

IFCC Paper

Amy K. Saenger, Allan S. Jaffe, Richard Body, Paul O. Collinson, Peter A. Kavsak, Carolyn S.P. Lam, Guillaume Lefèvre, Tobjørn Omland, Jordi Ordóñez-Llanos, Kari Pulkki and Fred S. Apple*

Cardiac troponin and natriuretic peptide analytical interferences from hemolysis and biotin: educational aids from the IFCC Committee on Cardiac Biomarkers (IFCC C-CB)

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Abstract: Two interferences recently brought to the forefront as patient safety issues include hemolysis (hemoglobin) and biotin (vitamin B7). The International Federation for Clinical Chemistry Committee on Cardiac Biomarkers (IFCC-CB) obtained input from a majority of cTn and NP assay manufacturers to collate information related to high-sensitivity (hs)-cTnI, hs-cTnT, contemporary, and POC cTn assays, and NP assays interferences due to hemolysis and biotin. The information contained in these tables was designed as educational tools to aid laboratory professionals and clinicians in troubleshooting cardiac biomarker analytical results that are discordant with the clinical situation.

Keywords: biotin; hemolysis; interferences; natriuretic peptide; troponin.

Cardiac troponin I and T (cTnI, cTnT) and the natriuretic peptides (NP; B-type natriuretic peptide, BNP; N Terminal-proBNP; NT-proBNP) are the primary cardiac biomarkers utilized in the diagnosis of myocardial injury and infarction (MI) and heart failure (HF), respectively. As with any clinical laboratory test, there are exogenous and endogenous factors that adversely interfere with the analytical performance of the cTn and NP assays, potentially resulting in inappropriate clinical interpretation of the results if the interferences are not identified. Analytical interferences are particularly concerning when dealing with cardiac biomarker assays, which are utilized to make time sensitive critical clinical decisions. Two interferences recently brought to the forefront as patient safety issues include hemolysis (hemoglobin) and biotin (vitamin B7, vitamin H, coenzyme R). The International Federation for Clinical Chemistry Committee on Cardiac Biomarkers (IFCC-CB) obtained input from a majority of cTn and

***Corresponding author: Fred S. Apple,** Hennepin County Medical Center, Department of Laboratory Medicine and Pathology, 701 Park Avenue, Minneapolis, MN 55415, USA; and Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA, Phone: +1 612 873-3324, Fax: +1 612 904-4229, E-mail: apple004@umn.edu

Amy K. Saenger: Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA

Allan S. Jaffe: Department of Laboratory Medicine and Pathology and Cardiology, Mayo Clinic, Rochester, MN, USA

Richard Body: Emergency Department, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; Cardiovascular Sciences Research Group, Core Technology Facility, Manchester, UK; and Healthcare Sciences Department, Manchester Metropolitan University, Manchester, UK

Paul O. Collinson: Department of Clinical Blood Sciences and Cardiology, St George's University Hospitals NHS Foundation Trust and St George's University of London, London, UK

Peter A. Kavsak: Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada

Carolyn S.P. Lam: National Heart Centre and Duke-National University of Singapore, Singapore, Singapore

Guillaume Lefèvre: Department of Biochemistry and Hormonology, Hospital Tenon, Sorbonne Universités GRC-14 BIOSFAST, AP-HP, Paris, France

Tobjørn Omland: Division of Medicine, Akershus University Hospital, Lørenskog, Norway; and Center for Heart Failure Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Jordi Ordóñez-Llanos: Servicio de Bioquímica Clínica, Institut d'Investigacions Biomèdiques Sant Pau, Barcelona, Spain; and Departamento de Bioquímica y Biología Molecular, Universidad Autónoma de Barcelona, Barcelona, Spain

Kari Pulkki: Department of Clinical Chemistry, University of Turku and Turku University Hospital, Turku, Finland

NP assay manufacturers to collate information related to high-sensitivity (hs)-cTnI, hs-cTnT, contemporary, and POC cTn assays (Table 1) [1], and NP assays (Table 2) [2] interferences due to hemolysis and biotin. The information contained in these tables was designed as educational tools to aid laboratory professionals and clinicians in troubleshooting cardiac biomarker analytical results that are discordant with the clinical situation.

