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Global Adoption of High-Sensitivity Cardiac Troponins and the Universal Definition of Myocardial Infarction

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BACKGROUND: The universal definition of myocardial infarction (UDMI) standardizes the approach to the diagnosis and management of myocardial infarction. High-sensitivity cardiac troponin testing is recommended because these assays have improved precision at low concentrations, but concerns over specificity may have limited their implementation.

METHODS: We undertook a global survey of 1902 medical centers in 23 countries evenly distributed across 5 continents to assess adoption of key recommendations from the UDMI. Respondents involved in the diagnosis and management of patients with suspected acute coronary syndrome completed a structured telephone questionnaire detailing the primary biomarker, diagnostic thresholds, and clinical pathways used to identify myocardial infarction.

RESULTS: Cardiac troponin was the primary diagnostic biomarker at 96% of surveyed sites. Only 41% of centers had adopted high-sensitivity assays, with wide variation from 7% in North America to 60% in Europe. Sites using high-sensitivity troponin more frequently used serial sampling pathways (91% vs 78%) and the 99th percentile diagnostic threshold (74% vs 66%) than sites using previous-generation assays. Furthermore, high-sensitivity institutions more often used earlier serial sampling (≤3 h) and accelerated diagnostic pathways. Fewer than 1 in 5 high-sensitivity sites had adopted sex-specific thresholds (18%).

CONCLUSIONS: There has been global progress toward the recommendations of the UDMI, particularly in the use of the 99th percentile diagnostic threshold and serial sampling. However, high-sensitivity assays are still used by a minority of sites, and sex-specific thresholds by even fewer. Additional efforts are required to improve risk stratification and diagnosis of patients with myocardial infarction.

A joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Foundation Task Force has recently presented the fourth universal definition of myocardial infarction (UDMI)[5] *(1)*. This landmark document continues efforts to standardize the classification of a condition that affects 790 000 patients each year in the US alone *(2)*. The following key recommendations were made. Cardiac troponin is the preferred biomarker of myocardial injury owing to its high specificity and sensitivity. Serial sampling should be performed at presentation and after 3–6 h to demonstrate a rise and/or fall in troponin or even earlier when high-sensitivity assays are used, which have been recommended since the third UDMI in 2012 *(3)*. The diagnostic threshold for myocardial infarction is defined by the 99th percentile upper reference limit (URL) of cardiac troponin in a healthy reference population. The task force emphasized analytical precision and recommend use of high-sensitivity cardiac troponin assays capable of <10% coefficient of variation at the diagnostic threshold. Finally, it was recommended that sex-specific thresholds be adopted with use of high-sensitivity assays when there is evidence of variation between healthy men and women in reference populations *(4, 5)*.

The adoption of high-sensitivity cardiac troponin assays is not without controversy; sensitivity gains are balanced with a potential reduction in specificity for detection of an acute plaque rupture event (type I myocardial infarction), particularly when testing is performed indiscriminately *(6)*. The fourth UDMI emphasizes this critical distinction between myocardial injury and myo-

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[5] Nonstandard abbreviations: UDMI, universal definition of myocardial infarction; URL, upper reference limit; CK-MB, creatine kinase-MB.

cardial infarction. Such concerns may have limited adoption of high-sensitivity assays in many settings. However, the enhanced precision of high-sensitivity assays permits novel approaches to exclude myocardial infarction at presentation in low-risk patients, potentially improving the efficacy of patient assessment in emergency departments *(7–9)*.

Since publication of prior guidance from the third UDMI in 2012, high-sensitivity cardiac troponin use has increased worldwide, but these assays have only recently been approved for use in the US. Accordingly, we assessed the adoption of these guideline recommendations through a comprehensive global survey.

