I (hs TnI)[3]
2	Dr. Pierre N. Bouchelouche	Sjællands Universitetshospital Klinisk biokemisk afdeling Lykkebækvej 1 Koge, Denmark	ADVIA Centaur XP	TNIH[1]
			Dimension Vista	Troponin I (CTNI)[4]
3	Christina Alf-Borszeki Process Leader, Unilabs Malin Wennerholm, Chemist Unilabs	Unilabs AB Laboratoriemedicin Mälardalenssjukhus Eskilstuna Gothenburg, Sweden	ADVIA Centaur XPT	TNIH[1]
			Roche ELECSYS	Troponin T hs (high sensitive) (TnT hs)[5]
4	Dr. Jennifer Spencer Clinical Scientist	Department of Blood Sciences Leeds General Infirmary Great George St Leeds LS1 3EX, Yorkshire, England	ADVIA Centaur XPT	TNIH[1]
			ADVIA Centaur XPT	TnI-Ultra[6]

Table 2. Assay precision requirements.[1]

Troponin I Level (ng/L)	Repeatability (within-run)	Total Precision (within-lab)
9–20	<10%	<12%
>20	<10%	<10%

Elevated cardiac troponin levels can be associated with multiple diseases

Troponin values for a few subjects with clinical diseases causing cardiac injury were presented as the fold difference (x) compared to the 99th percentile of each method: 47.3 ng/L for the ADVIA Centaur TNIH Assay and 26 ng/L for the ARCHITECT hs TnI assay.

Results and Discussion

Precision

Precision data are comparable to Siemens Healthineers IFU precision data when data from sites in four countries are combined (Tables 3 and 4) or presented by site (Tables 5 and 6). These results met the assay precision requirements listed in Table 2.[1]

Comparison of number of subjects with undetectable troponin

Since clinical data were not available, comparisons between the ADVIA Centaur TNIH Assay and the other assay at each site were performed for the number of subjects with values below the respective LoDs and below the respective 99th percentiles (Table 7). Fewer subjects had values <LoD for the ADVIA Centaur TNIH Assay than for Dimension Vista, TnI-Ultra, and ELECSYS TnT hs assays; the number of subjects with values <LoD was similar for the ADVIA Centaur TNIH Assay and the Abbott ARCHITECT hs TnI assay.

The number of subjects with values <99th percentile was similar between the ADVIA Centaur TNIH Assay and the other assay at each site except for the ADVIA Centaur TNIH vs. ELECSYS TnT hs assays (Table 8).

Normalized data comparison

Cardiac troponin assays are not standardized, and values obtained differ between assays; thus, the data were normalized by dividing values by the respective 99th percentile. The numbers of subjects falling within different value/99th percentile ratio categories were compared (Table 9). Similar numbers of patients were found to fall within each of the categories for the ADVIA Centaur TNIH versus the Abbott ARCHITECT hs TnI and Dimension Vista Troponin I (CTNI) assays. For the ELECSYS TnT hs assay, a greater proportion of patients were above the 99th percentile of 14 ng/L. A gray zone up to 50 ng/L has been described in the literature recommending a higher cutoff for the elderly population.[8,9] In the U.S. the cutoff has been claimed at 19 ng/L.[10]

Kinetics of cardiac troponin I

A kinetic study performed for a few subjects demonstrates similar trends for cardiac troponin I values for the ADVIA Centaur TNIH and the ARCHITECT hs TnI assays (Figure 1).