Hemolysis is one of the major causes of pre-analytical errors, reportedly accounting for 40%–70% of all specimen rejections [3]. Furthermore, a substantial volume of hemolyzed samples occur from specimens collected in the emergency department and from indwelling catheters in many intensive care units [4]. The accuracy of cTn results is of significant importance because it is heavily relied upon for making appropriate and rapid patient care decisions. If hemolysis thresholds are exceeded, the specimen needs to be recollected, resulting in delays in patient care and an increased risk of iatrogenic injury, infection, and adverse clinical management in the absence of objective information. Hemolysis is a known confounder of hs-cTn and cTn assays, causing false positive or false negative results; either situation may hinder interpretation of single or serial values [5]. Detection of hemolyzed samples occurs either manually (visual, qualitative assessment) or through automated detection (quantitative or semi-quantitative assessment) using indices on the clinical chemistry platform. The latter approach is supported as a benchmark of good laboratory practice due to the improved reliability, accuracy and standardized approach to reporting results within a laboratory when using automated mechanisms to assess hemolysis. For cTn assays with a low threshold for hemolysis (>100 mg/dL, i.e. >1 g/L) the reported rate of incorrectly released results is as high as 76% [6]. Not all immunoassay platforms or point-of-care devices have the ability to routinely perform automated hemolysis detection, presenting potential patient safety issues for reporting accurate cTn and NP results due to the subjective nature of visual detection of hemoglobin. Moreover, hemolysis will be missed if whole blood is used as the matrix for measurements.

Biotin interference is a relatively new challenge to laboratories and highlighted by the Food and Drug Administration (FDA) warning statement to clinical laboratories (<https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm586641.htm>). Investigation of potential interferences from biotin in immunoassays is similar to methods utilized for decades in clinical laboratories to probe analytical interferences. Biotin is a water-soluble vitamin with a half-life ranging from 8 to 16 h, depending on renal

function [7]. Adequate intake is defined at 0.03 mg/day, although consumption has expanded and retail sales of over-the-counter “mega” doses (2.5–10 mg) of biotin have increased significantly due to marketing efforts claiming healthier and stronger hair, skin and nails. Furthermore, individuals are often unaware that the supplements they are ingesting even contain biotin. There are ongoing randomized clinical trials in the US and Europe to evaluate biotin doses of 300 mg/day in patients with multiple sclerosis and other inflammatory diseases, resulting in circulating serum biotin concentrations between 170 and 700 µg/L [8]. Immunoassays comprised of biotin labeled antibodies or biotin-streptavidin labeled complexes are particularly susceptible to interferences for a wide array of clinical tests.

Data obtained from manufacturers regarding the analytical specificity and interference for the cTn and NP assays/platforms are presented in Tables 1 and 2, respectively. Interference thresholds were defined as the greatest concentration for either hemoglobin or biotin that did not compromise accuracy of the cTn or NP analytical results. When this threshold was exceeded results were classified as either falsely high or low, allowing laboratory professionals to ascertain the performance of their specific assay/platform in the scenario of gross hemolysis or potentially excessive endogenous biotin intake. Manufacturers defined their acceptance criteria when evaluating and validating interference thresholds. The “End User Assessment of Hemolysis” column in Tables 1 and 2 was designed to aid clinical laboratory personnel performing cardiac biomarker testing. If laboratory personnel must visually assess for hemolysis before reporting or releasing cTn results the assay was designated as “Qualitative”. If the instrument automatically assesses for hemolysis to allow erroneous results to be suppressed and alerting the laboratorian the threshold was exceeded, the assay was designated as “Quantitative”.