Methods

A structured telephone survey was completed with staff from the laboratory, emergency, or cardiology departments of 1902 clinical institutions across 23 countries between February and April 2016. This survey was undertaken by a specialist independent organization, with quota sampling to provide balanced representation from 5 geographical regions: North America (US and Canada), Europe (France, Germany, Italy, Spain, and UK), Latin America (Argentina, Brazil, and Mexico), Asia Pacific (Australia, China, India, and Japan), and the Middle East and Africa (Egypt, Kenya, Morocco, Saudi Arabia, South Africa, Tanzania, Turkey, Uganda, and United Arab Emirates). Screening questions were used to determine that data were only collected from respondents who confirmed knowledge of guidelines for the diagnosis and assessment of myocardial infarction at their institution, including laboratory biomarkers tested. The structured questionnaire recorded the sensitivity of biomarkers, thresholds for myocardial infarction, and diagnostic pathway for each institution (see Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol65/issue3).

Results

Cardiac troponin was the primary diagnostic biomarker for myocardial infarction in 96% of surveyed centers. Outside of Latin America, creatine kinase-MB (CK-MB) use was very limited (Table 1). Significant global variation was observed in the adoption of high-sensitivity cardiac troponin assays, from 7% in North America to 60% in Europe (Fig. 1, A and B). Overall, a minority (41%) of surveyed sites had adopted high-sensitivity assays. Sites using high-sensitivity assays more frequently used serial sampling strategies (91% vs 78%) and the 99th percentile diagnostic threshold (74% vs 66%) when compared to sites using contemporary assays (Fig. 1C).

Serial sampling 3–6 h after symptom onset was reported by 78% of high-sensitivity sites. There was a shift toward earlier serial sampling at ≤3 h in these institutions (52% vs 35% of contemporary users, Fig. 2). However, diagnostic pathways including sex-specific thresholds were only reported by a minority (18%) of high-sensitivity sites (Table 1).

Discussion

This survey of almost 2000 institutions across 5 continents addresses progress toward the aims of the Global Task Force and makes several important observations that are relevant for the implementation of the recently released fourth UDMI. First, cardiac troponin has become ubiquitous as the diagnostic biomarker of myocardial infarction, although CK-MB usage persists in some parts of Latin America. Second, although most centers have adopted the 99th percentile URL and serial testing at 3–6 h after symptom onset, only a minority are using high-sensitivity assays that provide increased precision and improved information at this threshold. Thirdly, few sites using high-sensitivity assays reported sex-specific diagnostic thresholds.

As recently as 2001, the Euro Heart study determined fewer than two-thirds of patients with suspected acute coronary syndrome were assessed with cardiac troponin, often in combination with a second biomarker *(10)*. Within 2 decades, we have observed a rapid shift to near-universal use of cardiac troponin. There is also clear evidence of movement toward lower diagnostic thresholds defined by healthy reference populations rather than limits of assay precision. The CARMAGUE survey in 2006 reported only 28% of troponin T and 42% of troponin I sites in Europe were using the 99th percentile URL *(11)*. This percentage had risen to 52% across both assays in a 2013 survey by the same group *(12)*. In this global study, use of the 99th percentile URL has risen to 70% across all sites whether using a high-sensitivity or previous-generation assay.

However, the clinical effect of lower diagnostic thresholds remains contentious, particularly in the era of high-sensitivity troponin assays. The potential benefits of increased sensitivity may be partially mitigated by reduced specificity for type 1 myocardial infarction with more frequent identification of type 2 events secondary to supply/demand imbalance and detection of myocardial injury *(13)*. However, this may be because many centers have previously not used the 99th percentile URL even with contemporary cardiac assays *(12, 14)*. It is therefore encouraging that 74% of high-sensitivity and 66% of contemporary troponin users report adoption of the recommended 99th percentile threshold.

We recently reported the outcomes from a stepped-wedge, cluster-randomized controlled trial of 48 282 consecutive patients with suspected acute coronary syn-