Elevated cardiac troponin levels suspected to be associated with the clinical context

Some subjects with clinical disease had elevated cardiac troponin I values as tested with ADVIA Centaur TNIH and ARCHITECT hs TnI assays (Table 10). Assessment was not made whether these patients also had an AMI. However, multiple disease states, including those in the table, have been associated with elevated or sustained elevated cardiac troponin concentrations in the possible absence of an AMI.[11] It is important to note that elevations in cardiac troponin reflect cardiac injury/necrosis and are not specific for AMI. An AMI diagnosis is made when a significant rise or fall of cardiac troponin is detected along with clinical assessment and electrocardiogram.[2]

Conclusions

This preliminary study demonstrated that the ADVIA Centaur TNIH Assay precision results generated at four independent sites in Europe were acceptable. Due to lack of standardization between assays, values could not be directly compared; however, normalizing the data to the 99th percentile allowed an initial comparison for the number of subjects falling within different cutoff categories. For a few patients tested at different times using the ADVIA Centaur TNIH and ARCHITECT hs TnI assays, similar kinetic trends in cardiac troponin I concentrations between the assays were observed. Some debilitating clinical conditions known to be associated with elevated troponin I values were identified and were possibly not non-acute coronary syndrome causes of troponin elevation.

Table 3. Reproducibility across the four sites for the ADVIA Centaur XP and XPT TNIH Assay.

				Mean	Combined Repeatability (within-run)		Between-day		Reproducibility Within-lab (total precision)	
Sample Type	n/Date	# Runs	n Replicates	ng/L	SD (ng/L)	%CV (ng/L)	SD (ng/L)	%CV (ng/L)	SD (ng/L)	%CV (ng/L)
Low Serum Pool	20	5	100	7.79	0.44	5.7	0.70	9.0	0.83	10.6
Bio-Rad Control 1	20	5	100	72.11	2.69	3.7	2.55	3.5	3.71	5.1
Bio-Rad Control 2	20	5	100	129.64	6.67	5.1	5.98	4.6	8.96	6.9
Bio-Rad Control 3	20	5	100	3445.42	54.85	1.6	87.09	2.5	102.93	3.0

Table 4. Precision for ADVIA Centaur TNIH Assay by system (two ADVIA Centaur XP or two ADVIA Centaur XPT) performed at four sites.

				Mean	Combined Repeatability (within-run)		Between-day		Reproducibility Within-lab (total precision)	
Sample Type	n/Date	# Runs	n Replicates	ng/L	SD (ng/L)	%CV (ng/L)	SD (ng/L)	%CV (ng/L)	SD (ng/L)	%CV (ng/L)
ADVIA Centaur XP System										
Low Serum Pool	10	5	50	7.91	0.34	4.3	0.83	10.5	0.89	11.3
Bio-Rad Control 1	10	5	50	72.19	1.23	1.7	2.44	3.4	2.74	3.8
Bio-Rad Control 2	10	5	50	129.15	1.87	1.5	10.28	8.0	10.45	8.1
Bio-Rad Control 3	10	5	50	3388.61	44.09	1.3	60.98	1.8	75.25	2.2
ADVIA Centaur XPT System										
Low Serum Pool	10	5	50	7.67	0.38	4.9	0.66	8.6	0.76	10.0
Bio-Rad Control 1	10	5	50	72.04	1.07	1.5	4.51	6.3	4.64	6.4
Bio-Rad Control 2	10	5	50	130.13	2.55	2.0	7.37	5.7	7.80	6.0
Bio-Rad Control 3	10	5	50	3502.22	35.11	1.0	88.66	2.5	95.36	2.7

Table 5. Precision results for the ADVIA Centaur XP TNIH Assay at two independent sites.

				Mean	Combined Repeatability (within-run)		Between-day		Reproducibility Within-lab (total precision)	
Sample Type	n/Date	# Runs	n Replicates	ng/L	SD (ng/L)	%CV (ng/L)	SD (ng/L)	%CV (ng/L)	SD (ng/L)	%CV (ng/L)
Site 1										
Low Serum Pool	5	5	25	7.51	0.39	5.2	0.62	8.2	0.73	9.7
Bio-Rad Control 1	5	5	25	73.19	1.19	1.6	3.13	4.3	3.35	4.6
Bio-Rad Control 2	5	5	25	134.05	1.98	1.5	8.93	6.7	9.14	6.8
Bio-Rad Control 3	5	5	25	3422.56	52.23	1.5	69.55	2.0	86.98	2.5
Site 2										
Low Serum Pool	5	5	25	8.30	0.27	3.3	0.88	10.6	0.92	11.1
Bio-Rad Control 1	5	5	25	71.18	1.28	1.8	1.09	1.5	1.68	2.4
Bio-Rad Control 2	5	5	25	124.25	1.77	1.4	9.91	8.0	10.07	8.1
Bio-Rad Control 3	5	5	25	3354.65	34.06	1.0	27.28	0.8	43.64	1.3