Biotin interference data in the tables state whether a biotinylated antibody is incorporated and/or if biotin is used in the assay configuration; it is notable that those assays with either characteristic are more susceptible to interference from endogenous biotin use. If high dose biotin supplementation is known or suspected due to results that do not correlate with the patient’s clinical condition, one possible mitigation strategy could involve analysis with another assay that is not susceptible to biotin interference. However, this is not always a practical solution and may be problematic due to the lack of standardization of cTn and NP assays. Other proposed strategies include adsorption of excess biotin

Table 1: IFCC Committee on Clinical Applications of Cardiac Biomarkers (C-CB) cardiac troponin assay interference table for hemolysis and biotin designated by manufacturer v072618.

Company	Assay	Platform	Hemolysis			Biotin						
			Hemolysis limit (no interference up to stated value)	Influence of hemolysis above the threshold (+/-)	End user hemolysis assessment	Acceptance criteria ^b	Biotinylated antibody	Biotin used in assay configuration	Interference threshold	Acceptance criteria ^b	Highest biotin concentration tested	Influence of biotin above the threshold (+/-)
Abbott Diagnostics, Alere	High Sensitive Troponin-I (3P25) ^a	ARCHITECT	5.0 g/L (500 mg/dL)	ND	Qualitative	≤10%	No	No	290 µg/L	≤10%	290 µg/L	ND
	High Sensitive Troponin-I (8P13) ^a	Alinity i	5.0 g/L (500 mg/dL)	ND	Qualitative	≤10%	No	No	290 µg/L	≤10%	290 µg/L	ND
	Contemporary Troponin-I (2K41) US	ARCHITECT	5.0 g/L (500 mg/dL)	ND	Qualitative	≤10%	No	No	290 µg/L	Undefined	290 µg/L	ND
Abbott POC	cTnI	i-STAT	6.0 g/L (600 mg/dL)	(-)			No	No	ND	ND	ND	
	Access hs-cTnI	DxI, Access 2	4.0 g/L (400 mg/dL)	ND	Quantitative if using Beckman's integrated platform	- ≤10% at hs-cTnI >11.5 ng/L - ≤2.30 ng/L at ≤11.5 ng/L	No	No	ND	ND	ND	NA
Beckman Coulter	cTnI (AccuTnI+3)	DxI, Access 2	5.0 g/L (500 mg/dL)	ND	Quantitative if using Beckman's integrated platform	- ≤10% at cTnI - 0.50 µg/L at -0.50 µg/L at -0.05 µg/L - ≤0.02 µg/L at -0.01 µg/L	No	No	290 µg/L	- ≤10% at cTnI ~0.50 µg/L - ≤0.006 µg/L at -0.05 µg/L ≤0.02 µg/L at -0.01 µg/L	290 µg/L	NA
	hs-cTnI	VIDAS	4.85 g/L (485 mg/dL)	ND	Qualitative	±10%	Yes	Yes	2000 µg/L	<10%	2000 µg/L	ND
ET Healthcare	hs-cTnI ^a	Pylon 3d	5.0 g/L (500 mg/dL)	(+)	Qualitative (serum/plasma); NA (whole blood)	±10%	Yes	Yes	200 µg/L	±10%	200,000 µg/L	ND
	hs-cTnI ^a	Lumipulse G1200 and G600II	5.10 g/L (510 mg/dL)	ND	CLSI EP7-A2	±10%	No	No	ND	NA	NA	NA
LSI Medience	hs-cTnI ^a	PATHFAST	10 g/L (1000 mg/dL)	(-)	Quantitative (cyanmethemoglobin method)		No	No	1500 µg/L	±20%	1500 µg/L	ND
	cTnI ^a	PATHFAST	10 g/L (1000 mg/dL)	(-)	Quantitative (cyanmethemoglobin method)		No	No	1500 µg/L	±20%	1500 µg/L	ND
Ortho-Clinical Diagnostics	cTnI-II	PATHFAST	10 g/L (1000 mg/dL)	(-)	Quantitative (cyanmethemoglobin method)		No	No	1500 µg/L	±20%	1500 µg/L	ND
	Troponin I ES	ECI/ECIQ, 3600, 5600	1.0 g/L (100 mg/dL) at cTnI conc. of 0.006 µg/L	(+)	Automated/Quantitative	≤10%	Yes	No	2.5 µg/L	≤10% at 0.400 µg/L	NA	NA
Quidel	cTnI	Triage	10 g/L (1000 mg/dL)	(-)	Qualitative	≤10%	No	No	ND	NA	NA	NA

