Myocardial Infarction Redefined: Role of Cardiac Troponin Testing

As we move into the new Millennium, "the times they are a changin" regarding the diagnostic criteria used to rule in and rule out acute myocardial infarction (AMI) *(1)*. The purpose of this editorial is to comment on the new cardiology guidelines for the redefinition of AMI and unstable angina, as well as to compare them with previously published laboratory medicine recommendations. Some of the new recommendations made by clinical groups may appear to be in conflict with those published previously by laboratory medicine groups; thus, we document the chronology and evolution of all guidelines on the use of cardiac markers.

Consensus documents recently published by the European Society of Cardiology (ESC), the American College of Cardiology (ACC), and the American Heart Association (AHA) make specific recommendations on the use of biomarkers for the detection of myocardial infarction (MI) *(2–5)*. The redefined criteria used to classify acute coronary syndrome (ACS) patients presenting with ischemic symptoms as acute, evolving, or recent MI are heavily predicated on an increased serum/plasma cardiac troponin (I or T) concentration *(2–4)*. Furthermore, in the new ACC/AHA guidelines for management of patients with unstable angina and non-ST-segment elevation MI (NSTEMI), an increased cardiac troponin value establishes the diagnosis of NSTEMI, whereas a normal cardiac troponin value establishes the diagnosis of unstable angina in ACS patients with ischemic discomfort *(5)*.

The new guidelines emphasize the following clinical issues. First, increases of cardiac troponins are indicative of myocardial injury but are not synonymous with MI or an ischemic mechanism of injury. If an ischemic mechanism of injury is unlikely, other etiologies of myocardial injury should be pursued. Second, increases in cardiac troponin likely reflect irreversible rather than reversible injury, although there is continuing debate on this issue. Third, the degree of the increase of cardiac troponin in ischemia-induced injury patients is related to the patient's prognosis. Fourth, patients who undergo interventional procedures, such as percutaneous transluminal coronary angioplasty (PTCA) or heart surgery, are likely to have increased cardiac troponin as a consequence of the procedure. In heart surgery patients, no biomarker is currently capable of distinguishing injury caused by a MI from the procedure-induced injury itself. However, increases of cardiac troponin after coronary angioplasty or stent placement is indicative of ischemic cell death and should be labeled as a MI.

The guidelines also emphasize the following laboratory (analytical) issues. First, the diversity of the various cardiac troponin assays, especially for cardiac troponin I (cTnI), has led to substantial confusion among both clinicians and laboratorians. Standardization issues will likely assist in resolving some of these concerns. Acceptance of individual troponin assays should be based on the peer-reviewed literature. Second, clinical studies in the peer-reviewed literature should provide information pertaining to an assay's imprecision (CV), reference intervals, potential analytical interferences, and acceptable specimen types. An upper reference limit, defined as the 99th percentile with an acceptable imprecision of $\leq$10%, has been proposed. This places a large responsibility on the manufacturers of all cardiac troponin assays to optimize the low end of their assays. Although it is presently recognized that relatively few, if any, companies can meet this recommendation, it was the intent of the cardiology community to challenge the troponin assay manufacturing industry to meet this critical issue because diagnostic and therapeutic decisions will be based on lower cardiac troponin cutpoints. Although the use of plasma (heparin) instead of serum had initially been advocated as a means of decreasing the overall turnaround time for reporting a result, recent studies have shown that several cardiac troponin assays may give variable and substantially lower concentrations for heparinized plasma vs serum *(6, 7)*. Therefore, each assay needs to be validated for both serum and plasma. Third, cardiac troponin concentrations should be measured on serial blood samples collected at least 6–9 h after onset of symptoms, before a patient is ruled in or ruled out for MI. Fourth, if cardiac troponin assays are not available, the best alternative is creatine kinase MB (CK-MB) mass. Rapidly appearing biomarkers, such as myoglobin or CK-MB isoforms, are recommended for patients in need of an early triage, but they do not confirm the diagnosis of MI. We completely support the new cardiology guidelines and support the evidence-based literature that demonstrates cardiac troponin as the definitive marker to be utilized for detection of the MI, risk stratification, and to assist clinicians in optimizing therapy.