Table 6. Precision results for the ADVIA Centaur XPT TNIH Assay at two independent sites.

			Mean	Combined Repeatability (within-run)		Between-day		Reproducibility Within-lab (total precision)	
Sample Type	n/Date	# Runs	ng/L	SD (ng/L)	%CV (ng/L)	SD (ng/L)	%CV (ng/L)	SD (ng/L)	%CV (ng/L)
Site 3									
Low Serum Pool	5	5	7.08	0.40	5.6	0.28	3.9	0.48	6.8
Bio-Rad Control 1	5	5	69.38	1.07	1.5	3.07	4.4	3.26	4.7
Bio-Rad Control 2	5	5	125.63	1.50	1.2	8.60	6.8	8.73	6.9
Bio-Rad Control 3	5	5	3448.44	40.17	1.2	59.26	1.7	71.60	2.1
Site 4									
Low Serum Pool	5	5	8.26	0.36	4.4	0.22	2.7	0.42	5.1
Bio-Rad Control 1	5	5	74.70	1.07	1.4	4.33	5.8	4.46	6.0
Bio-Rad Control 2	5	5	134.63	3.28	2.4	0.00	0.0	3.28	2.4
Bio-Rad Control 3	5	5	3556.01	29.18	0.8	83.69	2.4	88.63	2.5

Table 7. Values for 99th percentile for the different assays as found in the respective Instructions for Use.

Assay	n for 99th Percentile	99th Percentile (ng/L)	Confidence Interval (CI) (ng/L)
ADVIA Centaur TNIH[1]	2010 F: 1012, M: 984	47.3 F: 37, M: 57.3 F: 39.6(s), M: 58.1(s)	90% CI 36.39, 64.27 F: 30.22, 72.63; M: 38.58, 90.15 F: 29.62, 74.64(s); M: 37.50, 80.35(s)
ARCHITECT High Sensitivity Troponin I[3]	1531 F: 765, M: 766	26.2 F: 15.6, M: 34.2	90% CI 23.3, 29.7 F: 13.8, 17.5; M: 28.9, 39.2
Dimension Vista Troponin I (CTNI)[4]	998	45	N/A*
ELECSYS TnT hs[5]	533	14	95% CI 12.7, 24.9
ADVIA Centaur TnI-Ultra[6]	648	40	20–60

**N/A: Not available.*

Table 8. Comparison between the ADVIA Centaur TNIH Assay and Dimension Vista, ADVIA Centaur TnI-Ultra, Roche TnT, and Abbott ARCHITECT hs TnI assays for the number of subjects <99th Percentile, and <LoD for cardiac troponin (using the cutoff concentrations reported in the respective Instructions for Use).[1,3,5,6]

Site	Assay	<99th Percentile		LoD	<LoD		Range >LoD
		n	%	ng/L	n	%	ng/L
Site 1	ADVIA Centaur TNIH	185/283	65.4%	2.21	36/283	12.7%	2.21–16,472
	ARCHITECT High Sensitivity Troponin I	159/283	56.2%	1.9	41/283	14.5%	2.00–30,102
Site 2	ADVIA Centaur TNIH	165/247	66.8%	2.21	28/247	11.3%	2.24–23,084
	Dimension Vista Troponin I (CTNI)	157/247	63.6%	15	136/247	55.1%	15.6–36,154
Site 3	ADVIA Centaur TNIH	251/356	70.5%	2.21	36/356	10.1%	2.25–>25,000
	ELECSYS TnT hs (OUS)	140/356	39.3%	5	59/356	16.6%	5.04–>10,000
Site 4	ADVIA Centaur TNIH	113/331	34.1%	2.21	9/331	2.7%	2.26–>25,000
	ADVIA Centaur TnI-Ultra	105/331	31.7%	6	91/331	27.5%	7.72–>50,000