Table 1 (continued)

Company	Assay	Platform	Hemolysis			Biotin						
			Hemolysis limit (no interference up to stated value)	Influence of hemolysis above the threshold (+/-)	End user hemolysis assessment	Acceptance criteria ^b	Biotinylated antibody	Biotin used in assay configuration	Interference threshold	Acceptance criteria ^b	Highest biotin concentration tested	Influence of biotin above the threshold (+/-)
	cTnI SOB ^a	Triage	5.0 g/L (500 mg/dL)	(-)	Qualitative	≤10%	No	No	ND	NA	NA	NA
	cTnI Cardio ^a	Triage	1.0 g/L (100 mg/dL)	(-)	Qualitative	≤10%	No	No	ND	NA	NA	NA
Radiometer, POC	TnI ^b	AQT90 FLEX	10 g/L (1000 mg/dL)	No interference	Qualitative	NA	Yes (pre-bound)	Yes (pre-bound)	No interference up to 3 µg/L ^c	≤10%	3 µg/L ^c	NA ^c
Radiometer, POC	TnT ^a	AQT90 FLEX	2.0 g/L (200 mg/dL)	No interference	Qualitative	NA	No	No	No interference up to 50 µg/L ^c	≤9%	50 µg/L ^c	NA ^c
Response biomedical			No information provided				No information provided					
Roche Diagnostics	cTnT-hs ^a and TnT Gen 5 STAT	MODULAR E170, cobas e411, e601, e602, e801	1.0 g/L (100 mg/dL)	(-)	Serum indices on pre-analytic module; Qualitative	Recovery within ±1.4 ng/L with a conc. <14 ng/L; Recovery ±10% with a conc. ≥14 ng/L	Yes	Yes (as conjugated Ab, not as free biotin)	21 µg/L	Recovery within ±1.4 ng/L at <14 ng/L; Recovery within ±10% at ≥14 ng/L	70 µg/L	(-)
Roche Diagnostics POC	Roche CARDIAC POC Troponin T	cobas h 232 POC system	2.0 g/L (200 mg/dL)	(-)	Qualitative	Mean bias vs. reference sample: ≤±15% at 40–2000 µg/L	Yes	Yes (as conjugated Ab, not as free biotin)	200 µg/L	Mean bias vs. reference sample: ≤±15% between 40 and 2000 µg/L ±10%	1200 µg/L	(-)
Siemens Healthineers	High Sensitivity Troponin I (TNH) ^a	ADVIA Centaur [®] XP/XPT Systems	5 g/L (500 mg/dL)	ND	Qualitative	±10%	Yes	Yes	3500 µg/L	±10%	3500 µg/L	ND
	High Sensitivity Troponin I (TNH) ^a	Atellica [™] IM Analyzer	5.0 g/L (500 mg/dL)	ND	Quantitative	±10%	Yes	Yes	3500 µg/L	±10%	3500 µg/L	ND
	High Sensitivity Troponin I (TNH) ^a	Dimension [®] EXL [™] System	4.0 g/L (400 mg/dL)	ND	Quantitative	±10%	Yes	Yes	300 µg/L	±10%	1200 µg/L	(-)
	High Sensitivity Troponin I (TNH) ^a	Dimension Vista [®] System	4.0 g/L (400 mg/dL)	ND	Quantitative	±10%	Yes	Yes	300 µg/L	±10%	1200 µg/L	(-)

Table 1 (continued)