From a clinical perspective, there is clear evidence that any amount of detectable cardiac troponin release is associated with risk of adverse clinical events. For cardiac troponin T (cTnT), the FRISC II study demonstrated that risk stratification was achieved with use of a cutoff concentration at the 99th percentile (8.5% incidence of death or AMI at 12 months for cTnT $<$0.01 μg/L vs 18.0% for cTnT $\geq$0.01 μg/L; $P <$0.001) *(8)*. Similar results have been demonstrated for cTnI, where use of the 97.5th percentile cutoff of 0.1 μg/L produced significant odds ratios of 2.2 (confidence interval, 1.3–3.6), 2.8 (1.5–5.1), and 3.0 (1.5–5.7) with the Immuno 1 (Bayer), ACS:180 (Bayer), and Dimension RxL (Dade Behring) analyzers, respectively *(9)*. For each assay, the values at the 97.5th vs 99th percentiles are similar. Although preliminary trials show risk stratification benefits at the low end of cardiac troponin assays, as noted above, the majority of manufacturers cannot meet the 10% imprecision (CV) recommendations at the 99th percentile. It is our opinion, therefore, that in the context of clinical medicine, a predetermined higher concentration that meets the goal of 10% imprecision be used for each assay as a medical diagnostic guide

for therapy until the goal of a 10% CV can be achieved at the 99th percentile. The magnitude of the medical problem stemming from a CV-related misclassification of patients is unknown, but this likely will be answered over time. In any event, the clinical assessment of the patient still needs to be part of the medical decision process, as highlighted in the new guidelines *(2–5)*.

With these newly published guidelines, we feel it is important and timely to revisit the National Academy of Clinical Biochemistry (NACB) *(10)* and the IFCC *(11)* guidelines pertaining to the use of cardiac markers published in 1999, and compare and contrast them with the ACC/ESC/AHA guidelines. First, both the NACB and IFCC guidelines recommended the use of two markers (an early marker and a late marker). The NACB recommended specimen collection at admission, 2–4 h, 6–9 h, and an optional collection at 12–24 h, whereas the IFCC recommended specimen collection at admission, 4, 8, and 12 h (or next morning). The ESC/ACC and the ACC/AHA guidelines state that for early MI diagnosis (within 6 h of the onset of symptoms), an early biomarker of cardiac injury (myoglobin or CK-MB subforms) should be considered in addition to a definitive marker that increases later (troponin) *(2–4)*. It is inferred that use of an earlier marker would require collection of an earlier blood sample, between admission and 6 h. Thus, there appears to be a consensus between the laboratory and cardiology recommendations. Furthermore, both groups acknowledge that only cardiac troponin testing is necessary if a very early triage protocol is not being followed, and we concur with this. A similar approach was recommended by the American College of Emergency Physicians, who suggest a "repeat CK-MB at 2–3 h after baseline or repeat myoglobin at 1–2 h after baseline and utilization of the ΔCK-MB or Δ myoglobin . . . " *(12)*.

In the original criteria for MI, WHO listed unequivocal changes of serial enzyme measurements as one of the three criteria for diagnosis, the other two being electrocardiographic changes and clinical features such as chest pain *(13)*. With the development of protein markers such as myoglobin and cardiac troponin, the NACB and IFCC Committees made a recommendation to expand on the enzyme diagnostic criteria for MI to include proteins. However, the NACB recommendations stopped short of actually changing the definition of MI and instead stated that it was the responsibility of cardiology groups, and not laboratorians, to redefine all of the criteria for diagnosis of MI. Thus, the redefinition of MI proposed by the joint ESC/ACC Committee is the appropriate next step.