Table 9. Number and percentage of subjects within different categories after normalizing to the respective 99th percentile (ratio = value/99th percentile).

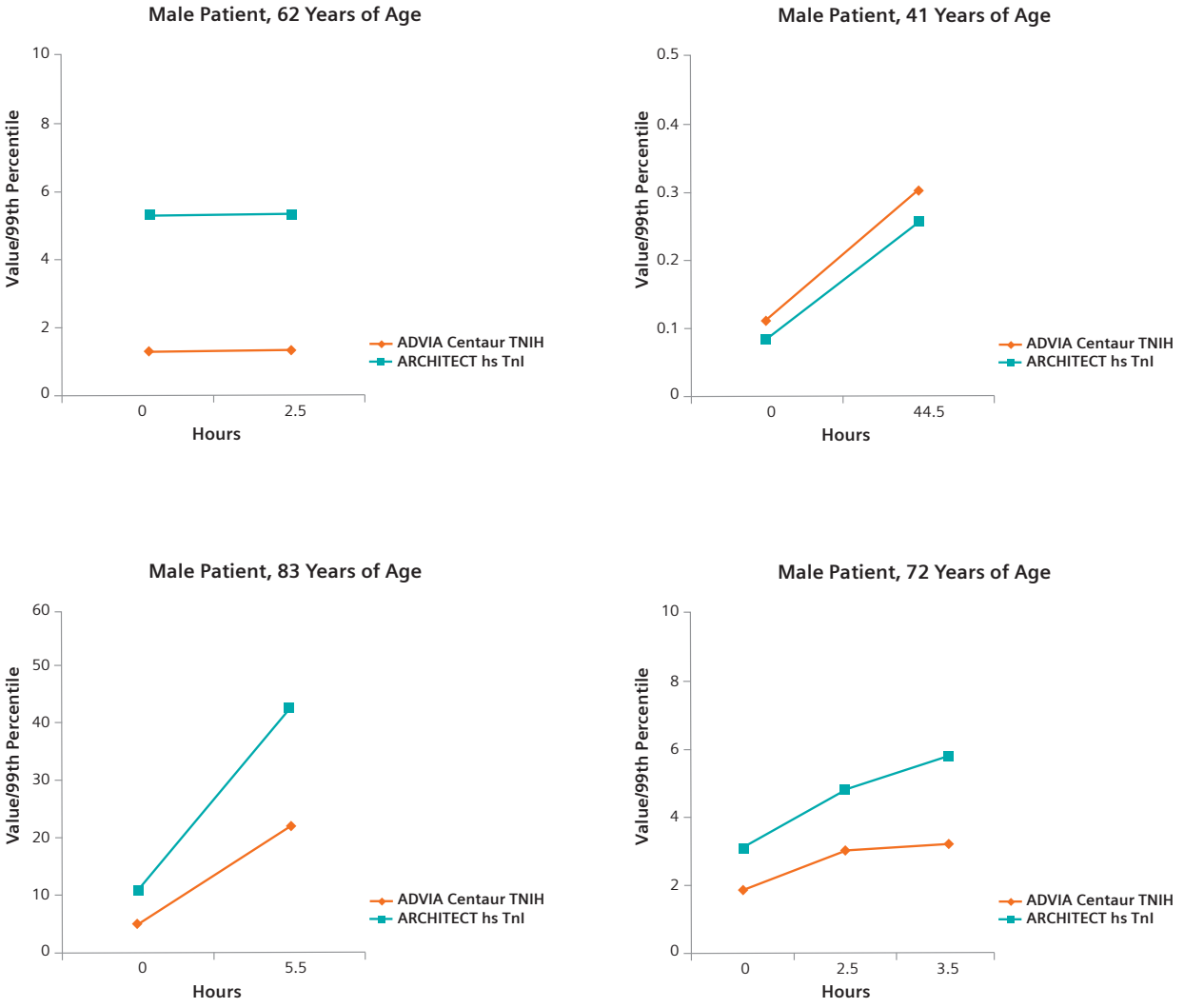
Site	Assay	<0.5		0.5–1.0		<1.0		1.0–2.0		>2.0	
		n	%	n	%	n	%	n	%	n	%
Site 1	ADVIA Centaur TNIH, n = 283 total	150	53	35	12.3	185	65.3	33	11.6	65	22.9
	ARCHITECT High Sensitivity Troponin I, n = 283	126	44.5	33	11.6	159	56.0	39	17.3	85	30.0
Site 2	ADVIA Centaur TNIH, n = 247	149	60.3	16	6.5	165	66.8	15	6.1	67	27.1
	Dimension Vista Troponin (CTNI), n = 247	143	57.9	14	5.7	158	64.0	14	5.7	75	30.6
Site 3	ADVIA Centaur TNIH, n = 356	200	60.4	51	14.5	251	71.5	25	7.6	80	24.2
	ELECSYS TnT hs, n = 356	79	22.2	61	17.1	140	39.3	70	19.7	146	41.0
Site 4	ADVIA Centaur TNIH , n = 331	92	27.8	13	3.9	105	31.7	41	12.4	185	55.9
	ADVIA Centaur TnI-Ultra, n = 331	31	9.4	15	4.5	46	13.9	45	13.6	240	72.5