Company	Assay	Platform	Hemolysis				Biotin					
			Hemolysis limit (no interference up to stated value)	Influence of hemolysis above the threshold (+/-)	End user hemolysis assessment	Acceptance criteria ^b	Biotinylated antibody	Biotin used in assay configuration	Interference threshold	Acceptance criteria ^b	Highest biotin concentration tested	Influence of biotin above the threshold (+/-)
Tni-Ultra	ADVIA Centaur® CP/XP/XPT Systems		5.0 g/L (500 mg/dL)	ND	Qualitative	±10%	Yes	Yes	10 µg/L	±10%	1500 µg/L	(-)
			5.0 g/L (500 mg/dL)	ND	Quantitative	±10%	Yes	Yes	10 µg/L	±10%	1500 µg/L	(-)
TNI	Dimension® EXL™ System		5.0 g/L (500 mg/dL)	ND	Quantitative	±10%	Yes	Yes	100 µg/L	±10%	1200 µg/L	(-)
CTNI	Dimension® RXL™ System		10 g/L (1000 mg/dL)	ND	Quantitative	±10%	No	No	ND	NA	NA	NA
CTNI	Dimension Vista® System		5.0 g/L (500 mg/dL)	ND	Quantitative	±10%	Yes	Yes	100 µg/L	±10%	1200 µg/L	(-)
Troponin-I	IMMULITE® 2000/2000 XPI Systems		5.0 g/L (512 mg/dL)	ND	Qualitative	±10%	Yes	Yes	1500 µg/L	±10%	1500 µg/L	ND
Troponin-I	IMMULITE® 1000 Systems		5.7 g/L (570 mg/dL)	ND	Qualitative	±10%	Yes	Yes	1500 µg/L	±10%	1500 µg/L	ND
Troponin-I	IMMULITE® Turbo System		5.12 g/L (512 mg/dL)	<10%	Qualitative	±10%	Yes	Yes	1500 µg/L	±10%	1500 µg/L	ND
Singulex	hs-cTnI Clarity		4.55 g/L (455 mg/dL)	(-)	Visual/qualitative	±10%	Yes	Yes	10,000 µg/L	±10%	10,000 µg/L	(-)
Tosoh	ST AIA-PACK cTnI 2nd Gen		4.3 g/L (430 mg/dL)			±10%	No	No	ND	NA	NA	NA

ND, not determined; NA, not applicable. ^aNot yet cleared by the FDA for clinical use in the US. ^bAcceptance criteria were those defined in the package insert for determining whether interference was considered significant or not. ^cUnder further investigation.

Table 2: IFCC Committee on Clinical Applications of Cardiac Biomarkers (C-CB) natriuretic peptide assay interference table for hemolysis and biotin designated by manufacturer v083018.