Second, regarding cutoff concentrations for cardiac markers, the NACB and IFCC recommended the use of two decision limits for cardiac troponin, a low limit that establishes the first presence of myocardial injury (97.5th percentile) and a high limit that establishes injury to the extent that it qualifies as MI (ROC curve determined), as defined previously by WHO. At that time, the NACB Committee was concerned about the "social, psychological, and socioeconomic" impact of designating patients with minor myocardial injury as MI, and by lowering the cutoff, the incidence of MI would dramatically increase. Again, the NACB Committee opined that "until the criteria for diagnosis of AMI are redefined by WHO or other clinical groups such as the American Heart Association or American College of Cardiology, the NACB Committee recommends a two-cutoff designation for cardiac troponin." The ESC/ACC Committee has noted that improvements in biomarker assay technologies have continuously led to a more accurate ability to diagnose MI, leading to a gradual increase in MI incidence over the years since the inception of the WHO criteria. The introduction of cardiac troponin is simply the next step in the ever-evolving medical technology. Again, we agree with this approach. As the joint ESC/ACC redefinition of MI is fully endorsed and implemented, there will no longer be the need for the NACB recommendation for two cutoff concentrations.

Third, in establishing the lower of the two cutoffs, the NACB and IFCC recommended use of the 97.5th percentile of the normal healthy population, consistent with other clinical laboratory tests. By definition, this will produce an analytical false-positive rate of 2.5%. The ESC/ACC and AHA/ACC guidelines have adopted a 99th percentile as a single cut point, which is between the low and high cutoffs recommended by the NACB and IFCC. The rationale for increasing the lower cutoff from the 97.5th to the 99th percentile was to limit the number of false-positive designations of myocardial injury. Manufacturers of cardiac troponin assays must now ensure that their assays have the necessary sensitivity and imprecision (CV $\leq$10%) to meet these new cutoffs. Although this process of improving imprecision will not occur overnight, we continually will stress the importance of improving low-end assay imprecision. We anticipate that, as CVs of 10% or less are achieved at concentrations corresponding to the 99th percentile for each assay, medical decision cutpoints will continue to be lowered *(8, 9)*. Nevertheless, as the precision and performance of cardiac troponin assays improve, more clinical trials will be necessary to define the optimal cutpoints for specific clinical decisions.

Finally, the NACB and IFCC recommended that cardiac troponin be the new biomarker standard for detection of myocardial damage. In the context of unstable angina, both the NACB and IFCC Committees stated that patients with small increases in cardiac troponin should be acutely treated to minimize the risk associated with myocardial injury. Other clinical groups have concurred with this recommendation. The ACC/AHA Task Force listed cardiac troponin as the preferred marker for early risk stratification *(5)*. Results of cardiac troponin were added to the Braunwald class IIIB classification of unstable angina *(14)*. The United States Agency for Health Care Policy and Research guidelines added an increased serum troponin I or T as one of the major criteria for entry of unstable angina patients into the high-risk group for short-term risk of adverse cardiac events *(15)*. The Cardiac Society of Australia and New Zealand also lists cardiac troponin as the marker of choice for ACS *(16)*.

Each of these clinical groups along with the laboratory community has independently reached the conclusion that cardiac troponin is the best marker for diagnosis, risk stratification, and guidance of therapy in ACS. Again, we totally support the recommendation that only cardiac troponin is necessary. We further recommend that clinicians begin moving away from the use of CK-MB as their primary marker of choice.

In summary, we feel the ESC/ACC and ACC/AHA guidelines *(2–4)* should now become required reading for all healthcare professionals, including clinicians, laboratorians, residents, students, hospital administrators, and industry personnel, as their medical and societal impact will be far reaching. We support the overall conclusions of the new cardiology guidelines that have underscored the initially published laboratory guidelines asserting that cardiac troponin testing is the new, definitive laboratory standard for the diagnosis of MI.

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