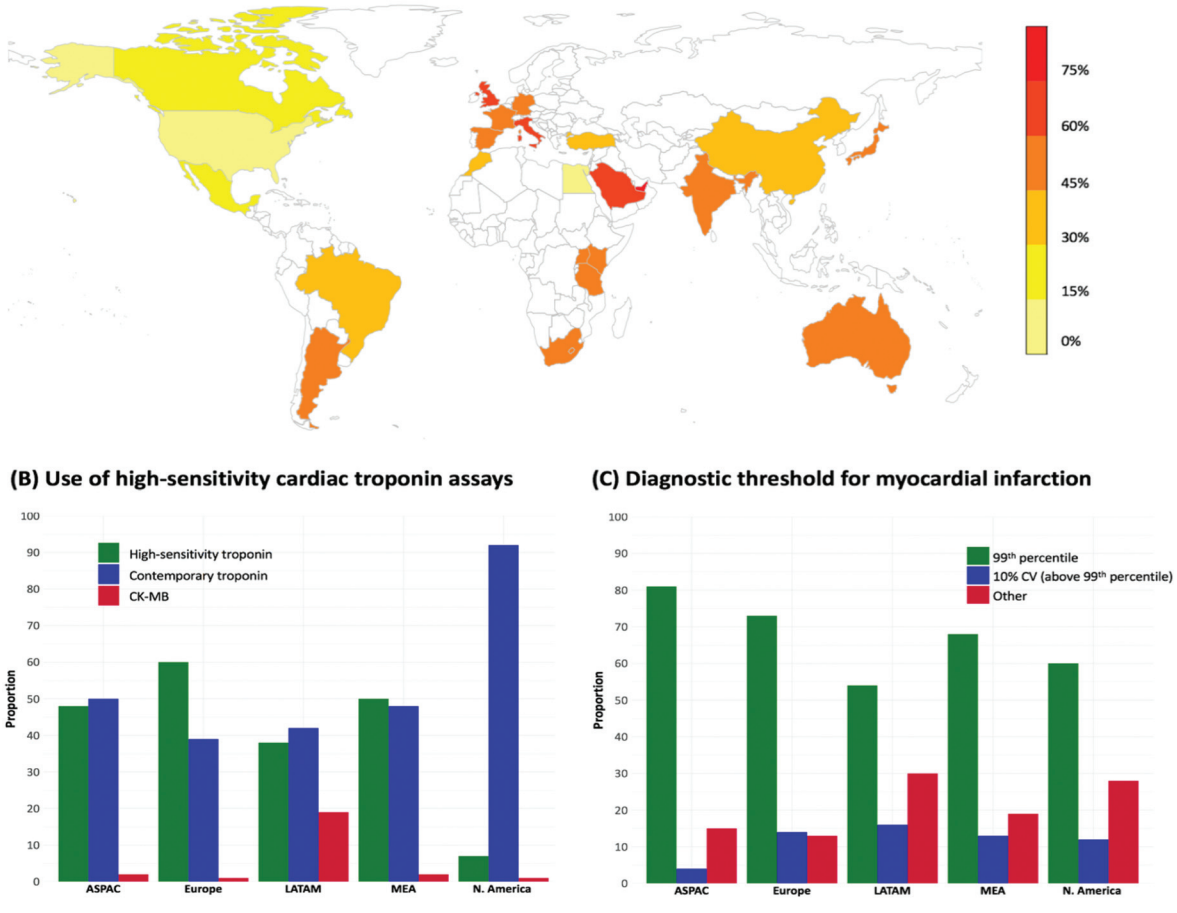
Table 1. Primary diagnostic assay and assessment of UDMI criteria among high-sensitivity cardiac troponin users by country.[a]