Company	Assay	Platform	Hemolysis			Biotin			Influence of biotin above the threshold			
			Hemolysis limit (no interference up to stated value)	Influence of hemolysis greater than the threshold (+/-)	Hemolysis assessment	Acceptance criteria ^a	Biotinylated antibody	Biotin used in assay configuration		Interference threshold	Acceptance criteria ^b	Highest biotin concentration tested
Abbott Diagnostics	BNP (8K28)	ARCHITECT	5.0 g/L (500 mg/dL)	ND	Qualitative	≤10%	No	No	ND	NA	ND	ND
	BNP (8P24) ^a	Alinity i	5.0 g/L (500 mg/dL)	ND	Qualitative	≤10%	No	No	ND	NA	ND	ND
Abbott POC	Alere NT-proBNP (2R10) ^a	ARCHITECT	10 g/L (1000 mg/dL)	ND	Qualitative	≤10%	Yes	No	4250 µg/L	≤10%	4250 µg/L	ND
	BNP	i-STAT	None	NA	Visual/ Qualitative	≤10%	No	No	ND	NA	NA	NA
	BNP	Access 2, UniCel Dxi	5.0 g/L (500 mg/dL)	(-)	Qualitative	≤10%	Yes (pre-bound)	Yes (pre-bound)	ND	NA	NA	NA
	NT-proBNP2	VIDAS	5.0 g/L (500 mg/dL)	ND	Qualitative	±10%	No	No	ND	NA	NA	NA
Healthcare Fujirebio	BNP*	Pylon 3d	10 g/L (1000 mg/dL)	(+)	Qualitative	±15%	Yes	No	200 µg/L	±10%	200 µg/L	ND
LSI Medicine	BNP	Lumipulse G1200/G600II	0.98 g/L (98 mg/dL)	ND	CLSI EP7-A2	±10%	No	No	ND	NA	NA	NA
	NT-proBNP	PATHFAST	1.4 g/L (1400 mg/dL)	(-)	Cyanmethemoglobin method Automated/ Quantitative	10%	No	No	1500 µg/L	±20%	1500 µg/L	ND
Ortho-Clinical Diagnostics	NT-proBNP	ECI/ECIQ, 3600, 5600	3.0 g/L (300 mg/dL)	(+)	Qualitative	≤10%	Yes	No	20 µg/L	≤10% at ~125 ng/L (14.8 pmol/L)	NA	NA
	BNP	Triage	at 88.4 ng/L (1000 mg/dL)	(+)	Qualitative	≤10%	No	No	ND	NA	NA	NA
Quidel/Alere	BNP SOB	Triage	5.0 g/L (500 mg/dL)	(+)	Qualitative	≤10%	No	No	ND	NA	NA	NA
	BNP Cardio ^a	Triage	1.0 g/L (100 mg/dL)	(+)	Qualitative	≤10%	No	No	ND	NA	NA	NA
Radiometer, POC	NT-proBNP ^a	Triage	5.0 g/L (500 mg/dL)	(-)	Qualitative	≤10%	No	No	ND	NA	NA	NA
	NT-proBNP ^a	AQT90 FLEX	2.0 g/L (200 mg/dL)	No interference	Qualitative	NA	Yes (pre-bound)	Yes (pre-bound)	NA ^d	NA ^d	NA ^d	NA ^d
Roche Diagnostics	proBNP II and proBNP II STAT	MODULAR E170, cobas e411, e601, e602, e801	10 g/L (1000 mg/dL)	(-)	Serum indices on pre-analytic module; Qualitative	Recovery ±20% at <100 ng/L; ±10% at ≥100 ng/L	Yes	Yes (as conjugated Ab, no free biotin added)	35 µg/L	Recovery of ±10 ng/L of initial value ±10% of initial value >100 ng/L <15% for biotin conc. up to 10 µg/L	35 µg/L	ND
	Roche diagnostics POC	Roche CARDIAC proBNP+	1.78 g/L (178 mg/dL)	(-)	Qualitative	Mean bias vs. reference sample: ≤± 34 ng/L (60–225 ng/L) and ≤± 15% (225–9000 ng/L)	Yes	Yes (as conjugated Ab, no free biotin added)	30 µg/L	reference sample: ≤± 34 ng/L (60–225 ng/L NT-proBNP) and ≤± 15% (225–9000 ng/L NT-proBNP)	30 µg/L	ND

Table 2 (continued)