Table 10. Elevated cardiac troponin levels were associated with multiple clinical cases. Clinical situations with elevated cardiac troponin I values presented as the fold difference (x) compared to the 99th percentile for each method: 47.3 ng/L for the ADVIA Centaur TNIH and 26 ng/L for the ARCHITECT hs TnI. Current AMI status was not assessed.

Patients	ADVIA Centaur TNIH (ng/L)	ARCHITECT hs TnI (ng/L)	ADVIA Centaur TNIH fold difference (x) vs. the 99th Percentile	ARCHITECT hs TnI fold difference (x) vs.the 99th Percentile	Clinical Context
Case 1	101.9; 99.1†	32; 31†	2.15x; 2.0	1.2x; 1.2x	Renal failure with increased blood pressure
Case 2	67	35	1.4x	1.35x	Multi-organ failure (MOF) with adenocarcinoma treated with anti-EGFR; cardiac toxicity?
Case 3	57; 57.3†	18.2; 16.9†	1.2x; 1.2x	0.7x; 0.65x	Previous AMI; pulmonary cancer; monoclonal Ab treatment (cardiac toxicity?)
Case 4	64.4	34	1.7x	1.3x	Septic shock with MOF; treated by monoclonal Ab (SIMULECT)
Case 5	131.3	17.9	2.8x	0.7x	Breast cancer; possible autoimmune disease; treated by antiaromatase drug (cardiac toxicity?)
Case 6	88.2	47.3	1.9x	1.8x	Retired farmer in kidney ICU
Case 7	163.7; 76.8†	22.5; 10.8†	3.7x; 1.75x†	0.9x; 0.4x†	Ovary cancer with systemic inflammatory response syndrome (SIRS); multiple blood transfusions in kidney ICU

†Rerun.

Figure 1. Kinetic profiles for four patients whose cardiac troponin levels were measured at presentation (0 hours) and after presentation. Similar trends were obtained for the ADVIA Centaur TNIH Assay and the ARCHITECT hs TnI assay.



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