		Primary diagnostic assay			UDMI Criteria for high-sensitivity sites (*n* = 774)			
Country	Number of sites	High-sensitivity cTn, n (%)[b]	Contemporary sensitivity cTn, n (%)	CK-MB, n (%)	99th percentile threshold, n (%)	Serial sampling, n (%)	Serial sample at 3–6 h, n (%)	Sex-specific thresholds, n (%)
United Arab Emirates	50	39 (78)	11 (22)	0 (0)	13/15 (87)	38/38 (100)	17/31 (55)	2/36 (6)
UK	80	58 (72)	22 (28)	0 (0)	34/43 (79)	56/57 (98)	42/54 (78)	22/58 (38)
Italy	82	55 (67)	26 (32)	1 (1)	29/47 (62)	54/55 (98)	49/54 (91)	21/55 (38)
Saudi Arabia	67	42 (63)	21 (31)	4 (6)	16/23 (70)	38/39 (97)	18/33 (55)	9/42 (21)
Africa[c]	10	6 (60)	4 (40)	0 (0)	0/1 (0)	6/6 (100)	5/5 (100)	0/6 (0)
France	80	46 (57)	34 (42)	0 (0)	29/41 (71)	45/46 (98)	37/44 (84)	10/46 (22)
Australia	100	55 (55)	45 (45)	0 (0)	45/46 (98)	53/55 (96)	40/47 (85)	11/54 (20)
Spain	80	44 (55)	36 (45)	0 (0)	32/37 (86)	42/43 (98)	31/41 (76)	5/44 (11)
India	100	53 (53)	45 (45)	2 (2)	43/48 (90)	36/46 (78)	32/35 (91)	4/52 (8)
Argentina	100	52 (52)	29 (29)	19 (19)	21/31 (68)	46/51 (90)	32/43 (74)	13/52 (25)
Germany	80	40 (50)	37 (46)	3 (4)	27/33 (82)	33/39 (85)	23/30 (77)	7/39 (18)
Japan	100	49 (49)	48 (48)	3 (3)	22/38 (58)	26/44 (59)	11/17 (65)	2/48 (4)
South Africa	121	58 (48)	61 (50)	2 (2)	33/41 (80)	53/56 (95)	38/45 (55)	2/58 (3)
Brazil	100	37 (37)	61 (61)	2 (2)	10/29 (34)	35/37 (95)	18/22 (82)	3/32 (9)
Turkey	122	45 (37)	74 (61)	3 (2)	17/26 (65)	35/37 (95)	13/24 (54)	9/44 (20)
Morocco	23	8 (35)	14 (61)	1 (4)	3/6 (50)	5/8 (63)	4/5 (80)	2/8 (25)
China	100	34 (34)	62 (62)	4 (4)	31/34 (91)	30/31 (97)	12/15 (80)	7/34 (21)
Canada	100	27 (27)	73 (73)	0 (0)	7/17 (41)	23/27 (85)	20/22 (91)	3/27 (11)
Mexico	100	26 (26)	37 (37)	37 (37)	10/17 (59)	18/25 (72)	14/16 (88)	6/26 (23)
Egypt	7	0 (0)	7 (100)	0 (0)	–	–	–	–
US	300	0 (0)	297 (99)	3 (1)	–	–	–	–
Total, n (%)	1902	774 (41)	1044 (55)	84 (4)	422/573 (74)	672/740 (91)	456/583 (78)	138/761 (18)

[a] For UDMI criteria, percentage per country calculated as a proportion of those sites providing a definitive response to each criterion.
[b] cTn, cardiac troponin.
[c] Africa = Kenya, Tanzania, and Uganda (results considered together).

drome, before and after implementation of a high-sensitivity cardiac troponin I assay *(15)*. Although the high-sensitivity assay newly reclassified 1 in 6 patients with myocardial injury or infarction, cardiovascular outcomes did not improve for these patients in the following year. This result may have been because only 1 in 3 of these reclassified patients experienced a type 1 myocardial infarction. Increased recognition of type 2 myocardial infarction with high-sensitivity assays may not advance patient outcomes, and formal treatment trials are lacking. These findings contrast a prior trial that demonstrated improved outcomes in patients with suspected acute coronary syndrome when lowering the diagnostic threshold with a contemporary sensitive assay *(16)*.

High-sensitivity assays allow precise quantification of very low cardiac troponin concentrations that may enable rapid exclusion of myocardial infarction with early patient reassurance and hospital discharge. Indeed, 1 approach to improve specificity is to assess dynamic changes in cardiac troponin concentration with early repeat testing. Although most sites follow the UDMI criteria for serial sampling at presentation and 3–6 h, it is clear those with access to high-sensitivity assays are increasingly performing rapid retesting at 1 and 2 h from presentation. Numerous strategies have been tested and some even recommended within regional guidelines, but controversy remains about optimum deployment of these early rule-out approaches *(7, 17–19)*. The fourth UDMI update acknowledges the emerging role of early rule-out thresholds well below the 99th percentile, but thresholds and exceptions have not been harmonized in the same manner as the 99th percentile diagnostic threshold.