Company	Assay	Platform	Hemolysis			Biotin			Influence of hemolysis greater than the threshold (+/-)	Hemolysis assessment	Acceptance criteria ^b	Biotinylated antibody	Biotin used in assay configuration	Interference threshold	Acceptance criteria ^b	Highest biotin concentration tested	Influence of biotin above the threshold
			limit (no interference up to stated value)	limit (no interference up to stated value)	influence of hemolysis greater than the threshold (+/-)	acceptance criteria ^b	acceptance criteria ^b										
Siemens Healthineers	BNP	ADVIA Centaur® CP System	1.0 g/L (100 mg/dL)	ND	Qualitative	±10%	Yes	250 µg/L ^c	±10%	Yes	250 µg/L ^c	±10%	1500 µg/L	(-)			
	BNP	ADVIA Centaur® XP/ XPT Systems	1.0 g/L (100 mg/dL)	ND	Qualitative	±10%	Yes	250 µg/L ^c	±10%	Yes	250 µg/L ^c	±10%	1500 µg/L	(-)			
	BNP	Atellica™ IM Analyzer	1.0 g/L (100 mg/dL)	ND	Quantitative	±10%	Yes	250 µg/L ^c	±10%	Yes	250 µg/L ^c	±10%	1500 µg/L	(-)			
	BNP	Dimension Vista® System	5.0 g/L (500 mg/dL)	ND	Quantitative	±10%	Yes	100 µg/L	±10%	Yes	100 µg/L	±10%	1200 µg/L	(-)			
	NT-proBNP	ADVIA Centaur® CP System	10 g/L (1000 mg/dL)	ND	Qualitative	±10%	Yes	75 µg/L	±10%	Yes	75 µg/L	±10%	1500 µg/L	(-)			
	NT-proBNP ^a	ADVIA Centaur® XP/ XPT Systems	10 g/L (1000 mg/dL)	ND	Qualitative	±10%	Yes	75 µg/L	±10%	Yes	75 µg/L	±10%	1500 µg/L	(-)			
	NT-proBNP	Atellica™ IM Analyzer	10 g/L (1000 mg/dL)	ND	Quantitative	±10%	Yes	75 µg/L	±10%	Yes	75 µg/L	±10%	1500 µg/L	(-)			
	NT-proBNP	Dimension® EXL™ System	10 g/L (1000 mg/dL)	ND	Quantitative	±10%	Yes	250 µg/L	±10%	Yes	250 µg/L	±10%	1200 µg/L	(-)			
	NT-proBNP	Dimension® RXL™ System	10 g/L (1000 mg/dL)	ND	Quantitative	±10%	No	NA	NA	No	NA	NA	NA	NA			
	NT-proBNP	Dimension Vista® System	10 g/L (1000 mg/dL)	ND	Quantitative	±10%	Yes	100 µg/L	±10%	Yes	100 µg/L	±10%	1200 µg/L	(-)			
	NT-proBNP ^a	IMMULITE® 2000/2000 XPI Systems	6.0 g/L (600 mg/dL)	ND	Qualitative	±10%	Yes	1500 µg/L	±10%	Yes	1500 µg/L	±10%	1500 µg/L	ND			
	Turbo NT-proBNP ^a	IMMULITE® Turbo 1000 Systems	6.0 g/L (600 mg/dL)	ND	Qualitative	±10%	Yes	1500 µg/L	±10%	Yes	1500 µg/L	±10%	1500 µg/L	ND			
Thermo Fisher	MR-proANP ^a	BRAHMS MRproANP Kryptor AIA series	10 g/L (1000 mg/dL)	ND	CLSI EP7-A2	CLSI EP7-A2	No information provided	ND	ND	ND	ND	ND	ND	ND			
	BNP		No information provided	No information provided			No information provided										

ND, not determined; NA, not applicable. ^aNot yet cleared by the FDA for clinical use in the US. ^bAcceptance criteria were those defined in the package insert for determining whether interference was considered significant or not. ^cNot in current Instructions for Use (IFU). ^dUnder further investigation.

using streptavidin-coated microparticles [8, 9], although this requires additional validation within the laboratory before implementation.

Cardiac biomarker assays, like a majority of clinical laboratory assays, are susceptible to endogenous and exogenous interferences to some extent, which may yield analytically incorrect results. There is particular concern about the effect of interferences with hs-cTn and NP assays, as these are widely used clinically in urgent care settings to guide critical clinical decisions but there is often less time to carefully consider potential analytical issues in this situation. For cTn assays, the analytical sensitivity and imprecision at the 99th percentile are of utmost importance and the consequences of false negative or false positive results at or near the 99th percentile due to hemolysis and/or biotin consumption have been highlighted in recent publications [10]. While diagnosis of acute MI, ischemia or heart failure should always be taken in conjunction with the clinical context of the patient, heightened awareness of these analytical issues and solutions should be implemented to avoid adverse events.

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