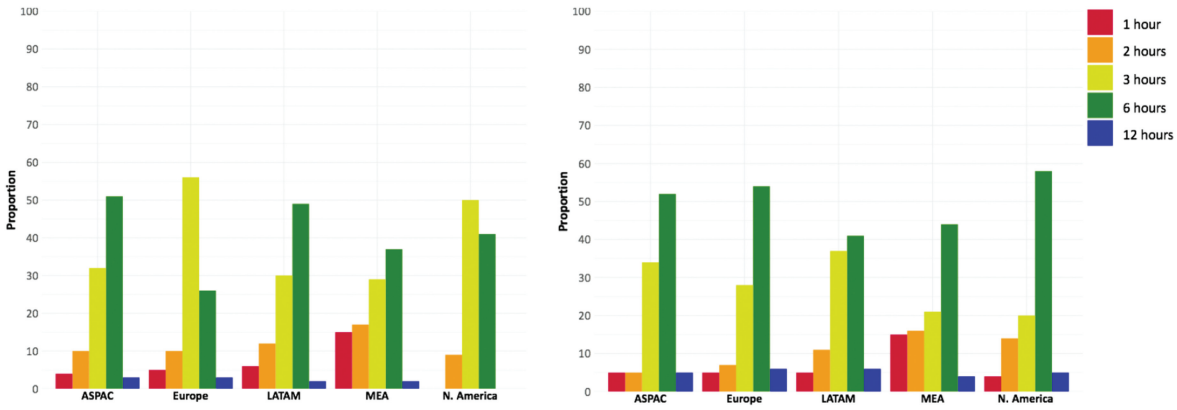


ASPAC, Asia-Pacific (Australia, China, lndia, and Japan); Europe (France, Germany, Italy, Spain, and UK); LATAM, Latin America (Argentina, Brazil, and Mexico); MEA, Middle East and Africa (Egypt, Kenya, Morocco, Saudi Arabia, South Africa, Tanzania, Turkey, Uganda, and United Arab Emirates); N. America, North America (US and Canada)

Fig. 1. Global adoption of high-sensitivity cardiac troponin assays and diagnostic thresholds for myocardial infarction.

Global variation in the selection of assay and diagnostic thresholds affects the reporting of myocardial infarction events in multicentered international trials that inform guidelines. This effect has been demonstrated across the 276 hospital laboratories contributing to the ISCHEMIA trial, in which 1 in 4 sites reported decision thresholds more than 5-fold greater than manufacturer recommendations, with the majority using contemporary cardiac troponin assays *(20)*. It is clear that variation also exists in the adoption of sex-specific diagnostic thresholds, despite evidence of potential benefit to reduce the underrecognition of myocardial infarction in women *(4, 21)*. This result may reflect dominance of the high-sensitivity cardiac troponin T assay that, until its US approval, has not recommended sex-specific cutoff values.

Our global survey does have some limitations. Not all countries could be included, but as the largest such study and the first to report across every continent, extensive efforts were made to provide representative sampling. We have taken a truly global perspective, including many developing countries. It is critical to continue standardization toward a global consensus on both the identification and safe rule-out of myocardial infarction. This standardization will improve the efficiency and efficacy of healthcare systems and permit comparisons between countries and regions to further enhance standards of care. Efforts are still required to ensure all countries have access to high-sensitivity troponin assays and report according to the guideline-recommended thresholds.



ASPAC, Asia-Pacific (Australia, China, India, and Japan); Europe (France, Germany, Italy, Spain, and UK); LATAM, Latin America (Argentina, Brazil, and Mexico); MEA, Middle East and Africa (Egypt, Kenya, Morocco, Saudi Arabia, South Africa, Tanzania, Turkey, Uganda, and United Arab Emirates); N. America, North America (US and Canada)

Fig. 2. Comparison of serial sampling patterns for high-sensitivity and contemporary sensitive cardiac troponin sites.

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